Unified Total Syntheses
of the Antibiotic Macrolides
Aldgamycin N and Mycinamicin IV
&
De novo Syntheses of their Carbohydrate Units

Dissertation

Zur Erlangung des akademischen Grades eines
Doktors der Naturwissenschaften
(Dr. rer. nat.)
Der Fakultät für Chemie und Chemische Biologie
der Technischen Universität Dortmund

vorgelegt von

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Mülheim an der Ruhr, 10.01.2022

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DANKSAGUNG

ABSTRACT

The present thesis provides a unified total synthesis approach to the 16-membered macrolide antibiotics aldgamycin N and mycinamicin IV. Both natural products represent two distinct series of macrolide targets, which are characterized by a highly conserved "eastern" acid half but subtle variations within their macrocyclic frameworks, as well as their specific glycosides. The unified total syntheses are enabled by the swift assembly of the macrocyclic frameworks by merging individual carbonyl and alkyne modules as the two main synthetic fragments and the subsequent ruthenium-catalyzed transformation of the C–C triple bonds into the key functionalities distinguishing the individual targets. The eastern carbonyl fragments are reached from a single common terminal alkene building block formed on multi-gram scale by an asymmetric vinylogous Mukaiyama-type aldol reaction. Wacker oxidation of the common alkene terminus provides a ketone as the anchor point towards aldgamycin N, while an unprecedented stereo- and branch-selective hydroformylation at this site controlled by a literature-reported rhodium complex furnishes an aldehyde to serve as the handle for the preparation of mycinamicin IV. After combination of these fragments with their respective alkyne counterparts by carbonyl addition and closure of the macrolactone rings by an unusual stannoxane-mediated transesterification, the individual target moieties are forged using ruthenium-catalyzed transformations of the propargylic alcohols obtained from the carbonyl additions. Specifically, these late-stage key steps comprise a regioselective hydrostannation/Chan-Lam-type oxygenative coupling sequence to unveil the acyloin of aldgamycin N, and a rare example of a rearrangement of a secondary propargylic alcohol into the unsaturated ketone of mycinamicin IV. Completion of the target syntheses by attachment of the carbohydrates proved challenging and required close attention to both the timing of the glycosidation events and the exact glycosylation conditions employed. Systematic screening of the glycosylation conditions showcases the crucial distinction in reactivity between different silyl triflates for the activation of trichloroacetimidate donors. The rare branched-chain octose D-aldgarose and the basic amino sugar D-desosamine, required as the 4,6-dideoxy carbohydrates at the C5 position of both natural products, are also reached by a unified approach. The employed common building block is synthesized using an enantioselective hetero-Diels-Alder reaction, and intermediates of both *de novo* syntheses may serve the practical preparation of other naturally occurring 4,6-dideoxy sugars as well as derivatives thereof.

ZUSAMMENFASSUNG

Die vorliegende Dissertation stellt einen vereinheitlichten Zugang zu den 16-gliedrigen Makrolidantibiotika Aldgamycin N und Mycinamicin IV per Totalsynthese dar. Beide Naturstoffe repräsentieren zwei eigene Reihen von Makroliden, die sich durch eine höchst konservierte „östliche" Carbonsäurehälfte aber dennoch einige Variationen in deren makrocyclischen Gerüste, sowie ihre spezifischen Kohlenhydrate, auf markante Weise auszeichnen. Die vereinheitlichten Totalsynthesen werden durch raschen Aufbau der Makrocyclen durch Verknüpfung individueller Carbonyl- und Alkin-Module als die beiden synthetischen Hauptfragmente und die nachfolgenden ruthenium-katalysierten Umwandlungen der C–C-Dreifachbindungen in die Funktionalitäten der individuellen Zielmoleküle ermöglicht. Die östlichen Carbonylfragmente werden von einem einzelnen terminalen Alken als gemeinsamen Baustein erhalten, der durch asymmetrische vinyloge Mukaiyama-Aldolreaktion im Maßstab von mehreren Gramm gebildet wird. Wacker-Oxidation des gemeinsamen Alken-Terminus stellt ein Keton als Ankerpunkt auf dem Weg zu Aldgamycin N zur Verfügung, während, ohne jegliche Präzedenz in vergleichbarem Kontext, eine stereoselektive Hydroformylierung mit einem literatur-bekannten Rhodium-Komplex an dieser Stelle bevorzugt zum verzweigten Aldehyd führt, der dem Zugang zu Mycinamicin IV dient. Nach Verknüpfung dieser Fragmente mit den dazugehörigen Alkin-Gegenstücken durch Carbonyladdition und Bildung der Makrolacton-Ringe durch eine ungewöhnliche stannoxan-vermittelte Umesterung, werden die charakteristischen Funktionalitäten der Zielmoleküle durch ruthenium-katalysierte Transformationen der sich aus den Carbonyladditionen ergebenden propargylischen Alkohole erschaffen. Im Detail umfassen diese späten Schlüsselschritte eine Sequenz von regioselektiver Hydrostannierung und Chan-Lam-artiger oxygenierender Kupplung zur Bildung des Acyloins von Aldgamycin N, sowie ein seltenes Beispiel einer Umlagerung eines sekundären propargylischen Alkohols in das ungesättigte Keton von Mycinamicin IV. Vervollständigung der Naturstoffsynthesen durch Anbringung der Kohlenhydrate offenbarte sich als herausfordernd und erforderte umfassende Untersuchungen sowohl hinsichtlich des Zeitpunkts als auch bezüglich der genauen Bedingungen der Glycosylierungen. Systematische Erfassung der Glycosylierungsbedingungen heben die essentiellen Reaktivitätsunterschiede verschiedener Silyltriflate als Aktivatoren für Trichloracetimidat-Donoren hervor. Die seltene Octose D-Aldgarose mit verzweigter Kette und der basische Aminozucker D-Desosamin, die als 4,6-Dideoxy-Kohlenhydrate an den C5-Positionen der Naturstoffe benötigt werden, werden ebenfalls durch einen einheitlichen Zugang erhalten. Der dazu eingesetzte gemeinsame Synthesebaustein wird durch eine enantioselektive Hetero-Diels-Alder-Reaktion erhalten. Die Intermediate beider *de-novo*-Synthesen könnten der Synthese weiterer in der Natur vorkommenden 4,6-Dideoxy-Zucker sowie Derivaten davon nützlich sein.

CONTENTS

ABBREVIATIONS

Ac	acetyl
acac	acetylacetonato
aq	aqueous
BOM	benzyloxymethyl
bp	boiling point
br	broad
CoA	coenzyme A
cod	cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dibal-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N'-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppb	bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
dTDP	deoxythymidine diphosphate
eda	ethylenediamine
EE	ethoxyethyl
HFIP	hexafluoroisopropanol
LLS	longest linear sequence
Mc	methylcarbonyl
m-CPBA	3-chloroperbenzoic acid
MOM	methoxymethyl
mp	melting point

MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
NIS	*N*-iodosuccinimide
NOE	nuclear Overhauser effect
pin	pinacolato
Piv	pivaloyl
PMB	4-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
SEM	(2-(trimethylsilyl)ethoxy)methyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBPA	tris(4-bromophenyl)ammoniumyl hexachloroantimonate
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
tfa	trifluoroacetate
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Chapter 1

Introduction

1.1 Antibiotics

Antibiotics (Greek for "against life") are chemical compounds with the characteristic property of either destroying bacterial life (bactericidal effect) or inhibiting its growth (bacteriostatic effect). They occur naturally as secondary metabolites produced by organisms to combat competing entities, or they are non-natural molecules specifically designed by humankind for the treatment of bacterial infections.[1] During the course of the 20th century, the discovery of antibiotics and their general supply mark a profound leap in modern medicine and deeply changed our civilization by enabling us to alleviate the course of infectious diseases, which once were severely life-threatening, if not meaning imminent death.[2] While epidemic courses of most of the "classical" bacterial diseases are largely prevented by systematic vaccination and higher infrastructural and sanitary standards, acute treatment of bacterial infections is subject to antibiotic therapy. Antibiotics play a key role in today's spectrum of medical care in a broader sense, *e.g.* in the prevention of postoperative infections after common surgeries or organ transplantations.[3] Aside from their significant impact on medicine, antibiotics have also become indispensable for the agricultural industry because of their use in crop growing[4] and veterinary context[5]: in large-scale animal husbandry antibiotics are administered to the livestock to promote its growth and to prevent diseases, which otherwise would be fatal in that situation.

While the first natural antibiotic to be described as such (mycophenolic acid; cf. figure 1.1) alongside the potential therapeutic use were initially overlooked after 1893,[6] the first synthetic antibiotic (Salvarsan) and its derivatives remained the standard medication for the treatment of syphilis for decades.[7] The invention and ultimate approval of the arsenical compound Salvarsan as a drug in 1910 resulted from a more general idea of "chemotherapia specifica" formulated by Paul Ehrlich. He was hoping to find a "magic bullet" ("Zauberkugel"), a substance capable of selectively killing pathogens causing the corresponding disease of a sick patient without dealing the patient any undesired harm in addition to the curing effect.[8]

mycophenolic acid

Salvarsan
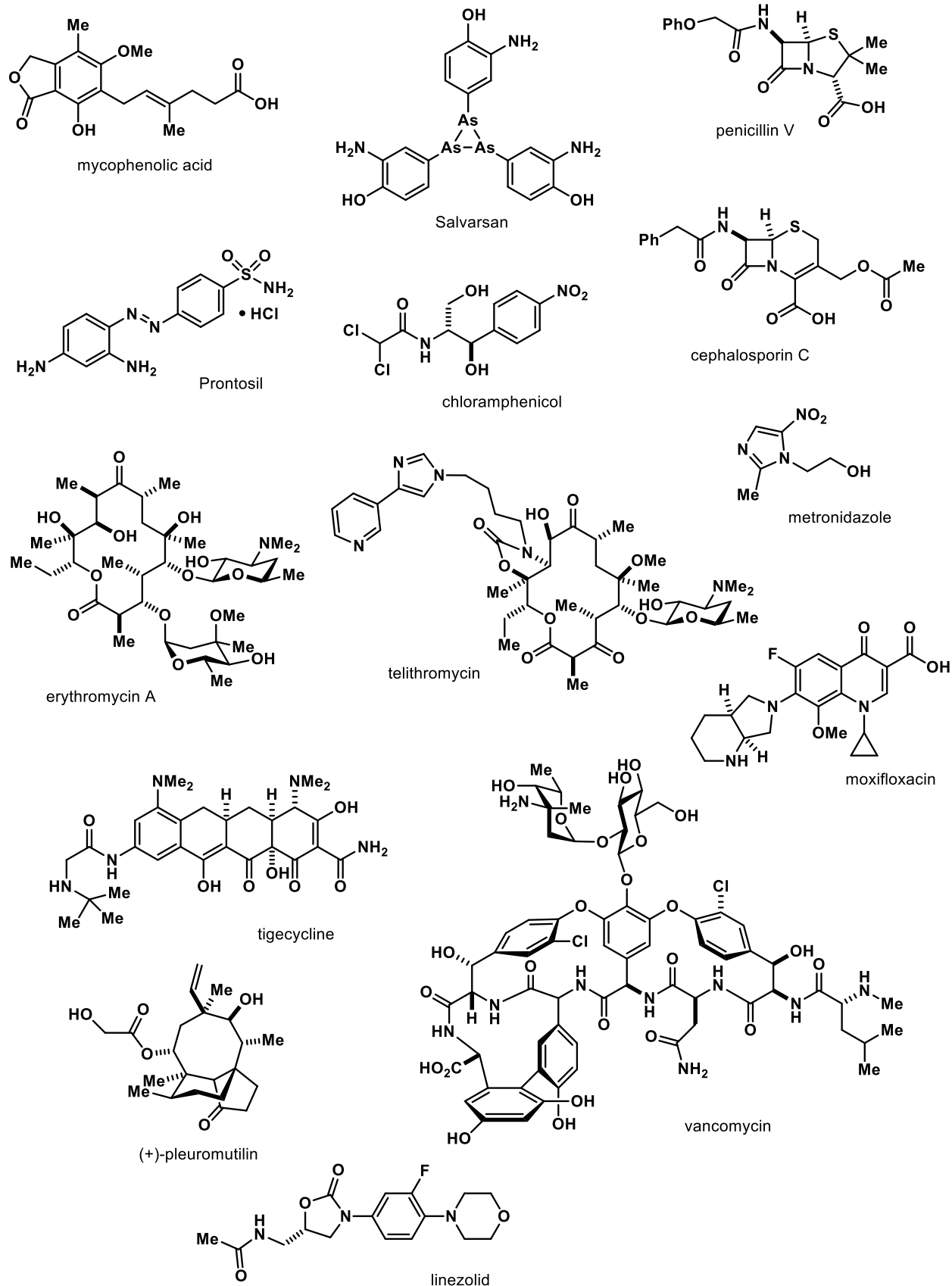
penicillin V

Prontosil

chloramphenicol

cephalosporin C

erythromycin A

telithromycin

metronidazole

moxifloxacin

tigecycline

vancomycin

(+)-pleuromutilin

linezolid

Figure 1.1: Select historic and recent examples of antibiotics.

Chapter 1. Introduction

In 1909, his fundamental research found recognition with the Nobel Prize in Physiology or Medicine together with Ilya Mechnikov.[9] The therapeutic relevance of Salvarsan was later raveled by arguably one of the greatest achievements of humankind during the last century:[10] the discovery of life-saving penicillin by Alexander Fleming in 1928.[11] Penicillin became available to the public after World War II and its discovery was rewarded with the Nobel Prize in Physiology or Medicine in 1945. Shortly thereafter, the structure of the penicillin family, which is centered around the highly strained 4,5-bicyclic β-lactam scaffold, was unambiguously proven by X-ray crystallographic analysis by Dorothy Crowfoot Hodgin (Nobel laureate in Chemistry, 1964).[12] With this, the 1940s started a "golden era" in the discovery of antibiotics. In addition to the β-lactam class and sulfonamides, the antibiotic effect of which had already been found coincidentally during the synthesis of an azo dye at Bayer in the mid-30s (Prontosil), most of the antibiotic classes still used today emerged in this era, most notably tetracyclines, macrolides, polypeptides, glycopeptides, aminoglycosides, quinolones and phenylpropanoids.

Many major milestones in the field of organic synthesis have accompanied the discovery of these antibiotic substances, and antibiotics continue to lend formidable targets to natural product synthesis. The first total synthesis of penicillin V was reported in 1957 by John Sheehan.[13] Obviously, the success of this total synthesis critically hinged on the late-stage closure of the sensitive β-lactam ring of the penicillin family. To this end, the Sheehan group developed the coupling of carboxylic acids with amines mediated by a carbodiimide (DCC), a methodology that is still regularly used today.[14] The total synthesis of the related cephalosporin C was presented by Robert B. Woodward in his Nobel lecture in 1965.[15] Woodward also coined the term "macrolide" to refer to antimicrobial agents characterized by a macrolactone ring.[16] Due to their structural features, the class of macrolide antibiotics has posed serious challenges early on to the synthetic community, and total syntheses of macrolides required advancements that today belong to the elementary tool-set of organic chemistry. The major challenges are stereocontrol in the creation of the carbon chain comprising the macrolide core with all its stereocenters, closure of the large lactone rings by esterification or olefination, and selective glycosidation.[17] The synthesis of methymycin by Masumene *et al.* in 1975 was the first total synthesis of a macrolide antibiotic.[18] In 1978, the group of E. J. Corey disclosed the first synthesis of erythronolide B,[19] and the total synthesis of the glycosylated macrolide antibiotic erythromycin A was reported in 1981 by the group of Woodward, who had passed away two years before the completion of that synthetic endeavor.[20] These classic landmarks of total synthesis, which still relied on traditional substrate control in the creation of the consecutive stereocenters found in the carbon chains of the macrolide antibiotics, illustrate solutions to some of the challenges posed by this natural product class. As synthetic methodology progressed, carbon–carbon bond-forming reactions like the aldol reaction made the selective creation of the macrolide cores by reagent- and catalyst-control possible. To this

3

end, the plethora of aldol reaction methodologies has grown to its own field[21] and also gave birth to the important concept of double stereocontrol/asymmetric induction.[22]

Although the first glycopeptide of the vancomycin family had already been isolated in 1953 and drug approval followed soon, it took the scientific community several decades to elucidate and assemble this impressive structure.[23] Vancomycin was first synthesized as its aglycon in the group of D. A. Evans in 1998, followed by preparation of the glycosylated target by K. C. Nicolaou *et al.* a year later.[24] Due to its antimicrobial activity against penicillin-resistant bacterial strains, vancomycin is today one of the last-resort antibiotics in clinical context when other antibiotics fail to exert their specific effect.

The therapeutic value and immense relevance of antibiotics for society notwithstanding, the decades following the golden era of antibiotic research during the period of 1940 – 1970 witnessed a large innovation gap until the beginning of this century. Indeed, one seemed to be convinced that the above-described antibiotic "wonder drugs" were a sufficient arsenal for the cure and prevention of bacterial infections.[25] This view has dramatically changed, however, with the increasing occurrence of bacterial strains exhibiting resistance against the same antibiotic agents, which formerly used to affect these strains.[26] Most strikingly, emergence of antibiotic resistance is especially prevalent in hospitals where antibiotics are both heavily used and needed.[27]

1.2 Antibiotic Resistance

In striking difference to most other drugs, the efficacy of antibiotic drugs is not perpetual due to the rise of resistant bacterial strains. First, the sheer existence of antibiotic resistance is of no great surprise, considering that the organism, which produces the antibiotic substance as a defense mechanism in its environment, will avoid to kill itself with its own metabolite (self-resistance).[1] The acquisition of secondary antibiotic resistance, however, is an inevitable consequence of evolutionary selection. Ironically, the evolutionary pressure in that selection process is not only induced by the use of antibiotics by humans for the treatment of bacterial infections, but has always been present due to the competition of bacteria against each other. The relatively short timescale of bacterial evolution becomes apparent when considering their rapid growth cycles ($\sim$30 min) and existence in extremely large numbers ($\sim$5 $\cdot$ 10^{31}), thus giving rise to high chances for mutations.[28] These rapidly occurring mutations may allow the microorganisms to eventually escape their antibiotic eradication. The mechanisms of antibiotic resistance have been identified to rely on (i) genetic changes that effect chemical modification or destruction of the antibiotic resulting in its deactivation (*e.g.* by enzymatic hydrolysis of β-lactams), (ii) expulsion of the antibiotic from the bacterial cell (efflux pumps), or (iii) alteration of the target under antibiotic attack (*e.g.* by exchange of structural amino acids). The Infectious Diseases Society of America has released a list of particularly concerning

bacterial pathogens, which already have developed multi-drug resistance and may thus cause difficult to treat infections.[26] Collectively, these are known as ESKAPE pathogens: vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Pseudomonas aeruginousa*, and *Enterobacter* species.

While the emergence of resistance can certainly be slowed down by careful use of antibiotics (*i.e.* avoiding overuse, choosing from the spectrum of different substances, correct dosage and compliance of the patients),[29][30] the urgency for new antibiotic substances and modifications of established ones in the race against resistance have been stressed lately.[31] Among others, recent subjects of antibiotic research and development are oxazolidinones (linezolid, US-approval in 2000), fluoroquinolones (*e.g.* moxifloxacin, US-approval in 1999) and tetracyclines (*e.g.* tigecycline, US-approval in 2005). Furthermore, much effort has been put into the modification of erythromycin, resulting in its ketolide derivatives, which are distinguished by the replacement of the neutral sugar at the 3-position of the erythromycin core for a simple ketone, rendering it more stable towards acidic hydrolysis (*e.g.* telithromycin, US-approval in 2004, later withdrawn from the market due to side reactions).[32] Under current clinical trial is the next-generation ketolide solithromycin.[33] As judged from these examples, antibiotic research has continued to predominantly focus on those compound families known for a long time. Critical in the combat of antibiotic resistance, however, is the discovery of new compounds with a different mode of action. A less-explored and very promising compound class due to their activity profile against otherwise resistant strains are cyclic polypeptides, some of which have only been discovered recently.[34] Another example for a novel molecular scaffold for potential clinical use are the pleuromutilins,[35] which have also attracted renewed attention in the total synthesis community.[36]

1.3 The Mycinamicin and Aldgamycin Families: Macrolides

With only a few exceptions, nature rather than a high-throughput screening approach driven by synthesis of small molecules continues to be the prime discovery source of antibiotics. Antibiotic substances are generally produced by microbes for chemical defense against other microorganisms. A particularly prolific source of antibiotics has been the widely spread class of Gram-positive actinobacteria.[37] Soil, a common habitat for actinobacteria, presented a well-accessible source of bacterial strains in the early decades of antibiotic research. The mycinamicin macrolides were first isolated in 1980 from *Micromonospora griseorubida* collected from Japanese soil.[38] With the rate of discovery from terrestrial samples declining over time, the exploration of bacterial strains has also expanded to more remote places; the (deep) sea naturally being an interesting choice of further research.[39] Recently, several novel aldgamycin macrolides were discovered from the marine *Streptomyces* strain HK-2006-1.[40][41] Important in the light of rising

antibiotic resistance is the fact that the members of both the mycinamicin and aldgamycin families exhibit significant and selective activity against various strains of *Staphylococcus aureus*, which belong to the particularly infamous ESKAPE pathogens (see last section).

The aldgamycins and mycinamicins are closely related macrolide antibiotics with an unsaturated 16-membered macrolactone core. Further relatives include the tianchimycin[42], swalpamycin[43] and chalcomycin[44] macrolides, all of which have a D-mycinose unit attached to the macrolactone core whenever the aglycon is glycosylated at the primary C20 hydroxyl group (figure 1.2). The distinguishing features between the members of this compound series are the specific glycosides at the C5 position and subtle alterations of unsaturation and oxygenation in the vicinity of the C9 ketone. Specifically, the aldgamycins carry the eponymous D-aldgarose at the C5 alcohol, an unusual, branched-chain octopyranose, which occurs both with and without a carbonate in the side chain. The sugars of the other natural product families at this position vary, but they all have in common to be 4,6-dideoxy sugars. The basic C5 amino glycoside of the mycinamicin family, D-desosamine, also occurs in erythromycin. Amongst the different families, another differentiating characteristic is the alkyl group branching off C15. For the aldgamycins, a methyl group is the rule, while an ethyl group branches off C15 for all mycinamicins. The eastern half (C1–C9) of the macrolactone core is highly conserved over the full range of compounds. As the only exception, C8 occasionally carries an additional tertiary alcohol.

The reason for such ample compound diversity among these macrolide antibiotics to blossom from a single conserved framework lies in their common biosynthetic origin. Macrolide antibiotics belong to the natural product class of polyketides (hence their name: macrolactone polyketides).[17] Therefore, the macrolide aglycons are constructed block-wise from acetyl and propionyl CoA, and their carboxylated derivatives malonyl and (2*S*)-methylmalonyl CoA respectively. These biosynthetic thioester building blocks are connected by sequential *pseudo*-Claisen condensations with concomitant decarboxylations mediated by the machinery of multi-enzyme complexes, called the polyketide synthases (PKSs). While the growing macrolide core chain is being processed down an enzymatic assembly line via thio-linkages to different domains of acyl carrier proteins (ACPs), diversification of the skeleton results from (partial) reduction and/or dehydration of the intermediates, leading to ketones, alcohols, alkenes, or methylene groups. A starting propionyl residue ends up as an ethyl branch at the O-terminus, as observed for the mycinamicins, and the incorporation of (2*S*)-methylmalonyl units gives rise to the stereospecific methyl branches. In some cases, different building blocks are incorporated for the chain-extension, *e.g.* ethyl- and hydroxymalonyl units. At the end of the machinery is located a thioesterase domain (TE) which effects the intramolecular transesterification to terminate the chain elongation and extrude the macrolactone.
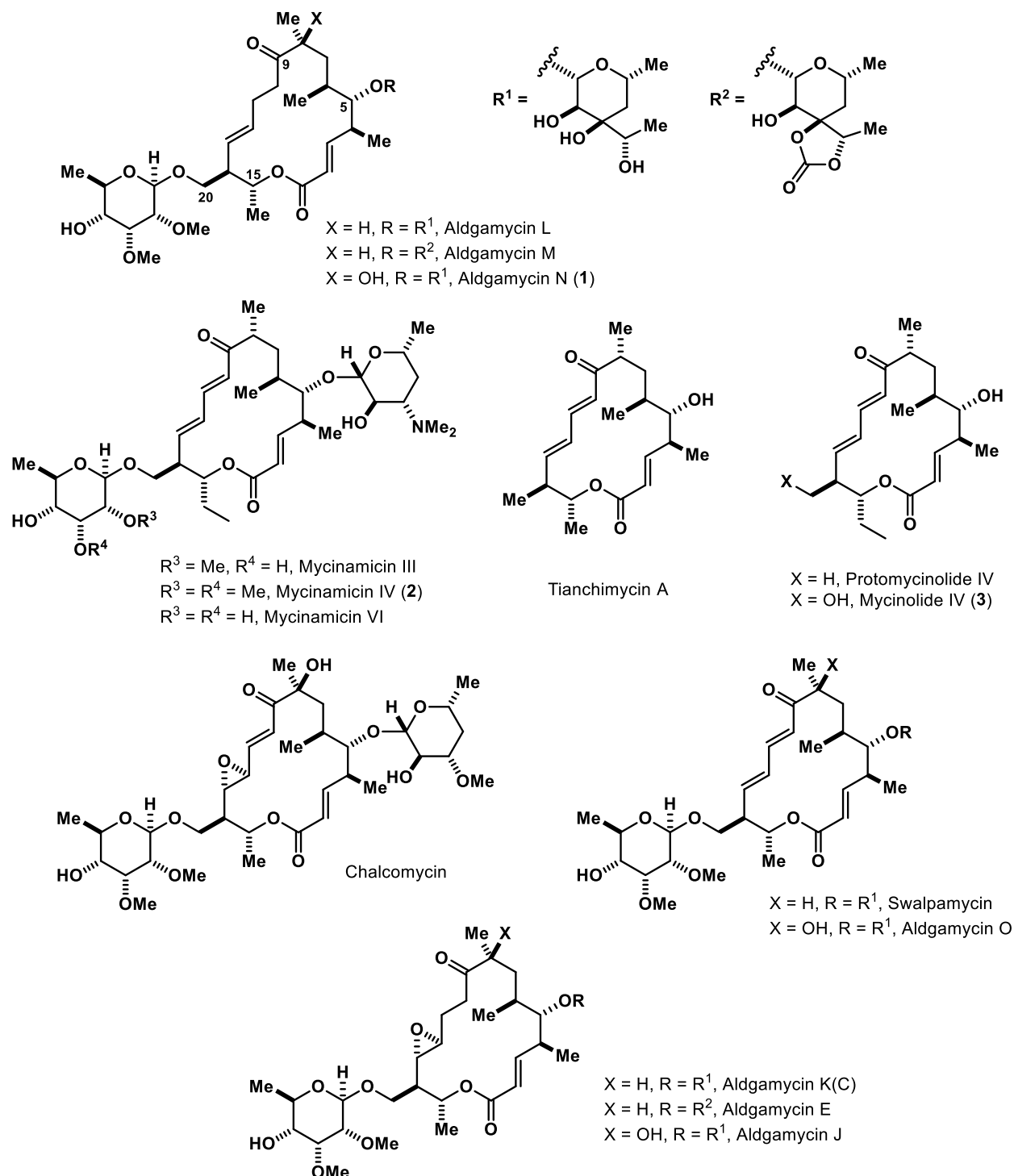
Figure 1.2: Select members of the aldgamycin, mycinamicin, tianchimycin, swalpamycin and chalcomycin macrolide families.

This modularity of enzymatic polyketide assembly and the genetics associated with it were first completely uncovered for the biosynthesis of 6-deoxyerythronolide B from *Saccharopolyspora erythraea* (DEB synthase, figure 1.3).[45] Enzymes outside the polyketide synthase complex may lead to additional functionalization to furnish the biologically active compounds. Besides hydroxylation and O-methylation,

7

by virtue of monooxygenases and methyl transferases respectively, these post-assembly line modifications include glycosylation mediated by glycosyl transferases. The sugar moieties are often vital for the affinity of the natural product to the biological binding site, and therefore for the resulting biological activity. For instance, the amino alcohol in the desosamine sugar is responsible for the binding of erythromycin to the bacterial ribosome, disrupting the protein synthesis during translation by sterically blocking the protein exit tunnel of the ribosome.[46]
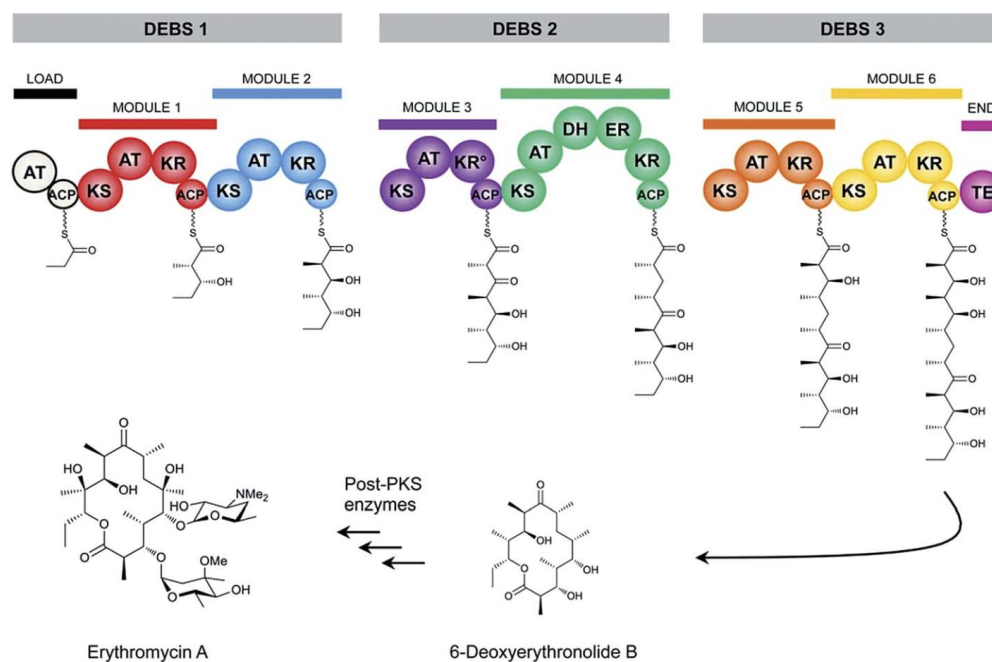
Figure 1.3: Schematic representation[45c] of the prototypical enzyme complexes responsible for the biosynthesis of deoxyerythronolide B (DEBS 1, 2, 3). The Acyltransferase (AT) transfers both the starting acetyl or priopionyl starting unit and the carboxylated chain-extending units. The acyl carrier protein (ACP) shuttles the growing polyketide along the domains, and the ketosynthase (KS) catalyzes the decarboxylative *pseudo*-Claisen condensation. The ketoreductase (KR), dehydrogenase (DH), and enoyl reductase (ER) effect the downstream adjustment of the oxidation state. The macrolactone closure is catalyzed by the thioesterase (TE). Post-PKS functionalizations furnish the biologically active natural product.

Several intermediates of the biosynthetic assembly of the macrolide core could be isolated up to the C15-C5 chain of the mycinamicins (mycinonic acids).[47] Interestingly, this discovery was made even before the underlying gene cluster producing the mycinamicins was known.[48] Furthermore, the seco-acid preceding the macrolactone of protomycinolide IV was the first seco-acid to be isolated from a fermentation culture as a biochemical intermediate towards a macrolide.[49] Radiolabeling studies showed that protomycinolide IV derives from five propionate and three acetate units as the primary biosynthetic intermediate, which subsequently is converted to the other mycinamicins by post-assembly line processes.[38e, 50] Very recently, mycinamicins were crystallized as binding complexes with the ribosome of a non-pathogenic model bacterium.[51] The data suggest a similar binding mode across all the different mycinamicins investigated and an analogous blocking or narrowing of the ribosomal protein exit tunnel as

previously described. The study emphasizes the underexplored therapeutic potential of 16-membered macrolides compared to the 14-membered congeners used since the early time of antibiotic therapy. A deeper extension into the ribosomal protein exit tunnel and their better gastrointestinal tolerance, lack of drug-drug interactions, as well as their activity against certain drug resistant bacterial strains are cited as their advantages.

Genetic studies confirmed that the remarkably similar structures of aldgamycins and chalcomycins in particular are indeed caused by their origin from a single gene cluster.[44, 52] Their biosynthesis was demonstrated to bifurcate at the stage of the C5 carbohydrate synthesis and attachment. It was suggested that the 4,6-dideoxy sugars D-chalcose and D-aldgarose are products of the same, well-examined biosynthetic route that delivers the amino sugar D-desosamine.[53] Biosynthesis of either a chalcomycin or aldgamycin derivative is initiated by carbonyl reduction or branching of a 3-keto sugar intermediate, respectively (figure 1.4). The two-carbon branching of aldgarose may evolve from nucleophilic addition of pyruvate to the keto sugar after Umpolung of the pyruvate keto group by binding to thiamine pyrophosphate and decarboxylation.[54]
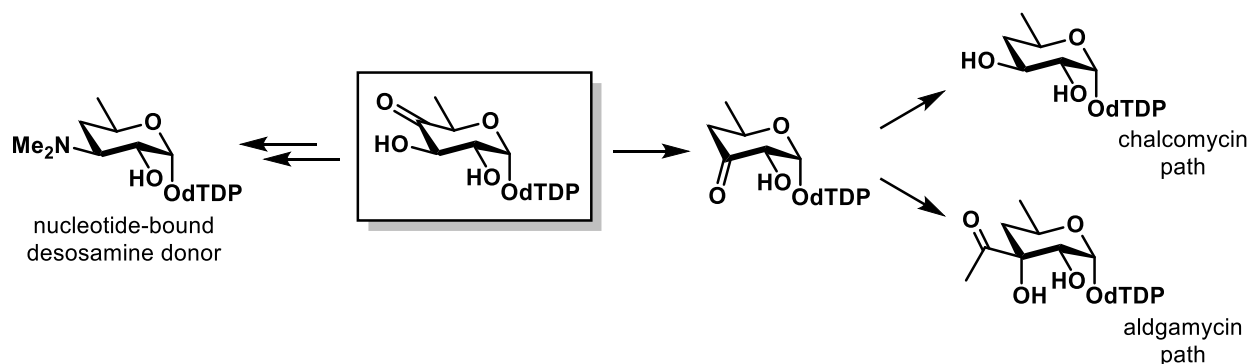
Figure 1.4: The bifurcation in the biosynthesis of chalcomycins and aldgamycins is located in the C5 carbohydrate syntheses (chalcose and aldgarose). Both rare 4,6-dideoxy sugars are suggested to originate from the same path as the amino sugar desosamine.

1.4 Previous Studies targeting the Mycinamicin Antibiotics

Among the compound families named in the previous section (figure 1.2), the members of the mycinamicins have been relatively prominent targets in natural product synthesis. In contrast, only a single (uncompleted) study towards a member of the aldgamycin estate had been disclosed before the work summarized in this thesis.[55]

M. Yamaguchi et al., 1984: Protomycinolide IV
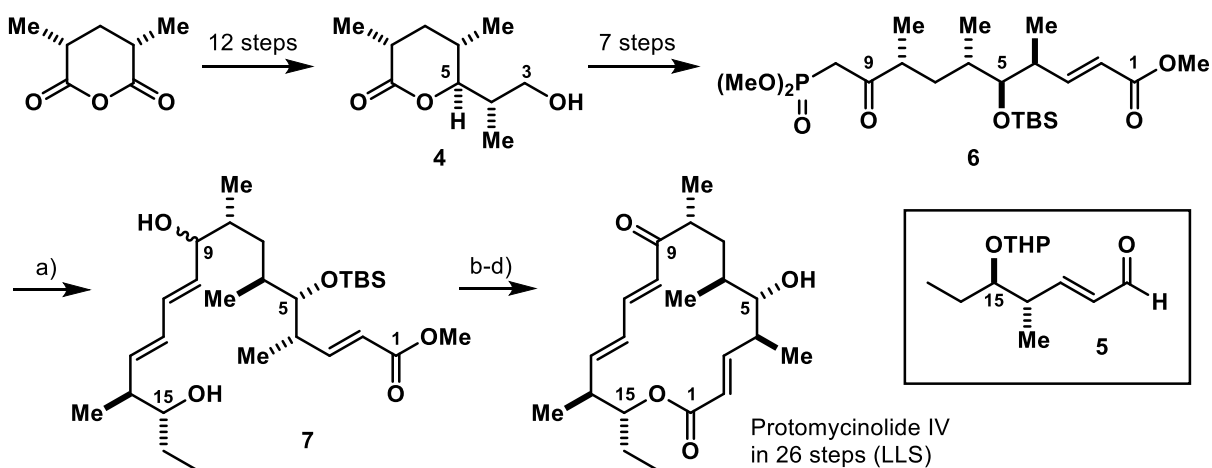
Scheme 1.1: Total synthesis of protomycinolide IV disclosed by M. Yamaguchi *et al.*. Conditions: a) (i) *t*-BuOK, THF/Et$_2$O, −78 °C → rt; (ii) **5**, −80 °C; (iii) PPTS, MeOH, 50 °C; (iv) NaBH$_4$, CeCl$_3$, MeOH, 0 °C, 74% (overall); b) KOH, MeOH/H$_2$O, 50 °C, 95%; c) (i) 2,4,6-trichlorobenzoyl chloride, NEt$_3$, THF; (ii) DMAP, toluene, reflux, high dilution, 53%; d) (i) Swern oxidation; (ii) HF, MeCN, 16% (over two steps).

The first total synthesis of a mycinamicin derivative was disclosed by Yamaguchi *et al.* in 1984.[56] Protomycinolide IV was accessed over a longest linear sequence of 26 steps (scheme 1.1). The synthesis started with dimethylated meso-glutaric anhydride to give the reduced form **4** of the Prelog-Djerassi lactone after several steps, which include a Sharpless asymmetric epoxidation to set the absolute stereochemistry of the intermediate. Further elaboration of this intermediate led to methyl ester **6** as the C1–C10 fragment with a terminal phosphonate in place for fragment merging by Horner-Wadsworth-Emmons condensation with aldehyde **5**, which itself had been obtained in nine steps. Interestingly, the C9 ketone had to be reduced at this stage before the seco-acid was liberated from **7** by basic saponification of the methyl ester, yet no explanation is provided by the authors. The oxidation state at the oxygenated C9 position was readjusted by Swern oxidation after the macrolactone had been closed selectively with the C15 alcohol employing the mixed anhydride method developed in the same group ("Yamaguchi macrolactonization").[57]

K. Suzuki et al., 1986: Protomycinolide IV
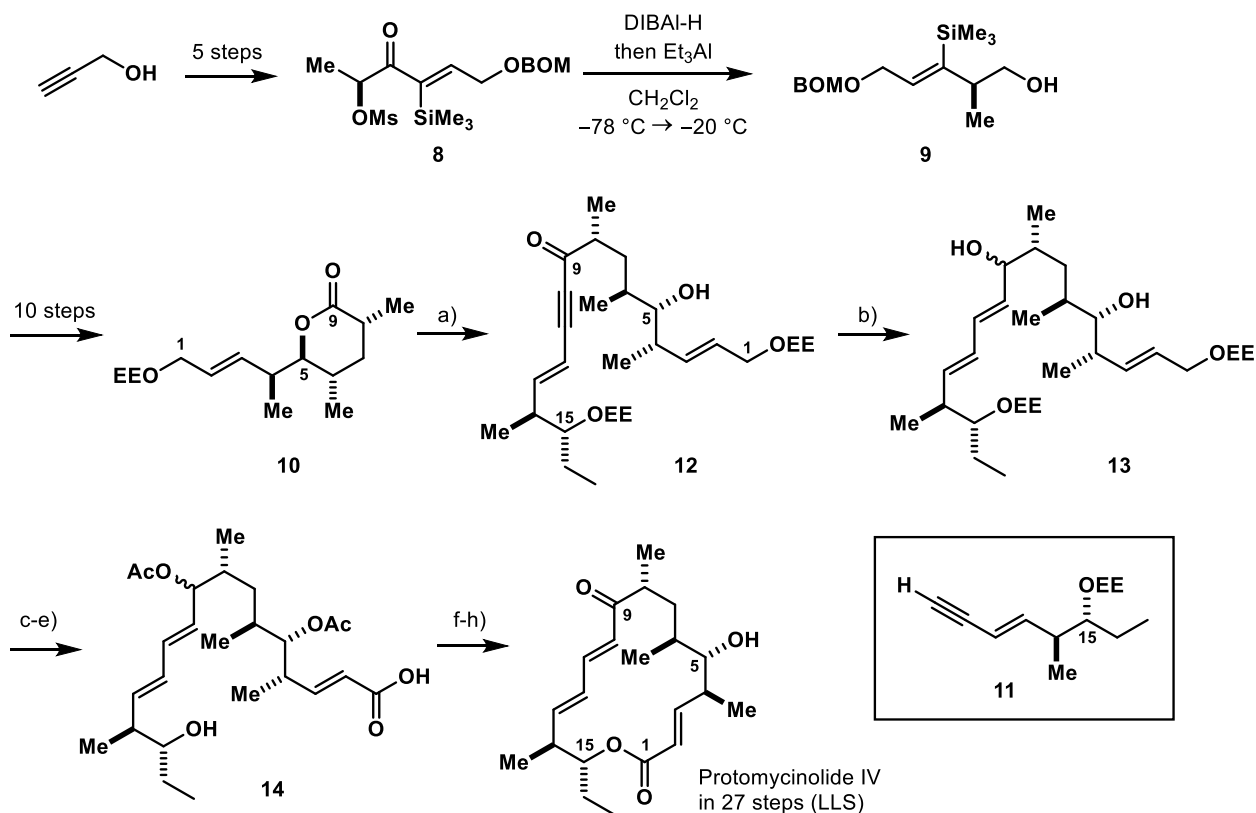
Scheme 1.2: Total synthesis of protomycinolide IV disclosed by K. Suzuki *et al.*. Conditions: a) **11**, *n*-BuLi, hexanes, 0 °C, 91%; b) LiAlH$_4$, THF, rt, 65%; c) Ac$_2$O, pyridine, rt, 98%; d) PPTS, MeOH, rt, 99%, e) (i) MnO$_2$, Et$_2$O, rt; (ii) NaClO$_2$, resorcinol/*t*-BuOH, pH 4 buffer, rt, 79%; f) (i) 2,4,6-trichlorobenzoyl chloride, NEt$_3$, THF, rt; (ii) 4-pyrrolidinopyridine, toluene, reflux, 58%; g) LiOH, MeOH/H$_2$O, rt, 44% or 46% (for separate C9 diastereomers); h) MnO$_2$, Et$_2$O, rt, 68% or 59% (for separate C9 diastereomers).

The protomycinolide IV synthesis by the group of K. Suzuki reported in 1986 started from propargyl alcohol and enantiopure lactic acid to give functionalized ketone **8** in five steps.[56] Reduction of the ketone induced a pinacol-type 1,2-rearrangement in presence of triethylaluminum to yield a suitable alcohol precursor **9** for the further elaboration into lactone **10** as the C1–C9 fragment (scheme 1.2). A similar approach furnished the C10–C17 fragment **11**, which contains a terminal enyne for the fragment coupling by nucleophilic lactone opening. At this stage, metal hydride reduction of the corresponding keto alkyne **12** gave the derived *trans*-configured allylic alcohol **13**, which would later lead to the enone motif of the natural product. The completed linear framework was prepared for macrolactonization by appropriate protecting group manipulations to liberate the C15 and C1 alcohols. Stepwise oxidation of the latter furnished the free carboxylic acid **14**. This hydroxy acid was cyclized once again by the Yamaguchi procedure, followed by cleavage of the acetyl protecting groups as well as oxidation of the C9 alcohol to furnish protomycinolide IV. The overall step count was similar to that needed in the total synthesis published before by the Yamaguchi group.

K. Suzuki et al., 1987/88: Mycinolide IV and Mycinamicin IV
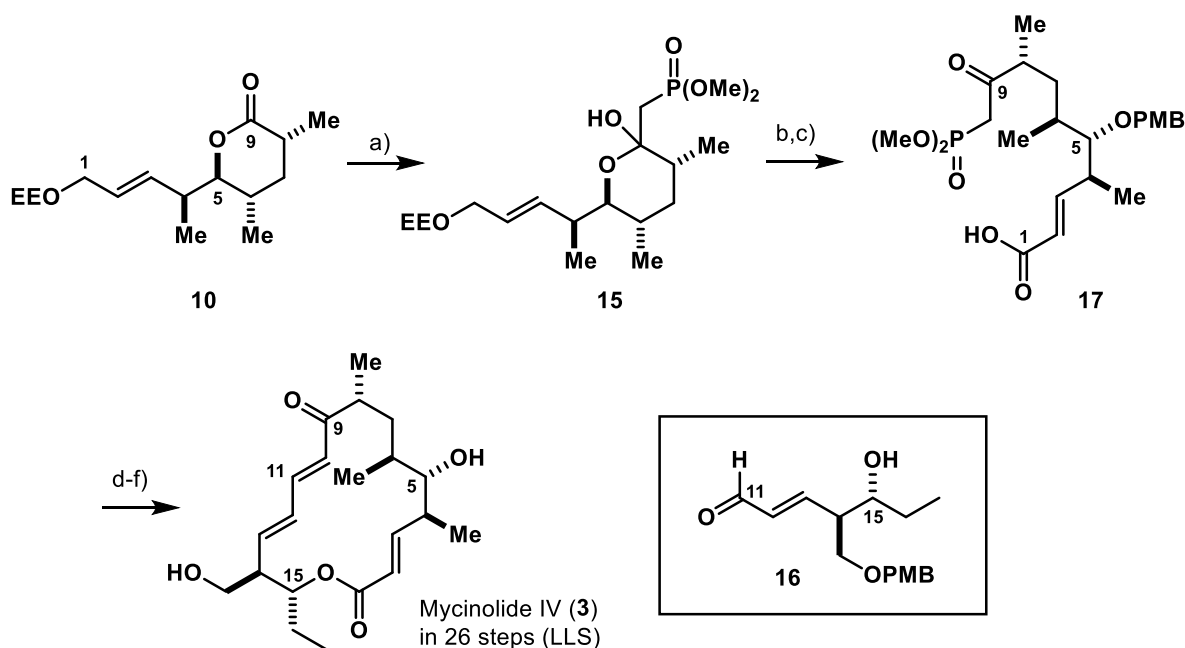
Scheme 1.3: Total synthesis of mycinolide IV disclosed by K. Suzuki *et al.*. Conditions: a) LiCH$_2$P(O)(OMe)$_2$, THF, −78 °C → rt, 77%; b) KH, PMBCl, THF, 80%; c) (i) PPTS, MeOH; (ii) MnO$_2$, Et$_2$O; (iii) NaClO$_2$, pH 4 buffer, 92% (over three steps); d) (i) 2,4,6-trichlorobenzoyl chloride, NEt$_3$, THF; (ii) DMAP, toluene, 60%; e) K$_2$CO$_3$, 18-crown-6, toluene, 70 °C, 35%; f) DDQ, CH$_2$Cl$_2$, H$_2$O, 91%.

After the disclosure of the protomycinolide IV synthesis, the group of K. Suzuki focussed its efforts on the oxygenated congener mycinolide IV and the glycosylated antibiotics mycinamicin VII and IV.[58] The total synthesis of mycinolide IV essentially followed the same blueprint as employed for the synthesis of protomycinolide IV with a few adjustments in the sequence of steps and the position of the central disconnection. To this end, the assembly of the macrolide core still relied on the same lactone fragment **10** (scheme 1.3). Just three simple operations furnished phosphonate **17** with the C1 carboxylate ready for intermolecular coupling with hydroxy aldehyde **16** by Yamaguchi esterifaction. The macrocycle was subsequently closed by intramolecular HWE condensation at the C10/C11 linkage, albeit in only 35% yield. Cleavage of both PMB ethers furnished the aglycon mycinolide IV (**3**) in 26 steps in the longest linear sequence. An improved access to the C11–C17 building block was published later.[59]
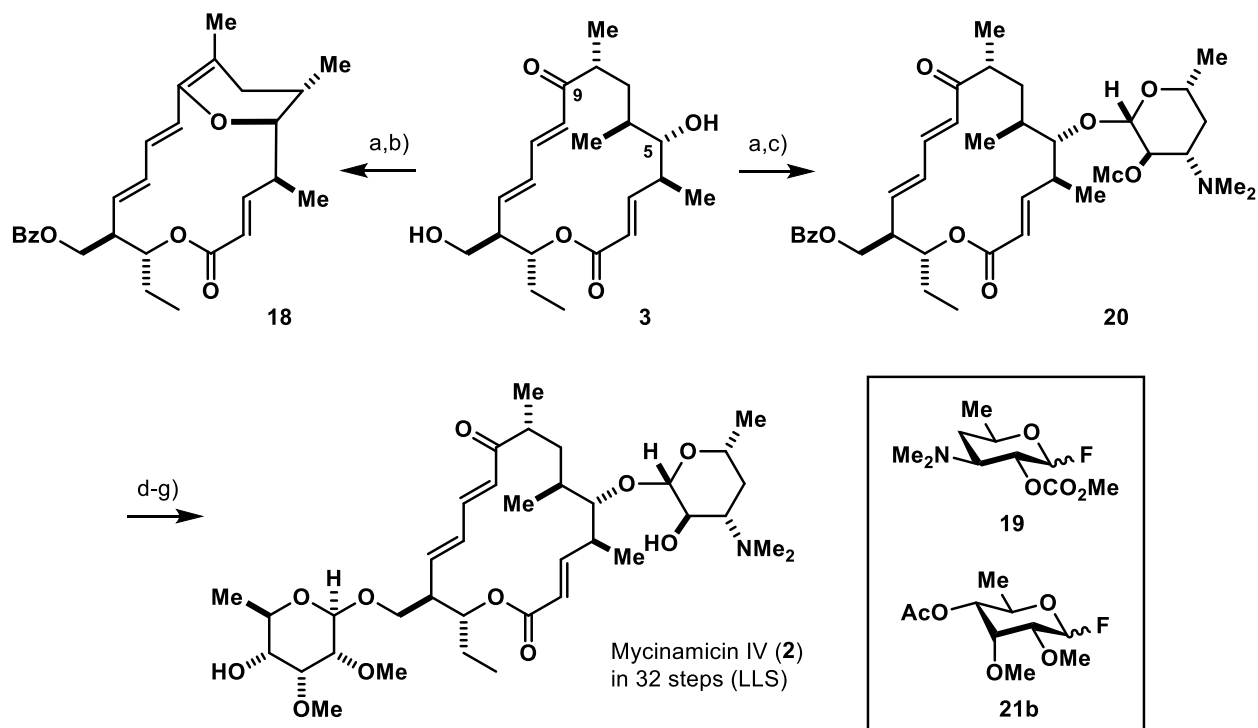
Scheme 1.4: Total synthesis of mycinamicin IV disclosed by K. Suzuki *et al.*. Conditions: a) PhCOCl, pyridine/CH$_2$Cl$_2$ (1:1), 0 °C, 1 h, 96%; b) "weakly acidic conditions", see text; c) **19** (3 equiv), Cp$_2$HfCl$_2$ (5 equiv), AgClO$_4$ (5 equiv), CH$_2$Cl$_2$, 0 – 5 °C, 2 h, 72% (α:β = 1:6); d) Et$_3$N/H$_2$O/MeOH (1:1:5), 70 °C, 3 h, 75%; e) ClCO$_2$Me, CH$_2$Cl$_2$, 0 °C, 1 h, 99%; f) **21b** (3 equiv), Cp$_2$ZrCl$_2$ (5 equiv), AgClO$_4$ (5 equiv), benzene, rt, 1 h, 86% (α:β = 1:26); g) Et$_3$N/H$_2$O/MeOH (1:1:5), rt, 16 h, 73%.

The glycosylation of the bare macrolide **3** proved challenging due to the propensity of the C5 alcohol to engage in the intramolecular formation of transannular enol ether **18** with the C9 ketone, even under "weakly acidic conditions". Since the back-then available glycosylation procedures were unsuccessful in delivering the desired glycoside, the development of a new metallocene-mediated glycosylation methodology using glycosyl fluorides was necessary.[60] With this methodology in hand, both carbohydrates of mycinamicin IV could be attached efficiently to the macrolide core. Thus, mycinolide IV was selectively acylated at the primary site with benzoyl chloride, and glycosylation of the remaining secondary alcohol was achieved with fluoride donor **19** of the basic carbohydrate desosamine. Since the primary alcohol of the macrolide could not be deprotected selectively, both carboxylates of **20** were removed (mycinamicin VII), and the protecting group at the C2' alcohol of the desosamine residue was carefully reattached. In the stereochemically challenging glycosylation of the primary C21 acceptor, the chosen mycinosyl donor **21b** is lacking a participating neighboring group next to the anomeric position. Despite this unfavorable preposition, an outstanding stereochemical preference (α:β = 1:26) for the desired β-anomer was achieved with the newly developed glycosylation methodology. After protecting group cleavage, mycinamicin IV was reached in 32 steps (longest linear sequence).

R. W. Hoffmann et al., 1990: Mycinolide V
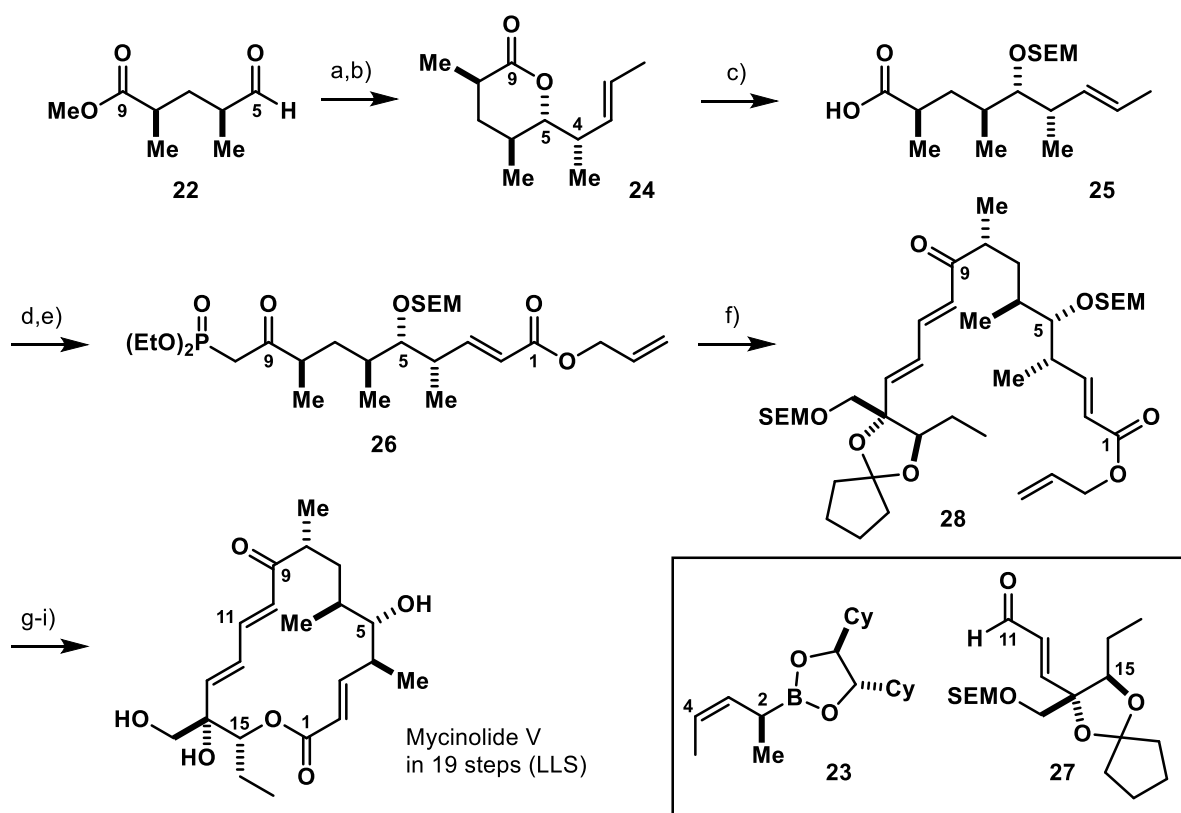
Scheme 1.5: Total synthesis of mycinolide V disclosed by R. W. Hoffmann *et al.*. Conditions: a) crotylation with **23**, 85% (dr > 95:5); b) lactonization, no yield given; c) (i) KOH (1 equiv), MeOH/H₂O, 60 °C, 3 h; (ii) SEMCl (3 equiv), (*i*-Pr)₂NEt (4 equiv), CH₂Cl₂, 20 °C, 3 d; (iii) 25% *w/w* aq. KOH, reflux, 4 h, 78% (over three steps); d) (i) Me₂C=CCl(NMe₂), CH₂Cl₂, 0 °C, 3 h; (ii) (EtO)₂P(O)CH₂Li, CuI, THF, 0 °C → 20 °C, 12 h, 65%; e) (i) O₃, CH₂Cl₂, −78 °C; (ii) Zn, AcOH, CH₂Cl₂, 20 °C, 2 h, 85%; (iii) (EtO)₂P(O)CH₂C(O)OCH₂CH=CH₂, *t*-BuOK, THF, −78 °C → rt, 84%; f) (i) *t*-BuOK, THF, −78 °C → 0 °C; (ii) **27**, THF, −78 °C → rt, 88%; g) Pd(OAc)₂, Ph₃P, morpholine, THF, 20 °C, 12 h, 95%; h) 1 M aq. HCl, MeCN, 20 °C, 4 h, 44% (with remaining starting material); i) (i) 2,4,6-trichlorobenzoyl chloride, NEt₃, THF; (ii) DMAP, benzene, 90 °C; (iii) LiBF₄ (8 equiv), MeCN/H₂O, 72 °C, 5 h, 33% (over three steps).

Mycinolide V belongs to the members of mycinamicins with an additional tertiary alcohol at C14. In the total synthesis by the group of R. W. Hoffmann, this alcohol is introduced within the C11–C17 aldehyde fragment **27**.[61] The central disconnection of the macrolide chain at C10 by HWE olefination and recourse to lactone **24** closely resemble the synthetic plan followed in the earlier syntheses of (proto)mycinolide IV by K. Suzuki *et al.*. Once again, the macrocycle is closed by the Yamaguchi macrolactonization procedure. Although the aldehyde fragment **27** was obtained over a rather lengthy 14-step route from the chiral pool, the overall synthesis is considerably shorter than the protomycinolide IV syntheses published earlier due to a streamlined route to the C1–C10 fragment enabled by asymmetric crotylation of glutaric hemi-aldehyde **22**, which can be prepared in four steps from meso-2,4-dimethylglutaric anhydride.[62]

Various fragments toward mycinamicins

Takano *et al.* disclosed a formal total synthesis of protomycinolide IV by describing alternative routes to building blocks anologous to those used in the total synthesis by the group of Suzuki.[63] The authors also provide access to the mycinonic acid methyl esters, which occur as intermediates in the biosynthesis of the polyketide. The synthesis of a C11–C17 fragment of mycinolide IV was also published by the same group.[64]

In 2005, the Mukaiyama group applied a diastereoselective samarium(II) iodide-mediated aldol reaction to find one more entry to the C11–C17 fragment **16** of mycinolide IV employed by Suzuki *et al.* (scheme 1.6).[65] Thus, ethyl dienoate **29** was selectively epoxidized at the terminal alkene, and the resulting product was coupled to an Evans oxazolidinone. After reduction of epoxy carboximide **30** with SmI_2, the derived dienolate **31** smoothly underwent an aldol reaction with propionaldehyde at the non-extended site to furnish alcohol **32** with good diastereoselectivity (dr = 8.7:1). Selective protection of the primary alcohol and reductive cleavage of the chiral auxiliary furnished diol **33**, which corresponds to an intermediate en route to fragment **16** in the total synthesis of the Suzuki group.[58a]
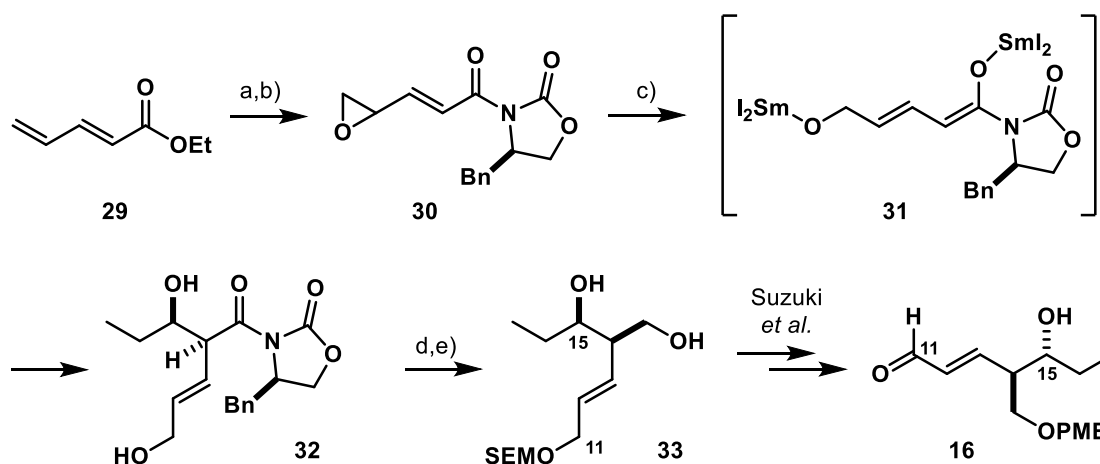
Scheme 1.6: Samarium(II) iodide-mediated aldol reaction enabling the synthesis of a C11–C17 fragment of mycinolide IV. Conditions: a) *m*-CPBA, dichloroethane, 60 °C, 60%; b) (i) LiOH, dioxane/MeOH, H_2O, 0 °C; (ii) PivCl, Et_3N, (4*R*)-4-benzyl-2-oxazolidinone, LiCl, 0 °C, 52% (over two steps); c) SmI_2, EtCHO, THF, −78 °C, 85% (dr = 8.7:1); d) SEMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 85%; e) $LiBH_4$, THF/EtOH, 0 °C, 87%.

In 2014, Hoveyda *et al.* published an asymmetric tandem addition of propargyl copper intermediates to aldehydes. The corresponding organometal compounds were generated from borylation of 1,3-enynes under copper catalysis with the commercially available bisphosphine **35** as the chiral ligand. The methodology could be employed to quickly access C12–C17 fragments of both the tylosin aglycon and mycinolide IV (scheme 1.7).[66] To this end, alkenyl boronate **38** was obtained as a potentially useful intermediate towards mycinolide IV in only six steps from simple enyne **34** and propionaldehyde.
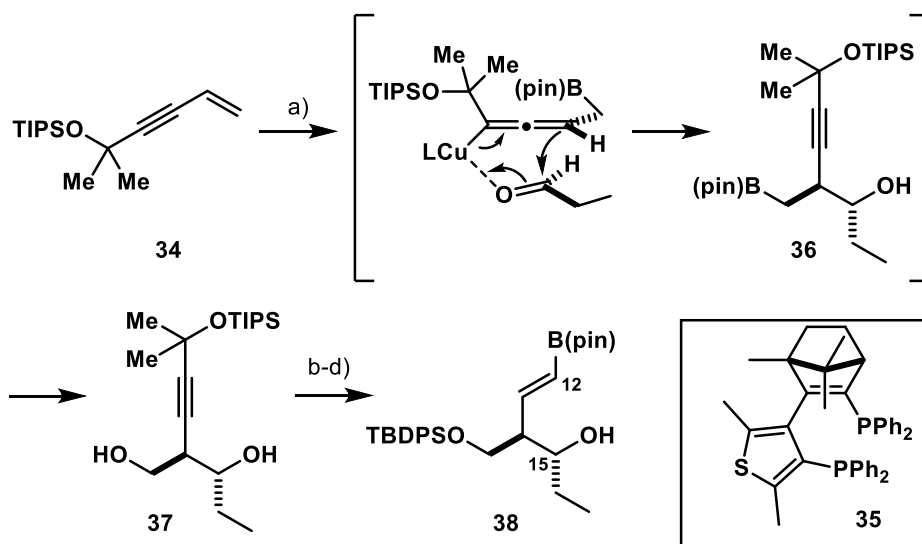
Scheme 1.7: Application of Hoveyda's copper-catalyzed aldehyde propargylation using 1,3-enynes for the synthesis of a C12–C17 mycinolide IV fragment. Conditions: a) (i) $B_2(pin)_2$ (1.1 equiv), CuCl (5 mol%), **35** (5 mol%), t-BuONa (20 mol%), THF, 22 °C, 8 h; (ii) $NaBO_3 \cdot 4 H_2O$, THF/H_2O, 22 °C, 4 h; b) (i) TBAF, THF, 22 °C, 12 h; (ii) NaOH, toluene, 110 °C, 1 h; c) TBDPSCl, imidazole, CH_2Cl_2, 22 °C, 2 h, 78% (overall, dr > 98:2, 90% *ee*); d) $B_2(pin)_2$ (1.1 equiv), MeOH (2.0 equiv), CuCl (5 mol%), 1,3-bisadamantylimidazolium tetrafluoroborate (5 mol%), t-BuONa (20 mol%), THF, 22 °C, 12 h, 85%.

1.5 This Work: A Unified Synthetic Approach

The previous two sections described the impressive diversity among a class of 16-membered macrolide antibiotics that results from subtle alterations of a conserved ichnography in nature. In an effort to address this diversity, the present work aimed at a collective rather than an individual total synthesis approach. It was envisioned that appropriate functionalization of a single, common intermediate might provide a unified access towards representative targets of these natural products. Since their structures are broadly covering the two subsets of targets, aldgamycin N (**1**) and mycinamicin IV (**2**) were chosen as initial targets for proof of concept: they (i) exhibit the different oxygenation pattern at C8, (ii) feature different levels of unsaturation in the vicinity of the C9 ketone, and (iii) represent the families with either a C15 methyl or a C15 ethyl branch. As a unifying blueprint, both compound series were traced back to a single, common synthon **VII** by the following retrosynthetic considerations (figure 1.5): the literature precedent of the mycinamicin IV total synthesis by K. Suzuki *et al.* suggests late-stage glycosylations of the macrolide aglycons, allowing preliminary retrosynthetic cleavage of the sugar moieties. Masking the C9 ketone of the aldgamycin series as an alkyne, and projecting the enone of the mycinamicins to derive from redox-isomerization of a secondary propargylic alcohol, delivers synthons **I** and **II**, respectively. These allow for a simplified entry to the series by carbonyl addition. Synthon **I** is subject to addition of alkyne fragment **III** to ketone **IV**, and

addition of enyne **VI** to aldehyde **V** would forge the propargylic alcohol of macrolide **II**. A stereo- and branch-selective hydroformylation of the terminal alkene in the common building block **VII** would furnish the required aldehyde, whereas Wacker oxidation would deliver the required ketone. With this plan in mind, a unified and potentially practical approach to the two natural product series seemed possible.
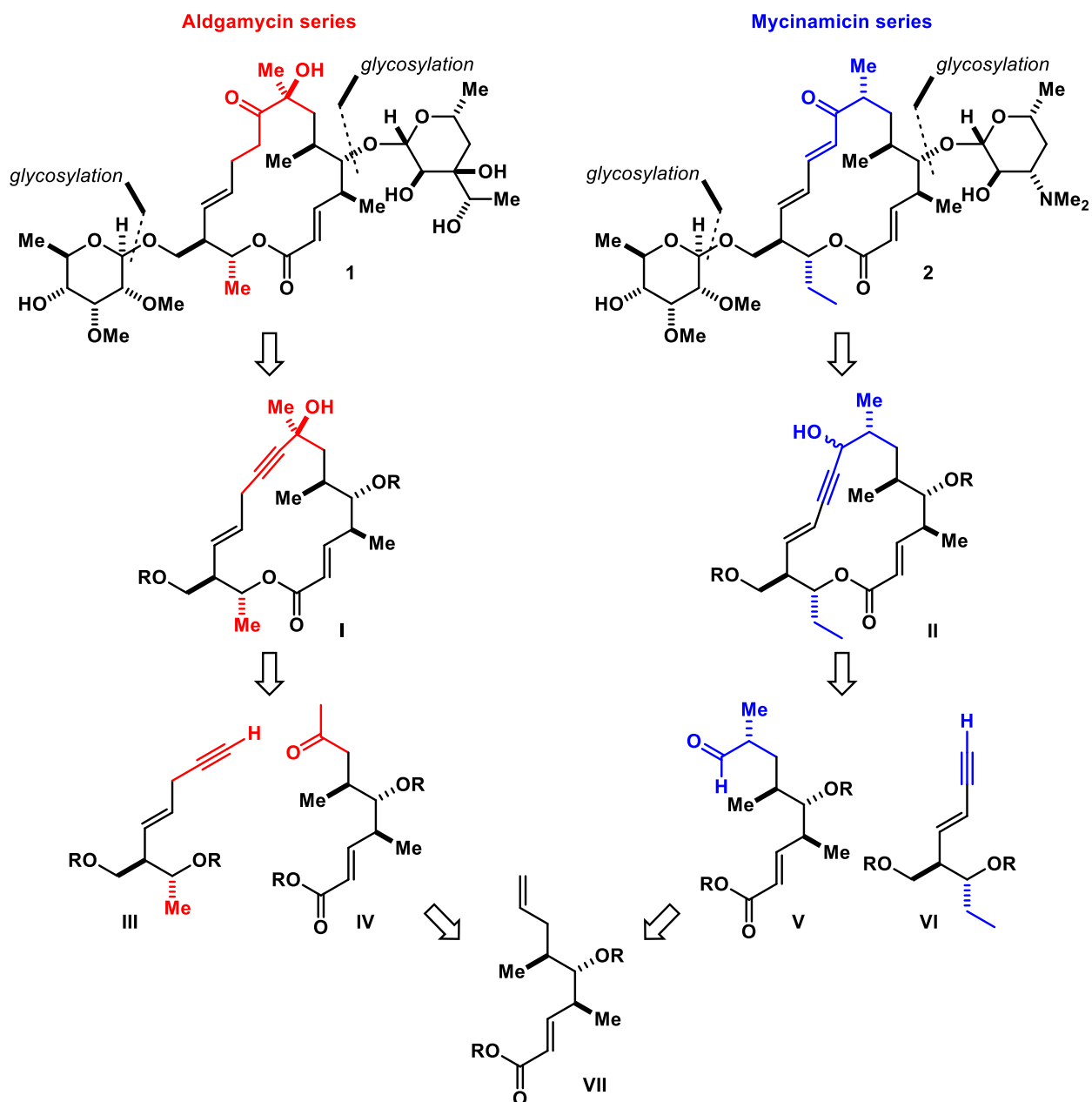
Figure 1.5: Unified layout for the collective total synthesis of aldgamycin and mycinamicin macrolides from a common intermediate.

Chapter 2

Results and Discussion

2.1 Synthesis of the Common Eastern Fragment

Remark: The synthetic work towards the common eastern fragment described in section 2.1 followed brief exploratory studies of Dr. M. Fernandez Bieber, and was otherwise conducted by Dr. B. Herlé.

A vinylogous aldol disconnection was deemed ideal for the efficient and scalable preparation of the anticipated common building block **39**. The synthetic endeavor would therefore commence with the synthesis of enantioenriched aldehyde **40** to be coupled with the known unsaturated silyl ketene acetal **41** (figure 2.1).
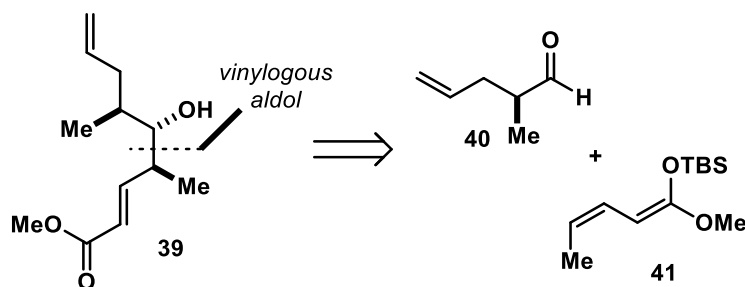
Figure 2.1: A vinylogous aldol reaction allows for a central disconnection of the common eastern fragment.

Concerning aldehyde **40**, initial reaction screening sorted out a chiral pool access from the enantiopure lactate **42**[67] as well as the organocatalytic allylation of propanal using SOMO catalysis[68], which either did not deliver the aldehyde in satisfactory enantiomeric purity, or in low conversion (scheme 2.1, parts a,b). Due to the laborious reaction sequence resulting from an auxiliary-based alkylation approach, the preparation of the required aldehyde by the assistance of Myers' pseudoephedrine amide **45** or Evans' carboximide **47** was also considered a non-ideal starting point.[69] Although the corresponding auxiliaries allowed the synthesis of aldehyde **40** in decent yield and high enantiopurity, provided that an appropriate condition was chosen for the oxidation of the corresponding alcohol **44**, the high volatility of the material after cleavage of the auxiliary presented an additional practical issue in these routes (scheme 2.1, part c).
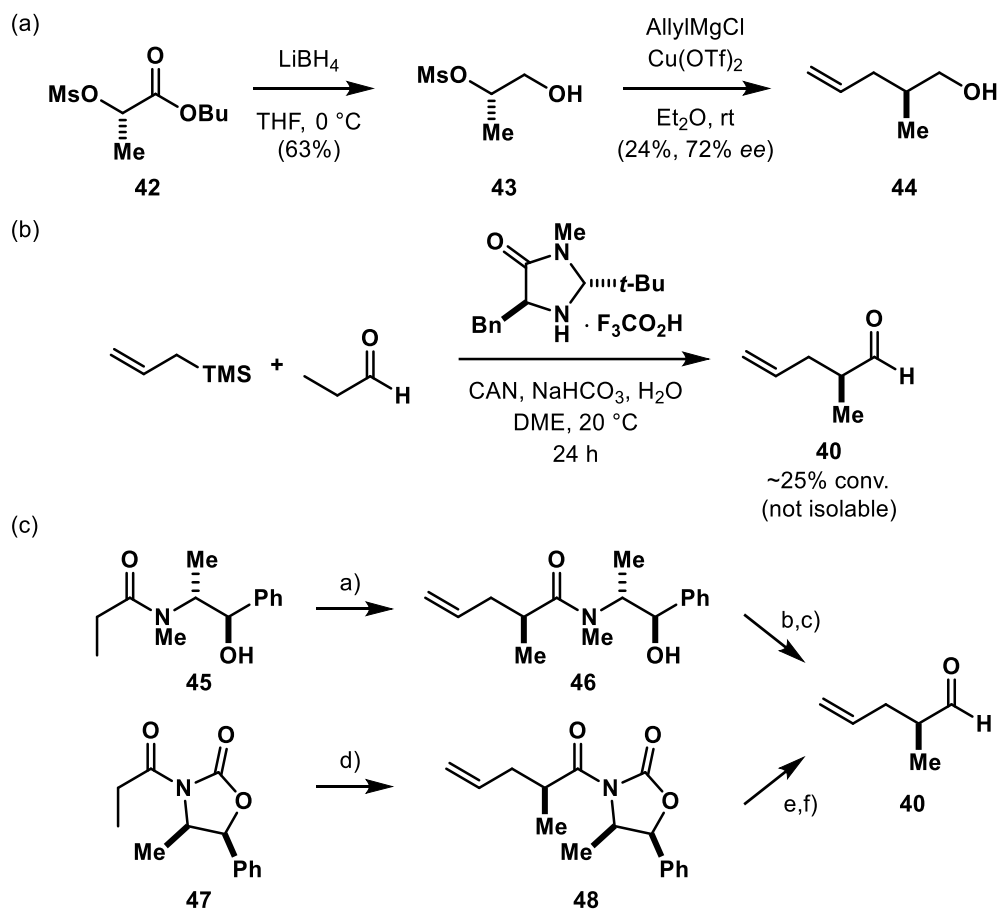
Scheme 2.1: (a) Nucleophilic allylation of a mesylate derived from naturally occurring (*S*)-lactate occurred only sluggishly with diminished enantiomeric purity; (b) MacMillan's organocatalytic allylation mediated by SOMO catalysis did not proceed with appreciable conversion. Isolation of the volatile aldehyde proved difficult due to the conditions employed; (c) auxiliary-based preparation of the required aldehyde was feasible but laborious. Conditions: a) LDA, allyl iodide, THF, −78 °C → 0 °C, 99% (dr > 98:2); b) LDA, H₃N · BH₃, THF, 0 °C → rt, 99%; c) DMP, CH₂Cl₂, rt, 71% (85% *ee*); d) NaHMDS, allyl bromide, THF, −78 °C, 82% (dr = 97:3); e) LiAlH₄, THF, −78 °C, 62% (93% *ee*); f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 °C, 57% (93% *ee*).

Enzymatic kinetic resolution of alcohol *rac*-**44** was eventually found to be far superior in providing multi-gram quantitites of the required aldehyde (scheme 2.2, part a). To this end, racemic carboxylic acid **49**, commercialized as an inexpensive food additive, was reduced to the corresponding alcohol, which was acylated with vinyl acetate in the presence of *Pseudomonas fluorescens* lipase. The desired (*S*)-enantiomer of the alcohol ended up to be acylated in 40% yield (of the possible 50%) with 94% *ee* on >20 g scale. This particular enzymatic resolution has already been used in tandem with an asymmetric Zr-catalyzed carboalumination to provide virtually enantiopure material.[70] The acetyl group of resulting **50** was cleaved by the addition of methyl lithium in diethyl ether, followed by quick aqueous removal of the formed lithium salts and careful evaporation of the ethereal solvent to minimize loss of the volatile material. Swern oxidation furnished aldehyde **40** without noticeable isomerization (by GC analysis), and provided a

sufficiently pure product after aqueous work-up for use in the next step without additional purification, again to prevent undue loss of material.
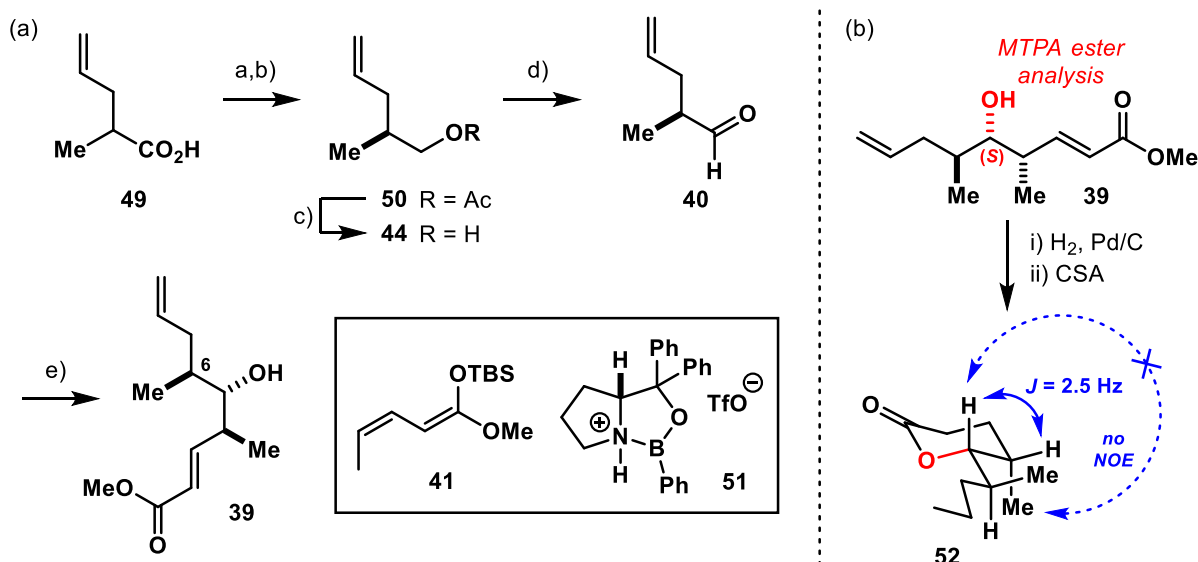
Scheme 2.2: (a) Final access to common eastern fragment **39** and preparation of the required aldehyde **40** by enzymatic resolution; (b) The absolute and relative stereochemistry of the eastern fragment was proven by Mosher's ester analysis and conversion into lactone **52**. Conditions: a) LiAlH$_4$, THF, 91%; b) vinyl acetate, Amano lipase (*Pseudomonas fluorescens*), THF, −20 °C, 40%, 94% *ee*; c) MeLi, Et$_2$O, −30 °C → rt, 75%; d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C → rt; e) **41**, **51** (50 mol%), *i*-PrOH, CH$_2$Cl$_2$ −78 °C, 69% (over two steps, dr = 89:11, C6 epimers).

With enantioenriched aldehyde **40** in hand, its coupling with ketene acetal **41** to give the required *syn/anti* stereotriad was optimized by the organocatalytic vinylogous Mukaiyama-type aldol reaction developed in the group of Kalesse.[71] Oxazaborolium triflate **51** derived from (*S*)-proline is employed as the catalyst in this reaction. Following the originally published methodology, the reaction outcome was erratic when the organocatalyst was prepared in-situ from PhBCl$_2$. Eventually it was found that preparation of the pre-catalyst in a separate step by condensation of phenylboronic acid with diphenylprolinol in a Dean-Stark trap,[72] followed by activation with triflic acid at low temperature in the set-up of the aldol reaction, gave a well-reproducible reaction outcome. In this way, product **39** was consistently obtained in fair yield and useful diastereomeric purity on a decent scale (69% yield over two steps, dr = 89:11, >10 g scale). Noticeably, the only reference found using this organocatalytic vinylogous aldol reaction in total synthesis also describes the preparation of catalyst **51** in a separate step rather than in-situ.[73] A control experiment with racemic aldehyde *rac*-**40** suggested that the diastereomers isolated from the reaction are epimeric at C6. Since the material of the enantioenriched aldehyde employed was isomerically pure, some scrambling of the α-stereogenic center of the aldehyde seems to occur under the reaction conditions of the aldol reaction, whereas the aldol coupling itself proceeds with practically exclusive stereocontrol. The absolute and relative stereochemistry of the common key building block **39** was proven by Mosher's ester analysis and by

conversion into lactone **52** to confirm the 4,5-*syn* configuration by an NOE magnetic resonance experiment (scheme 2.2, part b). The minor quantities of the undesired C6 diastereomer remaining in the isolated product after chromatography were carried through and separated during the subsequent steps.

2.2 Uniform Access to the Western Alkyne Fragments

Just as the common building block **39** will serve to provide the individual eastern fragments of the two natural product series, the required western alkyne fragments (synthons **III/VI**, figure 1.5) could also be reached by uniform routes. Starting with homologous *Z*-allylic alcohols **53a,b**, Sharpless asymmetric epoxidation and opening of the resulting epoxides **54a,b** with lithium acetylide ethylenediamine complex set the absolute and relative stereochemistry of the anticipated 1,3-diol with reasonable regiocontrol and furnished an alkyne handle for further chain extension (scheme 2.3).[74] In practical terms, the 1,2-diols resulting as minor regioisomers from the oxirane opening were easily discarded before chromatography by
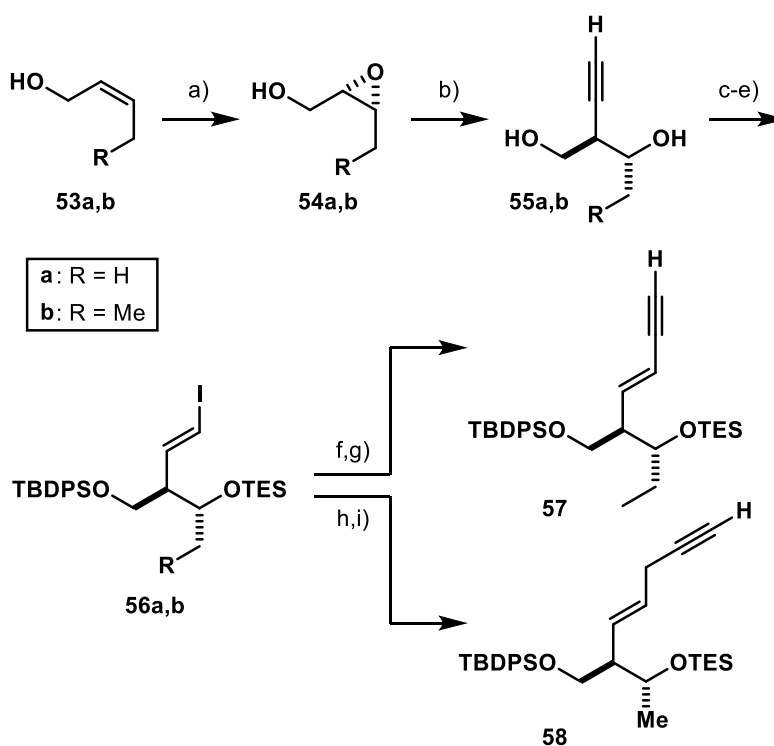
Scheme 2.3: Uniform strategy employed towards the western alkyne fragments. Conditions: a) cumene hydroperoxide, Ti(O*i*-Pr)$_4$, L-(+)-diisopropyl tartrate, CH$_2$Cl$_2$, −20 °C, 54% (**54a**, 92% *ee*), 73% (**54b**, 87% *ee*); b) (i) HCCLi · eda, THF, 0 °C → rt; (ii) NaIO$_4$, CH$_2$Cl$_2$/H$_2$O, 42% (**55a**), 29% (**55b**, 97% *ee* after recrystallization); c) TBDPSCl, imidazole, CH$_2$Cl$_2$, 83% (R = H); d) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C → rt, 96% (R = H), 91% (R = Me, over two steps); e) (i) Cp$_2$ZrCl$_2$, Dibal-H, THF, 0 °C → rt; (ii) I$_2$, 2,6-lutidine, THF, −78 °C, 65% (**56a**), 74% (**56b**); f) **56b**, TMSCCH, [(PPh$_3$)$_2$PdCl$_2$] (2.5 mol%), CuI, Et$_3$N; g) K$_2$CO$_3$, MeOH, THF, 96% (over two steps); h) TMSCCMe, *n*-BuLi, THF, −78 °C, then **56a**, CuI, DMAP, 0 °C → rt; i) K$_2$CO$_3$, MeOH, THF, 84% (over two steps).

an oxidative work-up with sodium periodate.[74] After selective protection of the alcohols with appropriate silyl groups that will allow for orthogonal cleavage at a later stage of the total syntheses, the terminal alkynes were subjected to a one-pot hydrozirconation/iodination sequence.[75] Negishi's reaction protocol had to be modified in that 2,6-lutidine was added prior to the oxidation with iodine to prevent cleavage of the acid-sensitive TES ether. Alkenyl iodide **56a** was cross-coupled with lithiated trimethylsilylpropyne mediated by DMAP-ligated copper(I) iodide to favor the propargylation over allene formation.[76] Selective C–Si bond cleavage furnished the required terminal alkyne **58** without any allene being observed in the crude reaction mixture neither before nor after desilylation. Sonogashira coupling of **56b** with trimethylsilylacetylene and subsequent desilylation smoothly afforded enyne **57** necessary for the mycinamicin series.[77]

As a more convergent entry to the western fragments, the direct opening of epoxides **54a,b** with metalated alkenyl iodides **59** and **60** was also investigated (scheme 2.4). These nucleophiles would already contain the capped terminal alkyne and hence shorten the linear sequence. Both the enyne and the skipped enyne pre-nucleophiles could be prepared from triisopropylsilylacetylene. Thus, dimerization of TIPS-capped propyne catalyzed by Wilkinson's catalyst followed by selective iododesilylation of the sp^2-C–Si bond furnished iodide **59** ready for addition of the conjugated enyne fragment.[78] Alkylation of magnesio-TIPS-propyne with propargyl bromide in the presence of copper(I) iodide provided the corresponding mono-silylated 1,4-pentadiyne. Subsequent hydrozirconation and iododezirconation occurred selectively at the uncapped triple bond to deliver iodide **60** of the skipped enyne fragment. Disappointingly, neither lithium nor magnesium reagents derived from these alkenyl iodides were able to open racemic samples of oxirane **54b** in the desired fashion.
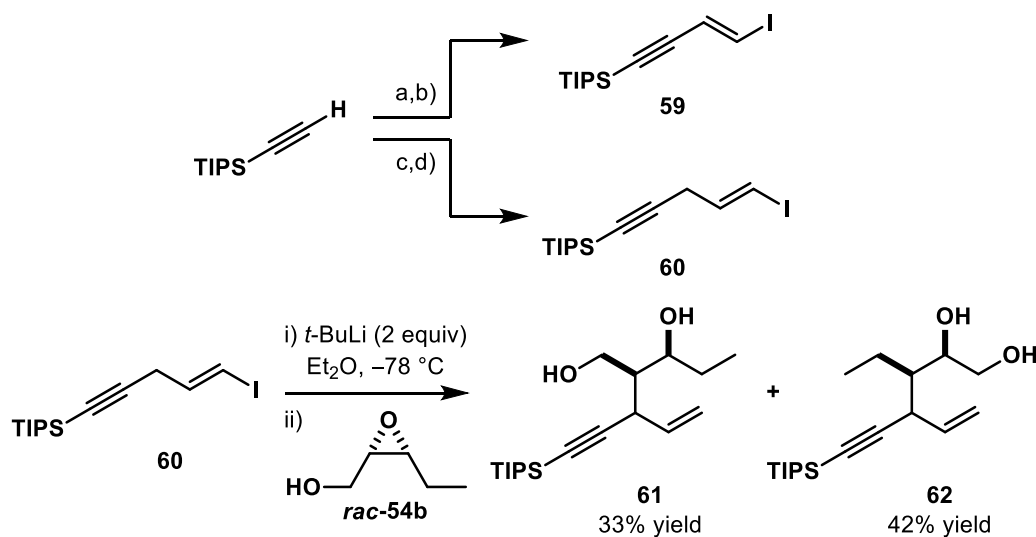
**Scheme 2.4:** Preparation of skipped and conjugated enyne building blocks for a more convergent epoxide-opening approach, and failed attempt of the epoxide opening with the lithiated skipped enyne. Conditions: a) [(PPh$_3$)$_3$ClRh] (5 mol%), toluene, 70 °C, 66%; b) NIS, Ag$_2$CO$_3$ (30 mol%), HFIP/CH$_2$Cl$_2$ (1:1), 0 °C, 79%; c) (i) EtMgBr, THF; (ii) propargyl bromide, CuI, 47%; d) (i) Cp$_2$ZrHCl, THF/toluene; (ii) I$_2$, 53%.

The branched oxirane-opening products **61** and **62** were isolated when skipped enyne **60** was metalated with *t*-BuLi at low temperature. Therefore, it seems that the alkenyl lithium compound formed by halogen-metal exchange from **60** had rearranged to the corresponding allyl lithium species before it opened the epoxide. When the corresponding magnesium reagent of **60** or the alkenyl lithium or magnesium reagents derived from iodide **59** were employed in the epoxide opening, only oligomerization of the epoxy alcohol was observed. Addition of catalytic amounts of copper(I) iodide or BF$_3$ etherate did not improve the reaction outcome. Since the regiocontrol in the epoxide opening with these larger nucleophiles seemed difficult to control anyway, this approach, though being more convergent, was not pursued any further.

2.3 Assembly of the Aldgamycin N Aglycon

With multi-gram amounts of the anticipated eastern and western fragments of both natural product series in hand, the bifurcation point in the syntheses was reached. En route to aldgamycin N, the alcohol of the common intermediate **39** was protected as its *p*-methoxybenzyl ether since the PMB protecting group proved to be advantageous in the selective liberation of the secondary C5 alcohol over the primary C20 alcohol later on. Whilst basic conditions for the introduction of the PMB ether led to decomposition of the starting material, classical acidic conditions employing the PMB trichloroacetimidate suffered from reagent-derived byproducts that were inseparable from the product. Quinolone ether **63** worked better and gave the clean PMB ether upon activation with a catalytic quantity of triflic acid (scheme 2.5).[79] The subsequent Tsuji/Wacker oxidation of the terminal alkene furnished ketone **64** in excellent yield.[80] The remote positioning of the stereocenters away from the ketone render a stereochemical control in the carbonyl addition of alkyne module **58** highly challenging. Indeed, when the lithium acetylide resulting from deprotonation with *n*-BuLi was reacted with the ketone in the presence of lithium chloride-complexed lanthanum(III) chloride to promote the 1,2-carbonyl addition,[81] the alkynylation took place with virtually no preference for any diastereomer of the resulting tertiary C8 alcohol, yet in high chemical yield. A brief screening showed that the reaction temperature had some influence on the stereoselectivity: the C8 alcohols were formed roughly as a 1:1 mixture at −78 °C, while minimal preference for the desired (8*S*)-isomer was found at higher temperatures (dr ≈ 60:40 at −20 °C). Even this small change of reaction parameters, however, led to increased side product formation: at −20 °C, no complete consumption of the ketone was reached, most likely due to enolization of the ketone by deprotonation by the lithium acetylide.
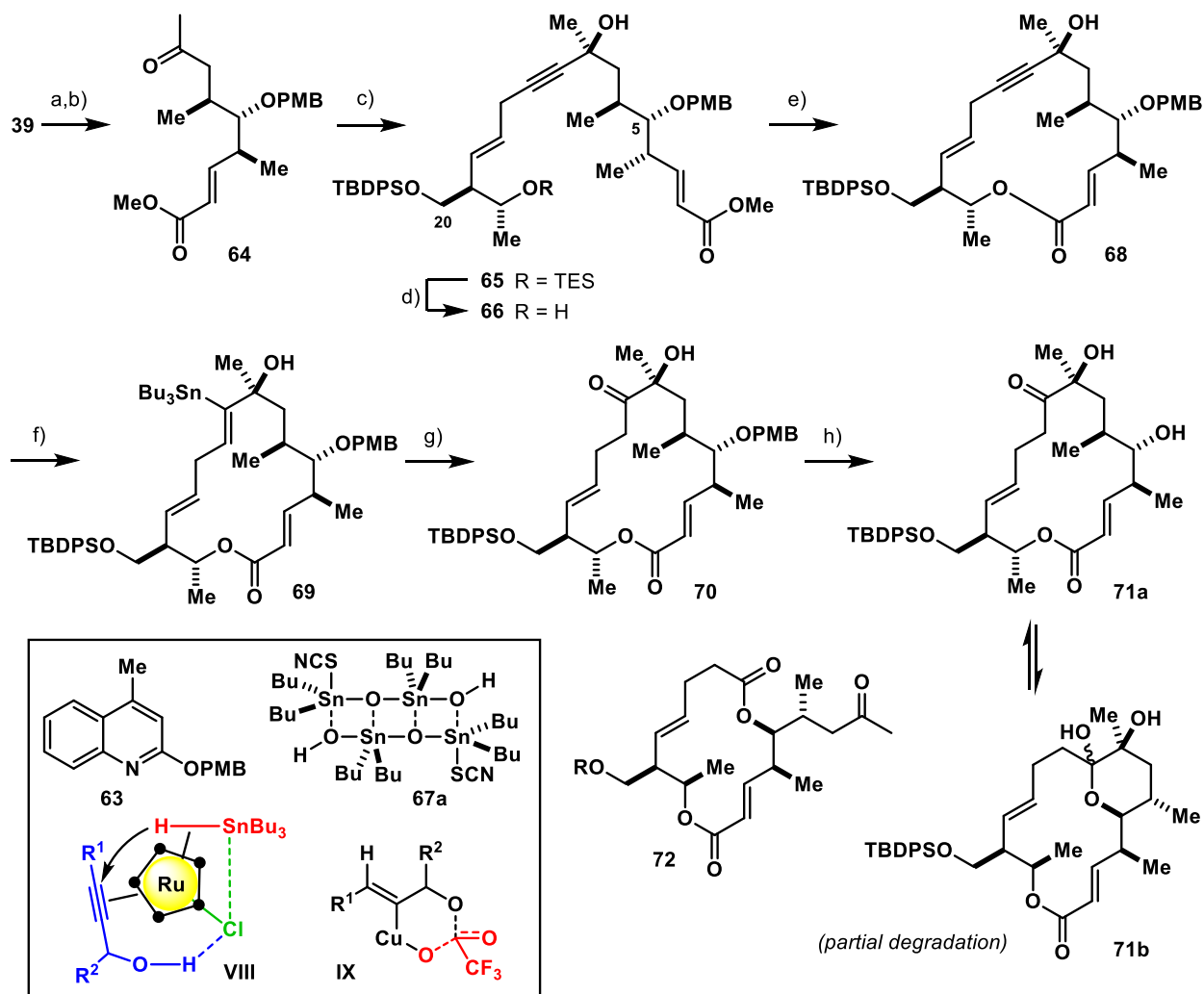
Scheme 2.5: Assembly of the aldgamycin core. Conditions: a) **63**, TfOH cat., CH$_2$Cl$_2$, −20 °C → rt, 68%; b) O$_2$, PdCl$_2$ (20 mol%), CuCl, THF, H$_2$O, 88%; c) **58**, n-BuLi, LaCl$_3$ · 2 LiCl, THF, −78 °C, 83% (dr ≈ 1:1); d) PPTS, EtOH, 0 °C, 89%; e) **67a**, toluene, reflux, 68%; f) [Cp*RuCl]$_4$ (12 mol%), Bu$_3$SnH, CH$_2$Cl$_2$, 72%; g) [Cu(tfa)$_2$] · H$_2$O, DMAP (40 mol%), DMSO, 45 °C, 83%; h) DDQ, CH$_2$Cl$_2$/H$_2$O, see text.

This and other side reactions of the enolate were also mainly observed in the absence of the lanthanum salt. The stereoselective formation of quaternary stereocenters from the alkynylation of ketones is still an unsolved problem, with only a few catalytic methods described in the literature for this challenging transformation.[82] For the coupling of skipped enyne **58** and ketone **64**, a recently published protocol for the enantioselective addition of zinc acetylides to aliphatic ketones under copper catalysis was to no avail.[83] Mixing of the alkyne in the lithiation step with either enantiomer of the chiral amino alcohol used in the enantioselective alkynylation of a trifluoromethyl ketone in Merck's Efavirenz synthesis was also without any success in bolstering the stereochemical outcome.[84] Ultimately, because the two C8 isomers were separable at this stage by preparative HPLC[85] and any detours from this alkynylation would have meant a considerably more lengthy route (*e.g.* via asymmetric dihydroxylation of a 1,1-disbstiuted alkene to forge the tertiary alcohol stereoselectively), no further effort was made to impose better control over the addition

process. Rather, the feasibility of the subsequent key steps to close the macrocylic core of aldgamycin N and its cousins was checked.

Selective cleavage of the secondary TES ether of adduct **65** was carefully performed in acidic, ice-cold alcoholic solvent without endangering the acid-sensitive tertiary propargylic alcohol. At this stage, formation of the macrocycle was originally anticipated by liberation of the seco-acid and lactonization by one of the many available procedures, *e.g.* by the Yamaguchi mixed anhydride method. Unfortunately, all attempts to hydrolyze the methyl ester of **73** were met with only poor yields or even complete failure at an earlier project stage when a TBS ether had still been used for the protection of the secondary C5 alcohol (table 2.1).

Table 2.1: Screening of reaction conditions for the liberation of the seco-acid in preparation of the macrocycle formation (n.i. = product not isolated).

73

74 R = TBDPS
75 R = H
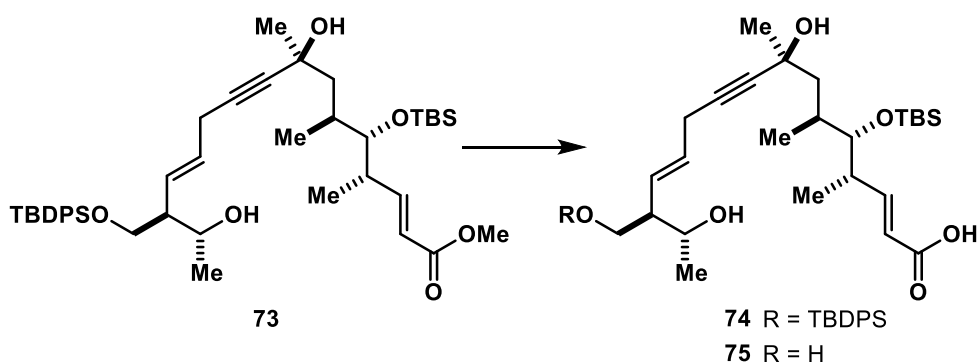
| entry	conditions	yield of 74	comment
1	LiOH (3 equiv) THF, MeOH, H₂O (3:2:1) [73] = 0.03 M, 40 °C, 14 h	0%	83% yield of **75** decreased reaction time and/or temperature led to mixtures of **74** and **75**
2	Me₃SnOH (24 equiv) 1,2-dichloroethane 70 °C, 55 h	n.i.	complex mixture of side products formed with remaining starting material
3	Ba(OH)₂ · 8 H₂O (6 equiv) MeOH, 40 °C, 48 h	0%	signals of enoate missing in ¹H NMR spectrum of crude reaction mixture
4	LiI (6.5 equiv) pyridine, reflux, 5 d	47%	with formation of side products and remaining starting material
5	LiI (6.5 equiv) 2,6-lutidine reflux, 2.5 h	44%	as entry 4
6	LiI (6.5 equiv) DMF 150 °C (ext.), 2.5 h	n.i.	low conversion

The major issue encountered under basic conditions (entries 1 – 3) was undesired cleavage of the primary TBDPS ether at C20. In addition, the formation of an ample variety of side products was observed under these conditions, probably resulting from the intra- and/or intermolecular addition of the tertiary C8 alcohol to the enoate moiety. Surprisingly, even the use of trimethyltin hydroxide in 1,2-dichloroethane furnished complex mixtures (entry 2).[86] The best results in delivering the seco-acid were found in the S_N2 demethylation with lithium iodide in pyridine solvents (entries 4 – 6).[87] However, the rather low yields (<50%) were not satisfying, and the possibility of a direct transformation of methyl ester **66** into the 16-membered lactone by intramolecular transesterification appeared as an attractive alternative.

The stannoxane-mediated transesterification developed in the group of Otera has been known for quite a long time, and certainly found its good use in intermolecular transesterifcations as well as for the formation of smaller ring sizes.[88] At the time of this project, only a single precedent for its employment in the setting of a macrolactonization in total synthesis had been described,[89] aside from its more recent application in the synthesis of a few natural-product-like macrodiolides.[90] Gratifyingly, this transformation immediately proved to be very well suited for the direct formation of macrocycle **68** from hydroxy ester **66**, even on a decent scale (68%, >400 mg, single largest batch). In practical terms, this reaction only required prolonged stirring of a dilute solution (2 mM) of ester **66** with a sub-stoichiometric amount of stannoxane **67a** in boiling toluene; while the stannoxane can be used in lower catalytic amounts, a higher catalyst loading was employed due to the already long reaction times (five days; more concentrated solutions furnished larger amounts of side products). Notably, this transformation was equally facile for both C8 diastereomers (69% yield for the (8R)-isomer, >100 mg scale). It was at this stage that the configuration at C8 could be tentatively assigned by comparison of the ¹H NMR signals at the C5 position for both epimers with the reported literature value of natural aldgamycin N (see experimental part). In the end, the resort to the stannoxane-mediated macrolactonization by transesterification not only salvaged the protecting group strategy in essence of the methyl ester but also saved a step in the longest linear sequence as it rendered the formation of the seco-acid unnecessary.

With the macrolactone ring closed, only the elaboration of the tertiary propargylic alcohol into the acyloin motif of aldgamycin N by unmasking the ketone from the triple bond remained to be done in order to gain access to the natural product aglycon. This late-stage chemistry worked particularly well in that case by employing the sequence of hydrostannylation and copper-mediated oxidative destannylation developed in the Fürstner laboratory.[91] Thus, propargylic alcohol **68** underwent a ruthenium-catalyzed *trans*-hydrostannylation at the proximal site of the alcohol moiety to give alkenylstannane **69** as a single regio- and stereoisomer. This regioselective outcome is thought to result from a highly ordered transition state **VIII** (scheme 2.5), in which the chloride ligand of the [Cp*RuCl] catalyst locks the substrate in place by interligand hydrogen bonding and at the same time steers the incoming stannane for hydride delivery by

coordinating the tin atom.[92] Alkenylstannane **69** was then subjected to slightly modified and further improved conditions of the oxygenative destannylation. Rather than resorting to Cu(OAc)$_2$ in DMSO/Et$_3$N to give the acylated acyloin as previously published, the possibility to form the free acyloin directly without an additional saponification step was explored. As a mechanistic rational of this Chan-Lam-type coupling, it may be understood that the alkene substituent of the stannane is first transmetalated to copper, either directly or by Brook-type participation of the free alcohol. The resulting organic copper carboxylate would then undergo acyl migration to the vicinal alcohol, followed by reductive elimination to an enol, which tautomerizes to the corresponding ketone (structure **IX**, scheme 2.5). It was hoped that a more acidic copper salt would render the intermediate acylated alcohol labile enough to suffer hydrolysis under the reaction conditions. Furthermore, a shorter life-time of the tertiary carboxylate in that particular case as well as less basic conditions in general were desired to prevent any damaging of the, probably sensitive, transient acyloin ester. To this end, a brief screening of reaction conditions for the given transformation of model substrate **76** revealed that destannylation with the trifluoroacetate salt Cu(tfa)$_2$ met these requirements (table 2.2): free acyloin **78** was obtained directly, and the reaction also proceed at room temperature within less than an hour, whereas the standard Cu(OAc)$_2$ required gentle heating overnight for complete conversion.[93] Interestingly, no base was required at all for the reaction to proceed efficiently, although a small amount of base (*e.g.* DMAP) might be advantageous to accelerate the solvolysis of the acyl intermediate and buffer traces of acid potentially formed from the turnover of the alcohol proton and/or the copper carboxylate hydrate salt (entries 6, 7). Along these lines, treatment of alkenylstannane **69** with a mixture of [Cu(tfa)$_2$] · H$_2$O and a sub-stoichiometric amount of DMAP in DMSO at 45 °C furnished free acyloin **70** in 83% yield (no reaction was observed at room temperature).

The stage was now set for the deprotection of the C5 and C20 alcohols to deliver the aglycon of aldgamycin N. Completion of the synthesis would require the selective liberation of the secondary and primary glycosyl acceptors for the attachment of the carbohydrates. Although the oxidative cleavage of the C5 PMB ether of **70** in itself worked well using DDQ, the liberated alcohol engaged the C9 ketone in an unforeseen transannular hemiketal formation. This internal cyclization to both diastereomers of **71b** occurred spontaneously and irrespectively of the reaction conditions. Therefore, uncyclized **71a** could not be isolated by chromatographic separation of the mixture with hemiketals **71b**, which were furthermore prone to partial degradation to unidentified side products. Though the reasons for this instability were not investigated in great detail, global deprotection of the C5 TBS ether anologous to **70** under acidic conditions (aq. HF, MeCN) led to the isolation of considerable amounts (~20%) of ring-contracted macrodiolide **72** (R = H), apparently formed by oxidative diol cleavage of the corresponding hemiketal.

Table 2.2: Screening of reaction conditions for the Chan-Lam-type oxygenative destannylation of a model alkenylstannane to forge an acyloin (n.f. = not found after chromatography).

Side products
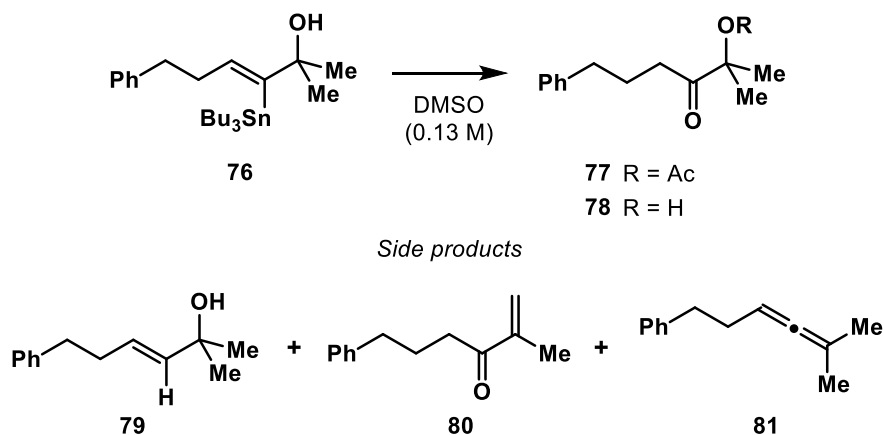
entry	conditions	time	crude ratio (^{1}H NMR)				isolated yields (%)		
			77/78	79	80	81	77/78	79	80
1	Cu(OAc)$_2$ · H$_2$O NEt$_3$ (2.0 equiv) 45 °C	16 h	79 (**77**)	21	0	0	69 (**77**)	15	n.f.
2	Cu(OTf)$_2$ NEt$_3$ (2.0 equiv) 45 °C	1.5 h	71 (**78**)	6	18	5	43 (**78**)	12	23
3	Cu(tfa)$_2$ · H$_2$O NEt$_3$ (2.0 equiv) 45 °C	1.5 h	89 (**78**)	4	7	0	71 (**78**)	5	12
4	Cu(tfa)$_2$ · H$_2$O DMAP (2.0 equiv) 45 °C	40 min	92 (**78**)	3	5	0	86 (**78**)	5	n.i.
5	Cu(tfa)$_2$ · H$_2$O DMAP (2.0 equiv) rt	1 h	>90% (**78**)		<5%		87 (**78**)	3	n.i.
6	Cu(tfa)$_2$ · H$_2$O DMAP (20 mol%) rt	30 min	>90% (**78**)		<5%		82 (**78**)	2	n.i.
7	Cu(tfa)$_2$ · H$_2$O no base rt	40 min	>90% (**78**)		<5%		72 (**78**)	n.i.	n.i.
8	Cu(tfa)$_2$ · H$_2$O, cat. DMAP (20 mol%) rt	16 h	mostly protodestannation, no full conversion						
9	Cu(tfa)$_2$ · H$_2$O DMAP (30 mol%) DMSO/THF, 0 °C		no reaction						

A similar decomposition mechanism is hence conceivable for **71a,b** obtained from cleavage of the PMB ether. Related problems of transannular hemiketal formation are known for other macrocyclic frameworks, including erythromycin B and derivatives thereof.[94] Notably, the problematic enol ether formation that impeded the initial glycosylation attempts in Suzuki's mycinamicin IV synthesis stems from this exact cyclization event (cf. scheme 1.4). However, transannular cyclization does not proceed spontaneously in this particular literature precedent.

Due to the instability and inconsistencies associated with the ketone and hemiketal mixtures of **71a,b**, as well as missing literature precedence for the glycosylation of such acceptor mixtures, the elaboration of these compounds into the glycosylated natural product seemed to no avail. Yet, the presented results were regarded as proof-of-concept towards the aldgamycin series, showing the viability of all key steps. Intriguingly, since the trouble-making transannular interference can only occur in presence of the ketone and the free C5 alcohol at the same time, unmasking the C9 ketone from the triple bond only after the C5 alcohol had already been glycosylated seemed to provide an opportunity to complete the target synthesis. This revision and the final completion of the synthesis of aldgamycin N are subject of section 2.8.

2.4 Assembly of the Mycinamicin IV Aglycon (Mycinolide IV)

Remark: The synthetic work towards mycinolide IV described in section 2.4 was conducted by Dr. B. Herlé, who established the transformation of common building block **39** into the derived aldehyde fragment by hydroformylation, followed by the stereochemical analysis of this key compound. After Dr. Herlé's exploration of the further elaboration into the natural product, Dr. L. Schreyer arranged the scale-up and optimization process of these steps and completed the total synthesis of mycinolide IV.

In the synthetic direction towards mycinolide IV, regio- and diastereoselective hydroformylation of the common building block **39** was necessary. Such transformation of a simple alkene bears evident synthetic potential.[95] Yet it is unprecedented in natural product synthesis: to this point, the arguably most advanced settings of branch-selective hydroformylations had been disclosed in the total synthesis of ambruticin and the studies towards tedanolide C by Jacobsen and Smith, respectively.[96] In these cases, however, 1,3-dienes served as substrates, which have an inherent electronic bias to favor the branched hydroformylation product by virtue of favorable allyl metal species.[97] The only other precedence for the synthetic application of asymmetric hydroformylations presented the elaboration of acrolein acetals and acrylic acid orthoesters into dictyostatin and the Prelog-Djerassi lactone, *i.e.* again the employment of alkene substrates with a certain substrate bias.[98]

Just as the alkynylation of ketone **64** en route to the aldgamycin core proved highly challenging due to the remote positioning of the stereocenters away from the carbonyl group, the same situation applies here for the hydroformylation of the terminal alkene in **39**. Such a stereo- and branch-selective transformation would require either exquisite catalyst control, or some sort of far-reaching directing group at the C5 alcohol of the substrate. Although the regiochemical steering of hydroformylations by means of a directing group is a well established tactic,[99] the need to screen for a suited directing group, as well as to introduce and later-on cleave this auxiliary, was deemed far from ideal. On the other hand, a suitable protecting group of the C5 alcohol would perhaps be needed for the down-stream elaboration into the macrocyclic core of the mycinamicin series. Despite the absence of a convincing literature precedent for the anticipated task, it was found after some experimentation that the hydroformylation catalyst formed from [Rh(acac)(CO)$_2$] and
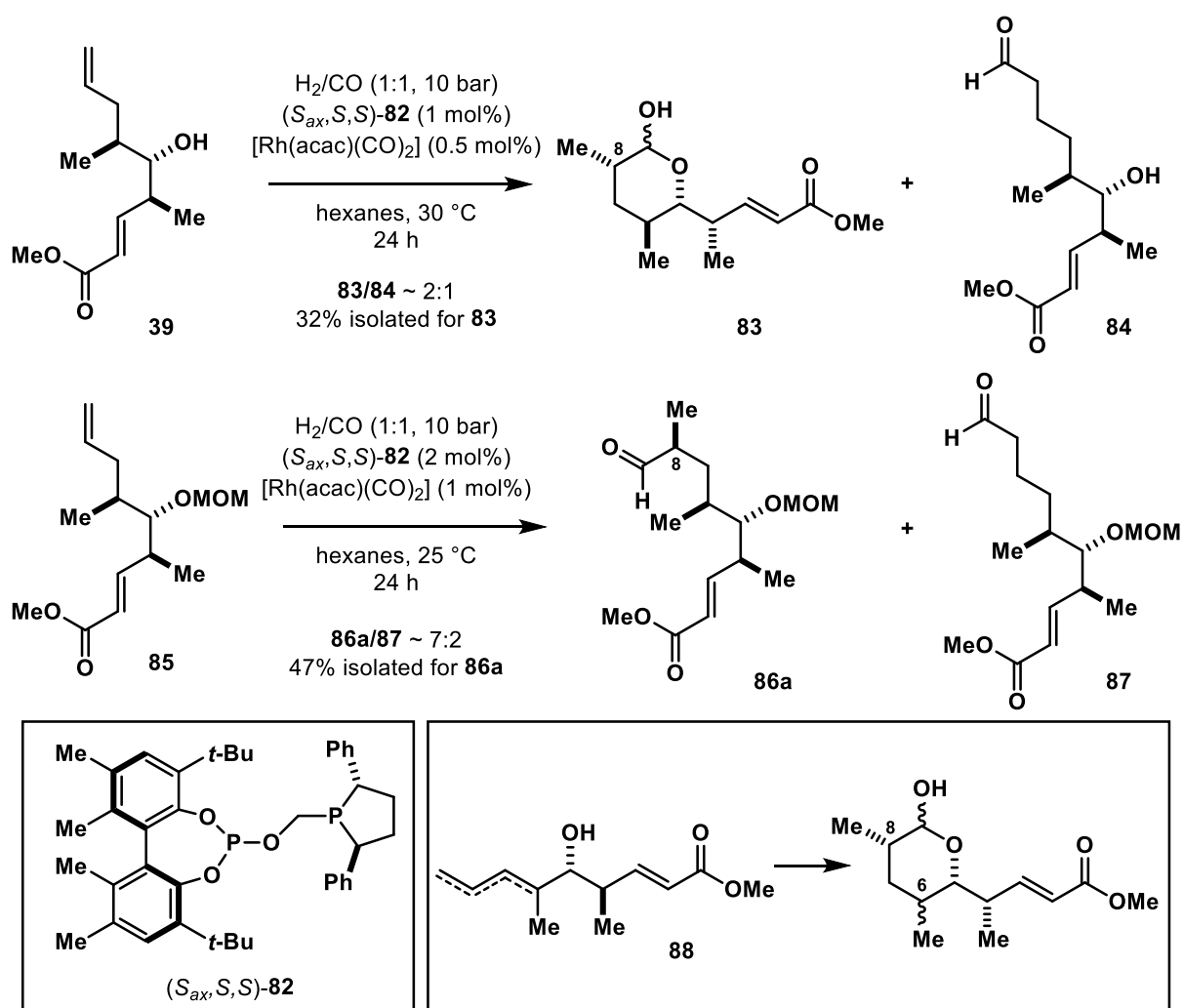

Scheme 2.6: Hydroformylation of the common alkene building block with selectivity for the branched aldehyde. A chain-walk mechanism may lead to epimerization of a remote methyl stereocenter during hydroformylation (see text).

the commercially available enantiomer of the mixed phosphine/phosphite ligand BOBPhos ((S_{ax},S,S)-**82**; "<u>b</u>est <u>of</u> <u>b</u>oth <u>ph</u>osphorous ligands") was able to effect the desired hydroformylation of alkene fragment **39**.[100] Even with the free C5 alcohol in place, the required branched aldehyde was formed with reasonable selectivity ($b/l \approx 2{:}1$) as virtually a single C8 epimer to form an anomeric mixture of lactols **83** (scheme 2.6). Gratifyingly, a MOM ether at C5 even improved this regiochemical outcome and circumvented the formation of lactol mixtures: the lactols showed some capricious behavior further down the route when their opening was explored by nucleophile addition or protecting group introduction (*e.g.* by silylation or alkylation of the C5 alcohol of the open-chain form in equilibrium with **83**).

Further optimization of the reaction showed that strictest temperature control during the hydroformylation step was crucial. While the lactol mixture **83** was obtained in the hydroformylation of **39** as a single C6 diastereomer at a reaction temperature of 30 °C, scrambling of this stereocenter was observed when the internal temperature was raised by only 5 °C. Stereochemical scrambling of this remote methyl substituent is best explained by reversible isomerization of the terminal alkene to the neighboring internal positions (cf. **88**, "chain walk"). Lowering the temperature by only 5 °C on the other hand, led to incomplete conversion of the substrate. Eventually, best results in terms of chemical yield for the branched hydroformylation product of MOM ether **85** were obtained under a total pressure of 15 bar of H_2/CO at $30-35$ °C in hexafluorobenzene instead of hexanes. This particular solvent had already been used in a more industry-oriented reaction setting to produce short-chain aldehydes, though the reason for its beneficial effect on the reaction outcome is unclear.[100c] A prolonged reaction time had to be avoided due to the additional hydroformylation of the enoate at some point. In order to rigorously prove the stereochemical identity of the produced branched aldehydes, the hydroformylation was also performed with the non-commercial (R_{ax},R,R)-enantiomer of phosphorous ligand **82**, synthesized following a multi-step literature procedure.[100c, 101] Thus, both hydroformylation products **86a,b** epimeric at C8 were subjected to (i) reduction of the aldehyde, (ii) acidic cleavage of the MOM protecting group, and (iii) oxidation/ring-closure under neutral conditions to lactones **90a,b** (scheme 2.7). Only the analytical data of lactone **90b**, obtained with (R_{ax},R,R)-**82**, displayed an excellent match with those reported for this exact same structure in the protomycinolide IV synthesis by the group of Yamaguchi (cf. section 1.4, and experimental part for details). The equally efficient performance of the enantiomeric phosphorous ligands in the stereochemical control during the creation of the C8 methyl branch by hydroformylation of alkene **85** (for both dr > 95:5) clearly confirms the catalyst- rather than substrate-control in the key step.
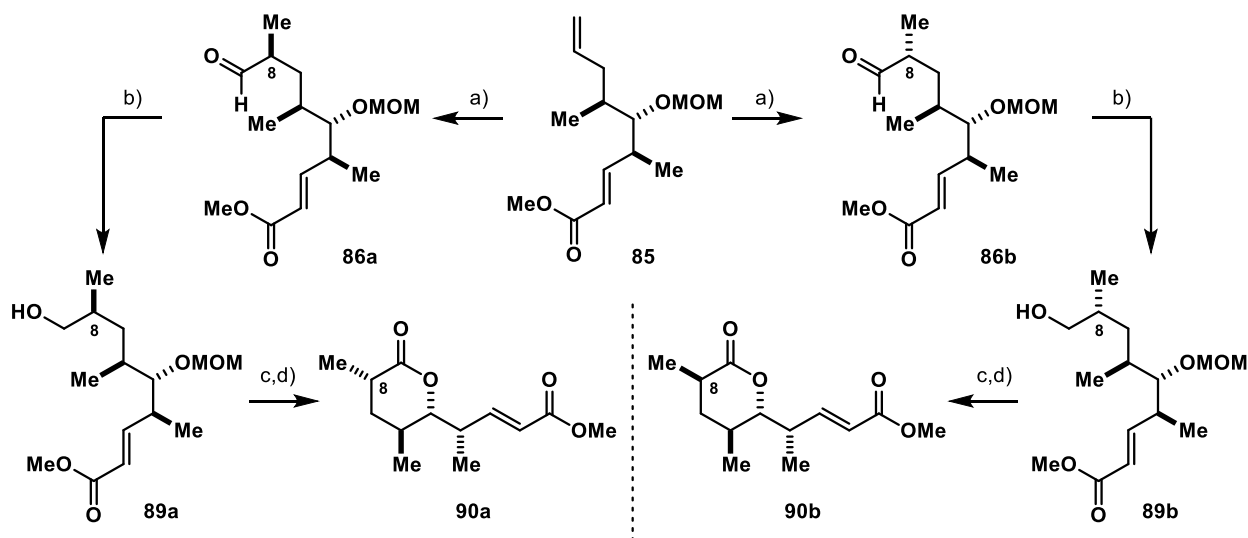
Scheme 2.7: Elaboration of the diastereomeric aldehydes obtained as products from hydroformylation of building block **85** with enantiomeric phosphorous ligands into six-membered lactones. Conditions: a) [Rh(acac)(CO)$_2$] (1 mol%), (S_{ax},S,S)-**82** (2 mol%, for **86a**) or (R_{ax},R,R)-**82** (2 mol%, for **86b**), H$_2$/CO (1:1, 15 bar), C$_6$F$_6$, 35 °C, 71% (**86a**, 24 h reaction time), 68% (**86b**, 3.5 d reaction time); b) NaBH$_4$, MeOH, 0 °C, 99% (**89a**), 52% (**89b**); c) HCl, MeOH/H$_2$O, rt; d) PhI(OAc)$_2$, TEMPO (20 mol%), MeCN/H$_2$O, 0 °C, 47% (**90a**, over two steps), 28% (**90b**, over two steps).

Following this stereochemical proof, the preparation of the desired branched aldehyde from common building block **39** was further fine-tuned for scale-up. Thus, MOM-protection of the C5 alcohol was accomplished by the action of phosphorous(V) oxide in anhydrous dimethoxymethane, avoiding the use of carcinogenic reagents (scheme 2.8). Under optimized conditions, the subsequent ligand-controlled hydroformylation of **85** (with remaining isomeric impurity epimeric at C6 from the vinylogous aldol reaction, dr = 87:13) could be performed on a decent scale: the required branched aldehyde **86b** was produced on gram-scale with excellent diastereoselectivity for the desired C8 isomer, which was isolated as a mixture with the branched reaction products epimeric at C8 and/or C6 derived from the impurity in the starting material (83:17 ratio of desired isomer to sum of all isomers; dr = 96:4 for formation of C8 stereocenter).

As aldehyde **86b** is prone to oxidation to the corresponding carboxylic acid under ambient atmosphere, it was reacted with lithiated enyne **57** without delay to furnish an inconsequential mixture of propargylic alcohols **91** in moderate yield (56 – 65% isolated). Though the chemical yield of this transformation certainly leaves room for improvement, initial efforts to optimize the reaction were corrupted by the instability of aldehyde **86b** upon storage, leading to erratic data. In the end, the above-described reaction outcome was deemed satisfactory in light of the simple conditions employed and the fact that no epimerization of the α-stereogenic center of the valuable aldehyde was observed under these conditions.
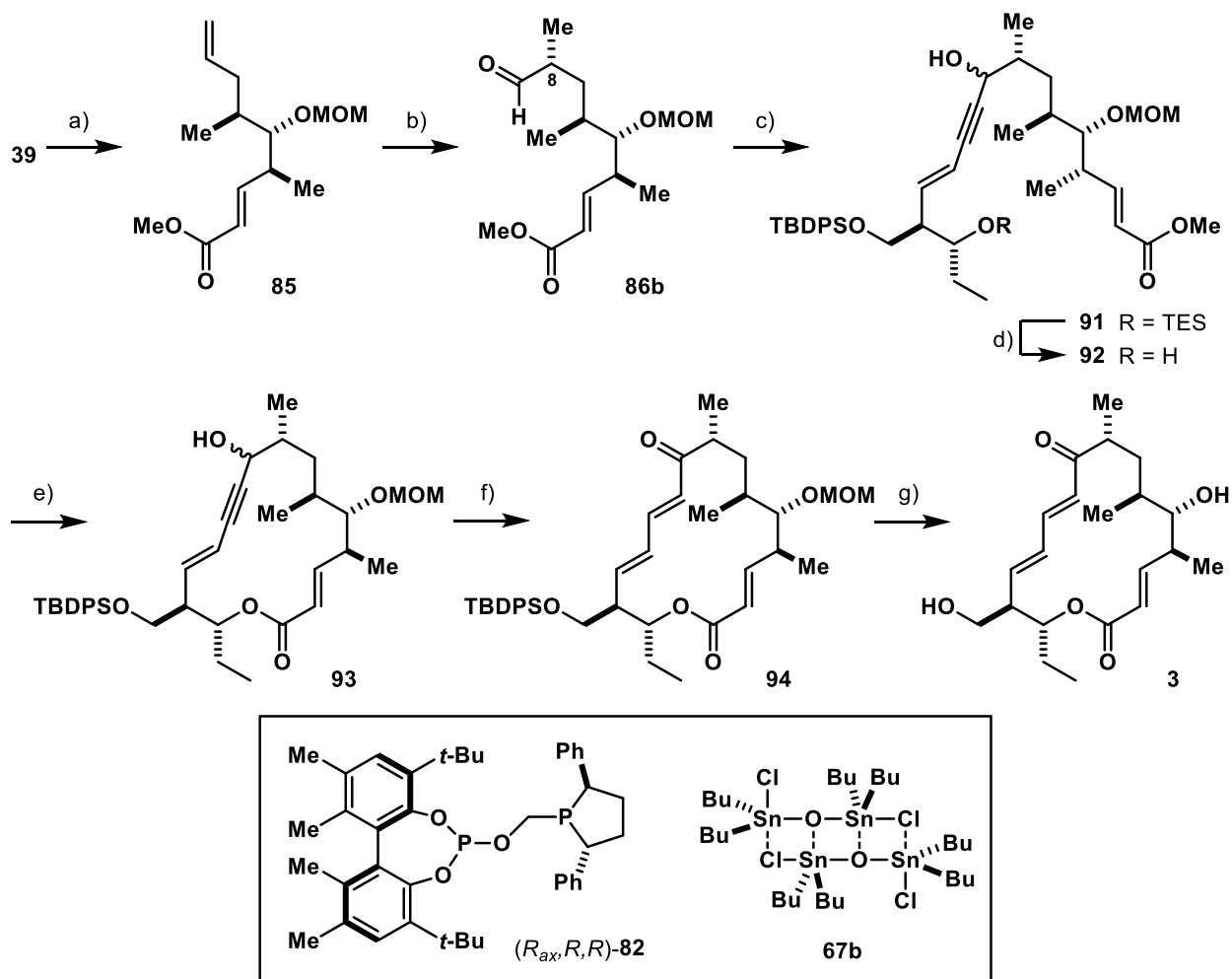
Scheme 2.8: Completion of the synthesis of mycinolide IV. Conditions: a) CH$_2$(OMe)$_2$, P$_4$O$_{10}$, CH$_2$Cl$_2$, 87% (dr = 87:13, see text); b) [Rh(acac)(CO)$_2$] (3.4 mol%), (R_{ax},R,R)-**82** (4.2 mol%), H$_2$/CO (1:1, 15 bar), C$_6$F$_6$, 30 °C, 60% (dr = 83:17, Σ of all isomers); c) **57**, n-BuLi, THF, −78 °C, 56 – 65% (dr = 1.4:1); d) CSA (5 mol%), CH$_2$Cl$_2$/MeOH, −20 °C, 86%; **67b**, chlorobenzene, reflux, 32 – 37%; f) [CpRu(MeCN)$_3$]BF$_4$ (50 mol%), PhPCy$_2$ (50 mol%), THF, reflux, 65%; g) aq. HCl (3 M), MeOH, 40 °C, 74%.

After the C15 triethylsilyl ether of propargylic alcohol **91** had been selectively cleaved with a catalytic amount of camphorsulfonic acid in methanolic dichloromethane at low temperature, the same problems as in the synthesis of the aldgamycin core were faced during attempted liberation of the seco-acid from **92**, aiming for a classical macrolactonization. Once again, these problems could be avoided because direct stannoxane-mediated transesterification of methyl ester **92** proved viable, though in this case the transformation was somewhat more difficult. Interestingly, the desired macrolactonization did not occur at all, when the ester was heated as a dilute solution in presence of stannoxanes **67a,b** in a closed system (table 2.3, entries 1, 2; Schlenk tube closed with cooling finger). Possibly, continuous evaporation of liberated methanol to remove it from the reaction equilibrium is necessary to drive the lactonization. Indeed, running the reaction as an open system, as it had previously been done in the synthesis of the aldgamycin core, consistently furnished desired macrolactone **93** in 30 – 40% yield. A few stannoxane catalysts **67a-e** with

Table 2.3: Screening of reaction conditions for the macrolactonization of methyl ester **92** by transesterification (n.i. = product not isolated).

R = n-Bu, X = OH, Y = SCN, **67a**
R = n-Bu, X = Y = Cl, **67b**
R = n-Oct, X = Y = Cl, **67c**
R = Me, X = Y = Cl, **67d**
R = n-Bu, X = Y = Br, **67e**
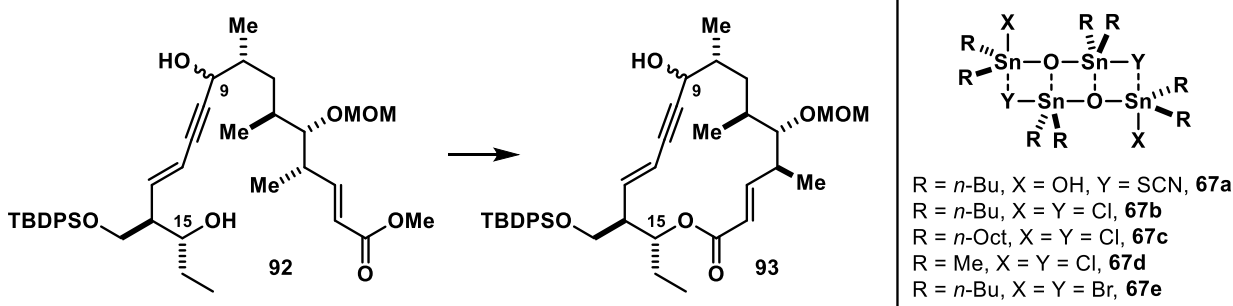
entry	conditions	time	yield	comment
1	**67a** (1.0 equiv) PhMe, reflux (closed set-up)	1 d	0%	desired product not found, only oxidation of the C9 alcohol observed
2	**67b** (1.0 equiv) PhMe, reflux (closed set-up)	1 d	0%	as entry 1
3	**67b** (2.0 equiv) PhCl, reflux	3 d	37%	17% isolated yield of seco-acid **67a** under the same conditions showed an inferior reaction profile by TLC analysis
4	**67e** (2.0 equiv) PhCl, reflux	3 d	24%	28% isolated yield of seco-acid
5	**67c** (2.0 equiv) PhCl, reflux	3 d	37%	
6	**67d** (2.0 equiv) PhCl, reflux	3 d	41%	
7	**67d** (2.0 equiv) PhCl, reflux	4 d	39%	
8	**67b** (2.0 equiv) trans-decalin, 140 °C	3 d	37%	
9	**67b** (2.0 equiv) MS 5Å PhCl, reflux	4 d	26%	
10	[(n-Oct)$_3$PMe][CO$_2$Me] (1.0 equiv) La(NO$_3$)$_3$ (1.0 equiv) cyclohexane, rt	7 h	0%	an undesired tetrahydropyran was formed as the major product (see experimental part)

different anions and alkyl residues were tested (entries 3 – 7), as well as different solvents. Perhaps unsurprisingly, the organic residue of the stannoxane had negligible influence on the reaction outcome. The *n*-butylstannoxanes, however, are preferable in terms of ease of preparation and lower toxicity.[102] Some influence was found for the anionic stannoxane constituents: among the *n*-butylstannoxane thiocyanate **67a**, chloride **67b** and bromide **67e**, the chloride performed best in the macrolactonization. Notably, a substantially larger amount of the uncyclized seco-acid was isolated in the case of the bromide, even if utmost care was taken in the drying of the glassware and reagents (entries 3, 4). The isolation of the seco-acid and the lower propensity of ester **92** to undergo the macrocyclization might be ascribed to a lower flexibility of the conjugated *E*-configured enyne in comparison to the skipped enyne subunit of **66**, which allows for rotation around the σ-bonds of the saturated carbon atom. In addition, the secondary propargylic alcohol of **92** at C9 rather than the tertiary alcohol of **66** might interfere in the template complex formation between the C15 alcohol and the methyl ester necessary for the macrocyclization.[88b] Ruthenium-catalyzed isomerization of this C9 alcohol to the corresponding dienone (see below) prior to the macrocyclization led to an inferior result, however; this might be due to an even lower flexibility of the dienone substrate. Addition of molecular sieves to the stannoxane system led to an inferior outcome, and employment of an alternative reagent system for transesterification based on lanthanum(III) nitrate was to no avail (entries 9, 10).[103] Eventually, macrocyclization of **92** was forged with the aid of stannoxane **67b** in chlorobenzene, furnishing macrolactone **93** on a preparatively useful scale (32% yield on 600 mg scale, single largest batch).

With the macrocycle closed, the stage was set for the final rearrangement of the propargylic alcohol to the corresponding unsaturated ketone characteristic for the mycinamicin series. This overall strategic transformation had previously been used in the total synthesis of protomycinolide IV by Suzuki *et al.*: classical reduction of a keto alkyne with lithium aluminum hydride and oxidation of the resulting *E*-allylic alcohol in a separate step ultimately led to the required target motif (cf. scheme 1.2). The success of the present work, however, depends on the rearrangement of propargylic alohol **93** into the ketone motif in a single step, since a multi-step sequence involving a strongly reducing metal hydride is not conceivable at the given macrolactone stage. The methodology of ruthenium-catalyzed redox-isomerization of propargylic alcohols into α,β-unsaturated ketones was originally introduced in the group of Trost,[104] and has since then been successfully used in another total synthesis in the Fürstner group.[105] The rearrangement is thought to proceed via a cationic [CpRuL₂] fragment (**X**), formed by chloride abstraction from precatalyst **95a** by the action of InCl₃ in the original procedure (figure 2.2, part a).
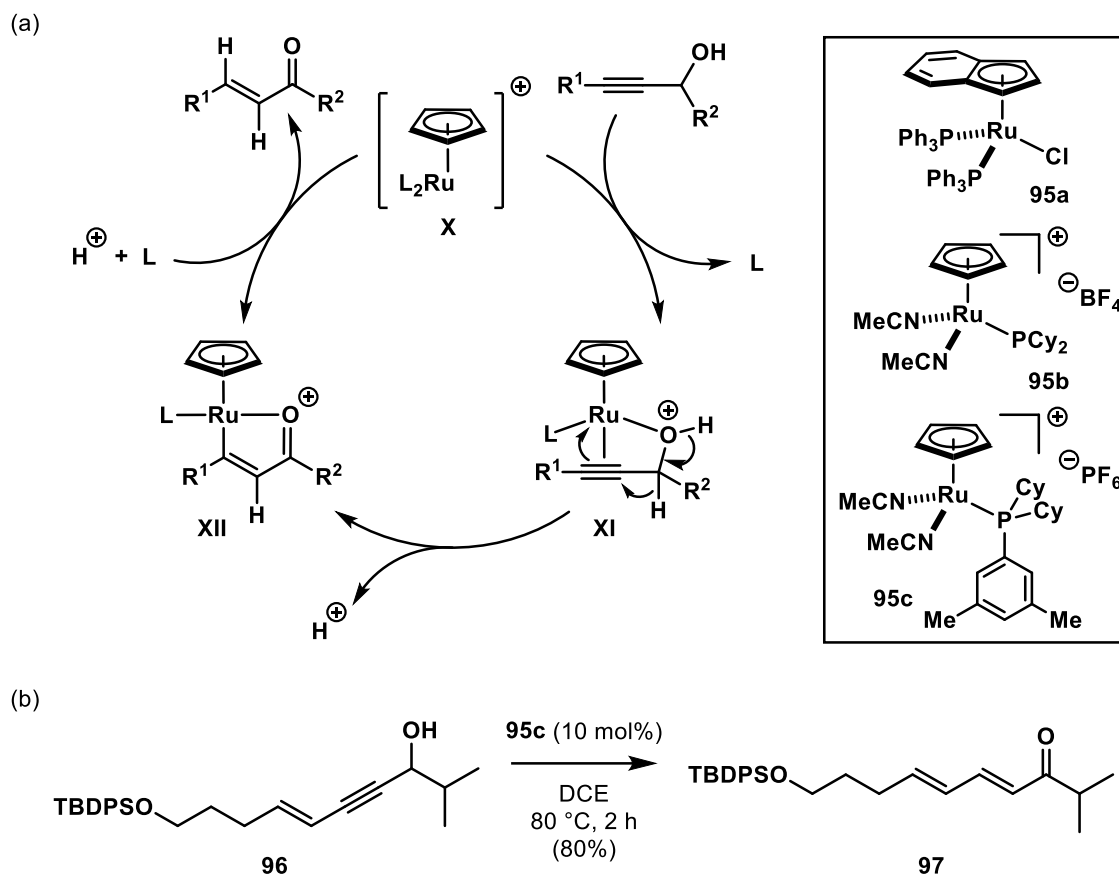
(a)

(b)

Figure 2.2: (a) Catalytic cycle for the redox-isomerization of propargylic alcohols into unsaturated ketones proposed in the original disclosure by Trost; (b) A model reaction indicates that the anticipated redox-isomerization of enynes into dienones is feasible, also without employment of an acid co-catalyst.

Substitution of one of the ligands by the propargylic alcohol leads to an active complex **XI** that undergoes stereospecific rearrangement to an *E*-alkenyl Ru intermediate **XII**, followed by protonolysis to deliver the enone product and release the Ru catalyst **X**. It was shown that the employment of cationic [CpRu] complexes **95b,c** obviates the use of InCl$_3$ to generate the active catalyst, avoiding possible side reactions arising from presence of this Lewis acid.[105a] In view of the catalytic cycle of this Ru-catalzyed transformation, the conjugated π-systems as present in enyne substrate **93** and the corresponding dienone product might inhibit or even stop the conversion to the rearrangement product by binding the active [CpRu] catalyst too tightly.[92c] However, a brief test reaction with model substrate **96** indicated the feasibility of this key step, and furthermore revealed that the rearrangement also proceeds efficiently in the absence of an acid co-catalyst (figure 2.2, part b). In the original methodological studies by the group of Trost, primary alcohols served as substrates for their rearrangement to aldehydes, which were described as unstable under the reaction conditions. The primary role of the acid co-catalyst might thus have been a merely circumstantial one to catalyze the in-situ acetalization of those aldehydes to prevent their decomposition.[104b] After all, subjecting propargylic alcohol **93** to ruthenium catalyst **95b** cleanly afforded

dienone **94** in refluxing tetrahydrofuran, even though a high catalyst loading was indeed necessary. This fact may reflect the initial concerns of catalyst quenching by the conjugated π-systems present.

When protected macrolide aglycon **94** was finally subjected to aqueous hydrochloric acid in methanol, global deprotection was achieved, furnishing mycinolide IV (**3**) in only twelve steps (longest linear sequence). The analytical and spectral data matched those previously reported[38c, 58a] and unequivocally confirmed the stereochemical assignments. The orthogonal cleavage of the C5 MOM ether and C21 TBDPS ether, as well as the attachment of the carbohydrates to yield the biologically active natural product mycinamicin IV, are discussed in section 2.9.

2.5 Synthesis of the Sugar at C5 of Aldgamycin: D-Aldgarose

The previous sections showed how the macrocyclic cores of the aldgamycin and mycinamicin families as two representatives of a larger estate of 16-membered macrolide antibiotics could be assembled by a unified approach, which relies on only a single building block for the highly conserved eastern sectors of these targets. In section 1.3 it was already pointed out, however, that typically only the glycosylated macrolides, *i.e.* the "complete" natural products, exhibit biological activity. The following three sections are therefore dedicated to the syntheses of the carbohydrates of the aldgamycins and mycinamicins: the sugars at their C5 positions, D-aldgarose and D-desosamine, and the sugar attached to the primary alcohols, D-mycinose.

During the time of this project when it was found that the free aglycon of aldgamycin N was not accessible due to the unforeseen engagement of the C5 alcohol in hemiketal formation with the C9 ketone, an efficient preparation of the branched 4,6-dideoxy octose D-aldgarose[106] became the highest priority. Only after preparation of this sugar, the revised plan could be scrutinized in which the critical glycosidation was timed before unveiling the carbonyl group by formal hydration of the triple bond. Although two syntheses of D-aldgarose had been disclosed in the literature, these syntheses were considered not satisfactory for the purposes of this project in view of the cumbersome access from the chiral pool via defunctionalization of D-galactose pentaacetate (**98**) or methyl α-D-glucopyranose (**103**, scheme 2.9).[107] From a strategic point of view, both syntheses introduce the C3 branch of aldgarose via carbonyl addition to the protected ketone intermediates **99** and **104**, respectively. Notably, addition of Seebach's lithio-dithiane to β-configured ulose **99** proceeds with low diastereoselectivity, whereas addition of vinyl Grignard reagent to the α-configured ulose **104** produces the desired equatorial branch as a single diastereomer. The transposition of the anomeric substituent is therefore of critical importance for the stereochemical outcome of a nucleophilic addition to the ketone at the 3-position. Sodium borohydride reduction of the keto branch obtained after mercury-mediated desulfurization of **100** actually formed the desired alcohol stereoisomer as

the minor isomer, ultimately furnishing methyl β-D-aldgaroside **102** with unfavorably low efficiency. On the other hand, epoxidation of the acetonide derived from **105** occurred with moderate diastereoselectivity in favor of the desired stereochemical arrangement in the C3 branch. However, this acetonide comes at the cost of two additional steps necessary for its introduction and cleavage, thus making this particular entry to methyl aldgaroside **102** again rather inefficient.
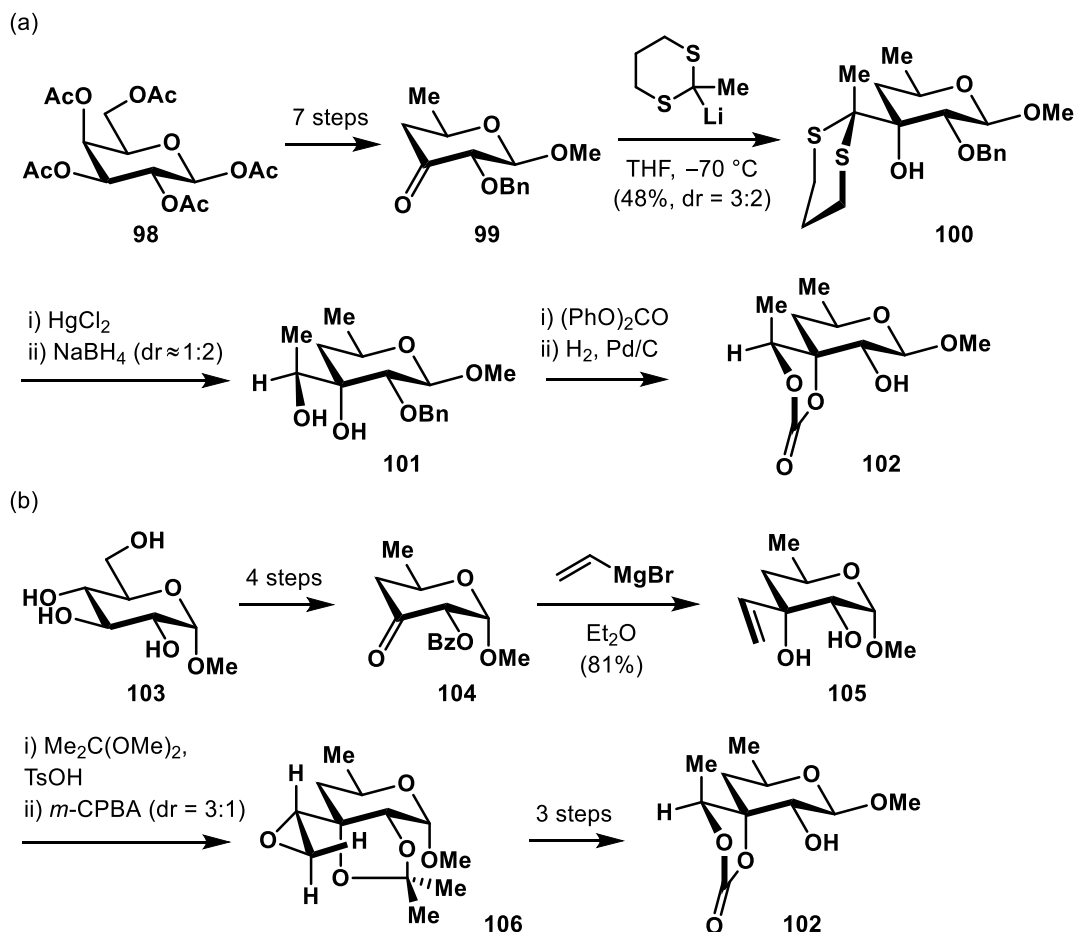
Scheme 2.9: Previous syntheses of methyl β-D-aldgaropyranoside (**102**) from naturally occurring carbohydrates: published by (a) Paulsen *et al.* in 1972 and (b) Brimacombe *et al.* in 1974.

In consideration of these lengthy routes, a completely new *de novo* access towards this rare but urgently needed carbohydrate was conceived. Retrosynthetically, build-up of the sugar by hetero-Diels-Alder reaction was anticipated. Thus, the C3 branch of a **XIII** might be introduced at a later stage by carbonyl addition to give protected ketol **XIV**, which could be traced back to dihydroxylation or epoxidation of enone **107**. Alternatively, a diene **XVIII** that already carries the side chain in its stereochemically fully developed form could be used, allowing a selective dihydroxylation of the endocyclic alkene of **XV** to forge the C2 and C3 alcohols (figure 2.3). Another approach to the side chain might be Mislow-Evans rearrangement of
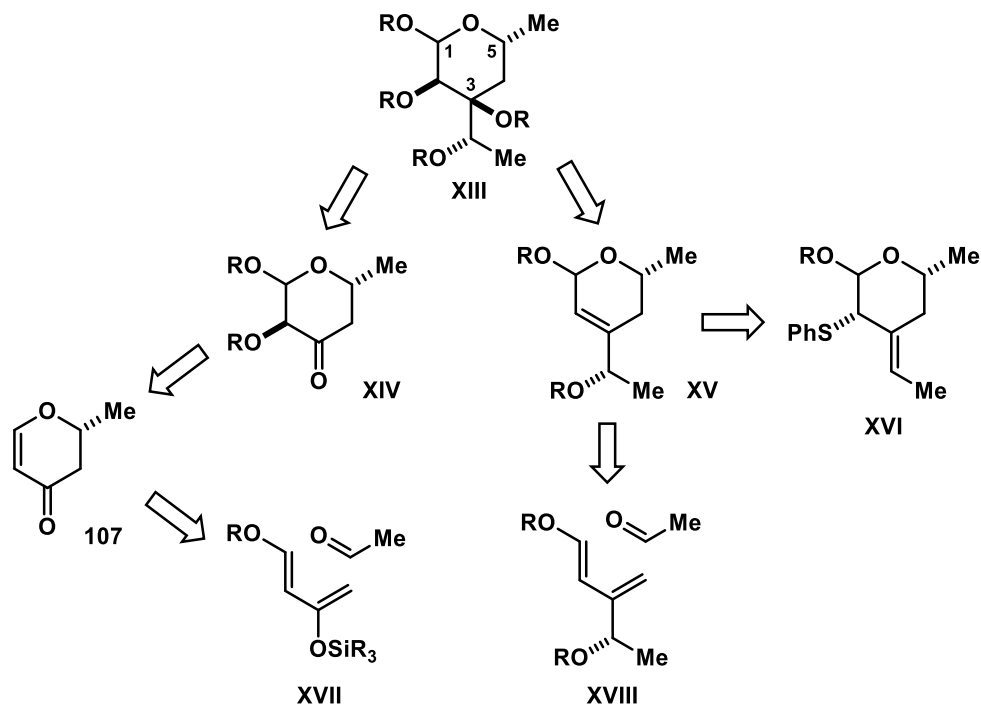
Figure 2.3: Retrosynthetic analysis of the branched aldgaroside **XIII** revealed two possible starting points for a synthetic approach by hetero-Diels-Alder reaction: either simple siloxy diene **XVII** or stereochemically defined diene **XVIII** with the two-carbon alcohol branch already in place.

thioether **XVI** with a tri-substituted alkene branching off C3. Preparation of this alkene as a single diastereomer seemed difficult, however, and no literature precedence could be found in support thereof. In contrast, both routes via either a classical Danishefsky diene **XVII** or branched diene **XVIII** appeared viable. The potentially more convergent synthesis via branched diene **XVIII** would first require the preparation of this building block in enantiomerically enriched form. The subsequent hetero-Diels-Alder reaction might then rely on substrate control to forge the C5 methyl substituent of **XV** stereoselectively, while an unfavorable stereochemical outcome might be overridden by additional catalyst control. The configuration of the anomeric position would be inconsequential in this route, although handling of a single anomer rather than an anomeric mixture would certainly be preferred for practical reasons.

To this end, the synthesis of the required diene started with a Morita-Baylis-Hillman reaction between acetaldehyde and ethyl acrylate to give racemic alcohol **108** (scheme 2.10). Kinetic resolution by acetylation with vinyl acetate catalyzed by Amano lipase PS from *Burkholderia cepacia* left back the desired enantiomer of the secondary alcohol in excellent yield and optical purity (5 g scale, 45% yield, 98% *ee*).[108] The alcohol was protected as its TBS ether in the next step, and the resulting ethyl ester **109** was then transformed into the corresponding aldehyde **110** by full reduction to the primary alcohol, followed by re-oxidation using the Parikh-Doering conditions. When this aldehyde was subjected to an ice-cold solution of the ylide formed from (methoxymethyl)triphenylphosphonium chloride and *t*-BuLi in diethyl ether, the

anticipated *E*-configured dienol ether **111** was formed selectively in decent yield.[109] Contrary to a few published thermal hetero-Diels-Alder reactions of branched dienes,[110] cyclocondensation of **111** with acetaldehyde to furnish endocyclic alkene **112** failed under various conditions. No defined product was found by stirring the dienol ether and acetaldehyde without a catalyst, or in presence of either achiral Lewis acids (BF$_3$ · OEt$_2$, ZnCl$_2$, Eu(fod)$_3$) or Jacobsen's chiral chromium catalyst (see below) in different solvents (CH$_2$Cl$_2$, THF, Et$_2$O).
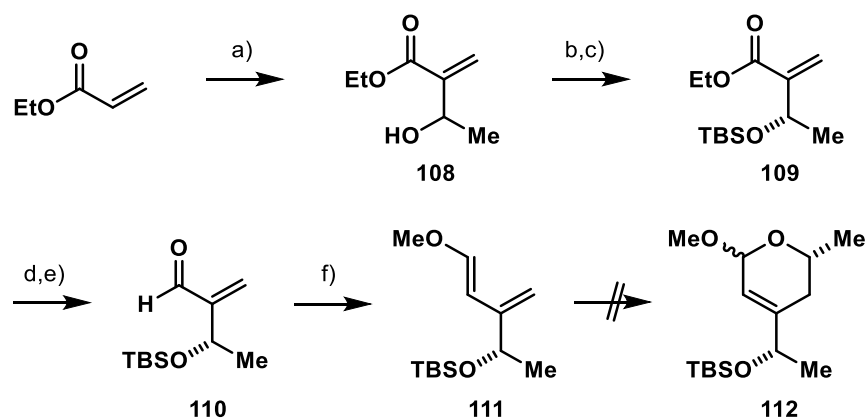
Scheme 2.10: Synthesis of an enantioenriched branched dienol ether for an attempted hetero-Diels-Alder reaction with acetaldehyde. Conditions: a) MeCHO, DABCO (5 mol%), neat, rt, 85%; b) vinyl acetate, Amano lipase PS (*Burkholderia cepacia*), MTBE, rt, 45%, 98% *ee*; c) TBSCl, imidazole, CH$_2$Cl$_2$, rt, 91%; d) Dibal-H, CH$_2$Cl$_2$, −78 °C, 95%; e) SO$_3$ · pyridine, DMSO, *i*-Pr$_2$NEt, CH$_2$Cl$_2$, −20 °C, 89%; f) (i) [Ph$_3$PCH$_2$OMe]Cl, *t*-BuLi, Et$_2$O, 0 °C; (ii) **110**, Et$_2$O, 0 °C, 72% (*E*/*Z* = 80:20, mixture isolated).

Therefore, the alternative approach to introduce the C3 branch of the sugar at a later stage was investigated next. While hetero-Diels-Alder reaction between Danishefsky's diene[111] **113a** and chromium salen catalyst **114a** had been described to deliver dihydropyranone **107** with only low enantiomeric purity (57% *ee*),[112] it was found that chromium complex **114b**, which had been optimized specifically for hetero-Diels-Alder reactions in the Jacobsen group,[113] catalyzes the same reaction with much better enantiocontrol (94% *ee*, scheme 2.11). The absolute configuration of **107** could be assigned by comparison of the optical rotatory power of the sample obtained to the literature value of the enantiomer.[114] After some experimentation, employment of the more stable triethylsilyl ether[115] **113b** proved superior for practical purposes, because it allowed for a much simpler separation of the initially formed silyl enol ether **115** from the self-addition side products of acetaldehyde also formed under the reaction conditions. Analytically pure dihydropyranone **107** was obtained in high enantiomeric purity (61% isolated yield, 93% *ee*) after chromatographic purification of the primary hetero-Diels-Alder product, followed by acidic cleavage of the silyl enol ether with trifluoroacetic acid in dichloromethane.[116]
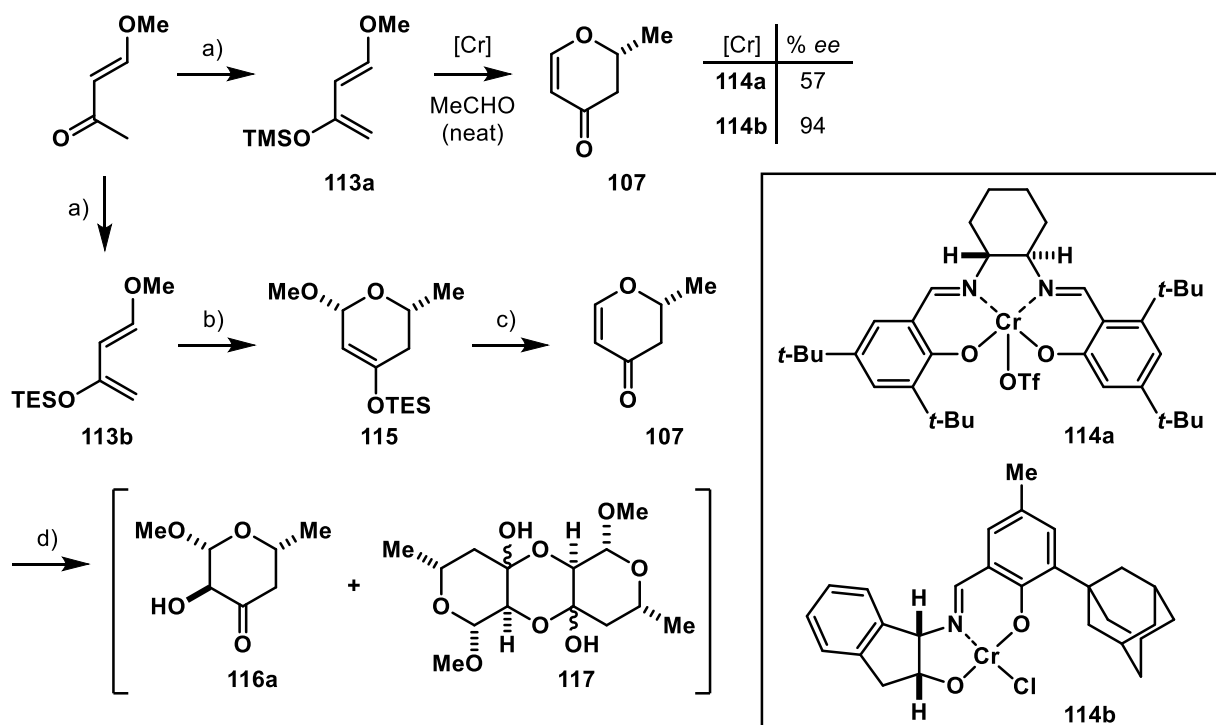
Scheme 2.11: Synthesis of an enantioenriched ketol as a useful intermediate for the carbohydrate syntheses. Conditions: a) TMSOTf for **113a** or TESOTf for **113b**, Et$_3$N, Et$_2$O, −20 °C, 81% (**113a**), 92% (**113b**); b) **114b** (1.5 mol%), MeCHO (neat), −20 °C → rt; c) TFA, CH$_2$Cl$_2$, 61% (over two steps, 93% *ee*); d) H$_2$O$_2$, MeOH, aq. NaOH, −45 °C, 70 – 90%.

Though dihydropyranone **107** was completely inert towards electrophilic epoxidation (*e.g.* by reaction with *m*-CBPA), it underwent clean epoxidation/ring-opening on exposure to hydrogen peroxide in methanol under basic Weitz-Scheffer conditions to afford the 1,2-*trans*-configured ketol **116a** and its derived dimer **117**.[117] With the ketol in hand, introduction of the C3 branch of aldgarose was now anticipated in analogous manner to the previous synthesis by Brimacombe *et al.* (cf. scheme 2.9, part b). Unfortunately, the obtained 1,2-*trans* configuration featuring an equatorial anomeric methoxy substituent was unfavorable for the stereochemical outcome of the carbonyl addition of vinyl Grignard reagent to the monomer/dimer mixture **116a/117** of the free ketol. Irrespectively of the solvent and temperature, addition of vinylmagnesium bromide delivered equimolar amounts of the two C3 diastereomers (scheme 2.12); all attempts failed to invert the anomeric methoxy substituent to its axial orientation to steer the carbonyl addition. Hence, it was decided to install a sterically demanding silyl ether at C2 in an attempt to improve the stereochemical outcome of the carbonyl addition. This also left the dimerization of the ketol inconsequential since a silyl chloride and imidazole cracked the dimer and furnished the silylated monomer exclusively. Addition of vinylmagnesium bromide to TIPS-protected ketol **116b** in ether at −78 °C proceeded with useful selectivity (dr ≈ 4:1), and the desired equatorially branched product could be isolated as a single diastereomer on multi-gram scale (46% yield from **107** over three steps). Gratifyingly, a TIPS ether not only favored the desired facial selectivity in the carbonyl addition, but also entailed the highly selective epoxidation of the resulting

allylic alcohol **118** by *m*-CPBA in the following step to give the required stereochemical arrangement in the side chain (dr = 10:1).[118] This excellent stereochemical outcome of the epoxidation might reflect a highly ordered transition state **XIX** in which the axial hydroxyl group directs the incoming reagent to the proper alkene face via hydrogen bonding, and also exerts a massive rate acceleration of the epoxidation by this preorganization.[119] Therefore, the seemingly disfavored orientation of the vinyl substituent towards the sterically demanding TIPS ether in structure **XIX** might be outweighed by this kinetic effect under the scenario of a Curtin-Hammett situation. The alternative arrangement with the vinyl group turned to the methylene side and the peracid approaching alongside the TIPS ether ought to be even less favorable.

R	dr
H (with dimer)	50:50
TBS	70:30
TIPS	85:15
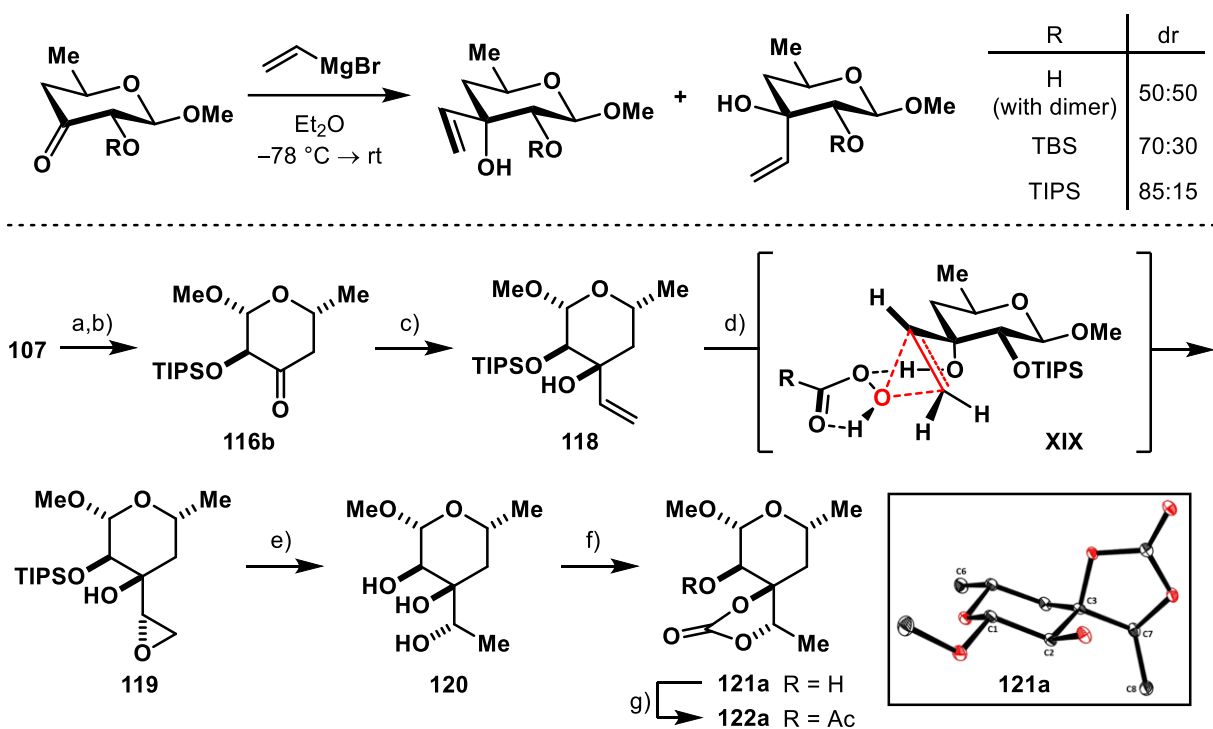
Scheme 2.12: Preparation of the methyl glycoside of D-aldgarose. Conditions: a) H_2O_2, MeOH, aq. NaOH, −45 °C; b) TIPSCl, imidazole, DMF; c) vinylmagnesium bromide, Et_2O, THF, −78°C, 46% (pure isomer, over three steps); d) *m*-CPBA, CH_2Cl_2, 0 °C → rt, 81% (dr = 10:1); e) $LiAlH_4$, Et_2O, 0 °C → rt, 91%; f) $COCl_2$, CH_2Cl_2, pyridine, 0 °C, 80%, g) Ac_2O, NEt_3, DMAP cat., 0 °C → rt, 81%.

With all chiral centers set, the epoxide was opened on treatment with lithium aluminum hydride, resulting in concomitant cleavage of the adjacent TIPS ether. This favorable outcome further increased the strategic value of this protecting group:[120] not only was it pivotal in the selective creation of two stereocenters, but also did it come without further cost in terms of the step count due to this reductive cleavage event. The resulting triol **120** underwent selective formation of the carbonate at the exocyclic site to give methyl β-D-aldgaropyranoside **121a**.[121] The analytical data of **121a** were in good agreement with the literature data,[107b] and NOE experiments allowed a preliminary confirmation of the proper stereochemical arrangement of the side chain. The rigorous stereochemical proof for this compound was provided by X-ray diffraction, which unambiguously confirmed the stereochemical identity of aldgarose (scheme 2.12, insert).

To prepare the carbohydrate for the upcoming glycosylation event en route to aldgamycin N, the C2 alcohol was acetylated (**122a**) to provide anchimeric assistance in favor of a β-selective glycosylation. In this effort, a panel of different glycosyl donors **122b-g** was synthesized by manipulation of the anomeric position (scheme 2.13).
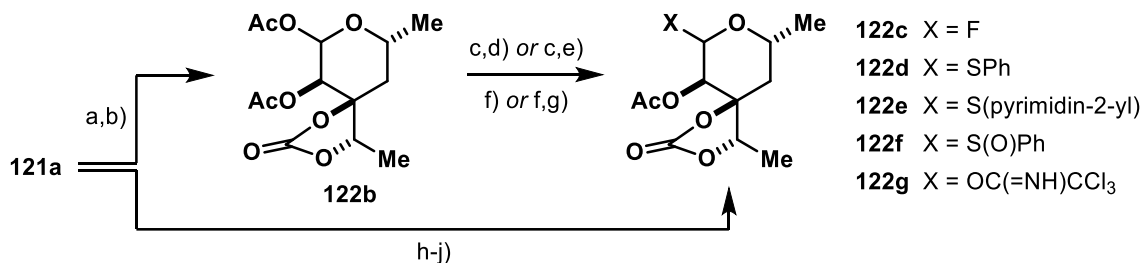
Scheme 2.13: Synthesis of D-aldgaropyranosyl donors. Conditions: a) Ac$_2$O, Et$_3$N, DMAP cat., 0 °C → rt, 81%; b) Ac$_2$O, H$_2$SO$_4$, 0 °C → rt, 98%; c) BnNH$_2$, THF, rt, 70% (α:β = 1:15); d) DAST, CH$_2$Cl$_2$, −15 °C, 78% (**122c**, α:β = 1:2); e) Cl$_3$CCN, DBU, CH$_2$Cl$_2$, 92% (**122g**, α:β = 1:3); f) PhSH, SnCl$_4$, CH$_2$Cl$_2$, 0 °C, 83% (**122d**, α:β ≈ 2:3); g) *m*-CPBA, CH$_2$Cl$_2$, 50% (**122f**); h) TFA/H$_2$O, 100 °C, 67%; i) PEt$_3$, (pyrimidin-2-yl)$_2$S$_2$, MeCN, 0 °C, 77%; j) Ac$_2$O, Et$_3$N, DMAP cat., rt, 71% (**122e**, β-anomer).

Fluoride donor **122c** and trichloroacetimidate **122g** were obtained from the corresponding 2-O-acetyl lactols upon treatment with DAST or trichloroacetonitrile in the presence of DBU, respectively. The anomeric acetate of **122b** was easily substituted by thiophenol with the aid of tin(IV) chloride to deliver thioglycoside **122d**, and subsequent oxidation furnished the corresponding sulfoxide donor **122f**. For the synthesis of the heterocyclic thioglycoside **122e**, a Mitsunobu-type procedure via the free sugar was followed.[122]

2.6 D-Desosamine: A unified Approach to 4,6-Dideoxy Sugars

Remark: The synthesis of racemic and enantioenriched nitro alcohol **125** from methyl vinyl ketone by Dr. L. Schreyer is gratefully acknowledged (cf. scheme 2.14).

The sugar at the C5 position of mycinamicin IV, D-desosamine, constitutes an important carbohydrate portion of several prominent macrolide antibiotics, most notably the erythromycins and (semi)-synthetic derivatives thereof. In fact, the acidic cleavage of erythromycin produced by fermentation is currently the most economical source of this basic 4,6-dideoxy amino sugar on large scale,[123] although several syntheses, both from the chiral pool and *de novo*, have been described.[124] The *de novo* synthesis of desosamine by the group of Myers is particularly noteworthy since it allows the preparation of both antipodes of the free amino sugar in only four steps from simple methyl vinyl ketone, and the synthetic procedures have been adapted to decagram scale (scheme 2.14).[124h] The synthesis commences with conjugate nitrite addition to methyl vinyl ketone and Corey-Bakshi-Shibata reduction of the resulting saturated ketone **123** to give nitro alcohol **125** in good yield with fair enantioselectivity (87% *ee*). Cyclization by Henry aldol addition with

glyoxal, employed as its trimer hydrate **126**, accompanied by intramolecular lactol formation under basic conditions furnish the properly configured nitro sugar **127** with improved enantiomeric purity as a single, thermodynamically favored diastereomer (>97% *ee*). Free desosamine **128** is easily obtained when **126** is subjected to palladium-catalyzed hydrogenation of the nitro group and reductive amination with formaldehyde under the same hydrogen atmosphere in a smooth one-pot operation.
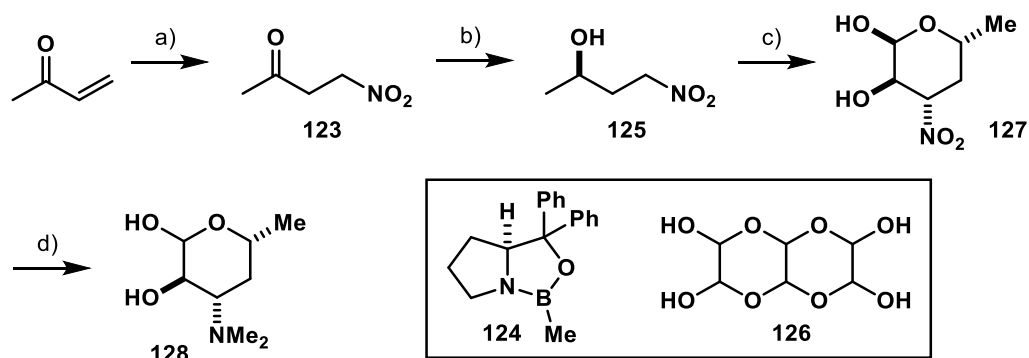
Scheme 2.14: Four-step *de novo* synthesis of D-desosamine by Myers *et al.*; results reproduced in this work in square brackets. Conditions: a) sodium nitrite, pyridinium trifluoroacetate, THF, 0 °C → rt, 78%; b) $BH_3 \cdot THF$, **124** (20 mol%), THF, −10 °C, 75% (87% *ee*, 46 g scale) [49% yield, 78% *ee*, 2.6 g scale], c) **126**, aq. Cs_2CO_3 (5 mol%), *n*-BuOH/H_2O/CH_2Cl_2, 50% (>97% *ee*, 30 g scale) [5% yield, 97% *ee*, 1.0 g scale]; d) H_2, $Pd(OH)_2$/C (10 mol%), MeOH/AcOH (9:1 *v/v*), then aq. CH_2O, 94% (α:β ≈ 1:1.6, 15 g scale).

Unfortunately, in the attempt to reproduce these results in this project, the cyclization step in particular was not nearly as facile as reported. Nitro intermediate **127** was merely obtained with a yield of 5% on gram-scale by the reported crystallization procedure. Alternative isolation by aqueous work-up followed by chromatography was significantly complicated by the high polarity and hydrophilicity of the compounds involved. Though the exact reasons for this issue remain unknown, the crystallization of nitro sugar **127** in the rather unique, biphasic solvent mixture might only work well on a larger scale, and certainly depends on the enantiomeric purity of the starting nitro alcohol **125**. This problematic crystallization might also present a driving force necessary for the reaction to proceed at all with decent conversion according to the principle of Le Chatelier.

Left unsatisfied with the above results, D-desosamine actually seemed within fairly straightforward reach when compared to ketol **116a** previously prepared to access the branched D-aldgarose. If successful, a newly developed synthesis of desosamine from this very same ketol appeared particularly attractive since it would definitely go in hand with the unified approach pursued for the assembly of the macrolide cores. Furthermore, an oxygenation of this ketol might even allow the access to D-mycinose, the terminal sugar constituent of both aldgamycin N and mycinamicin IV. In essence, the synthesis of desosamine would only require the stereoselective elaboration of a ketone into a tertiary amine. For the synthesis of the mycinose,

the very same C3 ketone might serve the functionalization of C4 via the enol(ate), followed by selective carbonyl reduction to the axial C3 alcohol (figure 2.4).
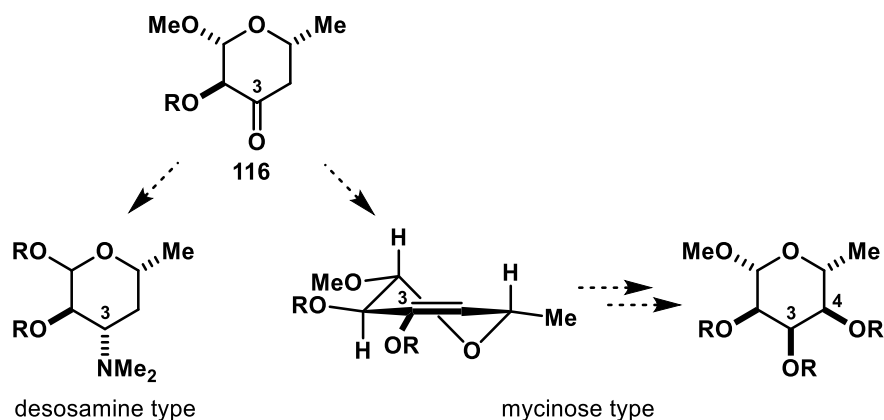

Figure 2.4: The close resemblance of ketol **116a** to the desosamine and mycinose carbohydrates might allow a unified synthesis of these deoxy sugars.

Towards desosamine, a direct transformation of the carbonyl group of free ketol **116a** into the required amino group was examined first. When the monomer/dimer mixture **116a/117** was treated with dimethylamine and NaHB(OAc)$_3$ in the presence of acetic acid, reductive amination to 1-O-methyl desosamine **130** as the major diastereomer was observed (scheme 2.15). However, separation from an impurity, tentatively assigned as the 2,3-*cis*-amino alcohol **131**, by chromatography or recrystallization of the hydrochloride was not possible, and the reaction yield was further diminished by the competing direct carbonyl reduction to *trans*-diol **129**. In order to avoid this side reaction, sequential formation of an oxime followed by reduction in a separate step was investigated: while oxime **132** was obtained from the ketol mixture without incident, the subsequent reduction with metal hydride reagents (NaBH$_4$, BH$_3$, LiAlH$_4$, Dibal-H) did not proceed stereoselectively. Surprisingly, heterogeneous hydrogenation/reductive amination over Pd(OH)$_2$/C furnished the required 2,3-*trans*-configured desosamine derivative **130** as an inseparable mixture with the *cis*-configured amino alcohol **134** as the major product, which exhibits an inverted stereocenter at the alcohol position (dr $\approx$ 3:1). A likely cause for the unexpected inversion at C2 is the stereospecific *cis*-hydrogenation of a transient enamine/enol form **133**.

Since the required amino alcohol configuration of desosamine could not be set by reductive amination of the ketol, the attention was next turned to an introduction of the amino group by S$_N$2 reaction. Stereoselective reduction of benzoate **116d** by equatorial hydride delivery was conceived by employment of bulky L-selectride to avoid non-bonding interactions with the axial hydrogen atoms at the 3-positions of the ketone. To our surprise, however, the unexpected *trans*-diol derivative **135** was formed selectively, possibly by a chelating effect of the 2-benzoate.[125]
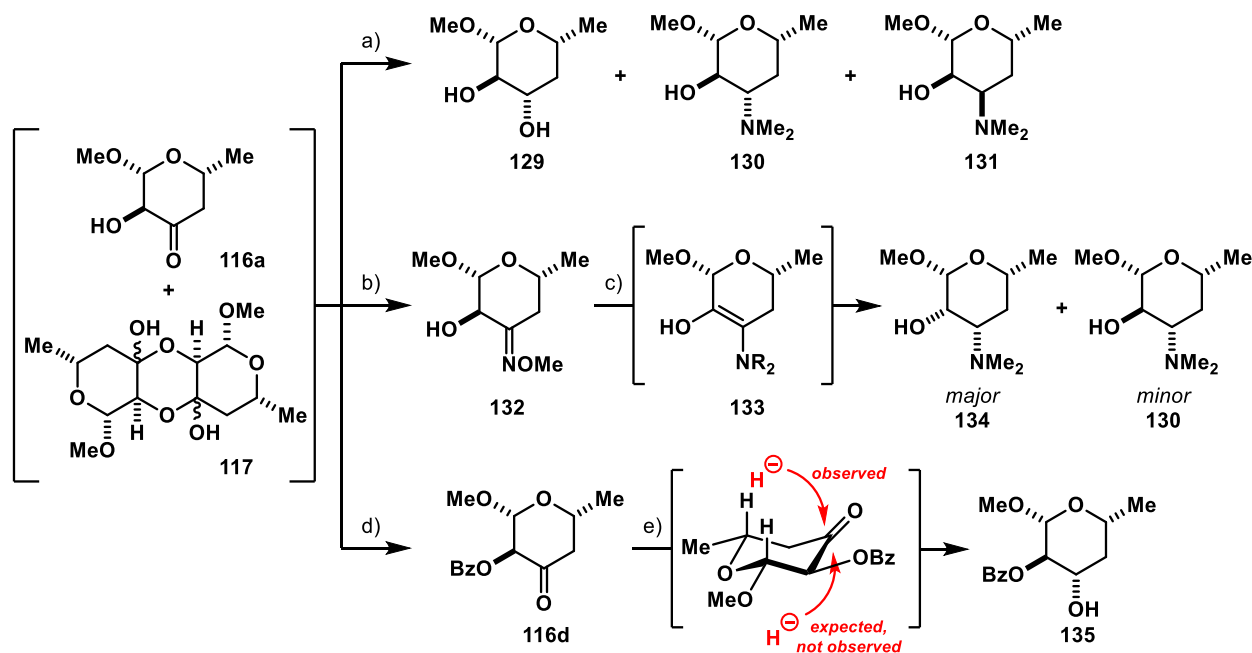
Scheme 2.15: Attempted elaboration of the ketol mixture **116a/117** into desosamine by reductive amination led to product mixtures. Reduction of benzoylated ketol **116d** with the bulky hydride donor L-selectride furnished *trans*-isomer **135**. Conditions: a) Me$_2$NH, AcOH, NaBH(OAc)$_3$, THF, see text; b) H$_2$NOMe · HCl, pyridine, MeOH, 88%; c) H$_2$, Pd(OH)$_2$/C cat., MeOH, AcOH, then aq. H$_2$CO, see text (dr ≈ 3:1); d) Bz$_2$O, pyridine, DMAP cat., CH$_2$Cl$_2$, 98%; e) L-selectride, THF, −78 °C, 75%.

Yet, *cis*-diol **136** required for the S$_N$2 approach could be obtained by treatment of the unprotected ketol monomer/dimer mixture with Dibal-H (scheme 2.16). Treatment of diol **136** with exactly one equivalent of benzoyl chloride in the presence of pyridine and catalytic DMAP selectively furnished equatorial benzoate **137**, as expected. This selectivity is ascribed to a higher stability of the bulky, tetrahedral intermediate at the equatorial rather than the axial site.
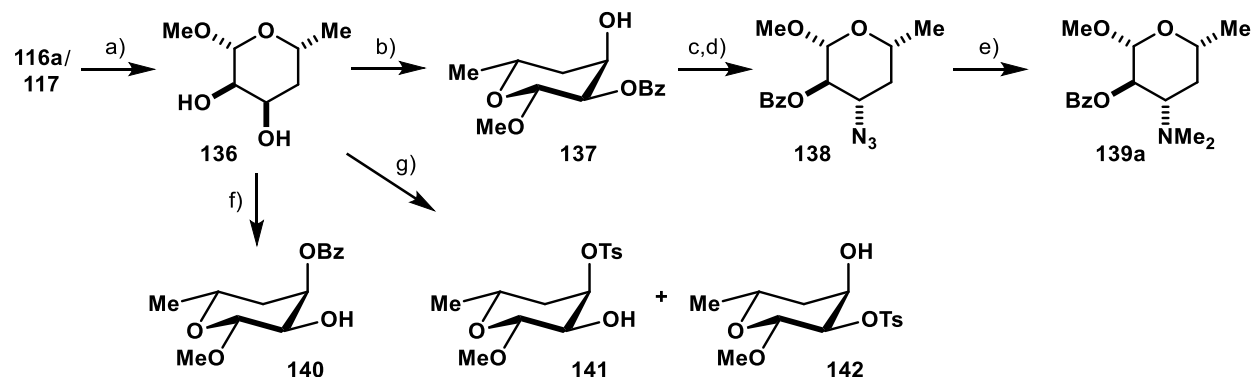
Scheme 2.16: Elaboration of *cis*-diol **136** into a desosamine derivative by selective protection and nucleophilic substitution. Conditions: a) Dibal-H, THF/toluene, −78 °C, 58% (from **107**), b) Bz$_2$O, DMAP cat., pyridine, CH$_2$Cl$_2$, 84%; c) MsCl, DMAP, pyridine, CH$_2$Cl$_2$, 99%; d) NaN$_3$, DMF, 90 °C, 82%; e) H$_2$, Pd(OH)$_2$/C cat., MeOH, EtOAc, then aq. H$_2$CO, 98%; f) (i) Bu$_2$SnO, toluene, reflux; (ii) Bz$_2$O, 80%; g) (i) Bu$_2$SnO, toluene, reflux; (ii) TsCl, DMF, 55% (**141**), 37% (**142**).

The remaining axial alcohol was activated as its mesylate, which succumbed to the anticipated stereo-inversion upon nucleophilic substitution with sodium azide at elevated temperature, furnishing azide **138** with all stereocenters set as needed. Interestingly, a selective acylation of diol **136** to yield axial benzoate **140** was also possible when the diol was first activated as a stannylene acetal and then treated with benzoyl chloride. This prompted the possibility to reverse the order of protection of the equatorial C2 alcohol by acylation and activation of the axial C3 alcohol by sulfonylation. Treatment of a stannylene acetal of diol **136** with tosyl chloride, however, only furnished a mixture of tosylates **141** and **142**. Though axial tosylate **141** was still the major isomer, the dramatically lower selectivity (55:37, isolated) as opposed to the exclusive benzoylation of the axial alcohol might be ascribed to the different substitution mechanism at sulfur and/or to the change of solvents from toluene to DMF, which was necessary for the tosylation to proceed.

The desired dimethylamine **139a** was finally obtained by heterogeneous hydrogenolysis/reductive amination of azide **138** with formaldehyde in a one-pot operation. A mixture of ethanol and ethyl acetate proved to be a suited solvent for this transformation; in methanol, the 2-benzoate was partially cleaved. Preparation of the glycosyl acetate **139b** by acidic cleavage of the methyl glycoside in acetic anhydride set the stage for the elaboration into fluoride **139c** and trichloroacetimidate **139d** as possible glycosyl donors for the decoration of the C5 alcohol of mycinolide IV (scheme 2.17). Additionally, free desosamine **128** was easily liberated by global saponification of the carboxylates in basic methanol (K$_2$CO$_3$, MeOH).
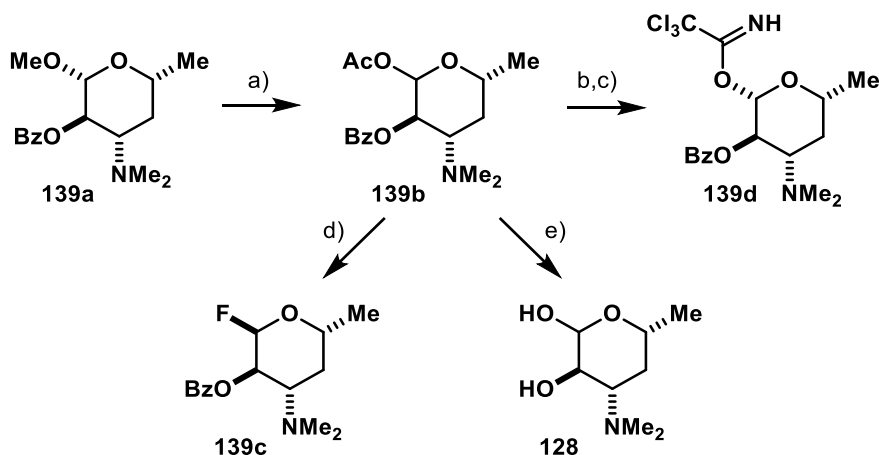
Scheme 2.17: Transformation of the desosamine methyl glycoside into glycosyl donors and synthesis of the free carbohydrate. Conditions: a) Ac$_2$O, H$_2$SO$_4$, 87%; b) NH$_3$, MeOH, THF, 0 °C, 85% (from **139a**), c) Cl$_3$CCN, DBU, CH$_2$Cl$_2$, 80%; d) HF · pyridine, CH$_2$Cl$_2$, 0 °C, 67%; e) K$_2$CO$_3$, MeOH, 96%.

In an effort to extend the unified approach also to the *de novo* synthesis of mycinose, the direct α-functionalization of the ketol as well as the transformation into epoxide **143** were investigated (figure 2.5). Considering the likely favored all-pseudo-equatorial half-chair conformation **XXI**, an electrophilic functionalization at the enol(ate) C4 atom was conceived to proceed selectively from the bottom face to give

the product **XXII** with the electrophile ending up in an axial orientation. Inversion of this stereocenter would furnish the required C4 configuration of the mycinose. The remaining tasks would be stereoselective carbonyl reduction of ketone **XXIII** and methylation of the C2 and C3 alcohols to complete the synthesis. The timing of the methylation event would depend on the protecting group strategy: methylation could either occur in one later operation for both alcohols, or already at the ketol stage for the C2 alcohol. Alternatively, the ketol could be elaborated into epoxide **143**, which might undergo stereospecific Fürst-Plattner opening of the oxirane selectively at C4 to furnish diaxial product **XXV**, in case that half-chair conformer **XXIV** was sufficiently favored. The resulting product **XXV** would already exhibit the necessary axial C3 alcohol, and a selective C3 methyl ether formation and liberation of the C4 alcohol would be straightforward if an appropriate oxygen nucleophile, *e.g.* benzyl alcohol (X = OBn), was employed in the epoxide opening. Completion of the synthesis following the latter approach would ultimately necessitate inversion of the C4 alcohol, perhaps by the mild Mitsunobu procedure.
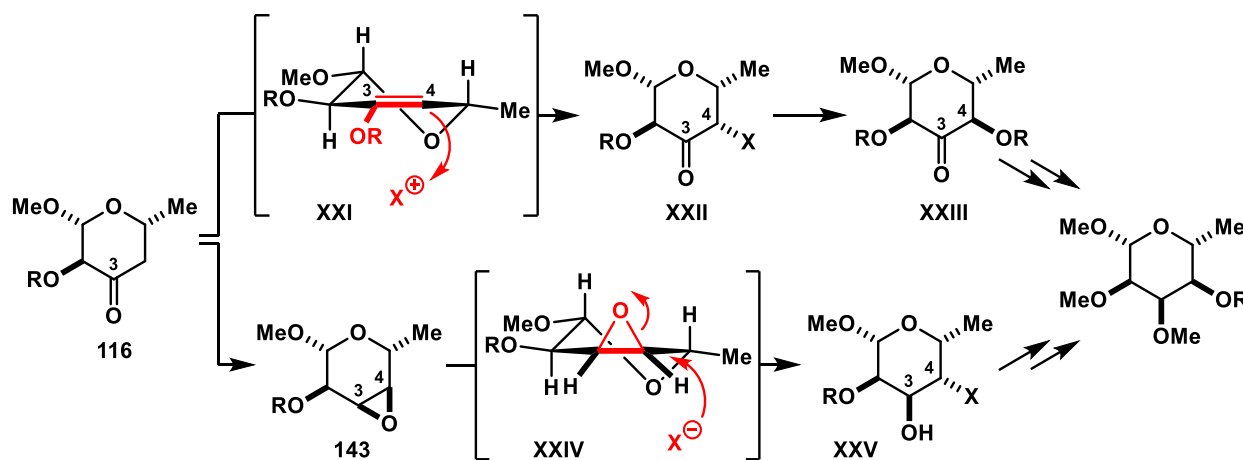

Figure 2.5: Direct α-functionalization and epoxide opening as two possible strategies to reach the 6-deoxy sugar mycinose from the commonly employed ketol for the access of aldgarose and desosamine.

In the forward direction, an early methylation of the ketol mixture **116a/117** proved rather inefficient: under a variety of conditions, both acidic and basic, the hydroxy group was either not sufficiently reactive towards an alkylation, or the hydroxy ketone was too prone to enolization to suffer from epimerization and/or methyl enol ether formation. Thus, treatment of the monomer/dimer mixture **116a/117** with an excess of methyl iodide and silver(I) oxide in acetonitrile furnished methyl ether **116e** as a mixture with dimethyl enol ether **144** in only low yield (scheme 2.18). Separation from this side product was possible after the trimethylsilyl enol ether **145e** had been obtained by selective deprotonation at C4 with LDA in the presence of trimethylsilyl chloride. Due to the problematic methylation, the analogous C4 enol ether was also prepared with a TBS group at O2 (**145c**), which was introduced without incident. With these enol ethers **145c,e** in hand, the subsequent electrophilic functionalization at C4 was examined. Starting with oxygenation, Davis' oxaziridine was simply too unreactive to produce the acyloin in presence of these silyl enol ethers.[126]

48
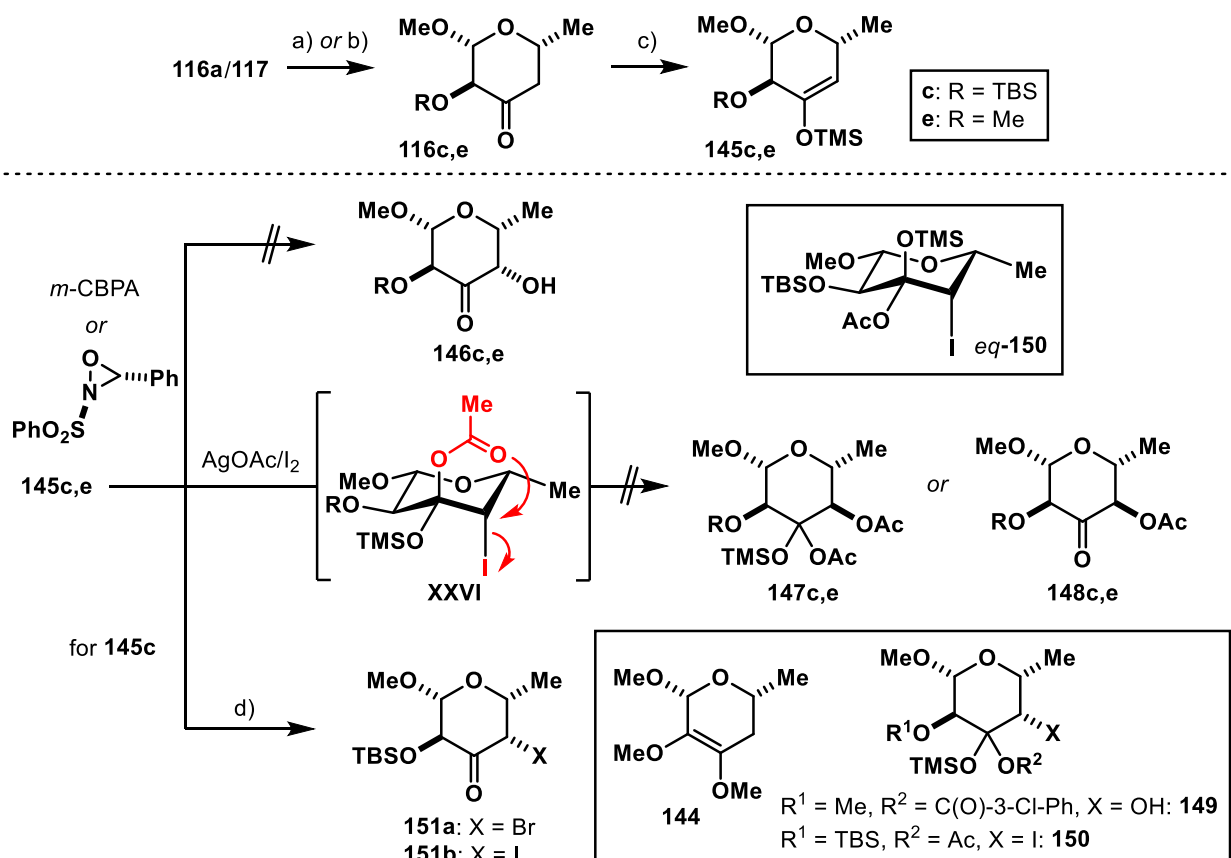
Scheme 2.18: Preparation and functionalization of a silyl enol ether obtained from the protected ketol. Conditions: a) MeI, Ag$_2$O, MeCN, reflux, ca. 30% (**116e**); b) TBSCl, imidazole, DMF, 93% (**116c**); c) LDA, TMSCl, THF, −78 °C, 90% (for **145e**), 95% (for **145c**); d) NBS (for **151a**) or NIS (for **151b**), THF, −78 °C → rt, 94% (for **151a**), 69% (for **151b**).

Trying to force the reaction by heating in dichloroethane led to decomposition of the enol ether. In the rather sluggish Rubottom oxidation of **145e** with *m*-CBPA,[127] addition of the acid byproduct to the primary reaction intermediate was observed, leading to ketal derivative **149**. Subsequent acidic or basic cleavage to give the desired hydroxy ketone was to no avail. The isolation of side product **149** suggests that desilylation of the C3 oxygen atom after an electrophile addition to the silyl enol ethers is rather slow and may be preceded by ketalization with an external nucleophile. It was therefore hoped that treatment of silyl enol ether **146c** with in-situ formed acetyl hypoiodite from a mixture of silver acetate and iodine might result in addition product **XXVI**: such intermediates have been shown to undergo rearrangement to acetoxy ketones.[128] Hence, employment of silyl enol ether **146c** under these conditions might enable an elegant transformation to ketone **148c** with the appropriately configured C4 acetate. Although a single diastereomer of α-iodo acetyl ketal **150** could indeed be isolated, no collapse to the desired acetates **147c/148c** was observed. As a second product in the reaction mixture, only α-iodo ketone **151b** was found, which was also formed upon prolonged standing of **150** in solution, presumably by hydrolysis of the acetyl ketal.
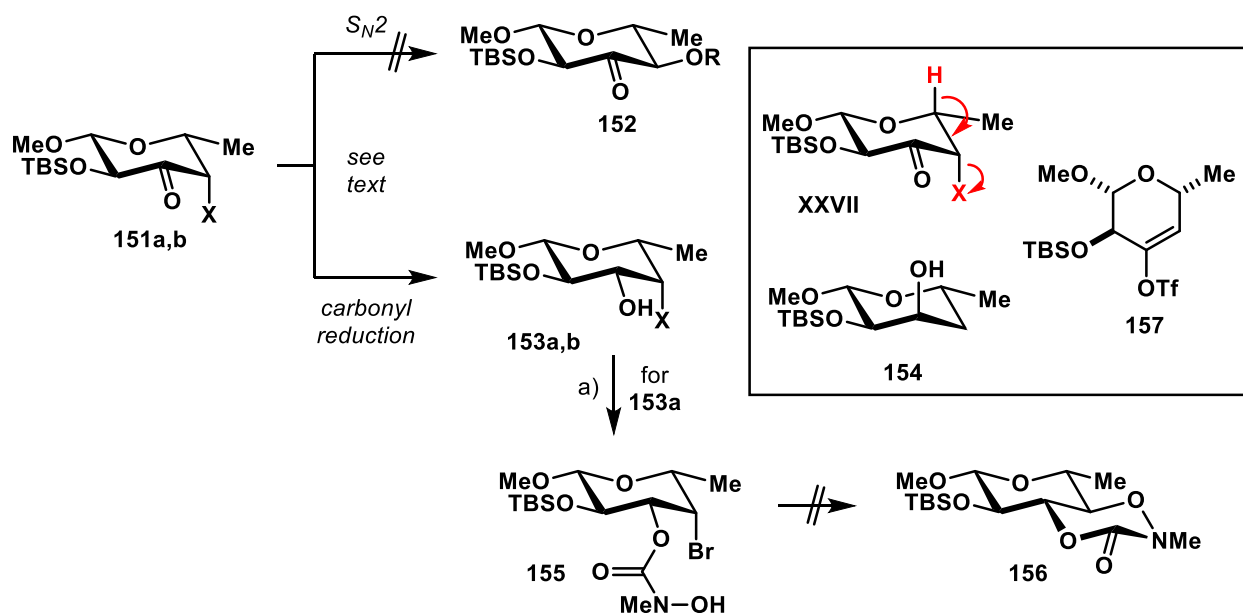
Scheme 2.19: Attempted S$_N$2 inversion of the axial halides **151a,b** or the equatorial alcohol **153a** were to no avail. Conditions: a) (i) triphosgene, pyridine, CH$_2$Cl$_2$, 0 °C; (ii) MeNHOH · HCl, i-Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C, 64%.

These findings suggest that ketal product **150** is most likely formed formed from equatorial rather than axial attack of the nucleophile to furnish equatorial acetate eq-**150** as a single isomer. This equatorial acetate, however, cannot overlap with the σ*-orbital of the C–I bond to extrude the iodide by backside attack due to the conformational constrains of the cyclic system, contrary to the anticipated axial isomer as in **XXVI**.

After these unproductive results, the synthetic utility of the α-halo ketone was examined: halogenation of silyl enol ether **145c** with NIS or NBS at low temperature smoothly afforded axial halides **151a,b** as single diastereomers. Unfortunately, any attempt to substitute the halide by oxygen nucleophiles failed due to the diaxial arrangement of the halide and its neighboring H5-atom and the correspondingly high propensity of **151a,b** to undergo E2 elimination (**XXVII**, scheme 2.19). Stereoselective carbonyl reduction to the axial halohydrins was to no avail either: metal hydride reduction of bromide **151a** with Dibal-H or NaBH$_4$, as well as Meerwein-Ponndorf-Verley reduction with (i-Bu)$_2$Al(O-i-Pr), only furnished the equatorial alcohol **153a** (84% yield for reduction with Diabal-H). Attempted reduction of bromide **151a** with L-selectride suffered from dehalogenation of the starting material and gave a mixture of bromohydrin **153a** and debrominated axial alcohol **154**. In order to invert the equatorial alcohol or the axial halide, Mitsunobu conditions and a sequence of either triflation/substitution or formation of carbamate **155** with subsequent cyclization were investigated. Unfortunately, no reaction was observed on treatment of alcohol **153a** under Mitsunobu conditions or upon heating of carbamate **155** in pyridine. The inversion of bromohydrin **153a** after triflation of the free alcohol suffered once again from elimination of the halide to furnish enol triflate **157**.
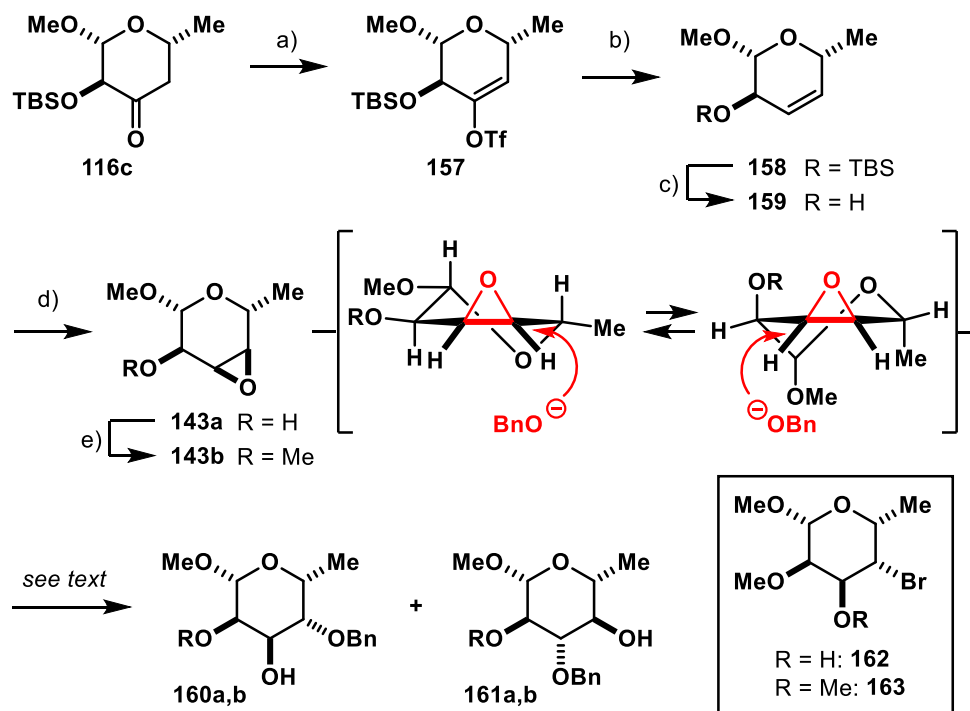
Scheme 2.20: Preparation of epoxides **143a,b** and attempted opening thereof. Conditions: a) LDA, THF, −78 °C; (ii) Comins' reagent, THF, −78 °C, 69%; b) Et₃SiH, Pd(OAc)₂ (10 mol%), dppf (10 mol%), DMF/THF, rt, 78%; c) TBAF, THF, rt, 72%; d) *m*-CPBA, CH₂Cl₂, rt, 80%; e) MeI, Ag₂O, MeCN, rt, 78%.

The alternative epoxide opening approach outlined in figure 2.5 mandates stereoselective synthesis of epoxide **143**. To this end, TBS-protected ketol **116c** was selectively deprotonated at C4 using LDA, and the resulting lithium enolate was trapped with Comins' reagent to deliver the corresponding enol triflate **157** (scheme 2.20).[129] Palladium-catalyzed triflate/hydrogen exchange by triethylsilane followed by cleavage of the C2 silyl ether with TBAF set the stage for the hydroxy-directed epoxidation of allylic alcohol **159**. Thus, *cis*-epoxy alcohol **143a** was obtained as a single diastereomer upon reaction with *m*-CPBA. The alcohol underwent clean O-methylation when treated with methyl iodide in the presence of silver oxide in acetonitrile. Although reaction of free epoxy alcohol **143a** or the derived methyl ether **143b** with either sodium or lithium benzylate in DMF led to the clean opening of the oxirane ring, the reaction did not occur selectively at C4 to give the desired axial C3 alcohols **160a,b**. Surprisingly, the regioisomeric products **161a,b** formed by epoxide opening at C3 were favored (ratio ≈ 4:1 for **143a**, 2:1 for **143b**). Reaction of the epoxides with benzyl alcohol under acidic conditions (CSA, Mg(OTf)₂, La(OTf)₃) led to complex mixtures.

It was eventually found that reaction of epoxide **143b** with magnesium bromide in diethyl ether cleanly affords bromohydrin **162** by selective attack of the bromide at C4. In addition, the C3 methyl ether **163** could be obtained with the aid of Meerwein's salt (Me₃OBF₄, 1,8-bis(dimethylamino)naphthalene, CH₂Cl₂) to avoid intramolecular cyclization of the bromohydrin back to the epoxide. At this point, however, the potential synthesis towards mycinose had already reached an inadequate number of steps. Furthermore, the

necessary inversion of the C4 bromide stereocenter of **160** would certainly not be a trivial task due to the propensity of the axial halide to suffer elimination with the neighboring axial hydrogen atom. This undertaking in the *de novo* synthesis of mycinose was therefore not pursued any further.

2.7 Synthesis of D-Mycinose from the Chiral Pool

Remark: Assistance in the scale-up of the synthesis of isoascorbic acid derivate **165** by Dr. L. Schreyer is gratefully acknowledged (cf. scheme 2.21).

D-Mycinose is the terminal sugar constituent of both aldgamycin N and mycinamicin IV. Although this 6-deoxy carbohydrate was not amenable to the unified synthesis approach described in the preceding section, it could be prepared efficiently from naturally occurring D-isoascorbic acid following a literature procedure with minor modifications (scheme 2.21).[130] Thus, D-isoascorbic acid (**164**) was treated with hydrogen bromide in acetic acid, followed by a hydrolytic work-up to cleave the intermediate secondary acetate. After selective methylation of the enediol with TMS diazomethane (instead of the more hazardous free diazomethane) to deliver primary bromide **165**, the carbon–bromine bond was cleaved by palladium-catalyzed hydrogenolysis. The free secondary alcohol was then used in a directed rhodium-catalyzed high-pressure hydrogenation of the double bond to forge the two new stereocenters of lactone **166** selectively.
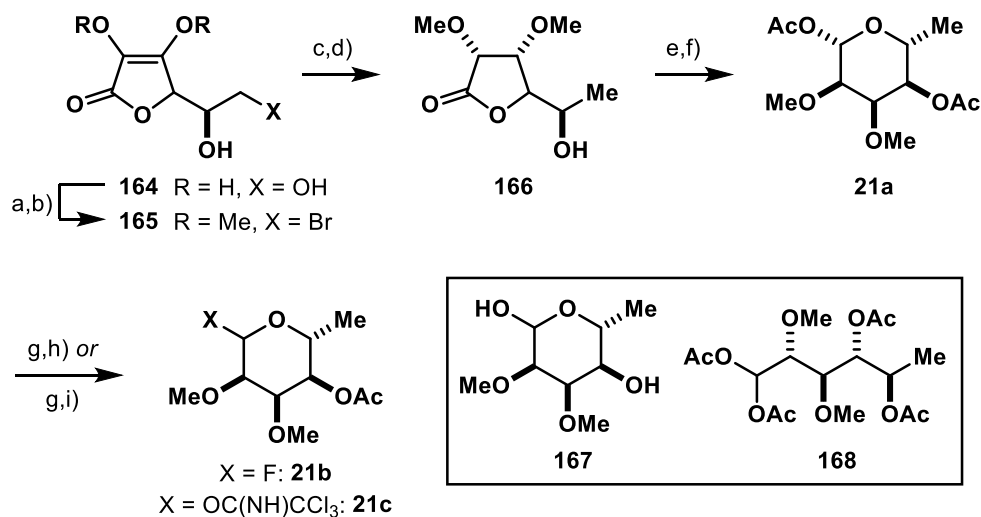
Scheme 2.21: Preparation of glycosyl donors of D-mycinose following a literature procedure from naturally occurring D-isoascorbic acid. Conditions: a) HBr, AcOH, then H_2O, 84%; b) $TMSCHN_2$, toluene, MeOH, 0 °C → rt, 78%; c) H_2 (1 bar), Pd/C (10% *w/w*), MeOH, Et_3N, 89%; d) [Rh(dppb)(cod)]BF_4 (10 mol%), H_2 (100 bar), CH_2Cl_2, 94%; e) Dibal-H, toluene, −78 °C → −55 °C; f) Ac_2O, H_2SO_4, 0 °C → rt, 48% (over two steps); g) $BnNH_2$, THF, 49%; h) HF · pyridine, CH_2Cl_2, 0 °C, 86% (α:β = 4:1); i) Cl_3CCN, DBU, CH_2Cl_2, 60% (α:β = 1:12).

The literature subsequently describes a lactone reduction with Dibal-H and rearrangement to free D-mycinose (**167**) with an excellent 87% yield. Attempts to reproduce this transformation in the present work, however, only furnished complex mixtures consisting of the corresponding anomeric furanose and pyranose isomers, as well as the open-chain sugar, even after repeated attempts using different work-up and isolation procedures.[131] Gratifyingly though, acid-mediated acylation of the crude mixture after reduction of dihyrofuranone **166** with Dibal-H proved viable and gave pyranosyl acetate **21a**, though still only in a modest yield (48% over two steps) due to the formation of the easily separable open-chain product **168**. With regard to the pending macrolide glycosylation, glycosyl acetate **21a** was elaborated into fluoride **21b** and trichloroacetimidate **21c** via the corresponding lactol, which was formed by selective aminolysis of the anomeric acetate.

2.8 Completion of the Total Synthesis of Aldgamycin N

With donors of all required carbohydrates in hand, the completion of the total syntheses of aldgamycin N and mycinamicin IV could be tackled. The branched octose at the C5 position of aldgamycin N was meant to be introduced at an early macrocylic stage with the C9 ketone still masked as a triple bond. In this way, the engagement of the acceptor alcohol with the ketone in a transannular ketalization would be avoided (figure 2.6; also cf. section 2.3).

This decisive task, however, turned out to be far from trivial for stability reasons: the tertiary propargylic C8 alcohol present at this early stage was by no means an innocent bystander, even when it was protected as a silyl ether before the C5 acceptor alcohol was liberated by oxidative cleavage of the C5 PMB ether (scheme 2.22). Considering the great success of a glycosyl fluoride donor in the total synthesis of mycinamicin IV by the group of K. Suzuki, much hope had been laid on aldgarosyl fluoride **122c** to install the branched sugar en route to aldgamycin N.[58b] Unfortunately, treatment of macrolide **169** in the presence of fluoride donor **122c** with a mixture of a metallocene chloride (Cp_2HfCl_2 or Cp_2ZrCl_2) and a silver salt (AgOTf or $AgClO_4$) not only resulted in the activation of the glycosyl donor towards glycosylation of the C5 alcohol but also in the destruction of the quaternary C8 stereocenter by elimination to enynes **170a,b** and internal cyclization to give the bicyclic ether **171**. This instability of the propargylic site was also encountered when thioglycosides **122d,e** were employed, which typically require similar activation conditions based on transition metal salts.[132] If successful at all, activation of these donors with $HgCl_2$, $Hg(NO_3)_2$, AgOTf or $Cu(OTf)_2$ furnished the desired β-glycoside **173** only in very low yield (ca. 20% yield in best cases) due to incomplete conversion of starting material even after long reaction times of up to several days. Moreover, the same elimination to furnish enynes **170a,b** as side products was observed.
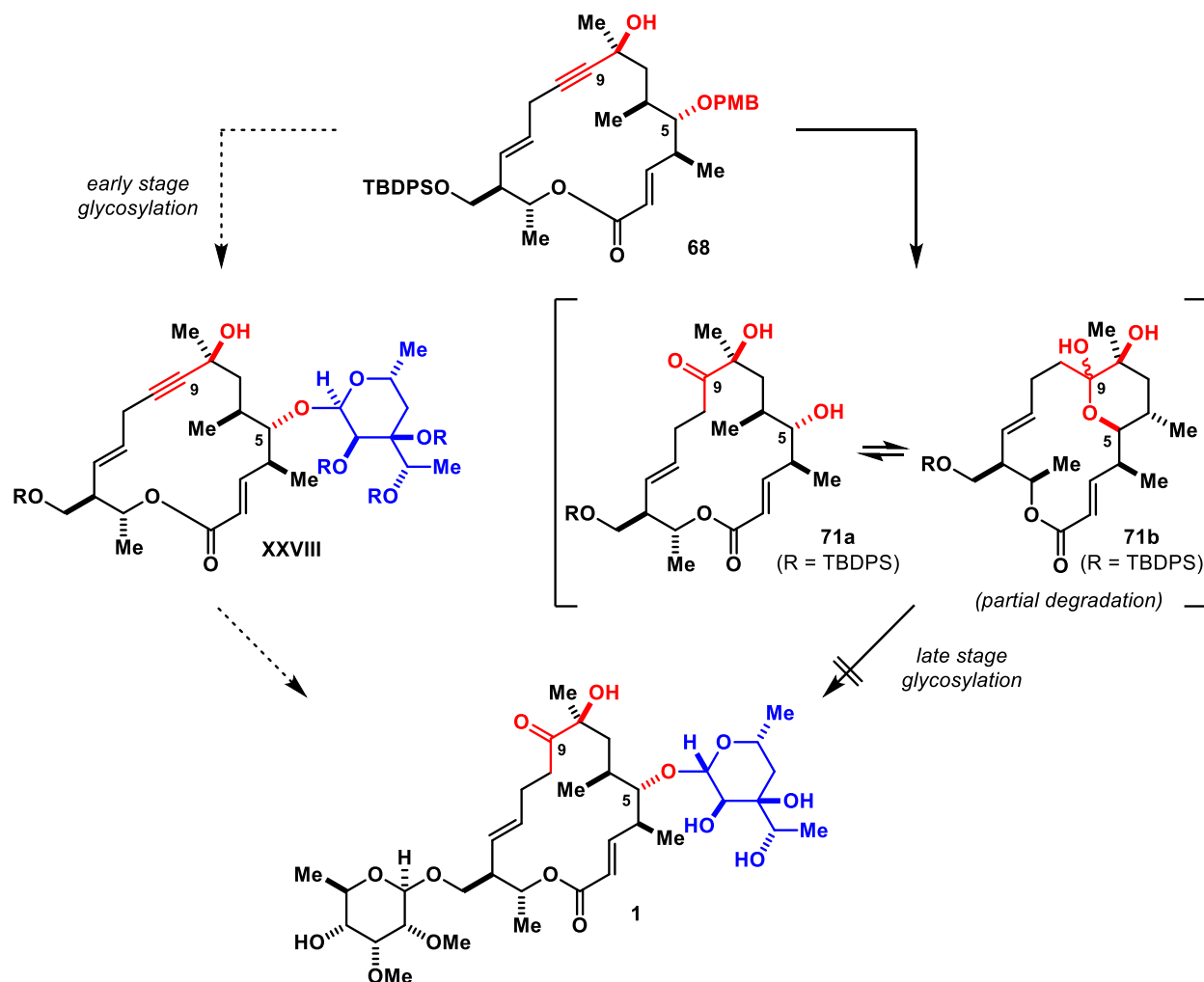
Figure 2.6: Revision of the synthetic plan towards aldgamycin N by an early glycosylation approach to prevent a transannular ketalization between the C5 acceptor alcohol and the C9 ketone.

Alternative donor activation by halogenation at sulfur (NBS or NIS in presence of Lewis acids),[133] one-electron transfer from **122d** with TBPA in acetonitrile[134] and alkylation (MeOTf) or protonation (PPTS or TfOH) of **122e** were to no avail either.[135] An initially promising result was found in the attempted glycosylation with heterocylic thioglycoside **122e** by activation with the sulfenylating agent DMTST.[136] Interestingly, under these conditions, the reaction did not suffer at all from enyne formation, but this activator also promoted an intermolecular transfer of the silyl group from the tertiary C8 position onto the C5 acceptor alcohol. Such silyl-shifting behavior of DMTST has been described elsewhere.[137] To our dismay, simply subjecting the analogous acceptor with an unprotected tertiary alcohol to the sulfenylating conditions only resulted in decomposition. A more sterically shielded TBS ether also suffered from the silyl shift, limiting the isolated yield of the desired glycosylation product once again to only 20 – 30% yield.

A high-yielding glycosylation of acceptor **169** hinges on reaction conditions that generate a powerful enough glycosylating agent but leave the propargylic alcohol motif intact. The methodologies described to this point are limited to temperatures above 0 °C and typically employ transition metal salts that might endanger the propargylic site by π-coordination. Low-temperature glycosidation with only a catalytic amount of an organic activating agent was therefore the last resort. While no defined product could be isolated when sulfoxide **122f** was treated with Tf$_2$O/DTBMP in presence of acceptor **169**,[138] employment of a silyl triflate as promotor for trichloroacetimidate **122g** gave a hit.[139] At a reaction temperature of −45 °C, the glycosidic bond was formed without incident, exclusively attaching the carbohydrate to the acceptor with the desired β-configuration, but the propargylic silyl ether at C8 was still too sensitive, and enyne **170a** was the only product in the reaction of acceptor **169** with trichloroacetimidate donor **122g** after catalytic activation with TMSOTf. Buffering of the reaction mixture with the pyridine base DTBMP (no reaction) or addition of molecular sieves (undefined decomposition) led to inferior reaction outcomes. Eventually, a solution was found by systematic screening of the silyl triflate activator. In the row of TMS-, TES-, TBS- and TIPSOTf the reactivity decreased with the size of the silyl group: at −78 °C, almost exclusively enyne **170a** was the product for the activation with TMSOTf, while no glycosylation at all was induced with TIPSOTf. The activator of choice turned out to be TESOTf, being the triflate promotor to display the necessary balance between appropriately strong donor activation and sufficiently low reactivity towards the propargylic C8 silyl ether. At this very fine balance, the glycoside formation almost stalled at the orthoester stage **172**, which slowly rearranged to the desired glycoside only on prolonged stirring at −78 °C; a sample of the orthoester could be isolated when the reaction was quenched within less than an hour. The formation of orthoesters is a well-known problem in the glycosylation of sterically encumbered acceptors with reactive donors.[140] Although these conditions were mild enough to suppress the elimination of the C8 OTES ether to enynes **170a,b**, the O–Si bond was still partially cleaved to deliver the free C8 hydroxyl group, which showed minor interference in an additional glycosylation at this site. Therefore, as well as to facilitate separation from the trichloroacetamide byproduct, the crude reaction product was treated with TASF in aqueous DMF to effect global desilylation.[141] The resulting diol **174** could be isolated as an analytically pure substance in fair yield in view of the challenges encountered (53% yield over both steps on 120 mg scale, single largest batch).
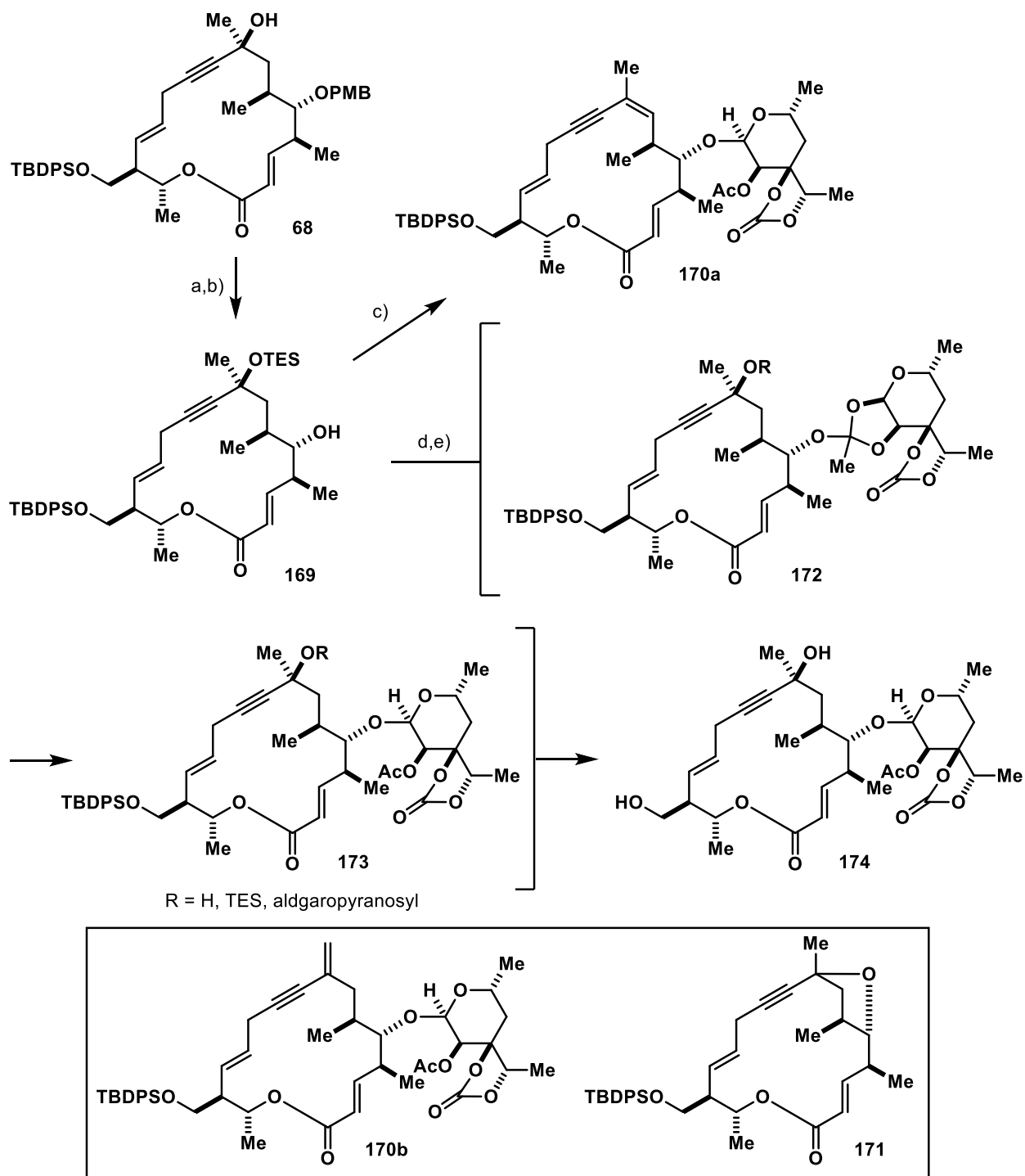
Scheme 2.22: Installation of the aldgaropyranose towards aldgamycin N at an early macrocylic stage before the C9 ketone is unveiled from the triple bond. Conditions: a) TESOTf, 2,6-lutidine, CH₂Cl₂, −25 °C, 91%; b) DDQ, CH₂Cl₂, H₂O, 86%; c) **122g**, TMSOTf cat., CH₂Cl₂, −45 °C, 66%; d) **122g**, TESOTf cat., CH₂Cl₂, −78 °C; e) TASF, DMF, H₂O, 0 °C → rt, 53% (over two steps).

The stage was now set once again for the key transformations to unveil the acyloin motif of the aldgamycins from the propargylic alcohol (scheme 2.23). Gratifyingly, the ruthenium-catalyzed *trans*-hydrostannylation still proceeded in good yield with direction to the proximal site of the tertiary alcohol despite the dense oxygen-rich decoration at the remote carbohydrate site of **174**, which might have inhibited the reaction by coordination of the transition metal. In the subsequent copper-mediated oxygenative destannylation, the previously optimized conditions using $Cu(tfa)_2$ rather than $Cu(OAc)_2$ not only proved advantageous with regard to the step count but even turned out to be instrumental: while $Cu(OAc)_2$ could cleave the alkenyl–Sn bond and most likely deliver the anticipated acyloin acetate in the first place, this tertiary acetate is unstable under the reaction conditions and underwent elimination to a complex mixture of undesired products, one of which could be identified as enone **176**. The reaction with $Cu(tfa)_2$ avoids this decomposition pathway since the derived trifluoroacetate rapidly succumbs to hydrolysis to the free alcohol, which is a much poorer leaving group under the reaction conditions than the acetate. Thus, treatment of alkenylstannane **175** with $Cu(tfa)_2$ in DMSO in the presence of 2,6-di-*tert*-butylpyridine as an acid-scavanger furnished free acyloin **177** in 61% yield, ready for the final glycosylation of the primary acceptor alcohol.[142]

In comparison to the installation of the branched aldgarose at C5, the glycosylation of the primary acceptor **177** cannot rely on anchimeric assistance to steer the stereochemical outcome, since the corresponding carbohydrate to be attached at this position carries a non-participating methyl ether neighboring the glycosidic site. In this regard, it was encouraging to note that the literature reported a highly β-selective glycosylation at the analogous position of mycinamicin IV using mycinosyl fluoride **21b**.[58b] Disappointingly, when transferred to acceptor **177**, these glycosylation conditions with a single equivalent of fluoride donor **21b** produced a mixture of unreacted starting material, the primary glycosylation product as a 1:1 mixture of anomers, and significant amounts of the double glycosylation product from additional reaction of the tertiary C8 alcohol. In contrast, employment of trichloroacetimidate donor **21c** at low temperature both solved the issue of regioselectivity in avoiding the competing glycosylation of the tertiary site and gave the possibility to bolster the stereochemical outcome by running the glycosylation in the presence of acetonitrile (for a more detailed discussion of the nitrile effect, see section 2.9).[143] Thus, pure β-glycoside **178** was obtained in 50% yield after chromatographic separation from the undesired α-anomer (27% yield) with modest selectivity when the glycosylation was carried out with TESOTf at −40 °C under high dilution in equal volumes of dichloromethane and acetonitrile.[144] It may be noted that the glycosylation of a precursor towards tylosin using a thioglycoside of the same carbohydrate proceeded with similar selectivity in neat acetonitrile as solvent.[145]
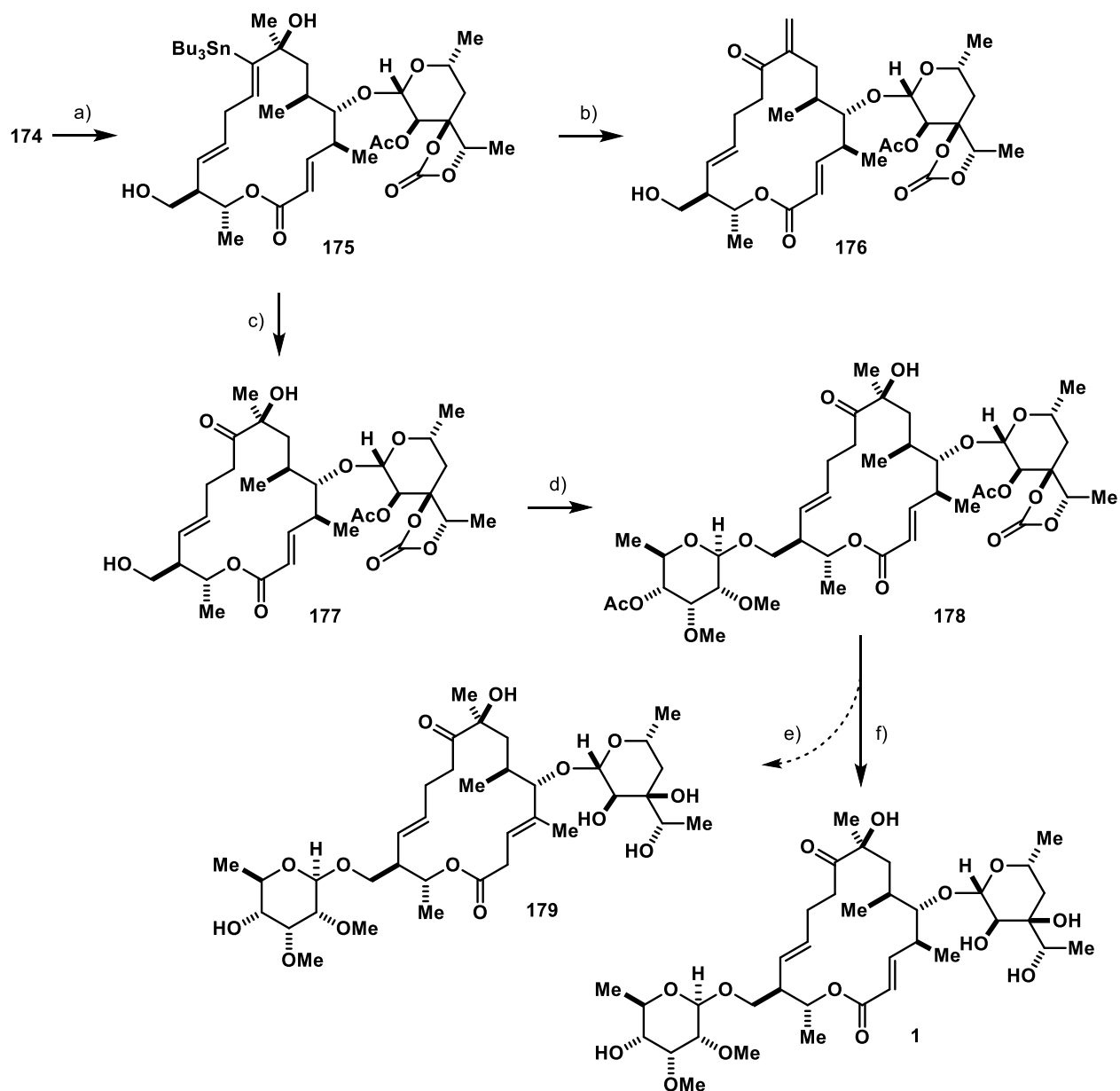
Scheme 2.23: End game comprising hydrostannylation/oxygenative destannylation and the second glycosylation to complete the total synthesis of aldgamycin N (**1**). Conditions: a) [Cp*RuCl]$_4$ (10 mol%), Bu$_3$SnH, CH$_2$Cl$_2$, 62%; b) Cu(OAc)$_2 \cdot$ H$_2$O, DMAP, DMSO, see text; c) Cu(tfa)$_2 \cdot$ H$_2$O, 2,6-di-*tert*-butylpyridine, DMSO, 48 °C, 61%; d) **21c**, TESOTf, CH$_2$Cl$_2$, MeCN, −40 °C, 50% (β-anomer), 27% (α-anomer); e) K$_2$CO$_3$, MeOH, rt, 32% (**1**), 8% (**179**); f) Ba(OH)$_2 \cdot$ 8 H$_2$O, H$_2$O, THF, 69% (**1**).

Finally, the natural product aldgamycin N (**1**) was obtained by global deprotection of macrolide **178** under basic conditions. To this end, Ba(OH)$_2$ in aqueous THF proved superior over K$_2$CO$_3$ in methanol, which, even at incomplete consumption of starting material, delivered substantial amounts of isomerization product **179**, in which the enoate double bond has migrated out of conjugation with the carbonyl group of the lactone to furnish the corresponding trisubstituted alkene. The analytical and spectral data of the synthetic aldgamycin N sample obtained in this way not only match well with reported data of the sample

isolated from nature,[40f] but the recorded ^{13}C NMR spectra even clearly reveal those signals that are hidden in the previously reported spectra due to massive line broadening.
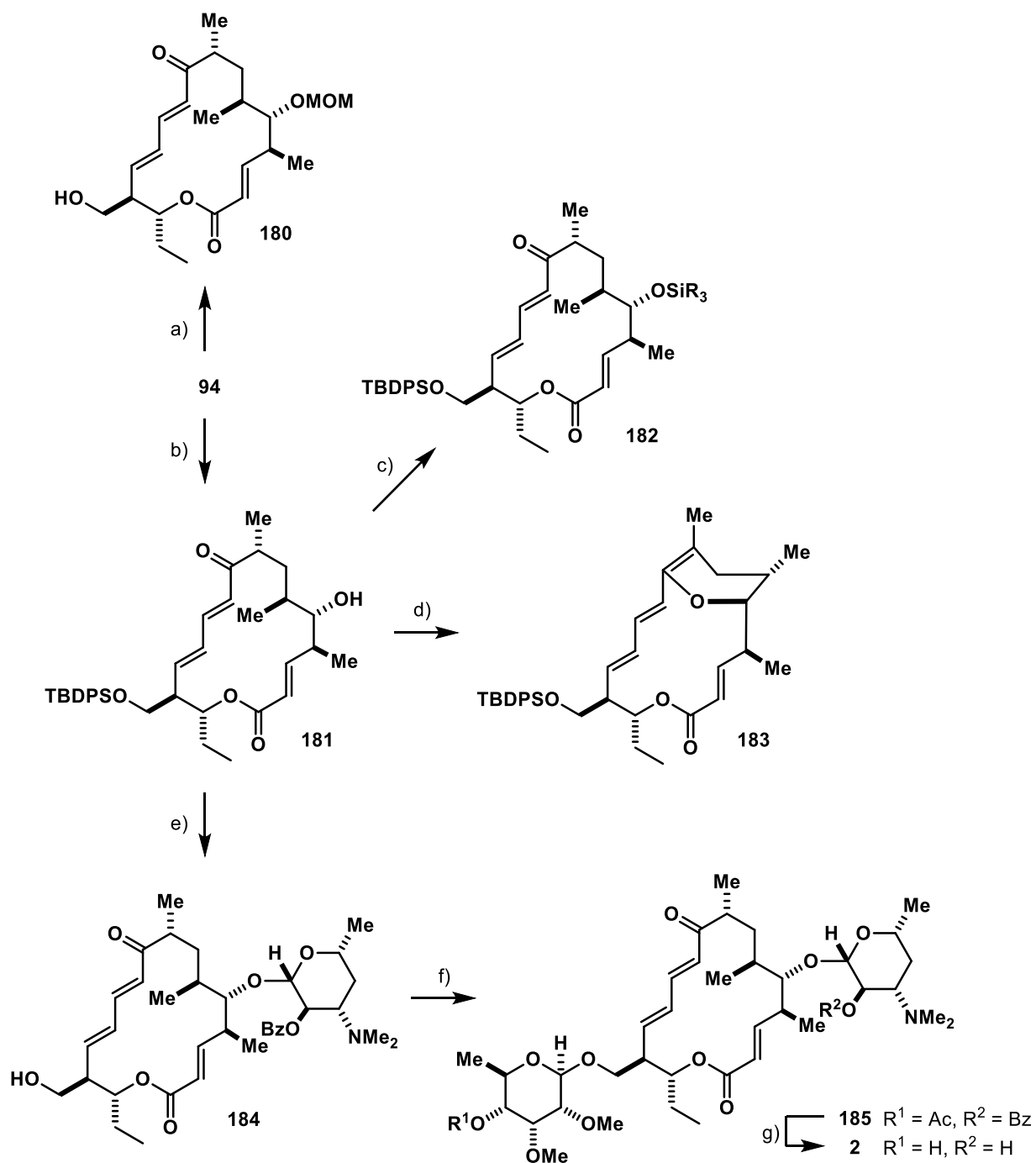
2.9 Completion of the Total Synthesis of Mycinamicin IV

Remark: Preliminary screening for the deprotection of macrolide **94** by a protic acid by Dr. L. Schreyer is gratefully acknowledged (cf. scheme 2.24).

In the group of K. Suzuki, the bare macrolide mycinolide IV (**3**) has already served for the total synthesis of the complete natural product decorated with its sugars.[58b] Therefore, the synthetic work described in section 2.4 represents a formal total synthesis of mycinamicin IV (**2**). Nonetheless, with suitable donors of both required carbohydrates in hand, and in regard of the close attention needed for the installation of the carbohydrates of aldgamycin N, it seemed desirable to also reach this complete natural product; not least because the required glycosylations had been referred to as an "extremely hard problem" in the literature. Furthermore, the intermediate macrolide **94** offers an attractive starting point for this venture upon orthogonal protecting group cleavage of the C5 and C21 alcohols. Specifically, the cleavage of the C5 MOM ether and installation of desosamine at this position would have to precede the glycosylation at C21. The other way around, cleavage of the C5 MOM ether mediated by a Lewis or Brønsted acid would likely not be feasible with a glycosidic bond already formed at the C21 alcohol.

Surprisingly, under the action of a protic acid in aqueous methanol the C21 TBDPS ether of **94** was cleaved faster than the C5 MOM ether. However, selective deprotection at C5 could be reached by careful treatment with dimethylboron bromide in dichloromethane at −78 °C (scheme 2.24).[146] The work-up of this reaction needed special care since the reaction did not deliver a uniform mixture right away but only after prolonged stirring with a solution of sodium carbonate in aqueous THF. Presumably, one of the primary acetal cleavage products is unusually long-lived before it decays to the desired free alcohol **181**.

For the following attachment of the basic amino sugar desosamine to the C5 alcohol, the literature precedent had specifically developed the hafnocene-mediated glycosylation with a glycosyl fluoride (cf. scheme 1.4).[58b, 60b] The authors were unable to glycosylate an acceptor closely related to **181** (benzoate instead of TBDPS ether at C21) with other then-available methodologies, including Schmidt's trichloroacetimidate method, due to the high propensity of the acceptor to form the transannular cylization product **18**. They describe the fluoride-mediated glycosylation as fast and mild enough to overcome this side reaction, and they were able to obtain the C5 β-glycoside with good yield and streocontrol following their newly developed method. Unfortunately, when we tried to harness these features for the glycosylation of acceptor **181** with fluoride donor **139c**, the results were not comparable.

Scheme 2.24: Completion of the mycinamicin IV total synthesis by selective deprotections and glycosylation. Conditions: a) aq. HCl, MeOH, rt, 52%; b) Me$_2$BBr, CH$_2$Cl$_2$, −78 °C, then aq. Na$_2$CO$_3$, THF, rt, 80%; c) **139d**, TMSOTf cat., CH$_2$Cl$_2$, rt, 44% (R = Me); d) **139d**, TMSOTf cat., CH$_2$Cl$_2$, −30 °C → rt, ≈30%; e) (i) **139d**, TBSOTf, CH$_2$Cl$_2$, rt; (ii) TBAF, THF, rt, 84% (over two steps); f) **21c**, TBSOTf, CH$_2$Cl$_2$, MeCN, rt, 33%; g) Et$_3$N, MeOH, H$_2$O, 70 °C, 71%.

Though the reasons for this irreproducibility were not examined to an extensive degree, the screening reactions suffered from incomplete consumption of the acceptor even when the glycosyl fluoride donor and the hafnocene/silver salt activator were used in large excess, or when the order of addition of donor and activator was inverted.[147][60c, d] In addition, as judged from NMR analysis of the crude mixtures, the reaction profile was nowhere clean as expected from the fine literature result.

Since the amount of remaining material to reach the final target was dwindling due to the failed attempts and the trichloroacetimidate method had proven far superior and amenable to a more rational reaction screening in the parallel conquest of aldgamycin N, the glycosylation with trichloroacetimidate **139d** was given full attention. It was indeed found that TMSOTf preferentially activated the C9 ketone of glycosyl acceptor **181** in presence of trichloroacetimidate **139d**, furnishing a non-polar and highly unstable non-glycosylated product when the reaction was run at or below 0 °C. By comparison to the literature,[58b] this side product was assigned as transannular enol ether **183**. Interestingly, the major product isolated from the same reaction run at room temperature was the O5 silyl ether, again without any substantial amounts of the desired glycosylation product. Whilst use of TESOTf essentially gave the same side products at the respective temperatures, the desired β-glycosidic bond was formed exclusively without the interference of any side products when TBSOTf was used as promotor at room temperature. Thus, glycosylated macrolide **184** was obtained as a single β-anomer in a very good 84% yield over both steps after subsequent cleavage of the C21 silyl ether with TBAF to undrape the primary alcohol ready for the next sugar attachment. After the experiences in the glycosylations towards aldgamycin N, these findings once again demonstrate the critical differences in the reactivity of silyl triflate activators in the glycosylation of sensitive targets. The literature reports of yet another example where the reaction screening with different silyl trifates in a glycosidation was instrumental for success.[148]

Similar problems in reproducing the exquisite results from the reported glycosylation with a glycosyl fluoride were faced in the installation of the mycinose moiety at the primary C21 alcohol. The reaction of acceptor **184** with either anomer of fluoride donor **21b** and $Cp_2ZrCl_2/AgClO_4$ as activator again suffered from incomplete conversion even with larger excess of reagents.[60a] Furthermore, the undesired α-anomer of glycosylation product **185** was even slightly favored over the β-anomer. In contrast, the literature claims an outstanding β/α ratio of 26:1 and a yield of 86% for their reaction employing closely related substrates differing from those of this work only in their protecting groups.[58b] Once again, resorting to trichloroacetimidate donor **21c** and TBSOTf as activator under high dilution[144] in a mixture of dichloromethane and acetonitrile furnished required glycoside **185** much more efficiently; this time, with the desired β-anomer observed exclusively by ^{1}H NMR in the crude reaction mixture, even so pure macrolide **185** was only obtained in a rather low yield of 33% after chromatographic purification. Final global protecting group cleavage was performed in a $Et_3N/MeOH/H_2O$ mixture at 70 °C,[58b] whereas the

benzoate at the desosamine residue proved to be stable in aqueous LiOH or Ba(OH)$_2$ at room temperature, or even in presence of NaOMe in methanol at 50 °C overnight. The analytical and spectral data of synthetic mycinamicin IV (**2**) thus obtained were in excellent agreement with the data published in the isolation paper.[38b]

The nitrile effect, which has paid great dividends in forging the glycosidic bonds at the primary acceptors towards both targets, deserves a brief discussion: in the quite challenging glycosylation towards mycinamicin IV, this solvent effect could be harnessed to form the required glycosidic bond with exclusive β-configuration. The nitrile effect was first observed in the late 1970s by several groups,[149] and is today understood as the intermediacy of an axial nitrilium ion **XXX** to favor overall equatorial selectivity in a glycosylation run in presence of a nitrile solvent, typically acetonitrile (scheme 2.25).[150]
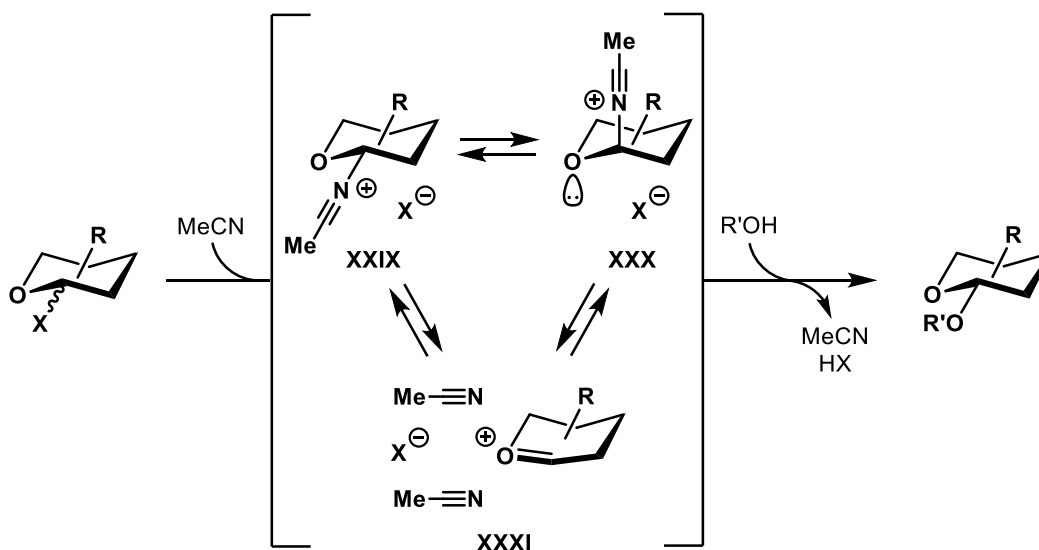

Scheme 2.25: Simplified mechanistic picture explaining the nitrile effect in a glycosidation.

The nitrile effect has been described employing basically all common types of glycosyl donors.[143, 151] Yet, the exact mechanistic features remain elusive beyond the generic assumption of a reactive axial nitrilium intermediate, which mainly derives from the isolation of various compounds resulting from trapping of this nitrilium anomer.[149a, d, 151c, d] The early publications of Schmidt *et al.*, who pioneered the nitrile effect in glycosylations using trichloroacetimidate donors, suggest a reaction under S$_N$1-type conditions that lead to an equilibrium between the axial and equatorial nitrilium species from a solvent-separated ion pair **XXXI**.[143] Though the equatorial nitrilium ion, or a conjugate thereof involving several solvent molecules, is argued to be thermodynamically more stable by virtue of the presumed but much debated "reverse anomeric effect",[143, 149c, 152] the preferential formation of the β-configured glycosylation product is explained by both a much faster formation and a much faster follow-up reaction of the axial rather than the equatorial nitrilium intermediate. Spectroscopic data suggesting the formation of an equatorial

nitrilium ion from glycosyl halides in acetonitrile, and apparently in absence of an acceptor, seem to support this hypothesis.[149c] However, no experimental details are provided in this reference and the spectroscopic data are limited to the ^{1}H NMR shift and the corresponding vicinal coupling constant of the anomeric hydrogen atom (6.30 ppm, $J_{1,2}$ = 8.0 Hz) as well as the characteristic IR absorption (1640 cm^{-1}) of a glucosyl nitrilium intermediate. As another hypothesis, the anomeric effect should render the axial nitrilium species more favorable than the equatorial ion both on kinetic and thermodynamic grounds.[151d] Still, regardless of which nitrilium anomer is favored thermodynamically, under this scenario, the reaction would not be under Curtin-Hammett control, which requires a fast equilibrium between both nitrilium ions.

Only a single more extensive NMR-spectroscopic characterization of glycosyl nitrilium ions has been disclosed.[153] This study also undertakes computational modeling and emphasizes the intermediacy of several possible non-chair conformers, which further complicate the mechanistic study of the nitrile effect.

In view of the widely appreciated synthetic utility of the nitrile effect, rigorous spectroscopic evidence missing in support of the above mechanistic picture appears somewhat unsatisfactory. In an effort to provide a contribution to remedy this instance, the activation of the mycinose trichloroacetimidate **21c** by addition of a silyl triflate was examined by low-temperature NMR spectroscopy. It was hoped that upon donor activation a glycosyl triflate and possibly an equilibirium with a nitrilium species might be observed when acetonitrile was present. Unfortunately, detection of a nitrilium species was unsuccessful, and several unidentifiable decomposition products were formed when trichloroacetimidate **21c** was activated with TBSOTf in a mixture of CD$_2$Cl$_2$ and D$_3$CCN at −78 °C, followed by gradual warming in the NMR spectrometer.
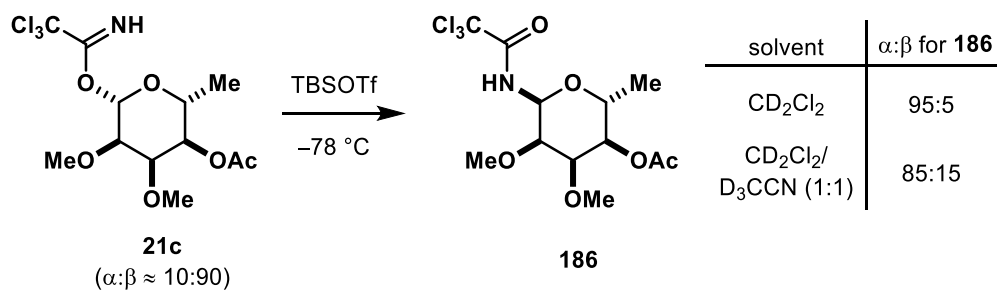
Scheme 2.26: Activation of the 4-O-acetyl mycinose trichloroacetimidate in an NMR experiment led to rearrangement to a glycosidic amide.

Some insight was gained, however, when this glycosyl donor (α:β ≈ 10:90) was activated with a catalytic amount of TBSOTf (10 mol%) at −78 °C in the absence of acetonitrile (scheme 2.26). Fast rearrangement to N-glycosyl amide **186** predominantly as its α-anomer was observed (α:β ≈ 95:5). A minor signal set with a low-field doublet (6.03 ppm, $J_{1,2}$ = 3.7 Hz), which completely disappeared after completion of this rearrangement, might indeed belong to an α-configured glycosyl triflate. The rearrangement was nearly

instantaneous at −78 °C when a stoichiometric amount of the silyl triflate was employed. Interestingly, amide **186** was also the major decomposition product in the reaction in presence of acetonitrile, yet with a lower preference for the α-anomer (α:β ≈ 85:15), which demonstrates that the nitrile effect is operative to some extent even in absence of an acceptor alcohol. Though trichloroacetimidates display an excellent leaving group potential, the above experiments suggest that formation of amides of the type of **186** might prevent the characterization of reactive intermediates formed from these donors in general. This might explain why thioglycosides and glycosyl sulfoxides, which can be activated in situ to generate virtually non-nucleophilic byproducts derived from the donor, have been much more popular in the study of reactive glycosylation intermediates.[150, 154]

Chapter 3

Conclusion

3.1 A Uniform Strategy and Contemporary Ruthenium Catalysis Enable the Practical Synthesis of Related Macrolide Antibiotics

Aldgamycin N and mycinamicin IV belong to a large estate of 16-membered macrolide antibiotics, which are characterized by a highly conserved "eastern" acid half but subtle variations within their macrocyclic frameworks, as well as the specific glycosides that they carry. In an effort to provide a foundation for a collective synthesis of either natural product family, the present thesis provides a unified synthesis blueprint to both natural products. As two representative targets of their families, aldgamycin N and mycinamicin IV exhibit a different oxygenation pattern at C8 as well as different levels of unsaturation in the vicinity of the C9 ketone, and constitute the natural products with either a C15 methyl or a C15 ethyl branch.

The unified approach to both targets is enabled by the swift assembly of the macrocyclic frameworks by merging individual carbonyl and alkyne modules as the two main synthetic fragments and the subsequent ruthenium-catalyzed transformation of the C–C triple bonds into the key functionalities distinguishing the individual targets (figure 3.1). The "eastern" carbonyl fragments were reached from a single common terminal alkene building block formed on deca-gram scale by an asymmetric vinylogous Mukaiyama-type aldol reaction. Wacker oxidation of the alkene terminus provided a ketone as the anchor point towards aldgamycin N, while the unified synthesis approach demanded the stereoselective formation of a branched aldehyde at this site to reach mycinamicin IV. In achievement of this task, the present thesis provides the first example of a diastereo- and regioselective hydroformylation of a terminal alkene in the setting of a natural product total synthesis. After careful optimization of the reaction conditions, the hydroformylation catalyst formed from [Rh(acac)(CO)$_2$] and the literature-known chiral phosphine/phosphite ligand BOBPhos allowed the preparation of the required aldehyde fragment on gram-scale. Similarly as the required carbonyl fragments were obtained by individual functionalization of just one common alkene building block, the "western" alkyne fragments were prepared following two individual but uniform routes on multi-gram scale as well. The stereocenters of the alkyne fragments were set by Sharpless asymmetric
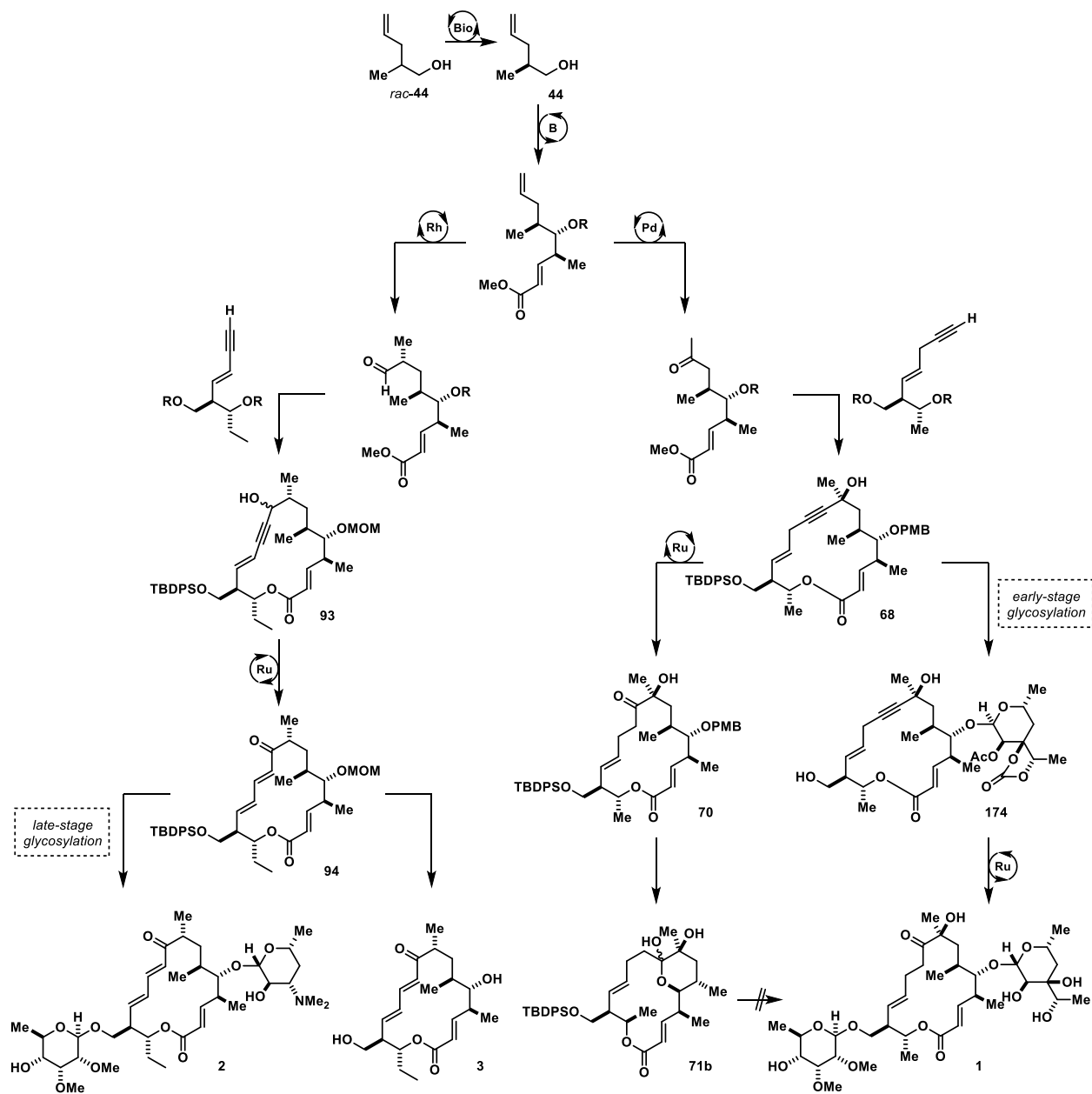
Figure 3.1: Schematic overview of the two total syntheses of the macrolide antibiotics aldgamycin N (right) and mycinamicin IV (left) by the unified approach described in this thesis. As shown, the key-steps are based on catalysis.

epoxidation of two simple allylic alcohols with the individual C15 alkyl branches followed by regioselective oxirane-opening by lithium acetylide. The resulting terminal alkynes served the elaboration of the specific patterns of unsaturation of the targets after conversion into the derived alkenyl iodides: copper-mediated propargylation gave the skipped enyne fragment necessary to reach aldgamycin N, whereas Sonogashira cross-coupling furnished the conjugated enyne for the preparation of mycinamicin IV.

Combination of the aldehyde and ketone fragments with their respective alkyne counterparts by carbonyl addition set the stage for macrolactonization. While attempted liberation of the respective seco-acids was to

no avail, the macrolactone rings could be closed by an unusual stannoxane-mediated transesterification from the methyl esters directly. After its disclosure in 1986, this transesterification methodology had served for a macrolactonization only once before in natural product synthesis. Both total syntheses described in this thesis, however, clearly showcase its mild reaction conditions as well as its attractive feature to save a step in the linear sequence by rendering the seco-acid formation unneccesary.

The specific transformation towards the acyloin motif of aldgamycin N comprises a novel sequence of a regioselective hydrostannation of the propargylic alcohol obtained from the carbonyl addition followed by a Chan-Lam-type oxygenative coupling of the resulting α-hydroxy alkenylstannane. The regio- (and stereo)-selective hydrostannation of the triple bond is enabled by $[Cp*RuCl]_4$ as catalyst, which locks the substrate and the stannane in a well-defined transition structure. Due to the highly oxygenated nature of the glycosylated substrate in the revised route to reach aldgamycin N (see below), the present thesis describes the arguably most advanced application of this methodology developed in the Fürstner group. Modification of the conditions previously reported in this research group for the subsequent Chan-Lam-type oxygenation of the alkenylstannane was instrumental to deliver the free acyloin right away rather than a less stable carboxylate. The modified procedure developed in the context of this thesis using copper(II) trifluoroacetate entails much milder conditions in the presence of only a catalytic amount of a weak pyridine base, allowing the reaction to proceed in typically less than an hour under gentle warming or even at room temperature.

The unsaturated ketone of mycinamicin IV was introduced by the ruthenium-catalyzed rearrangement of the secondary propargylic alcohol formed by the addition of the conjugated enyne to the aldehyde fragment. This rare redox-isomerization highlights the viability of the rearrangement of a 1,3-enyne-5-ol into a 1,3-diene-5-one derivative in a complex setting and remedies previous concerns of catalyst quenching by coordination of the transition metal by these conjugated π-functionalities.

3.2 A Flexible and Uniform De Novo Synthesis of 4,6-Dideoxy Sugars allows the Completion of the Aldgamycin N and Mycinamicin IV Total Syntheses

The final conquest of the two natural products by attachment of their specific glycosides demanded special attention. While the bare aglycon (mycinolide IV) could serve the total synthesis of mycinamicin IV as previously reported in the literature, the glycosylation conditions themselves needed considerable adjustment by resorting to trichloroacetimidates rather than glycosyl fluorides used as carbohydrate donors. In comparison to the total synthesis published by Suzuki and co-workers, the synthesis described in this
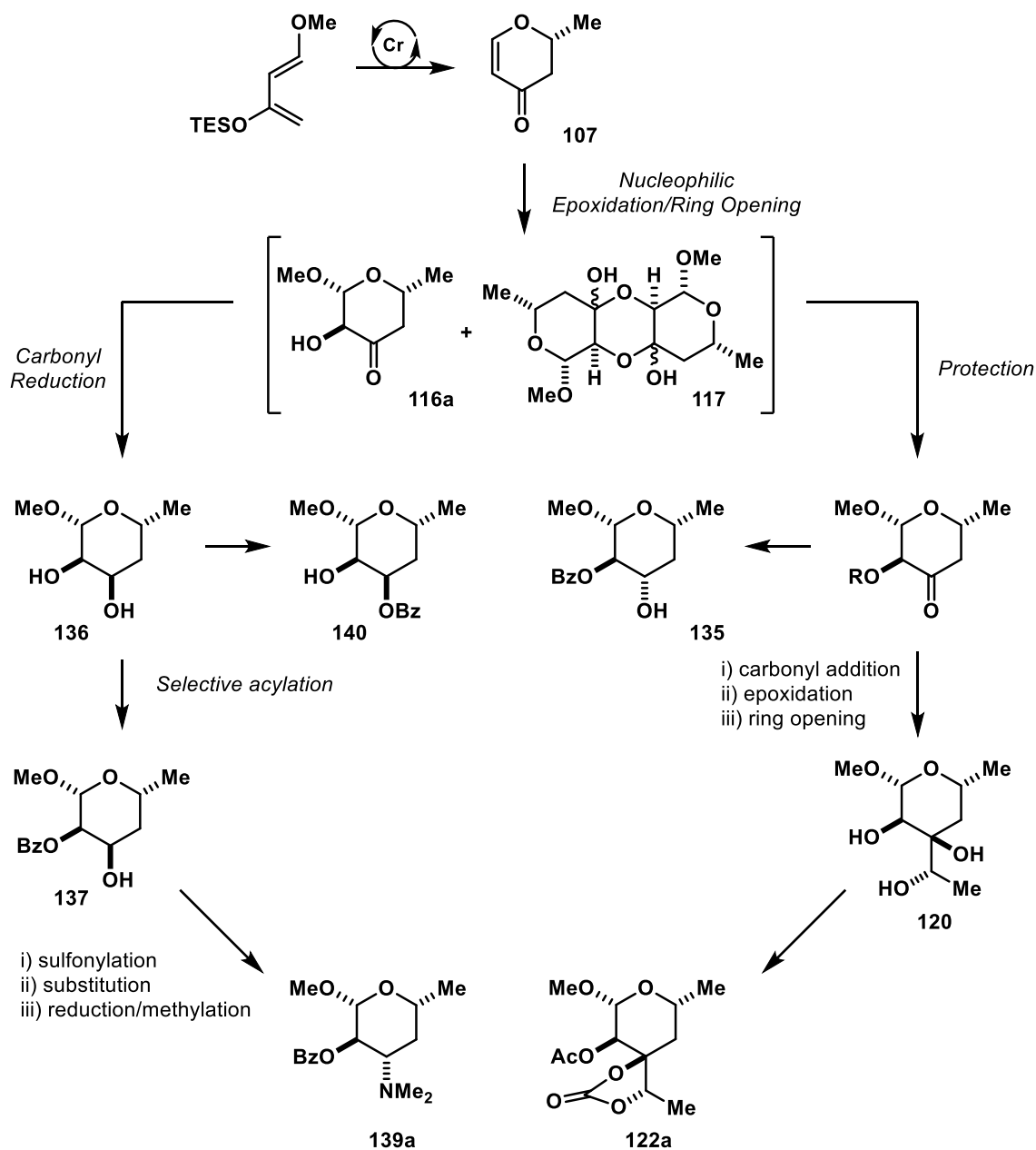
Figure 3.2: Schematic overview of the unified syntheses developed for the 4,6-dideoxy sugars D-desosamine (left) and D-aldgarose (right).

thesis offers the advantage of an orthogonal cleavage of the protecting groups of the mycinamicin core. In the case of aldgamycin N, a different glycosidation strategy had to be followed due to the formation of a transannular hemiketal once the C5 alcohol was liberated in presence of the C9 ketone in the attempt to reach the aglycon. Revision of the synthetic plan mandated to carry out the glycosylation of the secondary acceptor at an earlier stage with the ketone still masked as the C–C triple bond. Although this glycosylation turned out to be highly challenging due to the fragility of the propargylic alcohol functionality under typical glycosylation conditions, the synthetic revision was ultimately successful by the employment of a

trichloroacetimidate donor under carefully chosen conditions for the glycosylation. Both natural product syntheses strikingly demonstrate the underappreciated reactivity differences between different silyl triflate promotors in glycosylations: only after careful screening efforts, appropriate conditions were found for the glycosylations with the trichloroacetimidate donors. A fine reactivity balance was needed for success, at which the silyl triflate activated the glycosyl donor sufficiently towards the desired reaction on the one hand, while the glycosyl acceptor had to resist to undesired side reactions on the other hand. Overall, the present thesis shows that the glycosylation of elaborate targets remains far from routine, and that the final challenge of the synthesis of the biologically active natural product with all glycosides in place should not be underestimated.

The completion of the total syntheses described in this thesis, in particular due to the necessary early-stage glycosylation of the secondary acceptor towards aldgamycin N, required efficient syntheses of the sugar residues specific for the individual natural products. For both 4,6-dideoxy carbohydrates encountered in the targets, the branched octose D-aldgarose and the amino sugar D-desosamine, novel *de novo* syntheses were developed from a common intermediate, which was formed on multi-gram scale using a chromium-catalyzed asymmetric hetero-Diels-Alder reaction (figure 3.2). The synthesis diverts at the stage of ketol **116a**, which exists in equilibrium with its dimer **117**. After appropriate protection of this ketol, carbonyl addition provided a vinyl side chain, which was elaborated into the oxygenated two-carbon branch of aldgarose by epoxidation and ring opening. Alternatively, the ketol could be reduced to either acylated *trans*-diol **135** or *cis*-diol **136**, which served the synthesis of desosamine by selective protection and introduction of an azide group by nucleophilic substitution.

These routes not only feature robust and high-yielding steps, but also offer the advantage of high versatility. Specifically, access to both diols **135** and **136** may serve the preparation of stereoisomers of desosamine. Furthermore, these diols themselves are naturally occurring 4,6-dideoxy carbohydrate motifs.[155] With efficient procedures provided for the selective protection of diol **135**, regioisomers of desosamine are also within reach via the route described herein. Last but not least, the employment of asymmetric catalysis in the preparation of the common ketol intermediate allows for the equally facile access to the enantiomeric L-sugars, some of which actually occur in nature.[156]

3.3 The Virtues of the Herein Presented Uniform and Catalysis-based Approach to Macrolide Antibiotics

The step-count of only 16 steps in the longest linear sequence to create mycinamicin IV in this thesis demonstrates the significant progress in organic synthesis since the disclosure of the first conquest of

mycinamicin IV reported in 1981, which required 32 steps in its longest linear sequence. Following a unified blueprint, this thesis also describes the first total synthesis of a member of the aldgamycin family, to reach aldgamycin N in only 19 steps in the longest linear sequence. Whilst the first total synthesis of mycinamicin IV had completely resorted to the chiral pool to gain access to the natural product as a single enantiomer, the syntheses described herein are largely catalyst-based. As such, the underlying synthetic strategy embraces more than just one discipline of catalysis: biocatalysis allowed the enantioselective formation of the aldehyde needed for the common building block via lipase-catalyzed kinetic resolution. The realm of organocatalysis provided a chiral Lewis acid (boron) in the vinylogous aldol reaction and a mild, in two cases catalytic, activator (silicon) needed for the challenging glycosylations. Transition metal catalysis made the divergent functionalization of the common building block possible by either stereo- and branch-selective hydroformylation (rhodium) or Tsuji-Wacker oxidation (palladium). Furthermore, it served the enantioselective synthesis of the alkyne modules and carbohydrates by asymmetric epoxidation (titanium) and asymmetric hetero-Diels-Alder reaction (chromium). Both late-stage transformations to forge the key functionalities of the natural products (ruthenium) could not be imagined without the corresponding recent methodologies of transition metal catalysis. Catalysis not only enabled the unified synthetic approach presented in this thesis but it also rendered the underlying strategy indeed practical since the crucial intermediates of the syntheses could be prepared on multi-gram scale.

The collective synthesis of two or more targets within a single synthetic conquest is certainly not an unusal feature of contemporary total synthesis.[157] The present work described in this thesis, however, stands out amongst other collective efforts[158] in that it provides the access to two *distinct* series of natural products, which require *individual* main fragments and their coupling under *individual* conditions, followed by their specific elaboration into the final targets, while they are reached from a *common* intermediate or via a unifying strategy. In particular, this work is only the second effort to feature these modular virtues in the total synthesis of macrolide antibiotics. The only other, admittedly more extensive, example deals with the modular synthesis of mostly non-natural derivatives of erythromycin.[123, 159] The latter study clearly demonstrates that the underlying modularity is truly empowering in a medicinal context aiming at the discovery of synthetic analogoues with higher biological activity and stability, or even a completely different activity profile. These virtues might play an important role in the "race" against antibiotic resistance, to which the introduction of this thesis is alluding.

Chapter 4

Experimental Section

4.1 General

Unless otherwise stated, all reactions were conducted in oven-dried (80 °C) or flame-dried glassware in anhydrous solvents under argon applying standard Schlenk techniques, and the reaction mixtures were magnetically stirred. Dry argon (>99.5%) was purchased from Air Liquide.

The following solvents were purified by distillation over the indicated drying agents and transferred under argon: tetrahydrofuran and diethyl ether (Mg/anthracene), dichloromethane (CaH_2), hexanes and toluene (Na/K), methanol (Mg, stored over 3 Å molecular sieves). Acetonitrile, dimethyl sulfoxide, dimethylformamide, pyridine and triethylamine were dried using an adsorption (molecular sieves) solvent purification system. During work-up, solvents were generally removed under reduced pressure below 40 °C using a rotary evaporator.

Commercial technical-grade cumene hydroperoxide (Aldrich, 80 w-%) was used as received. Commercial titanium(IV) isopropoxide was distilled under reduced pressure and stored under argon at −20 °C. Amano Lipase (*Pseudomonas fluorenscens*) was purchased from Aldrich. The chiral ligand (S_{ax},*S*,*S*)-**82** (BOBPhos) was purchased from Strem chemicals. Silyl dienolate **41**[160], distannoxanes **67a-e**[102, 161], the chiral ligand (R_{ax},*R*,*R*)-**82**[100c, 101], siloxy diene **113b**[115], chromium catalyst **114b**[113] and dimethylboron bromide[162] were prepared following literature-reported procedures.
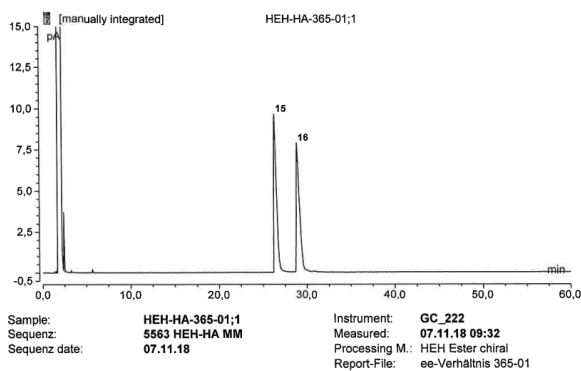
Thin layer chromatography (TLC) was performed on Macherey-Nagel precoated plates (POLYGRAM® SIL/UV254), and the compounds were detected by UV light (254 nm) or heating of the plate with a heat gun after treatment with a stain solution comprising either potassium permanganate, phosphomolybdic acid or vanillin. Flash chromatography was performed with VWR silica gel (particle size 40 – 63 µm). Automated column chromatography was conducted on a Biotage® Isolera™ or a Biotage® Selekt instrument, using the chromatography cartridges indicated in the respective procedure. Diastereomeric ratios of intermediates were determined by ^{1}H NMR spectroscopy from the relative integrals of sufficiently separated, characteristic signals of the respective intermediate.

NMR spectra were recorded on Bruker AV 400, AV 500 or AVIII 600 spectrometers in the solvents indicated. The solvent signals were used as references, chemical shifts were converted to the TMS scale and reported as follows: chemical shift in ppm (multiplicity, coupling constant J in Hz, number of protons). Multiplets are designated by the following abbreviations: s for singlet, d for doublet, t for triplet, q for quartet, quint for quintet, m for complex pattern; the abbreviation br indicates a broad signal. ^{13}C NMR spectra were recorded in ^{1}H-decoupled mode. Melting points were determined using a Büchi B-540 apparatus. IR spectra were recorded on a Bruker Alpha Platinum ATR spectrometer at room temperature. Mass spectrometric samples were measured using the following instruments: MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Bruker ESQ3000, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet) or Finnigan MAT 95. GC-MS samples were processed on a Shimadzu GCMS-QP2010 Ultrainstrument. Specific optical rotatory power ($[\alpha]_D$) was measured with the A-Krüss Otronic Model P8000-t polarimeter at a wavelength of 589 nm. The values are given with respect to exact temperature, concentration (c/(10mg/mL)) and solvent.

4.2 Preparation of the Common Eastern Fragment

(*S*)-2-Methylpent-4-en-1-yl acetate (50). A 1-L three-necked flask with cooling jacket equipped with an argon bubbler was charged with Amano Lipase (*Pseudomonas fluorenscens*) (2.15 g), tetrahydrofuran (430 mL) and 2-methyl-4-penten-1-ol (21.6 g, 215 mmol). The mixture was cooled to −20 °C using a cryostat while gently stirred (~250 rpm). Vinyl acetate (29.9 mL, 322 mmol) was added in one portion and stirring continued for 11.5 h at −20 °C. Once the reaction progress had been determined to have reached 45% (GC-FID), the enzyme was filtered off from the cold mixture using a fritted funnel. The filtrate was carefully concentrated to remove most of the solvent. Purification of the residue by flash chromatography (pentane/diethylether, 9:1) afforded the title compound as a colorless liquid (15.1 g, 40% yield, 94% *ee*). $[\alpha]_D^{20} = -2.3$ (*c* 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.83 – 5.70 (m, 1H), 5.07 – 5.00 (m, 2H), 3.96 (dd, *J* = 10.8, 6.1 Hz), 3.88 (dd, *J* = 10.8, 6.4 Hz) 2.20 – 2.11 (m, 1H), 2.06 (s, 3H), 1.99 – 1.81 (m, 2H), 1.36 – 1.18 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 171.4, 136.3, 116.7, 68.9, 37.9, 32.5, 21.1, 16.7. **IR (film):** 3078, 2964, 2934, 2914, 1738, 1642, 1461, 1441, 1390, 1366, 1232, 1035, 933, 912 cm^{-1}. **HRMS (GC-CI) m/z:** [M]$^+$ calcd for C$_8$H$_{15}$O$_2$ 143.1067; found 143.1066. The enantiomeric purity was determined by GC (see below).
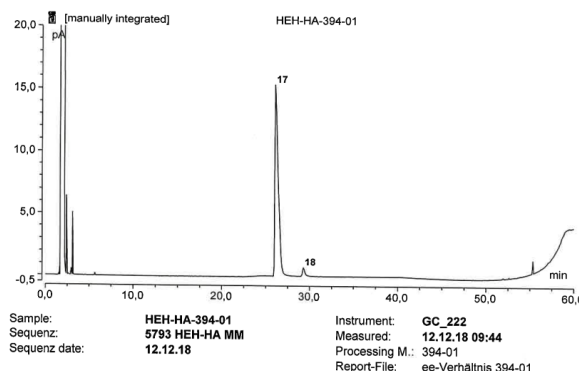
(S)-2-Methylpent-4-en-1-ol (44). Methyl lithium in diethyl ether (1.6 M, 64 mL, 102 mmol) was slowly added to a solution of acetate **50** (15.1 g, 85.0 mmol) in diethylether (200 mL) at −30 °C. Once the addition was complete, the mixture was warmed to room temperature and stirring was continued for another 3 h. The reaction was quenched by the addition of water and the mixture was extracted twice with diethyl ether. The combined organic phases were washed with brine and evaporated. The residue was purified by flash chromatography (pentane/diethyl ether, 5:1) to afford the title compound as a colorless liquid (6.40 g, 75% yield). $[\alpha]_D^{20} = -3.4$ (c 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.81 (ddt, J = 17.2, 10.1, 7.2 Hz, 1H), 5.08 – 4.99 (m, 2H), 3.55 – 3.43 (m, 2H), 2.18 (dddt, J = 14.3, 7.2, 6.0, 1.3 Hz, 1H), 2.00 – 1.90 (m, 1H), 1.81 – 1.68 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 137.1, 116.2, 68.1, 38.00, 35.8, 16.5. **IR (film):** 3321, 3077, 2957, 2913, 2875, 1640, 1456, 1439, 1378, 1040, 1028, 992, 909, 628 cm^{-1}. **HRMS-ESI m/z:** [M+H]$^+$ calcd for C$_6$H$_{13}$O 101.0961, found 101.0961.
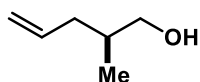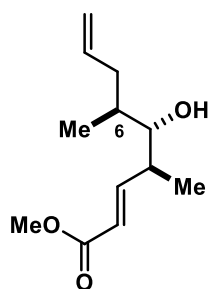
(S)-2-Methylpent-4-enal (40). In a 250-mL three-necked flask fitted with a dropping funnel, a thermometer and an argon inlet, dimethyl sulfoxide (14 mL, 200 mmol) was added over 5 min to a solution of oxalyl chloride (9.0 mL, 104 mmol) in dichloromethane (90 mL) at −78 °C, making sure the internal temperature stayed below −50 °C at all time. After an additional 5 min, alcohol **44** (9.50 g, 94.8 mmol) was added as a solution in dichloromethane (30 mL) over the course of 30 min. After stirring for additional 30 min, triethylamine (66 mL, 101 mmol) was introduced over 5 min, forming a thick white suspension, which was vigorously stirred. After 5 min, the mixture was warmed to room temperature and partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with an aqueous solution of HCl (0.5 M) and brine. The organic phases were dried over anhydrous magnesium sulfate, the drying
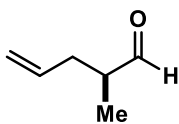
agent was filtered off, and the solution was concentrated under reduced pressure (800 mbar, 30 °C). Pentane was added to azeotropically remove most of the dimethylsulfide. Because of the volatility of the title compound, the resulting solution was used without further purification in the next step (29.0 g, ~29 w-% by ^{1}H NMR). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 9.66 (d, J = 1.4 Hz, 1H), 5.83 – 5.70 (m, 1H), 5.14 – 5.04 (m, 2H), 2.52 – 2.40 (m, 2H), 2.21 – 2.11 (m, 1H), 1.11 (d, J = 7.0 Hz, 3H).

Methyl (4S,5S,6S,E)-5-hydroxy-4,6-dimethylnona-2,8-dienoate (39). *Catalyst preparation:* A 100-mL two-necked flask equipped with a Dean-Stark trap topped by a reflux condenser and an argon bubbler was charged with (R)-diphenylprolinol (10.0 g, 38.8 mmol) and phenylboronic acid (4.98 g, 38.8 mmol). Toluene (200 mL) was added and the mixture was heated at reflux for 14 h. After cooling the reaction mixture to 50 °C, the Dean-Stark condenser was replaced by a connection to a vacuum manifold to remove the toluene in vacuum at 50 °C. The residue was dried in high vacuum for 2 h before the semisolid was dissolved in dichloromethane (530 mL).

A three-necked flask with cooling jacked equipped with a 100-mL dropping funnel and an argon bubbler was charged with this catalyst solution. The solution was cooled to −78 °C before freshly distilled triflic acid (2.8 mL, 32 mmol) was added in one portion, causing the immediate formation of a a red/orange precipitate. The mixture was stirred at −78 °C until all the solid material had disappeared (20 to 60 min). The dropping funnel was then charged with a solution of aldehyde **40** (28.7 g, 29 w-% in CH$_2$Cl$_2$, 86 mmol), dichloromethane (225 mL), ketene acetal **41** (16.0 g, 69.9 mmol) and isopropanol (5.4 mL, 70 mmol) in that order. The mixture in the dropping funnel was added over the course of 2 h to the catalyst solution at −78 °C. After complete addition, the mixture was stirred for an additional hour at this temperature before the reaction was quenched with saturated aqueous sodium bicarbonate solution (50 mL). The resulting mixture was warmed to room temperature, the aqueous phase was extracted thrice with dichloromethane, and the combined organic layers were stirred vigorously with an aqueous HCl solution (2 M, 400 mL) for 1 h. The resulting aqueous phase was extracted thrice with dichloromethane, and the combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The drying agent was filtered off, and the solution was concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 9:1) afforded the title compound admixed with the C6 epimer as a colorless oil (10.2 g, 48.1 mmol, 69% yield, 89:11 d.r.). $[\alpha]_D^{20}$ = −15.7 (c 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.97 (dd, J = 15.8, 7.6 Hz, 1H), 5.87 (dd, J = 15.8, 1.3 Hz, 1H), 5.84 – 5.73 (m, 1H), 5.08 – 4.99 (m, 2H), 3.73 (s, 3H), 3.36 (dt, J = 6.9, 5.0 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.40 – 2.31 (m, 1H), 1.95 (dtt, J = 13.9, 8.4, 1.1 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.58 (d, J = 5.2 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 152.4, 137.2, 121.0, 116.6, 78.1, 51.7, 39.5, 36.5, 36.1, 16.3, 12.9. **IR**

(film): 3470, 2969, 2932, 2910, 2879, 1704, 1653, 1642, 1456, 1436, 1276, 1195, 1178, 986, 911, 864 754 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for $C_{12}H_{20}O_3Na$ 235.1305, found 235.1306.

*Stereochemical Analysis of Product **39** formed by the Vinylogous Mukaiyama Aldol Reaction*

(1) The identity of the minor diastereoisomer (C6 epimer) was established by comparison of the crude mixture obtained under the reaction conditions described above to the reaction outcome with racemic aldehyde **40** under otherwise identical conditions. Since no other diastereomers were observed by NMR analysis of the crude product mixture, the aldol reaction itself seems to proceed with a stereoselectivity of *dr* > 98:2.

(2) The relative configuration at C5 was determined by Mosher ester analysis of alcohol **39**.

Table 4.1: Comparison of the chemical shifts of the ^1H NMR signals for (*S*)-MTPA (δ_S) and (*R*)-MTPA (δ_R) esters derived from alcohol **39**. The chemical shift differences for the ^1H atoms on the left side of the stereocenter exhibit negative values; those on the right side exhibit positive differences respectively. This analysis indicates the desired (*S*)-configuration of the C5 OH stereocenter.
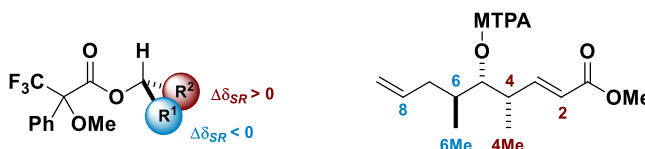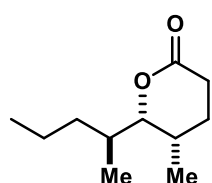

	δ_S	δ_R	$\Delta\delta_{SR}$
2	5.83	5.81	+0.02
3	6.85	6.82	+0.03
4	2.75	2.73	+0.02
4Me	1.02	0.99	+0.03
5	5.06	5.06	0.00
6	1.86	1.88	-0.02
6Me	0.86	0.89	-0.03
8	5.66	5.67	-0.01

(3) The relative configuration at C4 was determined by ^1H NMR analysis of the lactone formed by hydrogenation/cyclization (see below). The observed coupling constants and NOE interactions support the conformation and configuration shown below.
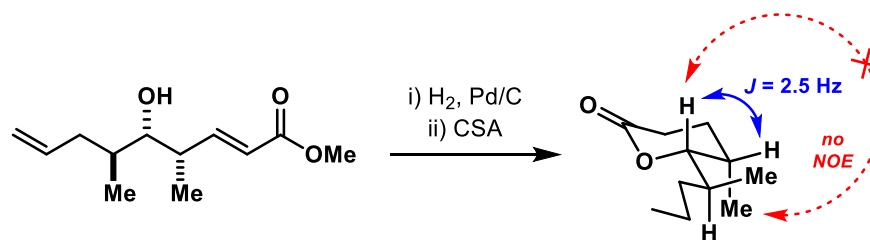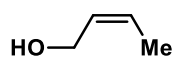
(5*S*,6*S*)-5-Methyl-6-((*S*)-pentan-2-yl)tetrahydro-2-pyran-2-one **(52).** A suspension of alcohol **39** (7.8 mg, 37 µmol) and Pd/C (5.2 mg) in ethyl acetate (1.0 mL) was stirred at room temperature for 2 h under hydrogen atmosphere. The suspension was filtered through Celite® and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (1.0 mL) and camphor-10-sulfonic acid (2.0 mg, 8.6 µmol) was added. After stirring at room temperature for 15.5 h, saturated aqueous sodium bicarbonate solution (1.0 mL) was added, the layers separated and the aqueous phase extracted with dichloromethane (3 × 1 mL). The combined organic layers were dried over anhydrous magnesium sulfate, the drying agent was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound as a colorless oil (6.2 mg, 34 µmol, 92% yield). $[\alpha]_D^{20}$ = −54.3 (*c* 0.78, CHCl$_3$); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 3.88 (dd, *J* = 10.1, 2.5 Hz, 1H), 2.52 (dd, *J* = 8.7, 6.3 Hz, 2H), 2.21 – 2.12 (m, 1H), 2.05 (dtd, *J* = 13.7, 8.7, 5.9 Hz, 1H), 1.82 (dddd, *J* = 13.6, 11.1, 5.6, 3.0 Hz, 1H), 1.74 – 1.68 (m, 1H), 1.66 (dtd, *J* = 13.7, 6.3, 3.0 Hz, 1H), 1.48 – 1.38 (m, 1H), 1.29 – 1.19 (m, 1H), 1.12 – 1.06 (m, 1H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 172.3, 86.7, 34.9, 34.5, 26.8, 26.7, 26.2, 19.6, 14.5, 14.3, 11.5. **IR (film):** 2959, 2932, 2873, 1734, 1457, 1383, 1325, 1238, 1201, 1126, 1062, 995, 980, 907, 738, 551 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{11}$H$_{20}$O$_2$Na$^+$ 207.1355, found 207.1357.

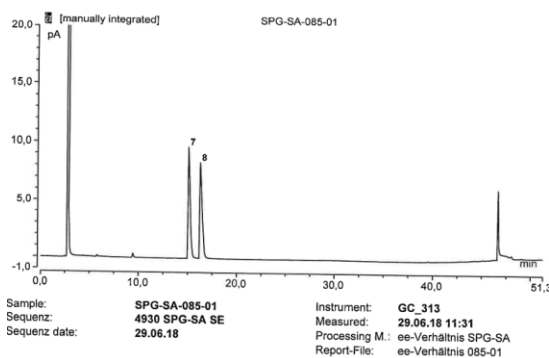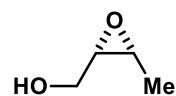## 4.3 Preparation of the Western Alkyne Fragments

(*Z*)-But-2-en-1-ol (53a). In a 500-mL three-necked round-bottomed flask under hydrogen atmosphere (two balloons), 2-butyn-1-ol (11 mL, 147 mmol) was added to a vigorously stirred suspension of Pd/BaSO$_4$ (10 w%, 1.07 g, 1.00 mmol) in diethyl ether (200 mL). The suspension was stirred under a hydrogen atmosphere for 44 h, until reaction monitoring by ^{1}H NMR indicated full consumption of the alkyne. For work-up, the flask was purged with argon and the suspension filtered through a pad of Celite®, which was rinsed with diethyl ether (5 × 15 mL). The combined filtrates were carefully evaporated (500 mbar, 36 °C) to give a yellowish liquid. Distillation at reduced pressure (5 cm Vigreux column; ~100 mbar, bp 60 – 65 °C) gave the title compound as a colorless liquid (5.6 g,

53% yield).**¹H NMR (400 MHz, CDCl₃):** δ 5.71 – 5.57 (m, 2H), 4.27 – 4.16 (m, 2H), 1.73 – 1.63 (m, 3H), 1.22 (br s, 1H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 129.4, 127.4, 58.4, 13.1.
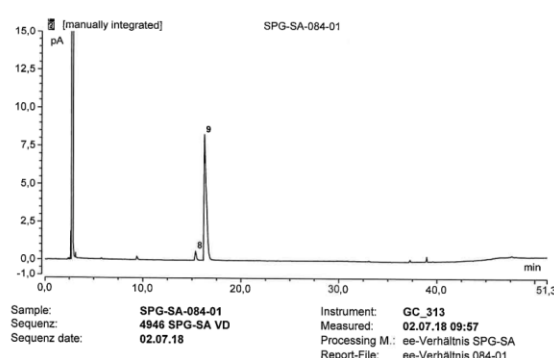
((2*S*,3*R*)-3-Methyloxiran-2-yl)methanol (54a). A 1-L Schlenk flask with cooling jacket was charged with powdered 4 Å molecular sieves (~6 g) and dichloromethane (320 mL). After the suspension had been cooled to −20 °C, titanium(IV) isopropoxide (5.0 mL, 17 mmol) and (+)-diisopropyl L-tartrate (4.2 mL, 20 mmol) were added and stirring was maintained for 20 min at −20 °C. Cumene hydroperoxide (80% technical grade, 27 mL, 146 mmol) was added and the resulting mixture stirred for 30 min before a mixture of allylic alcohol **53a** (6.04 g, 83.8 mmol) and powdered 4 Å molecular sieves (~1.5 g) in dichloromethane (40 mL) was introduced. Stirring was continued for another 14 h at −20 °C. After the addition of citric acid monohydrate (3.56 g) in diethyl ether/acetone (225 mL/25 mL), the mixture was warmed to room temperature and stirred for 30 min before the orange suspension was filtered through a short pad of Celite®, which was rinsed with dichloromethane (5 × 10 mL). The combined filtrates were concentrated under reduced pressure (150 mbar, 38 °C) and the residue was purified by flash chromatography (pentane/diethyl ether, 1:1) to give the title compound as a colorless liquid (3.98 g, 54% yield, 92% *ee*). $[\alpha]_D^{20}$ = −8.8 (*c* 1.2, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 3.90 – 3.80 (m, 1H), 3.75 – 3.65 (m, 1H), 3.19 – 3.11 (m, 2H), 1.75 – 1.69 (m, 1H), 1.33 (d, *J* = 5.7 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 60.7, 56.7, 52.8, 13.4. The enantiomeric purity was determined by GC (see below). The racemic sample was obtained by epoxidation of (*Z*)-2-buten-1-ol with 3-chloroperbenzoic acid. The analytical data are in agreement with those reported in the literature.[163]

((2S,3R)-3-Ethyloxiran-2-yl)methanol (54b). A 1-L Schlenk flask with cooling jacket was charged with powdered 4 Å molecular sieves (~1.5 g) and dichloromethane (60 mL). After the suspension had been cooled to −20 °C, titanium(IV) isopropoxide (1.1 mL, 3.7 mmol) and (+)-diisopropyl L-tartrate (0.95 mL, 4.5 mmol) were added and stirring was maintained for 20 min at −20 °C. Cumene hydroperoxide (80% technical grade, 6.5 mL, 35 mmol) was added and the resulting mixture stirred for 30 min before a mixture of commercial Z-2-penten-1-ol (**53b**) (1.9 mL, 19 mmol) and powdered 4 Å molecular sieves (~0.5 g) in dichloromethane (40 mL) was introduced. Stirring was continued for another 4.5 h at −20 °C. After the addition of citric acid monohydrate (775 mg) in diethyl ether/acetone (90 mL/10 mL), the mixture was warmed to room temperature and stirred for 30 min before the orange suspension was filtered through a short pad of Celite®, which was rinsed with dichloromethane (5 × 10 mL). The combined filtrates were concentrated under reduced pressure (150 mbar, 38 °C) and the residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give the title compound as a colorless liquid (1.40 g, 73% yield, 87% *ee*). $[\alpha]_D^{20} = -11.5$ (*c* 1.6, CH$_2$Cl$_2$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 3.86 (ddd, *J* = 11.8, 7.3, 4.2 Hz, 1H), 3.68 (ddd, *J* = 11.8, 6.9, 4.4 Hz, 1H), 3.17 (dt, *J* = 6.8, 4.2 Hz, 1H), 3.00 (ddd, *J* = 6.9, 6.0, 4.4 Hz, 1H), 1.70 – 1.48 (m, 3H), 1.05 (t, *J* = 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 60.9, 58.6, 57.2, 21.5, 10.8. The enantiomeric purity was determined by GC (see below). The analytical data are in agreement with those reported in the literature.[74b]

No.	Ret.Time min	area-% %	Peak Name
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2	37,60	49,87	
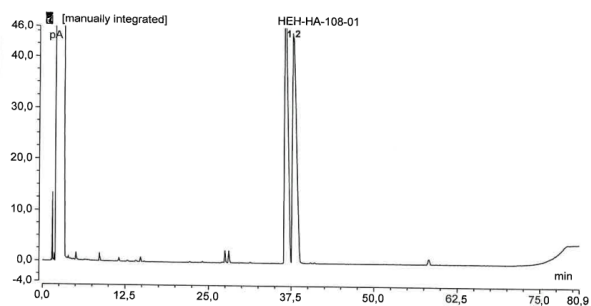
Sample: HEH-HA-108-01
Sequenz: 4299 HEHHA RO
Sequenz date: 22.02.18
Instrument: GC_122
Measured: 22.02.18 14:09
Processing M.: MPI
Report-File: Übersichtsanalyse

Instrument parameters:
Column: 25,0 m HYDRODEX BTBDAC G 664
Temperature: 230 80 1/MIN 150 8/MIN 220 3 MIN ISO 350
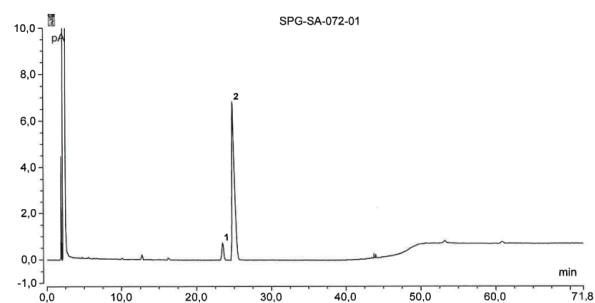Gas: 0,40 bar H2
Sample size: 1,0 µL

No.	Ret.Time min	area-% %	Peak Name
1	23,47	6,77	
2	24,80	93,23	

Sample: SPG-SA-072-01
Sequenz: 4862 SPG-SA RO
Sequenz date: 13.06.18
Instrument: GC_213
Measured: 13.06.18 12:02
Processing M.: MPI
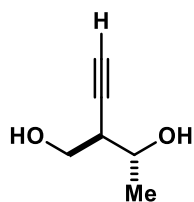Report-File: Übersichtsanalyse

Instrument parameters:
Column: 25,0 m HYDRODEX BTBDAC G 681
Temperature: 230 110 35 MIN ISO 9/MIN 220 3 MI ISO 350
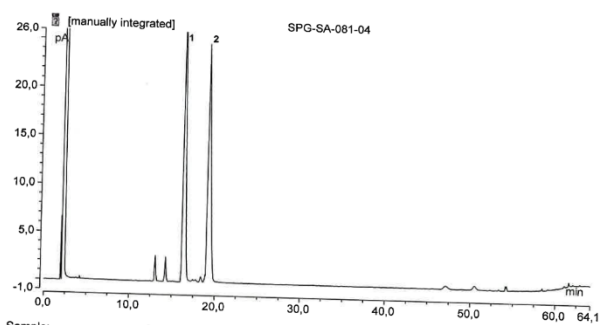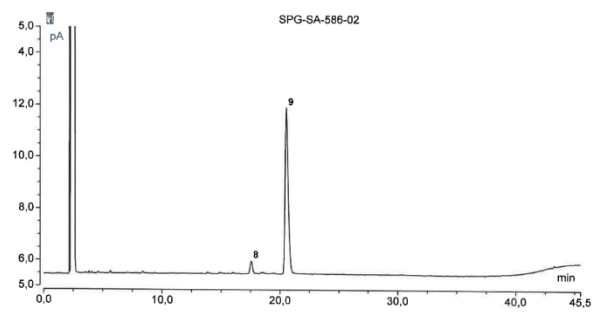Gas: 0,40 bar H2
Sample size: 1,0 µL

(2*R*,3*R*)-2-Ethynylbutane-1,3-diol (55a). In a 500-mL two-necked flask, a solution of epoxy alcohol **54a** (3.98 g, 45.2 mmol) in THF (30 mL) was added to a suspension of lithium acetylide ethylene diamine complex (13.6 g, 133 mmol) in THF (120 mL) at 0 °C (ice bath). The mixture was gradually warmed to ambient temperature while stirring for 19 h. The reaction was carefully quenched at 0 °C by the addition of aqueous HCl (1 M, 20 mL) and the resulting mixture was neutralized with concentrated (37% *w/w*) aqueous HCl. Half-saturated NaCl solution (60 mL) and *tert*-butyl methyl ether (40 mL) were added and the layers were separated. The aqueous layer was extracted with *tert*-butyl methyl ether (1 × 50 mL), before it was further extracted overnight with *tert*-butyl methyl ether using a continuous liquid/liquid extraction apparatus. The combined organic layers were concentrated under reduced pressure and the residue was dissolved in dichloromethane (35 mL). Water (1.0 mL) and sodium periodate (1.69 g) were added and the mixture was vigorously stirred at room temperature for 1 h. For work-up, anhydrous sodium sulfate was added until the organic layer became clear. The solid material was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:3) furnished the title compound as a light yellowish oil, which crystallized upon standing at −20 °C to give oily needles (2.18 g, 42% yield, 89% *ee*). $[\alpha]_D^{20} = -8.2$ (*c* 1.1, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.03 (qd, *J* = 6.3, 3.3 Hz, 1H), 3.90 – 3.78 (m, 2H), 2.63 (dddd, *J* = 6.1, 5.3, 3.3, 2.5 Hz, 1H), 2.35 (br s, 2H), 2.22 (d, *J* = 2.5 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 81.0, 73.3, 67.9, 63.9, 42.1, 21.3. **IR (film):** 3345, 3289, 2974, 2933, 2891, 1641, 1453, 1408, 1377, 1350, 1316, 1252, 1209, 1135, 1108, 1055, 1036, 986, 950, 904, 866, 809, 643, 554, 534, 490, 444 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_6$H$_{10}$O$_2$Na 137.0573; found 137.0573. The enantiomeric purity was determined by GC (see below).

No.	Ret.Time min	area-% %	Peak Name
1	16,17	50,90
2	19,03	49,10

Instrument parameters:
Column: 25,0 m HYDRODEX BTBDAC G 681
Temperature: 230 120 50 9/MIN 220 2 MIN ISO 350
Gas: 0,40 bar H2
Sample size: 1,0 µL

Sample: SPG-SA-081-04
Sequenz: 4947 SPG-SA RO
Sequenz date: 03.07.18
Instrument: GC_213
Measured: 04.07.18 09:39
Processing M.: MPI
Report-File: Übersichtsanalyse

chirale Messung, Verhältnis der Enantiomere
Zuordnung nach Racemat SPG-SA-081-04 18/4947 Box 82/D7

No.	Ret.Time min	Rel.Area %	Peak Name
8	17,55	5,62
9	20,51	94,38

Instrument parameters:
Column: 25,0 m Hydrodex-beta-TBDAc-CD 0,25/?df G/681
Temperature: 220/120 30 min iso 8/min 220, 3 min iso/350
Gas: 0,40 bar Hydrogen
Sample size: 1,0 µL

Sample: SPG-SA-586-02
Sequenz: 7361 SPG-SA SE
Sequenz date: 05.05.20
Instrument: GC_413
Measured: 05.05.20 10:35
Processing M.: SPG
Report-File: Verhältnis 586

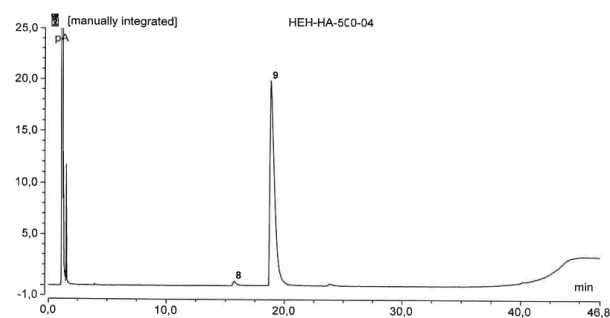**(2*R*,3*R*)-2-Ethynylpentane-1,3-diol (55b).** In a 250-mL two-necked flask, lithium acetylide ethylene diamine complex (8.60 g, 84.1 mmol) was added in one portion to a solution of epoxy alcohol **54b** (3.25 g, 31.8 mmol) in THF (100 mL) at 0 °C (ice bath). After stirring for 4.5 h, the reaction was carefully quenched at 0 °C by the addition of aqueous HCl (1 M, 10 mL), then neutralized by the addition of concentrated (37 w-%) aqueous HCl solution. Brine (40 mL) was added and the aqueous layer was extracted with *tert*-butyl methyl ether (3 × 50 mL), before it was further extracted overnight with *tert*-butyl methyl ether using a continuous liquid/liquid extraction apparatus. The combined organic layers were concentrated under reduced pressure and the residue was dissolved in dichloromethane (50 mL). Water (2.5 mL) and sodium periodate (1.36 g) were added and the mixture was vigorously stirred at room temperature for 1 h. Anhydrous sodium sulfate was added until the organic layer became clear. The solid material was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 1:1) gave the title compound as a light yellowish oil, which crystallized upon standing. Recrystallization from chloroform yielded the title compound as colorless needles in high enantiomeric purity (1.19 g, 29% yield, 97% *ee*). $[\alpha]_D^{20} = -1.1$ (*c* 1.0, CH₂Cl₂). **¹H NMR (400 MHz, CDCl₃):** δ 3.91 – 3.81 (m, 2H), 3.71 (ddd, *J* = 8.1, 5.7, 2.9 Hz, 1H), 2.70 (ddd, *J* = 6.1, 5.3, 2.7 Hz, 1H), 2.20 (d, *J* = 2.5 Hz, 1H), 0.98 (t, *J* = 7.5 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 80.9, 73.27, 73.23, 64.2, 40.4, 28.7, 10.3. **IR (film):** 3355 (br), 3295, 2965, 2938, 2880, 1462, 1411, 1340, 1243, 1124, 1046, 958, 803, 642 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C₇H₁₂O₂Na 151.0729; found 151.0730. The enantiomeric purity was determined by GC (see below). The spectroscopic data are in agreement with those reported in the literature.[66, 74b]

(2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-yn-2-ol (SI-1). In a 100-mL two-necked flask under argon, *tert*-butyldiphenylsilyl chloride (2.1 mL, 8.1 mmol) was added to a solution of diol **55a** (746 mg, 6.54 mmol) and imidazole (561 mg, 8.24 mmol) in dichloromethane (40 mL) at 0 °C. The ice bath was removed and the mixture stirred for 1 h at room temperature. The mixture was washed with saturated aqueous sodium bicarbonate solution (20 mL) and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 10:1) furnished the title compound as a colorless oil (1.92 g, 83% yield). $[\alpha]_D^{20}$ = +12.1 (*c* 1.3, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.74 – 7.64 (m, 4H), 7.48 – 7.35 (m, 6H), 4.14 (quintd, *J* = 6.4, 3.0 Hz, 1H), 3.94 – 3.80 (m, 2H), 2.62 (ddt, *J* = 7.5, 4.9, 2.5 Hz, 1H), 2.39 (d, *J* = 6.6 Hz, 1H), 2.14 (d, *J* = 2.5 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H), 1.07 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 135.8, 135.7, 134.9, 133.2, 133.0, 130.0, 129.8, 127.95, 127.92, 127.86, 81.2, 72.7, 66.9, 6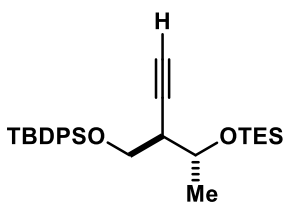4.7, 42.0, 27.0, 21.4, 19.4. **IR (film):** 3468, 3305, 3071, 3050, 2960, 2931, 2887, 2858, 1590, 1472, 1428, 1391, 1362, 1260, 1189, 1111, 998, 938, 823, 740, 702, 641, 613, 543, 505 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{22}$H$_{28}$O$_2$SiNa 375.1751; found 375.1752.
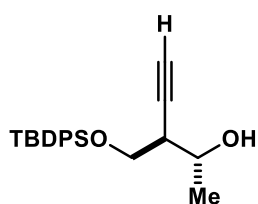
(2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-(triethylsilyloxy)-pent-4-yne (SI-2a). In a 100-mL two-necked flask under argon, triethylsilyl trifluoromethanesulfonate (2.7 mL, 12 mmol) was added to a solution of alcohol **SI-1** (3.27 g, 9.28 mmol) and 2,6-lutidine (1.7 mL, 15 mmol) in dichloromethane (60 mL) at 0 °C (ice bath). The mixture was gradually warmed to ambient temperature while stirring for 15 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (30 mL), and the mixture was diluted with dichloromethane (10 mL). The aqueous phase was extracted with dichloromethane (5 × 15 mL), the organic layers were washed with brine (20 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) furnished the title compound as a colorless oil (4.16 g, 96% yield). $[\alpha]_D^{20}$ = +15.7 (*c* 1.3, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.71 – 7.65 (m, 4H), 7.45 – 7.34 (m, 6H), 4.15 (qd, *J* = 6.3, 3.8 Hz, 1H), 3.89 – 3.74 (m, 2H), 2.55 (dddd, *J* = 7.0, 6.2, 3.8, 2.5 Hz, 1H), 2.05 (d, *J* = 2.5 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.67 – 0.50 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 135.8, 133.8, 129.8, 127.8, 83.1, 71.2, 66.7, 63.4, 43.3, 27.0, 21.8, 19.4, 7.05, 5.20. **IR (film):** 3312, 3072, 3051, 2955, 2933, 2910, 2876, 2859, 1590, 1462, 1428, 1414, 1377, 1362, 1239, 1188, 1148, 1110, 1077, 1006, 980, 939, 892, 823, 784, 738, 637, 613, 505 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{28}$H$_{42}$O$_2$Si$_2$Na 489.2616; found 489.2617.

(3R,4R)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-(triethylsilyloxy)-hex-5-yne (SI-2b). In a 100-mL round-bottomed flask, *tert*-butyldiphenylsilyl chloride (2.7 mL, 10 mmol) was added to a solution of diol **55b** (1.19 g, 9.30 mmol) and imidazole (760 mg, 11.2 mmol) in dichloromethane (60 mL) at 0 °C. The ice bath was removed and the mixture stirred for 4 h at room temperature. Filtration of the white suspension through a short plug of silica gel, which was rinsed with dichloromethane. Concentration of the combined filtrates under reduced pressure led to a colorless oil (3.78 g).

In a 100-mL two-necked flask, triethylsilyl trifluoromethanesulfonate (3.2 mL, 14 mmol) was added to a solution of this crude material and 2,6-lutidine (2.2 mL, 19 mmol) in dichloromethane (60 mL) at 0 °C (ice bath). The mixture was gradually warmed to ambient temperature while stirring for 14 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (20 mL), and the mixture was diluted with dichloromethane (15 mL). The aqueous phase was extracted with dichloromethane (3 × 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) furnished the title compound as a colorless oil (4.08 g, 91% yield). $[\alpha]_D^{20}$ = +15.8 (c 1.3, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.71 – 7.65 (m, 4H), 7.46 – 7.33 (m, 6H), 3.89 – 3.81 (m, 2H), 3.76 (dd, J = 9.8, 6.4 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.02 (d, J = 2.5 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.58 – 1.46 (m, 1H), 1.06 (s, 9H), 0.93 (t, J = 7.9 Hz, 9H), 0.86 (t, J = 7.8 Hz, 3H), 0.65 – 0.54 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 135.80, 135.77, 135.26, 133.78, 133.73, 129.79, 129.76, 127.78, 127.76, 127.5, 82.9, 72.2, 71.1, 63.5, 40.6, 28.2, 27.0, 19.4, 10.5, 7.10, 5.33. **IR (film):** 3311, 3072, 2958, 2934, 2877, 1462, 1428, 1380, 1239, 1112, 1010, 824, 739, 702, 637, 613, 506 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{29}$H$_{44}$O$_2$Si$_2$Na 503.2772; found 503.2771.
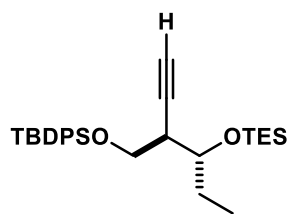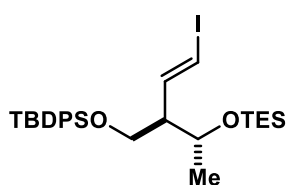
(2R,3R,E)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)-5-iodo-2-(triethylsilyloxy)-pent-4-ene (56a). In a 500-mL two-necked flask under argon, a solution of diisobutylaluminum hydride in hexanes (1.0 M, 24 mL, 24 mmol) was added over 10 min to a solution of zirconocene dichloride (6.96 g, 24.7 mmol) in THF (50 mL) at 0 °C (ice bath). After stirring for 30 min at this temperature, a solution of alkyne **SI-2a** (4.00 g, 8.32 mmol) in THF (50 mL) was added over 15 min, the cooling bath was removed, and stirring was continued for 1 h. During this time, the originally greyish suspension turned into a very dark green homogeneous solution. 2,6-Lutidine (3.1 mL, 27 mmol) was introduced, and the resulting mixture cooled to −78 °C. A solution of iodine (6.28 g, 24.7 mmol) in THF (40 mL) was added over 20 min and stirring was continued for 1 h at −78 °C. The reaction was quenched with a mixture of saturated aqueous

solutions of sodium bicarbonate and sodium thiosulfate (1:1 *v*/*v*, 100 mL), and the mixture was diluted with *tert*-butyl methyl ether (100 mL) and allowed to reach room temperature. After separation of the two layers in a separatory funnel, both were filtered separately through a pad Celite®, which was rinsed with *tert*-butyl methyl ether (3 × 20 mL). The aqueous filtrate was extracted with *tert*-butyl methyl ether (3 × 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1 → 15:1) furnished the title compound as a light amber oil (7.97 g, 65% yield). $[\alpha]_D^{20}$ = +23.6 (*c* 1.2, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 7.66 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 6.49 (dd, *J* = 14.5, 9.6 Hz, 1H), 5.99 (dd, *J* = 14.5, 0.6 Hz, 1H), 4.04 (qd, *J* = 6.37, 3.7 Hz, 1H), 3.73 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.56 (dd, *J* = 10.1, 6.5 Hz, 1H), 2.15 (ddt, *J* = 9.9, 6.4, 3.2 Hz, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.62 – 0.47 (m, 6H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 144.7, 135.8, 135.7, 133.80, 133.76, 129.81, 129.77, 127.82, 127.80, 127.7, 77.3, 66.9, 64.0, 56.8, 27.0, 22.3, 19.4, 7.08, 5.18. **IR (film):** 3071, 3050, 2956, 2931, 2910, 2875, 2858, 1603, 1590, 1471, 1462, 1428, 1376, 1361, 1259, 1241, 1178, 1146, 1111, 1092, 1008, 953, 824, 801, 738, 701, 614, 504, 489 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C₂₈H₄₃IO₂Si₂Na 617.1739; found 617.1744.
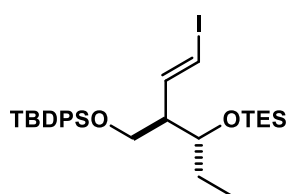
(3*R*,4*R*,*E*)-4-((((*tert*-Butyldiphenylsilyl)oxy)methyl)-6-iodo-3-(triethylsilyloxy)-hex-5-ene
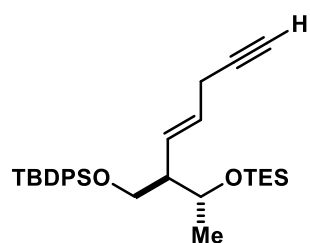

(56b). In a 100-mL two-necked flask under argon, a solution of diisobutylaluminum hydride in toluene (25 w-%, 7.0 mL, 9.8 mmol) was added to a solution of zirconocene dichloride (2.91 g, 10.3 mmol) in THF (20 mL) at 0 °C (ice bath). After stirring for 30 min at this temperature, a solution of alkyne **SI-2b** (4.00 g, 8.32 mmol) in THF (10 mL) was added over 5 min. The cooling bath was removed and stirring continued for 1 h, during which time the originally greyish suspension turned into a very dark green homogeneous solution. 2,6-Lutidine (1.3 mL, 11 mmol) was introduced and the mixture cooled to −78 °C. A solution of iodine (2.74 g, 10.8 mmol) in THF (15 mL) was added over 15 min and stirring was continued for 1 h at −78 °C. The reaction was quenched with a mixture of saturated aqueous solutions of sodium bicarbonate and sodium thiosulfate (1:1 *v*/*v*, 30 mL), the mixture was diluted with *tert*-butyl methyl ether (20 mL) and warmed to room temperature. The mixture was filtered through a short pad of Celite®, which was rinsed with *tert*-butyl methyl ether (5 × 10 mL). The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) led to the title compound as a light amber oil (3.76 g, 74% yield). $[\alpha]_D^{20}$ = +19.3 (*c* 1.2, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 7.68 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 6.46 (dd, *J* = 14.5, 9.6 Hz, 1H), 5.94 (dd, *J* = 14.5, 0.6 Hz, 1H), 3.79 – 3.68 (m, 2H), 3.54 (dd, *J* = 10.0, 6.9 Hz, 1H), 2.28 (ddt, *J* = 9.8, 6.8, 3.0 Hz, 1H),

1.47 – 1.38 (m, 2H), 1.05 (s, 9H), 0.90 (t, J = 7.9 Hz, 9H), 0.77 (t, J = 7.5 Hz, 3H), 0.61 – 0.48 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 144.3, 135.8, 135.7, 133.9, 133.8, 129.83, 129.76, 127.81, 127.79, 77.3, 72.4, 64.2, 53.3, 28.4, 27.0, 19.3, 9.95, 7.09, 5.30. IR (film): 3071, 3052, 2956, 2933, 2875, 1601, 1488, 1462, 1428, 1390, 1241, 1159, 1111, 1001, 970, 844, 824, 804, 767, 740, 616, 505, 488 cm^{-1}. HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{29}$H$_{45}$IO$_2$Si$_2$Na 631.1895; found 631.1893.

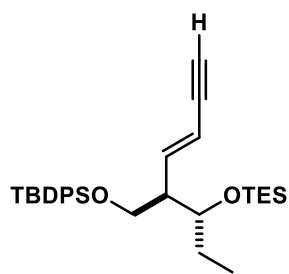(2*R*,3*R*,*E*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-(triethylsilyloxy)-oct-4-en-7-yne (58). In a 250-mL two-necked flask, *n*-BuLi (1.6 M in hexanes, 25 mL, 40 mmol) was added over 10 min to a solution of 1-(trimethylsilyl)propyne (7.8 mL, 53 mmol) in THF (100 mL) at −78 °C. The resulting pale yellowish solution was warmed to 0 °C and stirred for 1 h at this temperature. This solution was then transferred via cannula to a suspension of copper(I) iodide (7.67 g, 40.3 mmol) in THF (50 mL) at −78 °C in a 500-mL two-necked flask. After the addition, a greenish/sand-colored suspension had formed, which was stirred for additional 30 min. 4-(Dimethylamino)pyridine (4.91 g, 40.2 mmol) in THF (60 mL) was then introduced and the mixture was gradually warmed to −20 °C over 30 min, eventually leading to a clear, dark brown solution after stirring for further 20 min. At this point, a solution of alkenyl iodide **56a** (7.97 g, 13.4 mmol) in THF (40 mL) was added over 5 min. The mixture was stirred for 17 h, while being gradually warmed to room temperature. Saturated aqueous ammonium chloride solution (10 mL) was added, leading to a thick brown precipitation, which was filtered off through a glass frit (pore size 4), and the remaining solids were carefully rinsed with *tert*-butyl methyl ether (5 × 15 mL). The combined filtrates were washed with saturated aqueous ammonium chloride solution (3 × 75 mL) and the combined aqueous layers were extracted with *tert*-butyl methyl ether (3 × 30 mL). The organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) led to an amber oil (7.73 g).

Anhydrous potassium carbonate (3.70 g, 26.8 mmol) was added to a solution of this material in THF/methanol (1:1, 120 mL), and the resulting suspension was vigorously stirred for 4 h at room temperature (reaction monitoring by ^{1}H NMR). Volatile material was evaporated and the residue was dissolved in *tert*-butyl methyl ether (90 mL). Aqueous HCl (1 M, 80 mL) was carefully added at 0 °C (ice bath), the resulting aqueous phase was extracted with *tert*-butyl methyl ether (3 × 25 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) furnished the title compound as a light amber oil (5.72 g, 84% yield). $[\alpha]_D^{20}$ = +11.5 (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.70 – 7.60 (m, 4H), 7.45 – 7.33 (m, 6H), 5.68 (ddt, J = 15.4, 9.1, 1.7 Hz,

1H), 5.39 (dtd, J = 15.4, 5.6, 0.7 Hz, 1H), 4.10 (qd, J = 6.2, 3.7 Hz, 1H), 3.75 (dd, J = 10.0, 6.6 Hz, 1H), 3.58 (dd, J = 10.0, 6.2 Hz, 1H), 2.91 (ddd, J = 5.6, 2.7, 1.7 Hz, 2H), 2.14 (dtd, J = 9.8, 6.3, 3.6 Hz, 1H), 2.06 (t, J = 2.7 Hz, 1H), 1.09 (t, J = 6.3 Hz, 3H), 1.05 (s, 9H), 0.92 (t, J = 7.9 Hz, 9H), 0.63 – 0.48 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 135.80, 135.77, 134.1, 130.3, 129.66, 129.63, 127.7, 126.5, 82.2, 69.9, 67.6, 64.8, 53.0, 27.1, 22.2, 22.1, 19.4, 7.08, 5.24. **IR (film):** 3312, 3071, 3049, 2956, 2932, 2911, 2876, 2858, 1590, 1472, 1462, 1427, 1375, 1240, 1188, 1150, 1111, 1007, 972, 824, 807, 739, 702, 624, 614, 505, 489 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{31}$H$_{46}$O$_2$Si$_2$Na 529.2929; found 529.2927.

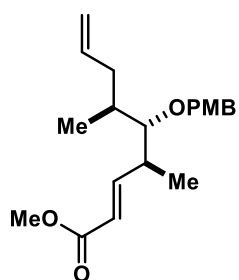**(3R,4R,E)-4-((($tert$-Butyldiphenylsilyl)oxy)methyl)-3-(triethylsilyloxy)-oct-5-en-7-yne (57).** In a 100-mL two-necked flask, bis(triphenylphosphine)palladium(II) dichloride (107 mg, 0.152 mmol) was added to a solution of alkenyl iodide **56b** (3.68 g, 6.05 mmol) in triethylamine (30 mL) at room temperature. The yellow mixture was stirred for 45 min at this temperature, before trimethylsilylacetylene (1.2 mL, 8.5 mmol) and copper(I) iodide (290 mg, 1.52 mmol) were added at 0 °C (ice bath). The originally yellow solution immediately turned into a brown suspension. After stirring for 20 min, the ice bath was removed and stirring continued for 18 h at room temperature. The mixture was diluted with $tert$-butyl methyl ether (35 mL) and filtered through filter paper, before it was washed with saturated aqueous ammonium chloride solution (2 × 25 mL). The combined aqueous phases were extracted with $tert$-butyl methyl ether (4 × 15 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 100:1) led to a yellowish oil (3.51 g).

Anhydrous potassium carbonate (1.68 g, 12.2 mmol) was added to a solution of this material in THF/methanol (1:1, 50 mL) at room temperature. Stirring was continued for 2.5 h before the mixture was concentrated under reduced pressure. The residue was dissolved in $tert$-butyl methyl ether (50 mL), the organic phase was washed with aqueous HCl (1 M, 30 mL), and the aqueous phase was extracted with $tert$-butyl methyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 100:1) furnished the title compound as a yellowish oil (2.93 g, 96% yield). $[\alpha]_D^{20}$ = +19.2 (c 1.2, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.67 – 7.62 (m, 4H), 7.45 – 7.34 (m, 6H), 6.18 (ddd, J = 16.1, 9.4, 0.6 Hz, 1H), 5.39 (ddd, J = 16.1, 2.2, 0.8 Hz, 1H), 3.82 (td, J = 6.8, 2.7 Hz, 1H), 3.75 (dd, J = 10.0, 7.1 Hz, 1H), 3.53 (dd, J = 10.0, 6.7 Hz, 1H), 2.80 (dd, J = 2.3, 0.62 Hz, 1H), 2.33 – 2.24 (m, 1H), 1.46 – 1.37 (m, 2H), 1.06 (s, 9H), 0.91 (t, J = 7.9 Hz, 9H), 0.77 (t, J = 7.5 Hz, 3H), 0.62 – 0.49 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 144.2, 135.8, 135.7, 133.9, 133.8, 129.8, 129.7, 127.77, 127.76, 111.4, 82.7, 76.1, 72.7, 64.5, 50.4, 28.5, 27.0, 19.4, 10.1, 7.10, 5.30.

IR (film): 3313, 3071, 2957, 2933, 2876, 2588, 1462, 1428, 1379, 1240, 1111, 1081, 1008, 963, 823, 738, 702, 612, 504 cm^{-1}. **HRMS-ESI m/z:** [M+H]$^+$ calcd for $C_{31}H_{47}O_2Si_2$ 507.3109; found 507.3114.
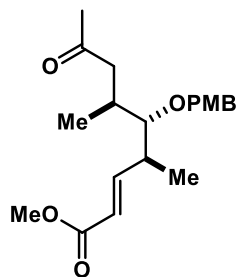
4.4 Completion of the Total Synthesis of Aldgamycin N

Methyl (4S,5S,6S,E)-5-((4-methoxybenzyl)oxy)-4,6-dimethylnona-2,8-dienoate (SI-3). In a 50-mL Schlenk tube, two drops of trifluoromethanesulfonic acid were added to a solution of alcohol **39** (1.19 g, 5.61 mmol) and 2-(4-methoxybenzyloxy)-4-methylquinoline (**63**) (3.16 g, 11.3 mmol) in dichloromethane (30 mL) at −20 °C. After 5 min, the cooling bath was removed and stirring continued for 67 h at ambient temperature. Triethylamine (0.03 mL) was added to the resulting white suspension, which was filtered through a pad Celite®, carefully rinsing with dichloromethane (5 × 15 mL). The combined filtrates were concentrated under reduced pressure and the residue was loaded onto Celite®. Purification by flash chromatography (hexanes/EtOAc, 25:1) furnished the title compound as a colorless oil (1.26 g, 68% yield). $[\alpha]_D^{20}$ = +11.3 (c 1.3, CHCl$_3$). **¹H NMR (400 MHz, CDCl₃):** δ 7.31 – 7.32 (m, 2H), 7.04 (dd, J = 15.8, 7.9 Hz, 1H), 6.90 – 6.83 (m, 2H), 5.86 (dd, J = 15.8, 1.3 Hz, 1H), 5.75 (dddd, J = 16.6, 10.3, 8.0, 6.2 Hz, 1H), 5.05 – 4.97 (m, 2H), 4.46 (s, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.17 (dd, J = 6.3, 5.0 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.43 – 2.34 (m, 1H), 1.91 (dddt, J = 13.7, 9.2, 8.0, 1.0 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.12 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 167.3, 159.3, 153.1, 137.6, 130.8, 129.5, 120.2, 116.2, 113.9, 86.4, 74.7, 55.4, 51.6, 39.5, 36.7, 36.2, 16.7, 14.2. **IR (film)** 3072, 2964, 2935, 2910, 2875, 2838, 1722, 1655, 1613, 1586, 1514, 1461, 1436, 1339, 1318, 1301, 1248, 1193, 1175, 1109, 1063, 1035, 1012, 990, 958, 913, 851, 823, 759, 731 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for $C_{20}H_{28}O_4Na$ 355.1880; found 355.1881.

Methyl (4S,5S,6S,E)-5-((4-methoxybenzyl)oxy)-4,6-dimethyl-8-oxonon-2-enoate (64). In a 100-mL two-necked flask, oxygen gas was bubbled via syringe needle through a mixture of THF and water (1:1 v/v, 40 mL) for 10 min. Copper(I) chloride (1.06 g, 10.7 mmol) and palladium(II) chloride (190 mg, 1.07 mmol) were added, followed by a solution of alkene **SI-3** (1.78 g, 5.35 mmol) in THF/water (1:1 v/v, 20 mL). The resulting greenish brown mixture was vigorously stirred under oxygen atmosphere (balloon) at room temperature. After 5 min, the mixture turned black and eventually became a green suspension, when TLC analysis (hexanes/EtOAc, 8:1) indicated full conversion of the starting material. The suspension was filtered through a pad of Celite®, which was rinsed with *tert*-butyl methyl ether (5 × 10 mL). The combined filtrates were washed with saturated aqueous ammonium chloride solution (80 mL) and the aqueous phase was extracted with *tert*-butyl methyl ether (6 × 20 mL). The

combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 7:2) furnished the title compound as a colorless oil (1.64 g, 88% yield). $[\alpha]_D^{20}$ = +12.0 (*c* 0.85, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.25 – 7.21 (m, 2H), 7.03 (dd, *J* = 15.8, 7.7 Hz, 1H), 6.90 – 6.85 (m, 2H), 5.85 (dd, *J* = 15.8, 1.4 Hz, 1H), 4.50 – 4.37 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.17 (t, *J* = 5.4 Hz, 1H), 2.68 – 2.55 (m, 2H), 2.32 – 2.19 (m, 2H), 2.06 (s, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 208.5, 167.1, 159.4, 152.3, 130.5, 129.6, 120.5, 114.0, 86.3, 74.5, 55.4, 51.7, 46.8, 39.4, 32.5, 30.4, 18.1, 14.3. **IR (film):** 2968, 2878, 2839, 1718, 1654, 1613, 1587, 1514, 1458, 1435, 1337, 1300, 1274, 1249, 1194, 1176, 1081, 1034, 992, 929, 866, 849, 821 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{20}$H$_{28}$O$_5$Na 371.1829; found 371.1832.

Addition products 65 and 8-*epi*-65. In a 100-mL two-necked flask, *n*-BuLi (1.6 M in hexanes, 4.9 mL,

7.8 mmol) was added over 10 min to a solution of alkyne **58** (4.06 g, 8.01 mmol) in THF (55 mL) at −50 °C and stirring was continued for 2 h.
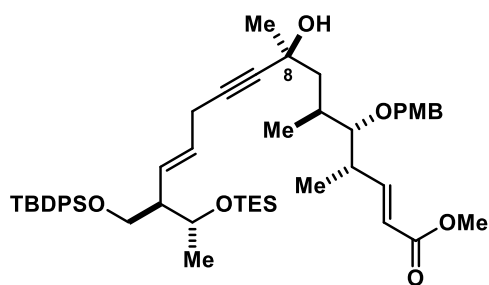
In a separate 250-mL two-necked flask, a solution of ketone **64** (1.64 g, 4.71 mmol) in THF (20 mL) was added to lanthanum(III) chloride bis(lithium chloride) complex (0.6 M in THF, 13 mL, 7.8 mmol) and the resulting mixture was stirred for 1 h at room temperature.

Both flasks were cooled to −78 °C and the solution of the lithium acetylide was transferred to the second flask containing the lanthanum chloride adduct via cannula. Stirring was continued for 1 h at this temperature before the mixture was diluted with *tert*-butyl methyl ether (50 mL) and washed with saturated aqueous ammonium chloride solution (80 mL). Both layers were carefully separated and the aqueous layer was filtered through a pad of Celite® to remove a white precipitate, which was carefully rinsed with *tert*-butyl methyl ether (5 × 15 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (5 × 25 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 20:1 → 12:1 → 6:1 → 4:1) furnished unreacted alkyne **58** (1.31 g, 2.58 mmol) and the title compound as a mixture of diastereomers (3.34 g, 83% yield, dr = 1:1).

The C8 epimers (3.34 g, 12 mL MeCN) were separated by preparative HPLC (stationary phase: Kromasil 100-5-C18, 2 × 150 mm length × 30 mm diameter, 5 μm (two columns used in series), eluent: MeCN/MeOH (95:5, v/v), 42.5 mL/min (6.5 MPa, 308 K, UV detection at 254 nm)). The desired 8-(*S*) epimer was eluted first (t_R = 22.0 min), then the undesired 8-(*R*) epimer (t_R = 24.5 min).

Analytical and spectral data of the desired epimer (8S)-65: colorless gum (1.00 g, 25% yield); $[\alpha]_D^{20}$ = +10.0 (*c* 0.62, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.69 – 7.60 (m, 4H), 7.45 – 7.32 (m, 6H), 7.27 – 7.22 (m, 2H), 7.01 (dd, *J* = 15.7, 7.9 Hz, 1H), 6.89 – 6.82 (m, 2H), 5.85 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.60 (ddt, *J* = 15.4, 9.2, 1.7 Hz, 1H), 5.36 (dt, *J* = 15.5, 5.7 Hz, 1H), 4.53 – 4.43 (m, 2H), 4.12 (qd, *J* = 6.3, 3.4 Hz, 1H), 3.78 (s, 3H), 3.76 – 3.71 (m, 4H), 3.54 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.13 (t, *J* = 5.6 Hz, 1H), 2.96 – 2.88 (m, 2H), 2.69 (s, 1H), 2.68 – 2.58 (m, 1H), 2.12 (dtd, *J* = 9.7, 6.5, 3.3 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.91 (dd, *J* = 14.4, 3.2 Hz, 1H), 1.53 (dd, *J* = 14.4, 6.9 Hz, 1H), 1.41 (s, 3H), 1.103 (d, *J* = 6.7 Hz, 3H), 1.100 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.62 – 0.49 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 159.4, 152.7, 135.77, 135.74, 134.13, 134.10, 130.3, 129.71, 129.68, 129.64, 129.5, 129.4, 127.7, 127.3, 120.4, 113.9, 87.7, 86.6, 81.1, 74.8, 67.8, 67.3, 64.9, 55.4, 53.0, 51.6, 45.8, 39.5, 33.2, 31.1, 27.1, 22.3, 22.2, 19.8, 19.4, 14.7, 7.11, 5.24. **IR (film):** 3480, 3070, 3050, 2957, 2932, 2876, 1724, 1656, 1613, 1588, 1514, 1462, 1428, 1374, 1335, 1301, 1248, 1193, 1175, 1152, 1111, 1080, 1036, 1011, 974, 824, 741, 703, 614, 567, 505, 492 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{51}$H$_{74}$O$_7$Si$_2$Na 877.4865; found 877.4857.

Analytical and spectral data of the undesired epimer (8R)-65: colorless gum (885 mg, 22% yield); $[\alpha]_D^{20}$ = +28.5 (*c* 1.3, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.67 – 7.7.61 (m, 4H), 7.44 – 7.32 (m, 6H), 7.25 – 7.21 (m, 2H), 7.09 (dd, *J* = 15.8, 7.3 Hz, 1H), 6.88 – 6.83 (m, 2H), 5.86 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.57 (ddt, *J* = 15.4, 9.1, 1.7 Hz, 1H), 5.35 (dt, *J* = 15.5, 5.5 Hz, 1H), 4.50 – 4.42 (m, 2H), 4.11 (qd, *J* = 6.3, 3.3 Hz, 1H), 3.79 (s, 3H), 3.77 – 3.72 (m, 4H), 3.55 (s, 1H), 3.53 (dd, *J* = 6.2, 10.0 Hz, 1H), 3.16 (dd, *J* = 7.3, 4.1 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.68 – 2.57 (m, 1H), 2.20 – 2.07 (m, 2H), 1.76 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.48 (dd, *J* = 14.5, 4.7 Hz, 1H), 1.41 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.63 – 0.47 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.3, 159.5, 153.3, 135.78, 135.74, 134.1, 130.0, 129.8, 129.7, 129.6, 129.3, 127.7, 127.6, 120.3, 113.9, 87.2, 86.1, 80.8, 74.4, 67.6, 67.3, 64.9, 55.4, 53.0, 51.7, 47.6, 41.5, 39.3, 33.3, 32.0, 29.2, 27.8, 27.1, 22.8, 22.4, 22.2, 20.6, 20.5, 19.6, 19.4, 14.5, 13.3, 7.11, 5.23. **IR (film):** 3435, 3071, 3051, 2956, 2932, 2876, 1724, 1655, 1613, 1588, 1514, 1462, 1428, 1373, 1321, 1301, 1249, 1176, 1151, 1111, 1078, 1036, 1011, 974, 824, 740, 703, 612, 556, 505 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{51}$H$_{74}$O$_7$Si$_2$Na 877.4865; found 877.4859.

Macrocyclization precursor 66. In a 10-mL round-bottom flask, pyridinium
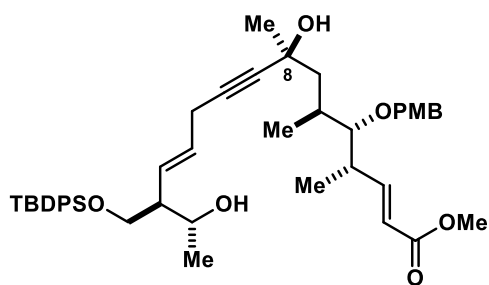
p-toluenesulfonate (18.5 mg, 73.6 µmol) was added to a solution of silyl ether **65** (523 mg, 0.612 mmol) in ethanol (10 mL) and THF (1.1 mL) at 0 °C (ice bath) and the resulting mixture was stirred at this temperature for 6.5 h. The mixture was then diluted with ethyl acetate (20 mL) and washed with half-saturated aqueous sodium bicarbonate solution (20 mL). The aqueous phase was extracted with ethyl acetate (6 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 3:1 → 2:1) furnished the title compound as a colorless gum (402 mg, 89% yield). $[\alpha]_D^{20}$ = +7.5 (*c* 0.05, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.68 – 7.62 (m, 4H), 7.47 – 7.35 (m, 6H), 7.26 – 7.22 (m, 2H), 7.01 (dd, *J* = 15.8, 7.9 Hz, 1H), 6.89 – 6.82 (m, 2H), 5.85 (dd, *J* = 15.7, 1.2 Hz, 1H), 5.71 (ddt, *J* = 15.4, 9.1, 1.7 Hz, 1H), 5.46 (dtd, *J* = 15.5, 5.5, 0.8 Hz, 1H), 4.52 – 4.44 (m, 2H), 4.07 (dtd, *J* = 10.2, 6.4, 3.9 Hz, 1H), 3.81 – 3.70 (m, 8H), 3.13 (t, *J* = 5.6 Hz, 1H), 2.98 – 2.92 (m, 2H), 2.71 (s, 1H), 2.69 – 2.59 (m, 2H), 2.24 (dq, *J* = 9.3, 4.8 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.91 (dd, *J* = 14.4, 3.3 Hz, 1H), 1.53 (dd, *J* = 14.4, 7.0 Hz, 1H), 1.42 (s, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.12 – 1.08 (m, 6H), 1.05 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 159.4, 152.7, 135.78, 135.72, 133.18, 133.13, 130.30, 129.98, 129.7, 128.5, 128.4, 127.9, 120.4, 113.9, 87.7, 86.9, 80.7, 74.8, 68.9, 67.8, 66.5, 55.4, 51.6, 50.8, 45.7, 39.5, 33.2, 31.2, 27.0, 22.4, 20.6, 19.8, 19.3, 14.7. **IR (film):** 3460, 2961, 2880, 1721, 1647, 1612, 1514, 1464, 1428, 1299, 1249, 1176, 1111, 1087, 1037, 1009, 850, 824, 740, 704, 617, 505, 490 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{45}$H$_{60}$O$_7$SiNa 763.4001; found 763.4002.

(8*R*)-Configured macrocyclization precursor 8-*epi*-66. Prepared analogously from 8-*epi*-**65** as a
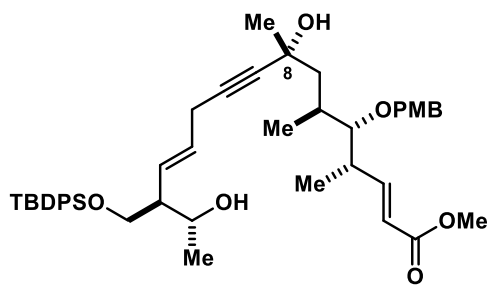
colorless gum (202 mg, 77% yield). $[\alpha]_D^{20}$ = +24.9 (*c* 0.92, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.68 – 7.62 (m, 4H), 7.47 – 7.35 (m, 6H), 7.26 – 7.20 (m, 2H), 7.09 (dd, *J* = 15.7, 7.3 Hz, 1H), 6.89 – 6.82 (m, 2H), 5.87 (dd, *J* = 15.8, 1.5 Hz, 1H), 5.69 (ddt, *J* = 15.4, 9.0, 1.7 Hz, 1H), 5.45 (dtd, *J* = 15.4, 5.5, 0.8 Hz, 1H), 4.51 – 4.42 (m, 2H), 4.07 (qd, *J* = 6.4, 3.6 Hz, 1H), 3.82 – 3.69 (m, 9H), 3.16 (dd, *J* = 7.4, 4.4 Hz, 1H), 2.98 – 2.91 (m, 2H), 2.69 – 2.57 (m, 1H), 2.29 – 2.20 (m, 1H), 2.20 – 2.09 (m, 1H), 1.76 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.49 (dd, *J* = 14.5, 4.5 Hz, 1H), 1.41 (s, 3H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.3, 159.5, 153.2, 135.8, 135.7, 133.2, 133.1, 130.03, 129.98, 129.96, 129.7, 128.6, 128.2, 127.9, 120.3, 113.9, 87.2, 86.5, 80.2, 74.5, 68.9, 67.6, 66.5, 55.4, 51.7, 50.7,

47.7, 39.2, 33.3, 32.0, 27.0, 22.4, 20.60, 20.56, 19.3, 13.2. **IR (film):** 3434, 3071, 3047, 2961, 2931, 2859, 1721, 1654, 1613, 1588, 1514, 1461, 1428, 1363, 1300, 1249, 1194, 1177, 1146, 1112, 1086, 1036, 941, 823, 742, 704, 613, 506 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{45}$H$_{60}$O$_7$SiNa 763.4001; found 730.4012.

Macrolactone 68. In a 500-mL round-bottomed flask equipped with a reflux condenser, distannoxane **67a** (457 mg, 0.410 mmol) was added to a solution of hydroxy ester **66** (402 mg, 0.543 mmol) in toluene (300 mL) and the resulting solution was stirred at reflux temperature for 5 d. After reaching room temperature, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (15 – 40 μm, hexanes/EtOAc, 5:1 → 4:1) to furnish the title compound as a pale yel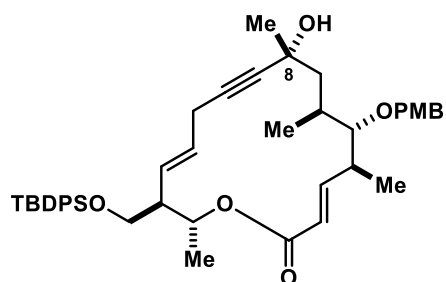lowish gum (260 mg, 68% yield). [α]$_D^{20}$ = +62.7 (*c* 0.07, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.66 – 7.59 (m, 4H), 7.45 – 7.33 (m, 6H), 7.30 – 7.25 (m, 2H), 6.90 – 6.85 (m, 2H), 6.76 (dd, *J* = 15.6, 9.5 Hz, 1H), 5.75 (dd, *J* = 15.7, 0.8 Hz, 1H), 5.58 (dd, *J* = 15.3, 9.4 Hz, 1H), 5.39 (ddd, *J* = 15.2, 7.8, 4.1 Hz, 1H), 5.23 (dq, *J* = 7.7, 6.3 Hz, 1H), 4.61 (d, *J* = 10.6 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 3.80 (s, 3H), 3.70 – 3.59 (m, 2H), 3.10 (dd, *J* = 9.8, 1.9 Hz, 1H), 2.93 (ddd, *J* = 18.2, 4.1, 1.9 Hz, 1H), 2.83 (ddd, *J* = 18.3, 7.9, 1.2 Hz, 1H), 2.58 (tdd, *J* = 9.6, 6.4, 3.1 Hz, 1H), 2.29 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 1.74 (dd, *J* = 14.5, 2.8 Hz, 1H), 1.69 (s, 1H), 1.59 (dd, *J* = 14.5, 10.5 Hz, 1H), 1.49 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.1, 159.4, 150.5, 135.8, 133.61, 133.56, 130.9, 129.9, 129.8, 129.7, 129.6, 127.9, 127.83, 127.81, 121.4, 114.0, 89.1, 81.9, 75.4, 69.5, 68.9, 64.4, 55.4, 52.0, 42.6, 40.8, 34.2, 33.1, 27.0, 22.6, 19.7, 19.4, 18.8, 18.1. **IR (film):** 3496, 3071, 3048, 2959, 2930, 2858, 1715, 1654, 1613, 1587, 1514, 1462, 1428, 1361, 1327, 1302, 1248, 1180, 1111, 1083, 1036, 986, 823, 741, 703, 610, 504 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{44}$H$_{56}$O$_6$SiNa 731.3738; found 731.3743.

(8*R*)-Configured macrolactone 8-*epi*-68. Prepared analogously from 8-*epi*-**66** as a colorless gum (113 mg, 69% yield). [α]$_D^{20}$ = +12.6 (*c* 1.2, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.65 – 7.60 (m, 4H), 7.44 – 7.32 (m, 6H), 7.29 – 7.25 (m, 2H), 6.98 (dd, *J* = 16.0, 6.8 Hz, 1H), 6.91 – 6.86 (m, 2H), 5.80 (dd, *J* = 15.9, 1.5 Hz, 1H), 5.66 (ddt, *J* = 15.4, 9.2, 1.7 Hz, 1H), 5.46 (ddd, 15.3, 6.3, 4.0 Hz, 1H), 5.28 (quint, *J* = 6.2 Hz, 1H), 4.59 – 4.48 (m, 2H), 3.80 (s, 3H), 3.70 (br s, 1H), 3.64 – 3.52 (m, 2H), 3.02 – 2.92 (m, 2H), 2.87 – 2.73 (m, 2H), 2.37 – 2.28 (m, 1H),

2.27 – 2.17 (m, 1H), 1.70 (dd, J = 14.4, 4.6 Hz, 1H), 1.53 (dd, J = 14.4, 5.4 Hz, 1H), 1.44 (s, 3H), 1.24 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.04 (s, 9H), 0.90 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 165.9, 159.6, 149.3, 135.80, 135.76, 133.7, 133.6, 130.1, 129.78, 129.75, 129.6, 128.5, 128.2, 127.79, 127.77, 122.0, 114.0, 87.9, 80.9, 72.6, 69.6, 68.2, 64.6, 55.4, 51.3, 48.3, 38.7, 33.8, 31.1, 27.0, 22.4, 19.8, 19.4, 19.0, 17.9. IR (film): 3406, 3071, 3046, 2959, 2931, 2858, 1714, 1655, 1612, 1587, 1514, 1462, 1428, 1363, 1302, 1249, 1180, 1111, 1086, 1037, 986, 823, 742, 704, 610, 504 cm^{-1}. HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{44}$H$_{56}$O$_6$SiNa 731.3738; found 731.3747.

The configuration at C8 was tentatively assigned at this point by comparison of the ^{1}H NMR signals at the C5 position for both epimers to the reported literature value of natural aldgamycin N (3.38 ppm, br d, 9.0 Hz).[40f] Whereas **68** exhibits for H5 a doublet of doublet with a similarly large coupling (3.10 ppm, J = 9.8, 1.9 Hz) as in the natural product, 8-*epi*-**65** exhibits for H5 a broad triplet (2.99 ppm, br t, J ~ 6 Hz). This assigment is confirmed by synthesis of the natural product aldgamycin N from **68**.

Chan-Lam-type oxygenative coupling of the model alkenylstannane 76

2-Hydroxy-2-methyl-6-phenylhexan-3-one (78). In a 10-mL Schlenk tube, 4-(dimethylamino)pyridine (3.4 mg, 28 μmol) and copper(II) trifluoroacetate monohydrate (93.0 mg, 321 μmol) were added to a solution of alkenylstannane **76**[91] (74.1 mg, 155 μmol) in DMSO (1.2 mL) at room temperature to give a light green, homogeneous solution. The mixture was stirred at this temperature for 30 min before it was diluted with *tert*-butyl methyl ether (10 mL) and washed with saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (4 × 5 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes, then hexanes/EtOAc, 20:1 → 10:1) to give the title compound as a light yellowish liquid (26.1 mg, 82% yield). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32 – 7.26 (m, 2H), 7.23 – 7.15 (m, 3H), 2.67 – 2.61 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.02 – 1.92 (m, 2H), 1.35 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 214.4, 141.4, 128.6, 128.6, 126.2, 76.3, 35.1, 34.7, 26.7, 25.2. IR (film): 3478, 3062, 3027, 2973, 2931, 2870, 1707, 1603, 1497, 1455, 1403, 1362, 1176, 1086, 10743, 1029, 967, 746, 700 cm^{-1}. HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{13}$H$_{18}$O$_2$Na 229.1199; found 229.1199.
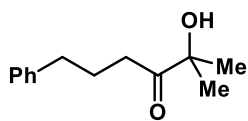
The side products **79**[164], **80**[165] and **81**[166] described in table 2.2 were isolated in the corresponding reactions following analogous procedures and identified by comparison to analytical data reported in the literature.

Attempted Liberation of the Aldgamycin N Aglycon.

Alkenylstannane 69. In a 10-mL Schlenk tube, a solution of [Cp*RuCl]$_4$ in dichloromethane (75 mg/mL, 0.20 mL, 14 µmol) was added to propargylic alcohol **68** (81.9 mg, 116 µmol) at room temperature, which caused the very dark green color of the catalyst solution to turn dark brown. A solution of tributyltin hydride in dichloromethane (0.35 M, 0.38 mL, 0.13 mmol) was then added over 1.5 h at room temperature. After complete addition, the dark red/brown solution was stirred for further 20 min before it was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes, then hexanes/EtOAc, 10:1) to furnish the title compound as a colorless gum (83.0 mg, 72% yield).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.67 – 7.61 (m, 4H), 7.45 – 7.32 (m, 6H), 7.30 – 7.25 (m, 2H), 6.90 – 6.85 (m, 2H), 6.73 (dd, J = 15.6, 9.5 Hz, 1H), 5.78 (dd, J = 15.6, 0.8 Hz, 1H), 5.71 (t, J = 6.8 Hz, 1H), 5.49 – 5.33 (m, 2H), 5.26 (quint, J = 6.3 Hz, 1H), 4.61 – 4.45 (m, 2H), 3.80 (s, 3H), 3.69 – 3.57 (m, 2H), 3.08 (dd, J = 9.5, 2.4 Hz, 1H), 2.78 – 2.53 (m, 3H), 2.29 – 2.20 (m, 1H), 2.07 – 1.95 (m, 1H), 1.83 – 1.73 (m, 1H), 1.50 – 1.38 (m, 7H), 1.32 – 1.24 (m, 6H), 1.24 – 1.20 (m, 6H), 1.12 (d, J = 6.7 Hz, 3H), 1.07 – 1.03 (m, 12H), 0.93 – 0.82 (m, 15H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.0, 150.6, 135.8, 135.6, 132.4, 131.0, 129.8, 129.7, 129.6, 127.80, 127.78, 121.5, 113.9, 88.4, 78.4, 74.2, 69.6, 64.4, 55.4, 52.6, 40.6, 36.0, 32.6, 29.4, 27.6, 27.0, 22.8, 19.4, 18.9, 18.7, 18.1, 13.9, 12.6. **IR (film):** 3499, 2956, 2928, 2870, 2857, 1717, 1700, 1652, 1613, 1513, 1462, 1428, 1375, 1248, 1173, 1111, 1071, 1039, 981, 940, 863, 824, 740, 702, 614, 505 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{56}$H$_{84}$O$_6$SiSnNa 1023.4962; found 1023.4962.

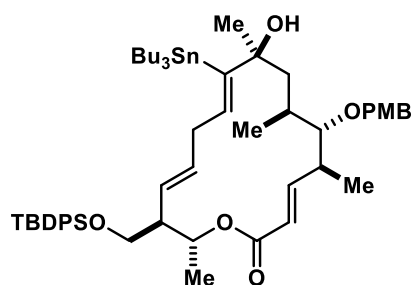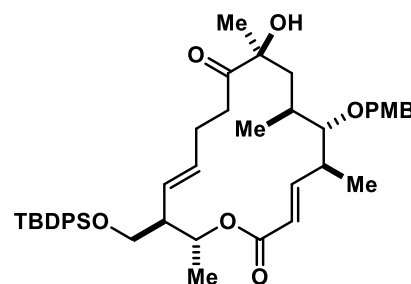**Acyloin 70.** In a 10-mL Schlenk tube, 4-(dimethylamino)pyridine (4.1 mg, 34 µmol) and copper(II) trifluoroacetate monohydrate (46.3 mg, 0.150 mmol) were added to a solution of alkenylstannane **69** (82.0 mg, 82.0 µmol) in DMSO (0.66 mL) at room temperature to give a green, homogeneous solution. The flask was immersed into a preheated oil bath at 45 – 50 °C and the mixture stirred at this temperature for 2 h. During this time, the color of the mixture became very dark green; eventually a fine, dark suspension was obtained. At this point, the mixture was diluted with *tert*-butyl methyl ether (10 mL) and washed with saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (5 × 10 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 8:1 → 4:1) to give the title compound as a colorless gum (49.5 mg, 83% yield). $[\alpha]_D^{20}$ = +18.6 (*c* 0.87, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):**

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stirred for 21 h at room temperature before it was diluted with ethyl acetate (10 mL) and carefully poured onto saturated aqueous sodium bicarbonate solution (10 mL). Both layers were separated and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (dichloromethane/methanol, 100:1 → 40:1). A fraction of macrodiolide **72** (5.4 mg, 20% yield) was eluted first, then a fraction containing a complex mixture of ketone **SI-5a** and hemiketals **SI-5b** (15.0 mg, ca. 56% yield), admixed with small amounts of unidentified impurities.

Analytical and spectral data of macrodiolide 72: colorless gum; $[\alpha]_D^{20} = -110.8$ (*c* 0.13, CHCl$_3$). **^{1}H NMR (600 MHz, CDCl$_3$):** δ 6.79 (dd, *J* = 16.0, 4.3 Hz, 1H), 5.75 (dd, 16.0, 2.0 Hz, 1H), 5.55 (dtd, *J* = 15.8, 6.9, 1.0 Hz, 1H), 5.42 (ddt, *J* = 15.8, 7.7, 1.2 Hz, 1H), 5.01 (dq, *J* = 7.5, 6.4 Hz, 1H), 4.94 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.60 (t, *J* = 6.2 Hz, 1H), 2.72 – 2.66 (m, 1H), 2.51 – 2.34 (m, 5H), 2.31 – 2.18 (m, 2H), 2.17 – 2.10 (m, 1H), 2.11 (s, 3H), 1.68 (t, *J* = 6.2 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 207.7, 173.0, 165.8, 150.7, 132.5, 128.9, 122.1, 78.4, 69.4, 62.6, 51.1, 47.6, 36.4, 34.2, 30.7, 30.6, 27.0, 19.0, 16.4, 10.2. **IR (film):** 3489, 2974, 2940, 2884, 1710, 1642, 1457, 1417, 1360, 1273, 1196, 1166, 1103, 1051, 977, 914, 866, 732 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{20}$H$_{30}$O$_6$Na 389.1935; found 389.1934.

Completion of the Total Synthesis of Aldgamycin N by Early-Stage Glycosylation

Protected Macrolactone SI-6. In a 10-mL Schlenk tube, triethylsilyl trifluoromethanesulfonate

(0.10 mL, 0.44 mmol) was added to a solution of propargylic alcohol **68** (222 mg, 0.313 mmol) and 2,6-lutidine (73 µL, 0.63 mmol) in dichloromethane (3.1 mL) at −25 °C. After 1 h, the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution (2 mL) at −25 °C. The mixture was warmed to room temperature, diluted with *tert*-butyl methyl

ether (20 mL) and washed with saturated aqueous sodium bicarbonate solution (15 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (4 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 15:1) furnished the title compound as a colorless gum (235 mg, 91% yield) $[\alpha]_D^{20} = +32.8$ (*c* 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.67 – 7.60 (m, 4H), 7.45 – 7.33 (m, 6H), 7.30 – 7.26 (m, 2H), 6.90 – 6.85 (m, 2H), 6.72 (dd, *J* = 15.7, 9.5 Hz, 1H), 5.79 – 5.65 (m, 1H), 5.74 (dd, *J* = 15.7, 0.8 Hz, 1H), 5.49 – 5.39 (m, 1H), 5.22 (quint, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 10.6 Hz, 1H), 4.44 (d, *J* = 10.6 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 10.2,
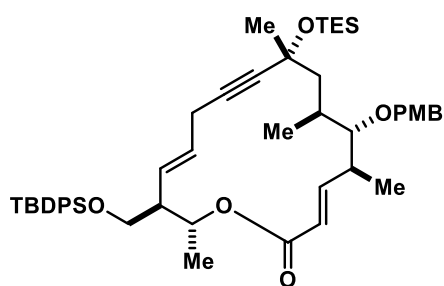
6.6 Hz, 1H), 3.59 (dd, $J = 10.2$, 5.5 Hz, 1H), 3.10 (dd, $J = 9.7$, 2.1 Hz, 1H), 2.97 – 2.79 (m, 2H), 2.56 (tq, $J = 9.6$, 6.7 Hz, 1H), 2.37 – 2.14 (m, 2H), 1.77 (br d, $J = 14.1$ Hz, 1H), 1.54 (dd, $J = 14.2$, 9.1 Hz, 1H), 1.44 (s, 3H), 1.23 (d, $J = 6.3$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 6.1$ Hz, 3H), 1.04 (s, 9H), 0.94 (t, $J = 7.9$ Hz, 9H), 0.72 – 0.56 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.1, 159.3, 150.3, 135.76, 135.74, 133.7, 133.6, 131.2, 129.81, 129.78, 129.4, 128.0, 127.8, 121.5, 113.9, 89.1, 89.0, 81.2, 69.8, 69.5, 64.3, 55.5, 51.5, 40.5, 27.0, 22.3, 19.4, 18.8, 18.5, 7.28, 6.37. **IR (film):** 3071, 3045, 2956, 2932, 2874, 1816, 1717, 1655, 1613, 1588, 1514, 1461, 1428, 1370, 1302, 1249, 1199, 1163, 1111, 1081, 1040, 1001, 986, 823, 785, 741, 703, 613, 505, 488, 431 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{50}$H$_{70}$O$_6$Si$_2$Na 845.4603; found 845.4608.

Glycosyl acceptor 169. In a 10-mL round-bottomed flask, DDQ (129 mg, 0.568 mmol) was added in one portion to a vigorously stirred solution of PMB ether **SI-6** (235 mg, 0.286 mmol) in dichloromethane (4.0 mL) and water (1.0 mL) at 0 °C (ice bath). After stirring for 1 h, the reaction mixture, which had turned from very dark green to brown, was diluted with *tert*-butyl methyl ether (20 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL, then 10 mL). The combined aqueous phases were extracted with *tert*-butyl methyl ether (4 × 10 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash (hexanes/EtOAc, 15:1 → 9:1) furnished the title compound as a colorless gum (173 mg, 86% yield). $[\alpha]_D^{20}$ = +45.0 (c 0.78, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.67 – 7.59 (m, 4H), 7.46 – 7.34 (m, 6H), 6.77 (dd, $J = 15.7$, 9.3 Hz, 1H), 5.76 (dd, $J = 15.7$ Hz, 0.8 Hz, 1H), 5.57 (dd, $J = 15.4$, 9.2 Hz, 1H), 5.38 (ddd, $J = 15.3$, 8.0, 4.1 Hz, 1H), 5.23 (dq, $J = 8.0$, 6.3 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.30 – 3.23 (m, 1H), 2.97 – 2.78 (m, 2H), 2.53 – 2.41 (m, 1H), 2.24 (tt, $J = 9.4$, 5.2 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.59 (dd, $J = 13.8$, 2.7 Hz, 1H), 1.51 – 1.43 (m, 4H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.05 (s, 9H), 0.94 (t, $J = 7.9$ Hz, 9H), 0.71 – 0.55 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.0, 150.2, 135.8, 133.62, 133.56, 129.85, 129.81, 129.76, 127.89, 127.83, 127.80, 121.5, 81.9, 81.5, 69.9, 69.4, 64.3, 52.0, 40.6, 34.4, 27.0, 22.6, 19.4, 18.9, 18.9, 18.0, 7.24, 6.36. **IR (film):** 3473, 3070, 3050, 2956, 2932, 2875, 1717, 1655, 1460, 1428, 1362, 1271, 1231, 1163, 1112, 1062, 1005, 985, 878, 824, 740, 703, 606, 505, 435, 420 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{42}$H$_{62}$O$_5$Si$_2$Na 725.4028; found 725.4034.

Propargylic alcohol 174. In a 25-mL Schlenk tube, a solution of triethylsilyl trifluoromethanesulfonate in dichloromethane (0.088 M, 0.29 mL, 0.026 mmol) was added to a solution of alcohol **169** (121 mg, 0.172 mmol) and trichloroacetimidate **122g** (91.4 mg, 0.226 mmol) in dichloromethane (6.9 mL) at −78 °C. The resulting mixture was stirred for 5 h at −78 °C before the reaction was quenched by the addition of triethylamine (0.10 mL) at this temperature Saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (5 mL) were added and it was warmed to room temperature while stirring. It was washed with saturated aqueous sodium bicarbonate solution (15 mL) and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure to give a pale yellowish oil (256 mg).
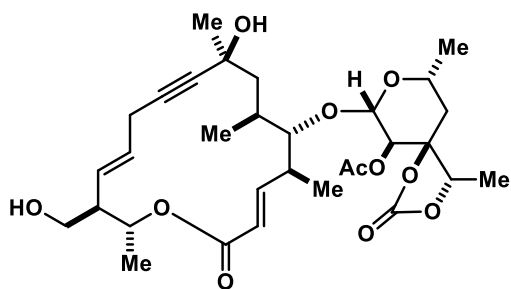
In a 25-mL Schlenk tube, TASF (0.51 M solution in DMF, 2.1 mL, 1.1 mmol) was added to a solution of this crude material in anhydrous DMF (5.8 mL) at 0 °C (ice bath). After stirring for 1 h at this temperature, water (35 μL, 1.9 mmol) was added and stirring continued at room temperature for 15 h. mixture was diluted ethyl acetate (30 mL) and washed with half-saturated aqueous sodium bicarbonate solution (50 mL) and brine (2 × 10 mL). The combined aqueous phases were extracted with ethyl acetate (5 × 15 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Remaining DMF was removed by co-evaporation with toluene (4 × 3 mL, 38 °C, 20 mbar) to give a thick, amber gum. Purification of the residue by flash chromatography (hexanes/EtOAc, 1:1 → 2:3) furnished the title compound as a thick, colorless gum (53.5 mg, 53% yield). $[\alpha]_D^{20} = +14.3$ (c 1.6, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.93 (dd, J = 15.8, 7.3 Hz, 1H), 5.77 (dd, J = 15.8, 1.4 Hz, 1H), 5.72 – 5.49 (m, 2H), 5.18 (qd, J = 6.4, 4.7 Hz, 1H), 4.95 (d, J = 7.8 Hz, 1H), 4.70 (d, J = 7.8 Hz, 1H), 4.38 (q, J = 6.7 Hz, 1H), 3.92 (dqd, J = 12.4, 6.1, 2.0 Hz, 1H), 3.55 – 3.42 (m, 2H), 3.38 – 3.27 (m, 1H), 3.06 – 2.89 (m, 2H), 2.62 – 2.48 (m, 1H), 2.37 (qd, J = 7.2, 4.6 Hz, 1H), 2.23 – 2.10 (m, 1H), 2.08 (s, 3H), 1.96 – 1.85 (m, 1H), 1.89 (dd, J = 14.3, 2.2 Hz, 1H), 1.63 (dd, J = 14.3, 11.3 Hz, 1H), 1.55 – 1.48 (m, 1H), 1.48 (m, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 168.9, 166.2, 153.7, 150.0, 129.1, 127.7, 121.2, 99.9 (br), 87.8, 85.5, 81.6 (br), 81.4, 81.1 (br), 70.3, 69.0, 68.75 (br), 68.66, 66.9, 63.0, 62.8, 51.3, 41.3, 39.6, 34.3, 22.3, 21.1, 20.6, 18.9, 18.0 (br), 16.6, 13.3. **IR (film):** 3481, 2976, 2933, 2881, 1804, 1754, 1707, 1656, 1452, 1378, 1328, 1278, 1229, 1197, 1157, 1116, 1087, 1069, 1051, 1010, 982, 914, 865, 826, 754, 687, 666, 618, 554, 513 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{31}$H$_{44}$O$_{11}$Na 615.2776; found 615.2775.

Alkenylstannane 175. In a 10-mL Schlenk tube, a solution of [Cp*RuCl]₄ in dichloromethane (30 mg/mL, 0.43 mL, 12 μmol) was added to propargylic alcohol **174** (69.8 mg, 118 μmol) at room temperature, which caused the very dark green color of the catalyst solution to turn dark brown. A solution of tributyltin hydride in dichloromethane (0.28 M, 0.47 mL, 0.13 mmol) was then added over 45 min at room temperature. After complete addition, the dark red/brown solution was stirred for further 10 min and then loaded directly onto silica gel (packed with hexanes/EtOAc, 4:1), eluting with hexanes (50 mL), then hexanes/EtOAc (4:1 → 3:1 → 2:1) to give the title compound as a slightly beige, amorphous solid (64.8 mg, 62% yield). **mp** = 140 – 143 °C. $[\alpha]_D^{20}$ = −46.9 (c 1.6, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 6.94 (dd, J = 15.9, 5.8 Hz, 1H), 5.89 (dd, J = 8.9, 5.8 Hz, 1H), 5.78 (dd, J = 15.9, 1.8 Hz, 1H), 5.78 – 5.69 (m, 1H), 5.37 – 5.27 (m, 1H), 5.25 (qd, J = 6.4, 2.3 Hz, 1H), 4.99 (d, J = 7.8 Hz, 1H), 4.72 (d, J = 7.8 Hz, 1H), 4.39 (q, J = 6.8 Hz, 1H), 3.95 (dqd, J = 12.5, 6.1, 2.0 Hz, 1H), 3.42 – 3.33 (m, 1H), 3.33 – 3.24 (m, 1H), 3.19 (dd, J = 9.0, 2.8 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.71 – 2.60 (m, 2H), 2.60 – 2.50 (m, 1H), 2.36 (tdd. J = 9.3, 6.6, 2.4 Hz, 1H), 2.11 (s, 3H), 2.10 – 2.01 (m, 1H), 1.92 (dd, J = 14.4, 2.1 Hz, 1H), 1.80 – 1.71 (m, 1H), 1.67 (dd, J = 14.4, 11.2 Hz, 1H), 1.49 – 1.40 (m, 6H), 1.40 – 1.34 (m, 5H), 1.33 – 1.22 (m, 20H), 1.10 (d, J = 6.6 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 7.3 Hz, 9H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 169.0, 166.4, 153.5, 149.1, 134.41 (br), 134.36, 126.2, 121.1, 100.9 (br), 88.5, 85.2, 81.3, 78.4, 70.2, 68.9, 67.3, 63.1, 51.4, 41.3, 38.5, 35.2 (br), 34.6 (br), 29.4, 28.0, 27.7, 21.1, 20.5, 19.0, 17.1, 15.7, 13.9, 13.3, 12.9. **¹¹⁹Sn{¹H} NMR (149 MHz, CDCl₃):** δ −58.7. **IR (film):** 3513, 2956, 2924, 2872, 2853, 1810, 1757, 1703, 1638, 1458, 1416, 1376, 1331, 1279, 1228, 1196, 1158, 1145, 1117, 1087, 1069, 1052, 1007, 983, 939, 914, 866, 771, 757, 688, 666, 628, 596, 533, 504 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C₄₃H₇₂O₁₁SnNa 907.3989; found 907.3997.

Acyloin 177. In a 10-mL Schlenk tube, 2,6-di-*tert*-butylpyridine (39 μL, 0.17 mmol) and copper(II) trifluoroacetate monohydrate (43.0 mg, 0.15 mmol) were added to a solution of alkenylstannane **175** (64.4 mg, 72.9 μmol) in anhydrous DMSO (0.97 mL, previously degassed with a stream of argon) at room temperature to give a green, homogeneous solution. The flask was immersed into a preheated oil bath at 48 °C, and the mixture stirred for 50 min. During this time, the color of the originally green solution slowly faded to become turbid yellow; eventually, a fine, amber suspension was obtained. At this point, the mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous ammonium chloride solution (2 × 10 mL). The combined aqueous phases were extracted
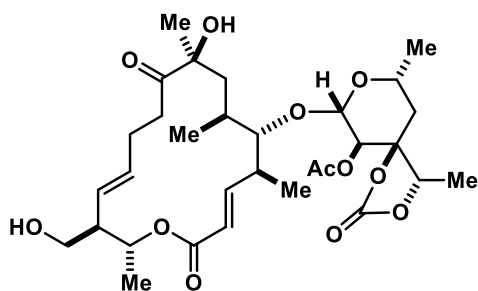
with ethyl acetate (5 × 10 mL) and the organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Most of the remaining DMSO was removed by co-evaporation with toluene (2 × 3 mL, 38 °C, 20 mbar), followed by drying of the residue under high vacuum (10^{-3} mbar, 1 h) to leave a thick, amber gum. The residue was purified by flash column chromatography (hexanes/EtOAc, 3:2 → 1:2) to give allene **SI-7** (8.9 mg, 21% yield) and hydroxy ketone **177**, still containing small amounts of stannoxane byproducts and DMSO. A second chromatographic purification of the latter sample with dichloromethane/methanol (60:1) as eluent completely removed remaining these impurities and furnished the title compound as a colorless foam (27.3 mg, 61% yield). $[\alpha]_D^{20} = -21.1$ (c 0.37, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 6.77 (dd, J = 15.8, 7.9 Hz, 1H), 5.75 (dd, J = 15.8, 1.2 Hz, 1H), 5.53 (ddd, J = 15.4, 8.8, 4.5 Hz, 1H), 5.29 (dd, J = 15.5, 9.3 Hz, 1H), 5.10 (dq, J = 8.0, 6.3 Hz, 1H), 4.94 (d, J = 7.7 Hz, 1H), 4.67 (d, J = 7.7 Hz, 1H), 4.39 (q, J = 6.8 Hz, 1H), 3.91 (dqd, J = 12.1, 5.9, 2.0 Hz, 1H), 3.70 (s, 1H), 3.60 – 3.42 (m, 2H), 3.27 (d, J = 8.1, 2.5 Hz, 1H), 2.72 – 2.48 (m, 2H), 2.45 – 2.25 (m, 3H), 2.25 – 2.15 (m, 1H), 2.09 (s, 3H), 1.90 (dd, J = 14.3, 2.2 Hz, 1H), 1.88 – 1.75 (m, 2H), 1.72 – 1.65 (m, 1H), 1.63 (dd, J = 14.3, 11.2 Hz, 1H), 1.39 – 1.34 (m, 1H), 1.37 (d, J = 6.8 Hz, 3H), 1.31 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 212.9, 168.9, 165.7, 153.7, 150.0, 133.6, 128.6 (br), 121.3, 99.4 (br), 87.5, 85.5, 81.3, 79.0, 70.4, 69.2, 66.9, 62.8, 52.6, 41.3, 40.2, 38.2 (br), 35.9, 33.3, 28.2, 26.1, 21.1, 20.5, 18.96, 18.88 (br), 17.2, 13.3. **IR (film):** 3488, 2971, 2932, 2881, 1807, 1754, 1707, 1652, 1597, 1456, 1379, 1328, 1281, 1229, 1196, 1157, 1143, 1115, 1088, 1070, 1052, 1008, 982, 957, 914, 868, 827, 755, 687, 667, 616, 561, 547 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C₃₁H₄₆O₁₂Na 633.2881; found 633.2880.

Analytical Data of the allene side product (SI-7): $[\alpha]_D^{20} = +72.3$ (c 0.57, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 6.78 (dd, J = 15.7, 8.7 Hz, 1H), 5.73 (dd, J = 15.7, 1.1 Hz, 1H), 5.64 (dt, J = 15.6, 5.7 Hz, 1H), 5.31 (ddt, J = 15.6, 9.0, 1.7 Hz, 1H), 5.14 – 5.03 (m, 2H), 4.95 (d, J = 7.8 Hz, 1H), 4.71 (d, J = 7.8 Hz, 1H), 4.38 (q, J = 6.8 Hz, 1H), 3.92 (dqd, J = 12.3, 6.2, 2.1 Hz, 1H), 3.60 – 3.43 (m, 2H), 3.29 (dd, J = 7.7, 3.1 Hz, 1H), 2.73 – 2.67 (m, 2H), 2.60 – 2.49 (m, 1H), 2.38 – 2.29 (m, 1H), 2.23 – 2.15 (m, 1H), 2.08 (s, 3H), 1.90 (dd, J = 14.3, 2.2 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.66 (d, J = 2.9 Hz, 3H), 1.64 (dd, J = 14.3, 11.3 Hz, 1H), 1.56 – 1.46 (m, 1H), 1.37 (d, J = 6.8 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 201.3, 169.0, 165.9, 153.7, 149.9, 133.5, 127.5, 121.4, 100.1, 99.3 (br), 89.2 (br), 87.2, 85.6, 81.4, 70.5, 69.2, 66.9, 63.0, 51.9, 41.4, 40.8, 35.1 (br), 34.8, 32.2, 21.1, 20.6, 20.4 (br), 18.9, 17.4, 16.4 (br), 13.3. **IR (film):** 3500, 2973, 2930, 1809, 1756, 1712, 1654, 1457, 1378,
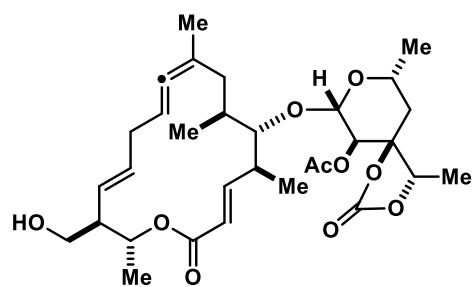
1281, 1229, 1196, 1157, 1143, 1088, 1070, 1052, 1010, 914, 772, 733, 687, 619 cm^{-1}. **HRMS-ESI m/z:** [M+H]$^+$ calcd for C$_{31}$H$_{45}$O$_{10}$ 577.3007; found 577.3009.

Glycosylated macrolide 178. In a 10-mL Schlenk tube with cooling jacket, a solution of alcohol **177** (25.2 mg, 41.3 μmol) and trichloroacetimidate **21c** (34 mg, 90 mmol) in dichloromethane/acetonitrile (1:1, 1.40 mL) was cooled to −40 °C before a solution of triethylsilyl trifluoromethanesulfonate in dichloromethane (0.088 M, 0.11 mL, 9.7 μmol) was added. After 1.5 h, a second batch of the same triethylsilyl trifluoromethanesulfonate solution (0.10 mL, 8.8 μmol) was introduced and stirring was continued for another 4.5 h. The reaction was quenched by the addition of triethylamine (58 μL, 0.42 mmol) at −40 °C. Saturated aqueous sodium bicarbonate solution (1 mL) and ethyl acetate (3 mL) were added. The mixture was warmed to room temperature and washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/acetone, 4:1 → 3:1) furnished the title compound as a colorless wax (17.1 mg, 50% yield; for analytical purposes, the sample was re-chromatographed with dichloromethane/methanol (90:1) to remove trace impurities: 14.8 mg, 43% yield). A second fraction contained the corresponding α-anomer (9.1 mg, 27% yield).
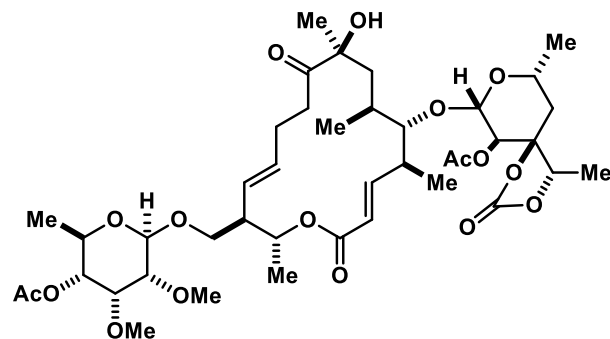
*Analytical and spectral data of the β-anomer **178***: $[\alpha]_D^{20}$ = −9.7 (*c* 0.72, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.68 (dd, *J* = 15.6, 9.4 Hz, 1H), 5.75 (dd, *J* = 15.6, 0.9 Hz, 1H), 5.45 – 5.29 (m, 2H), 5.08 (dq, *J* = 9.2, 6.3 Hz, 1H), 4.94 (d, *J* = 7.7 Hz, 1H), 4.67 (d, *J* = 7.7 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.44 (dd, *J* = 9.9, 2.6 Hz, 1H), 4.38 (q, *J* = 6.8 Hz, 1H), 3.97 – 3.85 (m, 4H), 3.68 (br s, 1H), 3.53 – 3.51 (m, 6H), 3.46 (dd, *J* = 9.5, 6.3 Hz, 1H), 3.26 (br d, *J* = 9.2 Hz, 1H), 3.05 (dd, *J* = 8.0, 2.9 Hz, 1H), 2.70 – 2.48 (m, 2H), 2.40 – 2.13 (m, 4H), 2.12 – 2.09 (m, 6H), 1.89 (dd, *J* = 14.3, 2.2 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.62 (dd, *J* = 14.4, 11.2 Hz, 1H), 1.56 – 1.43 (br m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.32 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 212.8, 170.3, 168.9, 165.5, 153.7, 150.1, 132.0, 129.9 (br), 121.7, 101.2, 99.7, 87.7, 85.6, 81.4, 80.7, 79.0, 78.0, 74.9, 70.5, 70.2, 70.0, 67.4, 66.8, 61.7, 59.8, 50.8 (br), 41.3, 40.8, 37.6 (br), 36.6 (br), 33.5, 28.3 (br), 26.1, 21.1 (2C), 20.5, 19.2 (br), 19.1, 18.1, 17.5, 13.3. **IR (film):** 3469, 2927, 2854, 1808, 1740, 1711, 1652, 1455, 1376, 1230, 1196, 1157, 1142, 1086,

1069, 1047, 1008, 963, 914, 868, 803, 754, 687, 666, 614, 549, 509 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{41}$H$_{62}$O$_{17}$Na 849.3879; found 849.3882.

Analytical and spectral data of the α-anomer: $[\alpha]_D^{20} = +20.5$ (*c* 0.60, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.69 (dd, *J* = 15.6, 9.4 Hz, 1H), 5.76 (dd, *J* = 15.6, 0.8 Hz, 1H), 5.50 – 5.30 (m, 2H), 5.12 (dq, *J* = 9.1, 6.2 Hz, 1H), 4.95 (d, *J* = 7.7 Hz, 1H), 4.83 (d, *J* = 4.1 Hz, 1H), 4.67 (d, *J* = 7.7 Hz, 1H), 4.47 (dd, *J* = 10.0, 2.7 Hz, 1H), 4.38 (q, *J* = 6.7 Hz, 1H), 4.20 (dq, *J* = 9.9, 6.3 Hz, 1H), 3.95 (t, *J* = 2.8 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.77 – 3.66 (m, 2H), 3.52 (s, 3H), 3.48 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.42 (s, 3H), 3.31 (dd, *J* = 4.1, 2.9 Hz, 1H), 3.25 (br d, *J* = 9.9 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.61 – 2.49 (m, 1H), 2.48 – 2.38 (m, 1H), 2.37 – 2.14 (m, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 1.89 (dd, *J* = 14.4, 2.1 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.62 (dd, *J* = 14.3, 11.3 Hz, 1H), 1.54 – 1.44 (m, 1H), 1.38 (d, *J* = 6.7 Hz, 3H), 1.33 (s, 3H), 1.32 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 213.0, 170.5, 168.9, 165.5, 153.7, 150.0, 131.9, 129.9 (br), 121.8, 99.8, 97.1, 87.8, 85.6, 81.4, 79.1, 78.8, 75.5, 74.5, 70.5, 70.3, 69.7, 66.8, 61.8, 61.0, 57.4, 50.5, 41.3, 40.9 (br), 37.4 (br), 36.7 (br), 33.7, 28.6 (br), 26.2 (br), 21.22, 21.12, 20.5, 19.1 (2C), 18.2, 17.1, 13.3. **IR (film):** 3420, 2973, 2930, 1809, 1754, 1740, 1712, 1651, 1597, 1456, 1377, 1327, 1280, 1231, 1197, 1179, 1157, 1108, 1088, 1070, 1050, 1010, 982, 914, 869, 831, 772, 755, 716, 687, 614, 546 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{41}$H$_{62}$O$_{17}$Na 849.3879; found 849.3876.
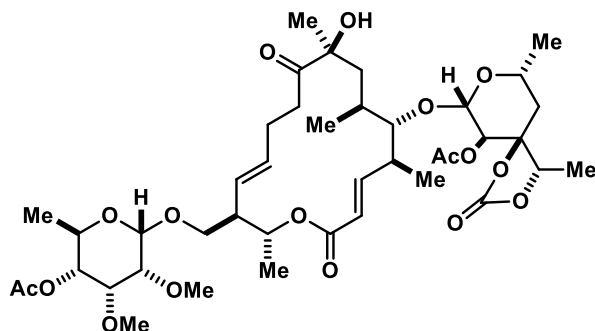
Aldgamycin N (1). Barium hydroxide octahydrate (31.0 mg, 98.3 μmol) was added in one portion to a solution of **178** (11.3 mg, 13.7 μmol) in THF/water (1:1 *v/v*, 1.2 mL) and the resulting mixture was vigorously stirred at room temperature. Over the course of the reaction, a fine white suspension formed. After 2 h, the mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced
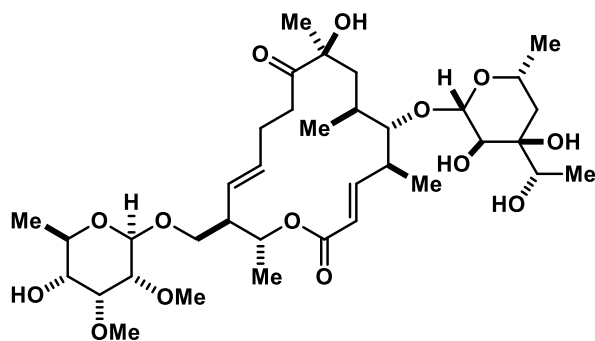
pressure. Purification of the residue by flash chromatography (dichloromethane/methanol, 30:1 → 25:1) furnished the title compound as a colorless gum containing trace impurities (6.8 mg, 69% yield).

Analytically pure Aldgamycin N was obtained by preparative HPLC: Agilent 1260 Infinity pump, 150 mm length × 10 mm diameter YMC Triart C18 5 μm column, acetonitrile/water (40:60 v/v, 4.7 mL/min, 8.3 MPa, 298 K) eluent, UV-detection at 200 nm.

Analytical and spectral data of synthetic Aldgamycin N: $[\alpha]_D^{27} = -15.1$ (*c* 0.13, CHCl$_3$), lit.: $[\alpha]_D^{27} = -13.2$ (*c* 0.5, CHCl$_3$).[40f] **^{1}H NMR (600 MHz, CDCl$_3$):** δ 6.72 (dd, *J* = 15.5, 10.0 Hz, 1H, 3-H), 5.79 (d, *J* = 15.5 Hz, 1H, 2-H), 5.49 – 5.27 (m, 2H, 12-H, 13-H), 5.10 (dq, *J* = 8.9, 6.3 Hz, 1H, 15-H), 4.63 (d, *J* = 7.5 Hz, 1H, 1'-H), 4.56 (d, *J* = 7.7 Hz, 1H, 1''-H), 3.99 – 3.89 (m, 2H, 5'-H, 20-H^a), 3.74 (t, *J* = 3.1 Hz, 1H, 3''-H), 3.70 (br s, 1H, 8-OH), 3.68 – 3.60 (m, 2H, 2'-H, 7'-H), 3.61 (s, 3H, 8''-H$_3$), 3.53 (s, 3H, 7''-H$_3$), 3.53 – 3.48 (m, 1H, 5''-H), 3.45 (dd, *J* = 9.5, 6.4 Hz, 1H, 20-H^b), 3.36 (br d, *J* = 8.7 Hz, 1H, 5-H). 3.24 (d, *J* = 2.1 Hz, 1H, 3'-OH), 3.18 (ddd, *J* = 11.2, 9.3, 3.3 Hz, 1H, 4''-H), 3.04 (dd, *J* = 7.8, 2.9 Hz, 1H, 2''-H), 2.80 – 2.60 (m, 3H, 2'-OH, 10-H^a, 4-H), 2.45 (d, *J* = 8.5 Hz, 1H, 7'-OH), 2.39 – 2.32 (m, 1H, 14-H), 2.30 (d, *J* = 11.2 Hz, 1H, 4''-OH), 2.30 – 2.12 (m, 3H, 11-H^a, 10-H^b, 11-H^b), 1.86 – 1.71 (m, 2H, 7-H$_2$), 1.50 (dd, *J* = 13.6, 2.2 Hz, 1H, 4'-H^a), 1.40 – 1.31 (m, 1H, 4'-H^b), 1.33 (s, 3H, 19-H$_3$), 1.30 (d, *J* = 6.3 Hz, 3H, 16-H$_3$), 1.28 (d, *J* = 6.6 Hz, 3H, 8'-H$_3$), 1.25 (d, *J* = 6.3 Hz, 3H, 6''-H$_3$), 1.17 (d, *J* = 6.7 Hz, 3H, 17-H$_3$), 1.17 (d, *J* = 6.3 Hz, 3H, 6'-H$_3$), 1.00 (d, *J* = 6.9 Hz, 3H, 18-H$_3$). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 212.7 (9-C), 165.5 (1-C), 150.8 (3-C), 132.0 (12-C), 129.6 (br, 13-C), 121.5 (2-C), 101.4 (1'-C), 101.0 (1''-C), 86.8 (5-C), 81.9 (2''-C), 79.9 (3''-C), 79.1 (8-C), 73.9 (7'-C), 73.8 (3'-C), 72.7 (4''-C), 72.5 (2'-C), 70.6 (5''-C), 69.9 (20-C), 69.7 (15-C), 66.8 (5'-C), 61.7 (8''-C), 59.8 (7''-C), 51.0 (br, 14-C), 41.1 (4-C), 39.4 (4'-C), 38.1 (br, 7-C), 36.7 (br, 10-C), 34.0 (6-C), 28.6 (br, 19-C), 25.9 (11-C), 20.7 (6'-C), 18.9 (16-C), 18.7 (17-C, 18-C), 18.2 (8'-C), 17.8 (6''-C). **IR (film):** 3469, 2973, 2931, 2884, 2838, 1705, 1651, 1454, 1378, 1355, 1323, 1279, 1234, 1162, 1081, 987, 963, 933, 893, 866, 806, 754, 667 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{36}$H$_{60}$O$_{14}$Na 739.3875; found 739.3885.

Double bond isomer 179: This compound was formed as a side product (ca. 8% yield) in analogous reactions with K$_2$CO$_3$/MeOH instead of Ba(OH)$_2$ · 8 H$_2$O; it analyzed as follows: **^{1}H NMR (600 MHz, CDCl$_3$):** δ 5.64 – 5.55 (m, 2H), 5.28 (ddt, *J* = 15.7, 9.0, 1.6 Hz, 1H), 5.12 (qd, *J* = 6.2, 5.1 Hz, 1H), 4.56 (d, *J* = 7.7 Hz, 1H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 1H), 3.95 (dqd, *J* = 12.5, 6.2, 2.2 Hz, 1H), 3.83 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.75 (t, *J* = 3.1 Hz, 1H), 3.67 – 3.60 (m, 3H), 3.62 (s, 3H), 3.55 – 3.48 (m, 1H), 3.52 (s, 3H), 3.41 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.21 – 3.12 (m, 3H), 3.08 (ddd, *J* = 17.9, 5.5, 1.0 Hz, 1H), 2.88 (dt, *J* = 19.0, 6.4 Hz, 1H), 2.64 (dt, *J* = 19.0, 6.4 Hz, 1H), 2.42 – 2.26 (m, 6H), 1.93 (dd, *J* = 14.5, 3.2 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.65 (br s, 3H), 1.61 (dd, *J* = 14.6, 7.5 Hz, 1H), 1.55 – 1.52 (m, 1H), 1.41 (ddd, *J* = 13.2, 11.2, 1.6 Hz, 1H), 1.33 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H),

1.22 (d, $J = 6.2$ Hz, 3H), 1.20 (d, $J = 6.4$ Hz, 3H), 0.99 (d, $J = 7.0$ Hz, 3H). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 213.7, 170.6, 136.8, 132.1, 126.5, 121.5, 100.5, 98.3, 84.8, 81.9, 79.6, 79.4, 73.7, 73.5, 72.7, 72.0, 70.6, 70.3, 69.7, 67.1, 61.6, 59.6, 48.5, 40.2, 39.3, 35.9, 34.6, 34.2, 27.3, 24.9, 20.8, 18.6, 18.5, 18.2, 17.8, 14.4. **IR (film):** 3467, 2974, 2929, 1712, 1455, 1379, 1265, 1162, 1080, 1026, 961, 917, 732 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{36}$H$_{60}$O$_{14}$Na 739.3875; found 739.3876.

NMR Spectroscopic Comparison of Natural and Synthetic Aldgamycin N
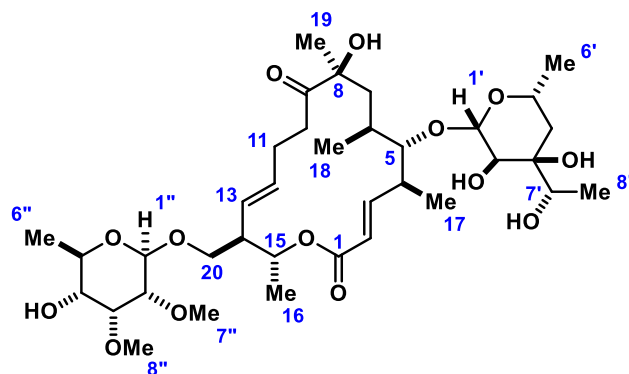
Table 4.2: Comparison of the NMR Data of Natural[40f] and Synthetic Aldgamycin N: Signals of the Aglycon (Numbering as shown above; indiscernible signals reported without designating any multiplicity)

Position	δ_C natural	δ_C synthetic	Deviation $\Delta\delta_C$	δ_H (J/Hz) natural	δ_H (J/Hz) synthetic	Deviation $\Delta\delta_H$
1	165.5	165.5	0.0	-	-	-
2	121.5	121.5	0.0	5.80 d (15.5)	5.79 d (15.5)	-0.01
3	150.7	150.8	+0.1	6.72 dd (15.5, 9.9)	6.72 dd (15.5, 10.0)	0.00
4	40.8	41.1	+0.3	2.61	2.67	+0.06
5	86.9	86.8	-0.1	3.38 br d (9.0)	3.36 br d (8.7)	-0.02
6	34.1	34.0	-0.1	1.35	* see below *	
7	38.0	38.1 (br)	+0.1	1.78	1.78	0.00
8	79.1	79.1	0.0	-	-	-
9	212.7	212.7	0.0	-	-	-
10	36.5	36.7 (br)	+0.2	2.69	2.69	0.00
				2.22	2.22	0.00
11	26.0	25.9	-0.1	2.27	2.27	0.00
				2.19	2.17	-0.02
12	132.0	132.0	0.0	5.41 ddd (15.2, 9.3, 3.0)	5.41	0.00
13	129.3	129.6 (br)	+0.3	5.36 dd (15.2, 9.3)	5.35 dd (14.7, 9.8)	-0.01
14	51.0	51.0 (br)	0.0	2.32	2.35	+0.03
15	69.8	69.7	-0.1	5.10 dq (9.0, 6.5)	5.10 dq (8.9, 6.3)	0.00
16	18.8	18.9	+0.1	1.29 d (6.5)	1.30 d (6.3)	+0.01
17	20.6	18.7	-1.9	1.18 d (6.4)	1.17 d (6.7)	-0.01
18	18.7	18.7	0.0	1.02 d (6.7)	1.00 d (6.9)	-0.02
19	28.3	28.6 (br)	+0.3	1.33 s	1.33	0.00
20	69.9	69.9	0.0	3.94 dd (9.4, 5.0)	3.95 dd (9.3, 4.7)	+0.01
				3.46 dd (9.4, 5.0)	3.45 dd (9.5, 6.4)	-0.0

Table 4.3: Comparison of the NMR Data of Natural[40f] and Synthetic Aldgamycin N: Signals of the Carbohydrates (Numbering as shown above; indiscernible signals reported without designating any multiplicity)

Position	δ_C natural	δ_C synthetic	Deviation $\Delta\delta_C$	δ_H (J/Hz) natural	δ_H (J/Hz) synthetic	Deviation $\Delta\delta_H$
1'	101.4	101.4	0.0	4.64 d (7.6)	4.63 d (7.5 Hz)	-0.01
2'	72.7	72.5	-0.2	3.62	3.62	0.00
3'	73.9	73.8	-0.1	-	-	-
4'	39.5	39.4	-0.1	1.50 br d (13.0)	1.50 dd (13.6, 2.2)	0.00
				1.36 d	1.35	-0.01
5'	66.9	66.8	-0.1	3.95	3.95	0.00
6'	20.6	20.7	+0.1	1.18 d (6.4)	1.17 d (6.3)	-0.01
7'	73.8	73.9	+0.1	3.65	3.65	0.00
8'	18.2	18.2	0.0	1.26 d (6.2)	1.28 d (6.6)	+0.02
1"	101.0	101.0	0.0	4.56 d (7.9)	4.56 d (7.7)	0.00
2"	82.0	81.9	-0.1	3.04 dd (7.9, 2.9)	3.04 dd (7.8, 2.9)	0.00
3"	79.9	79.9	0.0	3.75 t (2.9)	3.74 t (3.1)	-0.01
4"	72.6	72.7	+0.1	3.18 dd (9.2, 2.9)	3.18 ddd (11.2, 9.3, 3.3)	0.00
5"	70.7	70.6	-0.1	3.50	3.50	0.00
6"	17.8	17.8	0.0	1.25 d (6.2)	1.25 d (6.3)	0.00
7"	59.8	59.8	0.0	3.53 s	3.53 s	0.00
8"	61.7	61.7	0.0	3.62 s	3.61 s	-0.01

For H-6 (lit. 1.35 ppm, overlapping with complex multiplicity), un unambiguous the ^{1}H NMR spectroscopic assignment was not possible because no correlation with H5, H7 or H18 was found in COSY, and no correlation with C7 or C8 was found in HMBC. Moreover, even though C6 shows a sharp ^{13}C{^{1}H} resonance (34.0 ppm), no HSQC correlation was found. However, selective 1D-COSY and 1D-TOCSY experiments suggest for H6 a broad resonance at ~1.48 ppm (figure 4.1). Noticeably, H6 also appears as a very broad multiplet for both C-1" anomers at the stage of still protected **178** (cf. copies of spectra and figure 4.2).

The ^{13}C resonance for C17 was assigned by HSQC measurement (figure 4.3), indicating that C17 is overlapping with C18 rather than with C6' (however H17 and H6' overlap in ^{1}H NMR spectrum).

The ^{1}H resonances for the hydroxy groups at C8, C2', C3', C7' and C4" varied for different samples. For C7, C10, C13, C14 and C19, particularly broad ^{13}C{^{1}H} NMR signals were observed at 298 K (cf. copies of spectra). Measurements at 288 K and 308 K did not lead to any significant line sharpening.
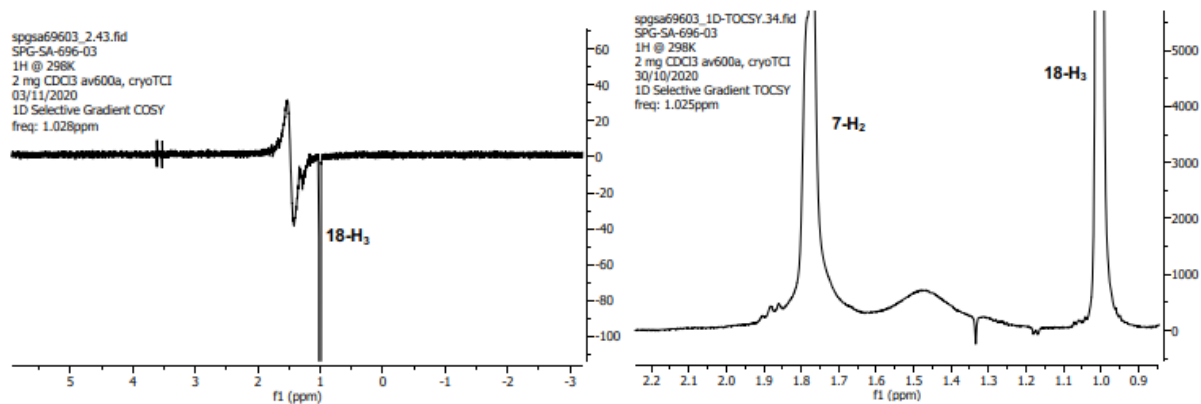
Figure 4.1: Selective 1D-COSY (left) and 1D-TOCSY (right) measurement for the ^{1}H assignment of H-6 (excitation of 18-H$_3$), see text.
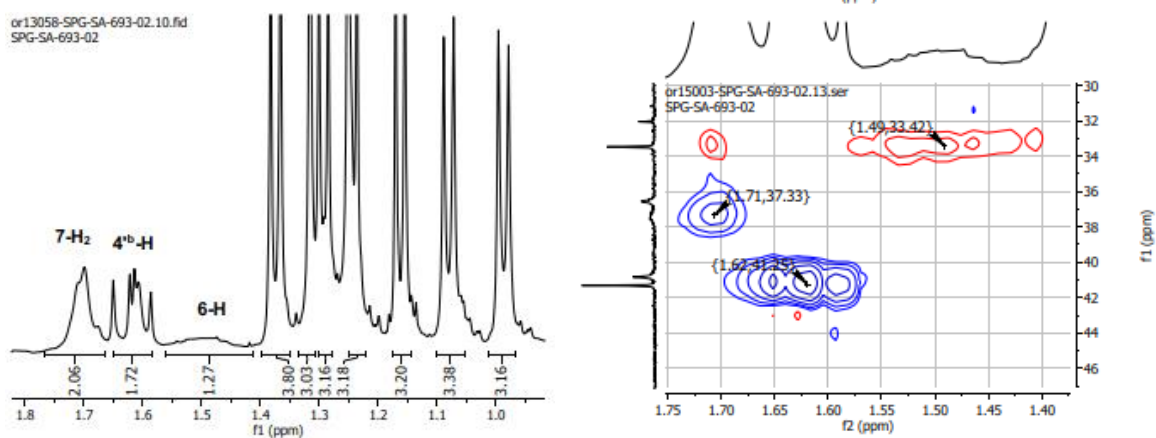
Figure 4.2: H6 exhibits a very broad ^{1}H resonance also at the stage of protected **178** (CDCl$_3$, H6: δ_H 1.56 – 1.43 (m), C6: δ_C 33.4).
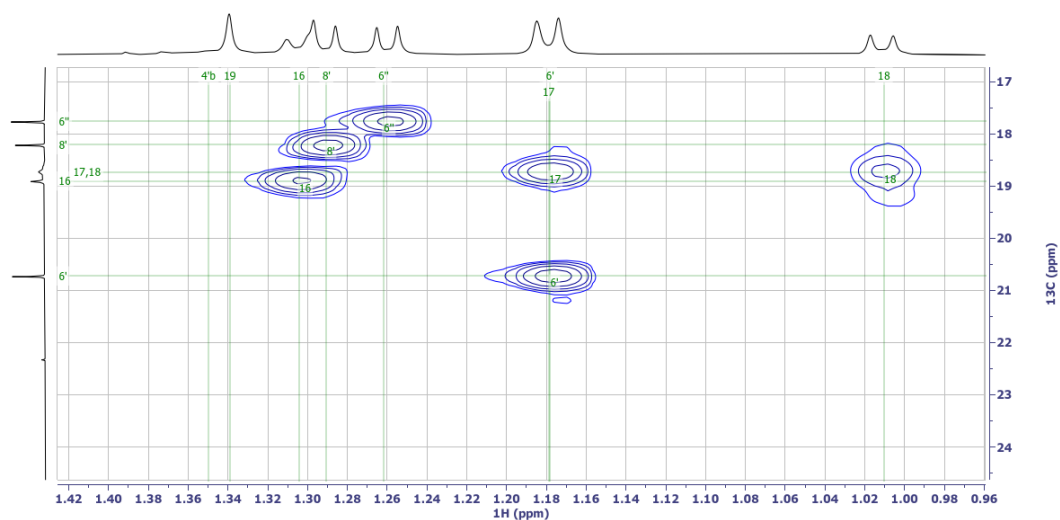
Figure 4.3: Selective HSQC measurement for the ^{13}C assignment of C17 and C6'.
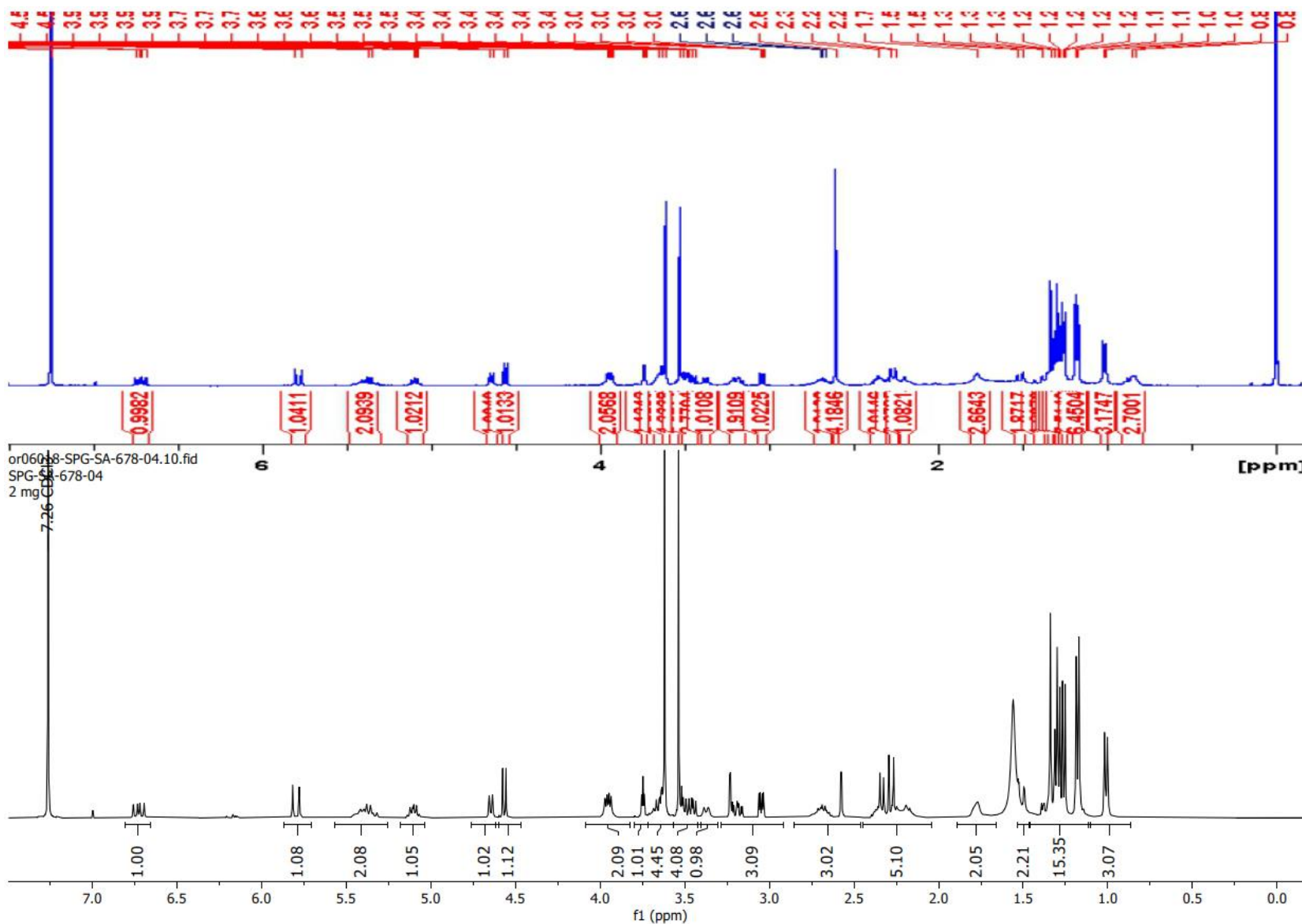
Figure 4.4: Comparison of ^{1}H NMR spectra of natural (top, 400 MHz, CDCl₃) and synthetic Aldgamycin N (bottom, 400 MHz, CDCl₃).[40f]
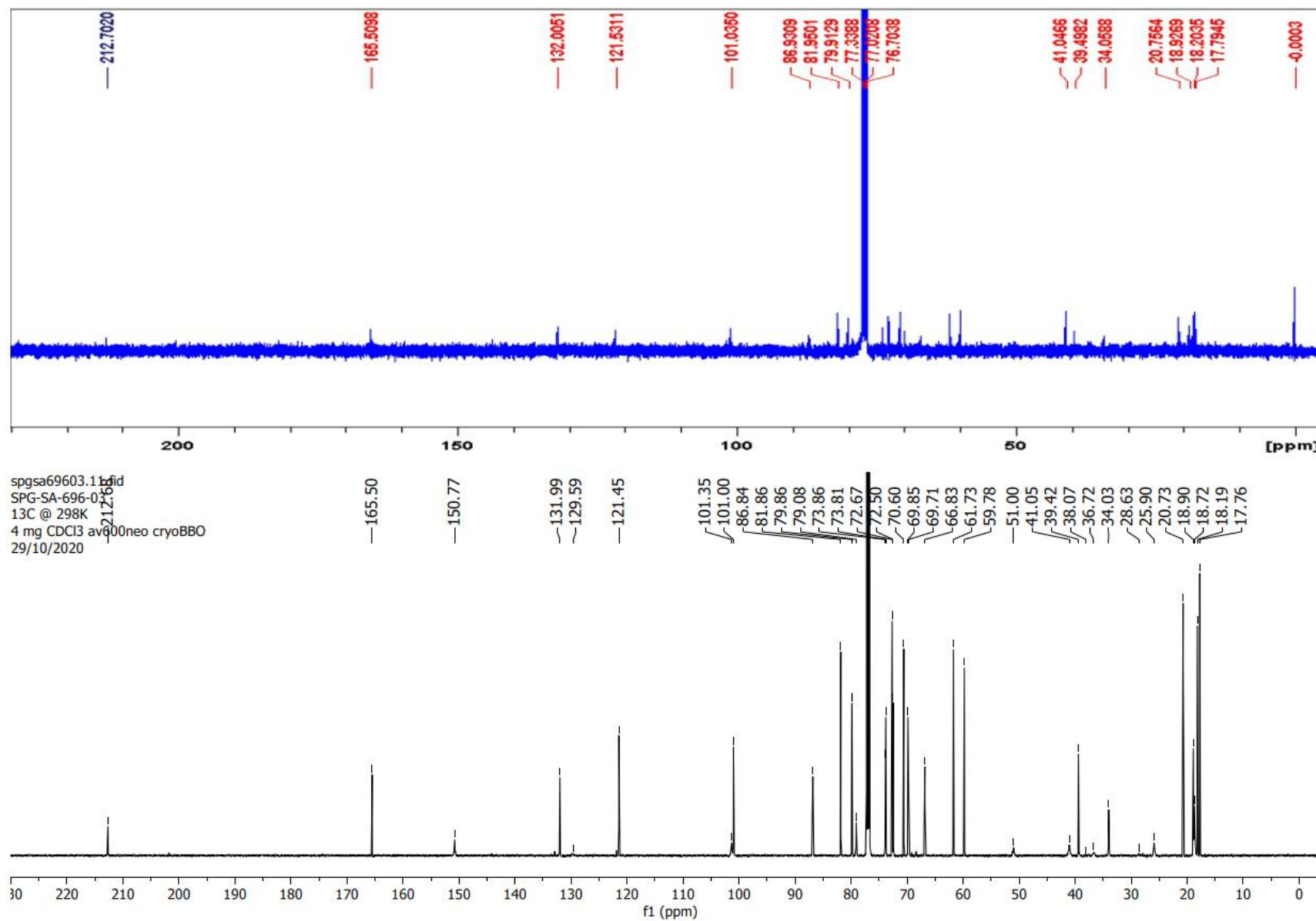
Figure 4.5: Comparison of $^{13}C\{^1H\}$ NMR spectra of natural (top, 100 MHz, CDCl₃) and synthetic Aldgamycin N (bottom, 151 MHz, CDCl₃).[40f]

4.5 Completion of the Total Syntheses of Mycinolide IV and Mycinamicin IV

Methyl (4*S*,5*S*,6*S*,*E*)-5-(methoxymethoxy)-4,6-dimethylnona-2,8-dienoate (85). Phosphorus pentoxide (1.45 g, 5.11 mmol) was added in one portion to a solution of alcohol **39** (1.09 g, 5.12 mmol) and dimethoxymethane (4.1 mL, 46 mmol) in dichloromethane (46 mL) at room temperature, resulting in the formation of a suspension with a rapidly darkening solid. After 16 h, the mixture was filtered through a pad of aluminum oxide (neutral), which was rinsed with ethyl acetate in dichloromethane (20% *v/v*, 100 mL). The combined filtrates were concentrated, giving a light yellow liquid. Purification by automated column chromatography (Biotage® 25 g SNAP Ultra HP-Sphere™ 25µm cartridge, loading as solution in hexanes; gradient of 8 − 66% EtOAc in hexanes over 15 column volumes) afforded the title compound as a colorless liquid (1.05 g, 87% yield, 87:13 d.r.). $[\alpha]_D^{20}$ = −16.0 (*c* 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.00 (dd, *J* = 15.8, 7.8 Hz, 1H), 5.84 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.75 (dddd, *J* = 16.7, 10.3, 7.8, 6.3 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.65 – 4.60 (m, 2H), 3.73 (s, 3H), 3.39 (s, 3H), 3.29 (t, *J* = 5.4 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.36 – 2.28 (m, 1H), 1.91 – 1.82 (m, 1H), 1.80 – 1.68 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.0, 152.4, 137.3, 120.2, 116.1, 98.1, 85.9, 56.1, 51.5, 39.1, 36.4, 35.8, 16.4, 14.4. **IR (film):** 2951, 2887, 1772, 1655, 1642, 1436, 1270, 1147, 1092, 1027, 990, 915, 728 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{14}$H$_{24}$O$_4$Na 279.1566; found 279.1567.
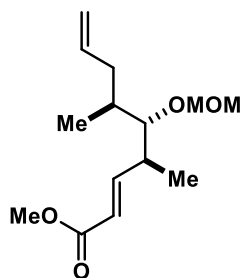
Methyl (4*S*,5*S*,6*S*,8*R*,*E*)-5-(methoxymethoxy)-4,6,8-trimethyl-9-oxonon-2-enoate (86b). Rh(acac)(CO)$_2$ (34 mg, 132 µmol) and (*R$_{ax}$,R,R*)-BOBPhos (**82**) (108 mg, 165 µmol) were added to toluene (previously degassed with argon; 3.5 mL) in a Schlenk tube, resulting in immediate gas evolution and the formation of a clear, yellow solution. This solution was transferred into an oven-dried (80 °C), argon-flushed autoclave equipped with a glass-inlet and stirring bar, pre-charged with hexafluorobenzene (140 mL). The autoclave was sealed, pressurized with hydrogen (7.5 bar) and carbon monoxide (7.5 bar) and heated to 50 °C (external temperature) while the mixture was vigorously stirred.
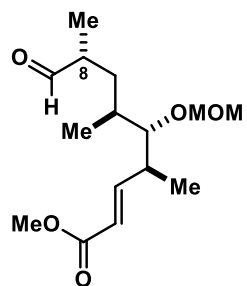
After 1 h, the autoclave was cooled to room temperature, overpressure was released and a solution of olefin **85** (1.00 g, 3.92 mmol) in hexafluorobenzene (5 mL) was added to the catalyst solution through an argon counter-flow. The autoclave was again sealed, pressurized with hydrogen/carbon monoxide (7.5 bar each) and warmed to 31 °C (internal temperature after equilibration) while the mixture was vigorously stirred.

After 3 d, the overpressure was released, and the crude reaction mixture was directly subjected to flash chromatography on silica gel (15 − 40 μm particle size, gradient of 1 – 10% EtOAc in hexanes), affording the title compound as a yellow liquid (675 mg, 60% yield, **86b/86a** = 96:4, d.r. (**86b/Σ** of all diastereomers) = 83:17). $[\alpha]_D^{20}$ = −31.1 (*c* 0.99, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 9.52 (d, *J* = 2.8 Hz, 1H), 6.95 (dd, *J* = 15.7, 8.0 Hz, 1H), 5.85 (dd, *J* = 15.7, 1.3 Hz, 1H), 4.65 – 4.61 (m, 2H), 3.73 (s, 3H), 3.39 (s, 3H), 3.25 (dd, *J* = 6.0, 4.6 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.51 – 2.38 (m, 1H), 1.94 (ddd, *J* = 13.7, 9.9, 3.4 Hz, 1H), 1.75 – 1.62 (m, 1H), 1.22 – 1.13 (m, 1H), 1.10 (d, 4.2 Hz, 3H), 1.09 (d, *J* = 3.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 205.0, 166.9, 151.8, 120.5, 98.1, 86.5, 56.1, 51.5, 44.1, 39.4, 33.6, 33.1, 17.3, 15.0, 14.9. **IR (film):** 2964, 2935, 2881, 1720, 1665, 1459, 1436, 1273, 1193, 1177, 1147, 1093, 1029, 988, 919, 864, 753 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C$_{15}$H$_{26}$O$_5$Na 309.1672; found 309.1675.

Stereochemical Analysis of the Hydroformylation Product

The analogous reaction using the enantiomeric ligand (*S$_{ax}$,S,S*)-**82** gave **86a** as the major product (see below); **86a** and **86b** were then transformed into the corresponding lactones **90a** and **90b**. The NMR data of these samples could be compared to those of authentic **90b** reported in the literature[56]: as shown in table 4.5, an excellent match with the reported ¹H NMR data was found for the lactone obtained from aldehyde **86b**, which was formed with the aid of (*R$_{ax}$,R,R*)-(**82**) as the chiral ligand.
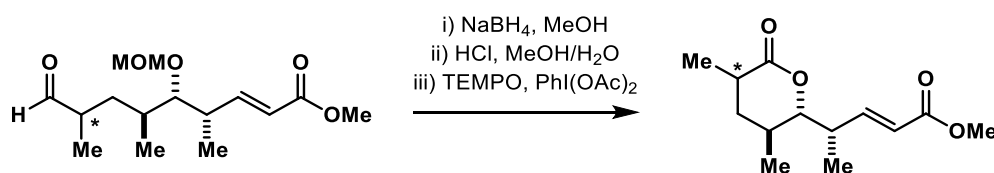
Table 4.5. Comparison of ¹H NMR data of lactone **90b** obtained from aldehyde **86b** with the reported data[56] of an authentic sample confirms the desired configuration at C8.

90b (reported)				90b (obtained from aldehyde 86b)					Deviation		
δ (ppm)		*J* (Hz)		δ (ppm)		*J* (Hz)			δ (ppm)	*J* (Hz)	
7.08	dd	15.8	7.2	7.07	dd	15.8	7.4		-0.01	0.0	0.2
5.88	dd	15.8	1.3	5.88	dd	15.8	1.4		0.00	0.0	0.1
4.04	dd	10.0	2.3	4.02	dd	10.0	2.3		-0.02	0.0	0.0
3.73	s			3.73	s				0.00		
				2.64	m					n.a.	
2.57	m								0.00		
				2.50	ddt	14.2	13.1	6.5		n.a.	
n.a.				1.94	m				n.a.		
n.a.				1.38	dt	13.9	12.4		n.a.		
1.27	d	7.0		1.28	d	7.1			0.01	0.0	
1.11	d	7.0		1.10	d	6.9			0.01	-0.1	
1.01	d	6.4		1.01	d	6.4			0.00	0.0	

Methyl (4S,5S,6S,8S,E)-5-(methoxymethoxy)-4,6,8-trimethyl-9-oxonon-2-enoate (86a). A 10-mL Schlenk tube was charged with Rh(acac)(CO)$_2$ (1.0 mg, 3.9 µmol), (S$_{ax}$,S,S)-BOBPhos (**82**) (5.0 mg, 7.7 µmol) and hexafluorobenzene (6 mL). The mixture was sonicated until all solids had disappeared. This solution was then transferred into an oven-dried (80 °C), argon-flushed autoclave equipped with a glass-inlet and stirring bar. The autoclave was sealed, pressurized with hydrogen (7.5 bar) and carbon monoxide (7.5 bar) and the resulting mixture vigorously stirred at 50 °C (external temperature).
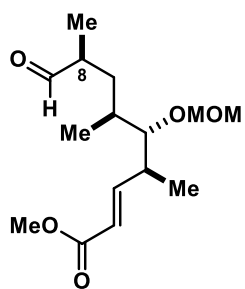
After 1 h, the autoclave was cooled to room temperature, overpressure was released and a solution of olefin **85** (50.0 mg, 0.195 mmol) in hexafluorobenzene (3 mL) was added to this catalyst solution through an argon counter-flow. The autoclave was again sealed, pressurized with hydrogen/carbon monoxide (7.5 bar each) and warmed to 30 °C (internal temperature after equilibration) while the mixture was vigorously stirred. After 24 h, the overpressure was released, and the contents were transferred to a round-bottom flask. Volatile material was removed under high vacuum and the residue was subjected to flash chromatography (hexanes/EtOAc/dichloromethane, 8:1:1) to afford the title compound as a colorless liquid (39.9 mg, 71% yield, **86a**/**86b** = 96:4; **86a**:Σ of all diastereomers = 72:28). $[\alpha]_D^{20}$ = −32.0 (c 0.99, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 9.62 (d, J = 1.7 Hz, 1H), 6.93 (dd, J = 15.8, 8.2 Hz, 1H), 5.83 (dd, J = 15.8, 1.2 Hz, 1H), 4.63 (d, J = 1.2 Hz, 2H), 3.73 (s, 3H), 3.38 (s, 3H), 3.31 – 3.25 (m, 1H), 2.62 (dtd, J = 7.9, 6.5, 1.3 Hz, 1H), 2.36 (dddd, J = 10.0, 7.1, 4.5, 1.7 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.63 – 1.53 (m, 1H), 1.43 (ddd, J = 13.6, 10.0, 3.3 Hz, 1H), 1.10 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 205.1, 167.1, 151.8, 120.7, 98.5, 86.8, 56.3, 51.7, 44.3, 39.7, 33.4, 31.7, 16.9, 15.3, 13.0. **IR (film):** 2964, 2937, 2882, 2824, 1723, 1656, 1460, 1437, 1380, 1273, 1178, 1149, 1093, 1033, 920 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{15}$H$_{26}$O$_5$Na 309.1672; found 309.1667.

Methyl (4S,5S,6S,8R,E)-9-hydroxy-5-(methoxymethoxy)-4,6,8-trimethylnon-2-enoate (89b). Sodium borohydride (6.3 mg, 0.17 mmol) was added in one portion to a solution of aldehyde **86b** (14.5 mg, 50.2 µmol) in methanol (0.5 mL) at −78 °C and the resulting mixture was slowly warmed to room temperature. The mixture was concentrated under reduced pressure, the residue was diluted with *tert*-butyl methyl ether and the organic layer was washed with water. The aqueous phase was extracted with *tert*-butyl methyl ether and the combined organic layers were dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Flash chromatography (hexanes/EtOAc, 1:1) afforded the title compound as a colorless oil (7.6 mg, 52% yield). $[\alpha]_D^{20}$ = −28.1 (c 0.62, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 6.96 (dd, J = 15.8,
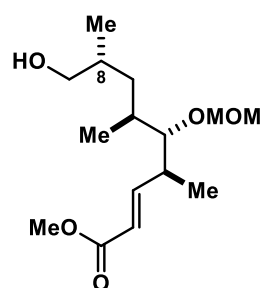
8.2 Hz, 1H), 5.84 (dd, J = 15.7, 1.2 Hz, 1H), 4.63 (q, J = 6.8 Hz, 2H), 3.73 (s, 3H), 3.48 (dd, J = 10.6, 4.9 Hz, 1H), 3.42 – 3.37 (m, 4H), 3.26 (dd, J = 6.0, 4.6 Hz, 1H), 2.62 (dddd, J = 8.1, 7.1, 6.0, 1.3 Hz, 1H), 1.82 – 1.64 (m, 2H), 1.57 (ddd, J = 13.9, 8.6, 4.1 Hz, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.96 (m, J = 6.8, 2.2 Hz, 7H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 152.3, 120.2, 98.1, 86.5, 67.3, 56.1, 51.6, 39.3, 35.7, 33.7, 33.3, 18.3, 17.6, 15.2. **IR (film):** 3434, 2953, 2931, 2881, 2824, 1722, 1654, 1459, 1437, 1273, 1177, 1148, 1094, 1030, 988, 919 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{15}$H$_{28}$O$_5$Na 311.1829; found 311.1831.

Methyl (4S,5S,6S,8S,E)-9-hydroxy-5-(methoxymethoxy)-4,6,8-trimethylnon-2-enoate (89a).
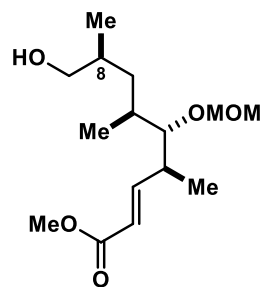
Prepared analogously from **86a** as a colorless oil (23 mg, 99% yield). $[\alpha]_D^{20}$ = −30.9 (c 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.95 (dd, J = 15.7, 8.2 Hz, 1H), 5.83 (dd, J = 15.8, 1.2 Hz, 1H), 4.66 – 4.61 (m, 2H), 3.73 (s, 3H), 3.47 – 3.41 (m, 2H), 3.38 (s, 3H), 3.26 (dd, J = 6.1, 4.5 Hz, 1H), 2.68 – 2.58 (m, 1H), 1.79 – 1.63 (m, 2H), 1.26 – 1.21 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 152.3, 120.4, 98.4, 87.2, 69.4, 56.2, 51.7, 39.6, 34.7, 33.4, 33.2, 17.1, 15.9, 15.3. **IR (film):** 3461, 2956, 2932, 2879, 2825, 1724, 1655, 1460, 1437, 1273, 1195, 1094, 1034, 989, 919 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{15}$H$_{28}$O$_5$Na$^+$ 311.1829, found 311.1827.

Lactone 90b. Concentrated aqueous HCl (0.1 mL) was added to a solution of acetal **89b** (7.8 mg, 27 µmol) in acetonitrile (0.4 mL) and the resulting mixture was stirred for 16 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate and the drying agent was filtered off. The solvent was removed under reduced pressure to give a colorless oil (6.4 mg).
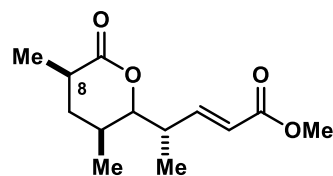
In a 10-mL round-bottom flask, bis(acetoxy)iodobenzene (19 mg, 0.054 mmol) and TEMPO (0.8 mg, 0.005 mmol) were added to a solution of this crude material in acetonitrile/water (1:1 v/v, 0.25 mL) at 0 °C (ice bath). After stirring for 24 h at room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with dichloromethane (3 ×1 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Flash chromatography (hexanes/EtOAc, 6:1 → 1:1) afforded the title compound as a colorless oil (1.8 mg, 28% yield). $[\alpha]_D^{20}$ = −98.3 (c 0.18, MeOH). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.07 (dd, J = 15.8, 7.4 Hz, 1H), 5.88 (dd, J = 15.8, 1.4 Hz, 1H), 4.02 (dd, J = 10.0, 2.3 Hz, 1H), 3.73 (s, 3H), 2.68 – 2.59 (m, 1H), 2.56 – 2.44 (m, 1H), 1.98 – 1.89 (m, 2H), 1.38 (dt, J = 13.9, 12.4 Hz, 1H), 1.28 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 174.0, 166.8, 150.4, 121.4, 88.4, 51.5, 38.2, 37.5, 36.2, 31.0, 17.3, 11.7. **IR (film):**

2969, 2936, 2881, 1724, 1658, 1459, 1436, 1380, 1322, 1273, 1256, 1192, 1165, 1108, 1039, 994 cm^{-1}.
HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{13}$H$_{20}$O$_4$Na$^+$ 263.1254, found 263.1259.

Lactone 90a. Prepared analogously from **89a** as a colorless oil (2 mg, 47% yield). $[\alpha]_D^{20}$ = +75.0 (*c* 0.13,
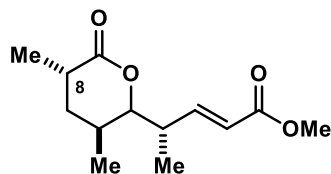
MeOH). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.02 (dd, *J* = 15.8, 7.6 Hz, 1H),
5.88 (dd, *J* = 15.8, 1.3 Hz, 1H), 3.98 (dd, *J* = 9.7, 2.9 Hz, 1H), 3.72 (s, 3H),
2.67 – 2.58 (m, 2H), 2.00 (dq, *J* = 9.7, 7.1 Hz, 1H), 1.70 (ddd, *J* = 8.2, 7.5,
5.7 Hz, 2H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.02 (d,

J = 6.8 Hz, 3H).**^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 175.7, 166.8, 150.2, 121.4, 84.8, 51.5, 37.9, 34.9, 32.3, 28.6, 17.7, 16.4, 12.0. **IR (film):** 3287, 2952, 2840, 1647, 1450, 1407, 1197, 1113, 1014, 533, 447 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{13}$H$_{20}$O$_4$Na$^+$ 263.1254, found 263.1254.

Fragment Coupling and Total Synthesis of Mycinolide IV

Propargylic Alcohol 91. *n*-BuLi (1.6 M in hexanes, 1.8 mL, 2.9 mmol) was added to a solution of alkyne
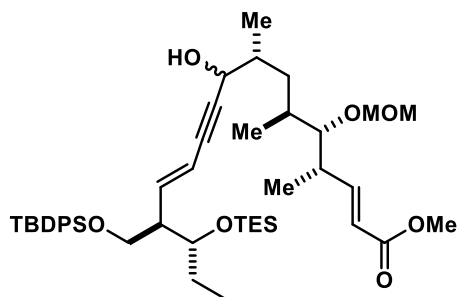
57 (1.44 g, 2.84 mmol) in THF (40 mL) at −78 °C, giving a pale
yellow solution. After 1 h, a solution of aldehyde **86b** (675 mg,
2.36 mmol) in THF (7 mL) was added, and the resulting mixture
was stirred at −78 °C for 1.5 h. Pentane (40 mL) was added, the
reaction was quenched with water (20 mL) and the mixture
allowed to warm to room temperature. Saturated aqueous sodium

chloride (10 mL) was introdced, the layers were separated and the aqueous phase was extracted with pentane (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and the drying agent was filtered off. The filtrate was evaporated to dryness, giving a pale yellow oil. Purification by automated column chromatography (for each half of the crude product using a Biotage$^®$ 50 g SNAP Ultra HP-Sphere^{TM} 25μm cartridge, loading as a solution in hexanes, gradient of 4 − 50% EtOAc in hexanes over 15 column volumes) afforded the title compound as a colorless oil (1.04 g, 56% yield, 1.4:1.0 ratio of C9 epimers). *Analytical and spectral data for the mixture of C9 epimers (NMR integrals of overlapping signals given with respect to single epimer)*: **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.69 – 7.59 (m, 4H), 7.46 – 7.32 (m, 6H), 7.02 – 6.89 (m, 1H), 6.10 – 6.00 (m, 1H), 5.89 – 5.80 (m, 1H), 5.46 – 5.38 (m, 1H), 4.68 – 4.58 (m, 2H), 4.43 – 4.39 (m, 1H, *single epimer*), 4.36 – 4.31 (m, 1H, *single epimer*), 3.85 – 3.79 (m, 1H), 3.78 – 3.72 (m, 1H), 3.72 (s, 3H, *single epimer*), 3.70 (s, 3H, *single epimer*), 3.55 – 3.48 (m, 1H), 3.38 (s, 3H, *single epimer*), 3.37 (s, 3H, *single epimer*), 3.29 – 3.23 (m, 1H), 2.70 – 2.55 (m, 1H), 2.32 – 2.23 (m, 1H), 1.90 – 1.75 (m, 3H), 1.74 – 1.64 (m, 1H), 1.47 – 1.36 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 3H, *single epimer*), 1.08 (d, *J* = 6.7 Hz, 3H, *single epimer*), 1.05 (s, 9H), 1.02 (d, *J* = 6.7 Hz, 3H, *single epimer*), 1.01 (d, *J* = 6.4 Hz, 3H, *single epimer*), 0.97 (d, *J* = 6.8 Hz,

3H, *single epimer*), 0.96 (d, *J* = 6.7 Hz, *single epimer*), 0.91 (t, *J* = 7.9 Hz, 9H), 0.772 (t, *J* = 7.5 Hz, 3H, *single epimer*), 0.769 (t, *J* = 7.4 Hz, 1H, *single epimer*), 0.61 – 0.50 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 167.2, 167.1, 152.32, 152.25, 142.2, 142.0, 135.7, 135.6, 133.8, 133.7, 129.63, 129.56, 127.6, 120.34, 120.29, 111.9, 111.8, 98.01, 98.00, 88.2, 87.2, 86.4, 86.2, 84.8, 84.2, 72.5, 66.8, 65.7, 64.4, 56.04, 56.01, 51.5, 51.4, 50.2, 39.3, 39.2, 37.12, 37.10, 35.6, 34.5, 33.8, 33.7, 28.3, 26.9, 19.2, 17.83, 17.79, 16.1, 16.0, 15.3, 15.1, 9.9, 6.9, 5.1. **IR (film):** 2957, 2933, 2875, 1724, 1655, 1461, 1428, 1378, 1337, 1243, 1148, 1084, 1031, 962, 920, 822, 737, 701, 612, 503, 488 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{46}$H$_{72}$O$_7$Si$_2$Na 815.4709; found 815.4700.

Macrocyclization Precursor 92. Camphor-10-sulfonic acid (12 mg, 52 µmol) was added to solution of
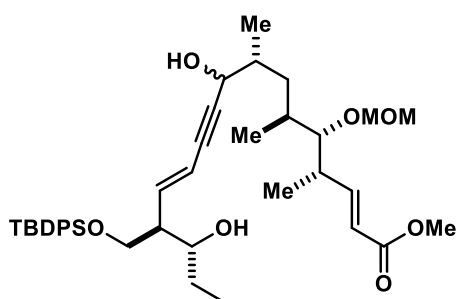
compound **91** (818 mg, 1.03 mmol) in MeOH/CH$_2$Cl$_2$ (each 23 mL) at −20 °C and the resulting mixture was stirred at this temperature for 2 h. *tert*-Butyl methyl ether (40 mL) and half-saturated aqueous sodium bicarbonate solution (20 mL) were introduced and the mixture was warmed to room temperature. The layers were separated and the aqueous phase was extracted with

tert-butyl methyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, and the drying agent was filtered off. The filtrate was evaporated to dryness, affording a pale yellow oil. Purification of the residue by automated column chromatography (Biotage® 50 g SNAP Ultra HP-Sphere^{TM} 25µm cartridge, loading as a solution in CH$_2$Cl$_2$/hexanes = 1:1, gradient of 4 – 50% EtOAc in hexanes over 20 column volumes) yielded the title compound as a colorless oil (601 mg, 86% yield, 1.4:1.0 ratio of C9 epimers). *Analytical data for the mixture of C9 epimers (NMR integrals of overlapping signals given with respect to single epimer)*: **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.69 – 7.62 (m, 4H), 7.49–7.34 (m, 6H), 7.02 – 6.89 (m, 1H), 6.27 – 6.15 (m, 1H), 5.89 – 5.80 (m, 1H), 5.58 – 5.48 (m, 1H), 4.68 – 4.58 (m, 2H), 4.44 – 4.39 (m, 1H, *single epimer*), 4.35 (dd, *J* = 5.1, 1.8 Hz, 1H, *single epimer*), 3.85 – 3.74 (m, 3H), 3.72 (s, 3H, *single epimer*), 3.70 (s, 3H, *single epimer*), 3.379 (s, 3H, *single epimer*), 3.376 (s, 3H, *single epimer*), 3.30 – 3.23 (m, 1H), 2.69 – 2.56 (m, 1H), 2.37 – 2.26 (m, 1H), 1.91 – 1.73 (m, 3H), 1.72 – 1.62 (m, 1H), 1.55 – 1.34 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 3H, *single epimer*), 1.08 (d, *J* = 6.8 Hz, 3H, *single epimer*), 1.06 (s, 9H), 1.021 (d, *J* = 6.7 Hz, 3H, *single epimer*), 1.016 (d, *J* = 6.4 Hz, 3H, *single epimer*), 0.98 (d, *J* = 6.9 Hz, 3H, *single epimer*), 0.97 (d, *J* = 6.7 Hz, 3H, *single epimer*), 0.922 (t, *J* = 7.4 Hz, 3H, *single epimer*), 0.920 (t, *J* = 7.4 Hz, 3H, *single epimer*). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$)** δ 167.24, 167.15, 152.3, 152.2, 141.2, 140.9, 135.6, 135.5, 133.01, 132.97, 132.85, 132.80, 129.9, 127.8, 120.4, 120.3, 112.44, 112.38, 98.02, 97.98, 88.8, 87.7, 86.3, 86.2, 84.4, 83.8, 73.9, 73.8, 66.7, 66.3, 66.1, 65.7, 56.1, 56.0, 51.53, 51.50, 49.7, 49.6, 39.3, 39.2, 37.1, 37.0, 35.4, 34.5, 33.8, 33.6, 27.8, 26.9, 19.2, 17.8, 17.7, 16.2, 16.0, 15.5, 15.1, 10.3. **IR (film):** 3454, 2959, 2931, 1721, 1654, 1461, 1428, 1380, 1278, 1147,

1106, 1030, 961, 914, 864, 823, 801, 736, 702, 613, 504, 433 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{40}$H$_{58}$O$_7$SiNa 701.3844; found 701.3840.

Macrolactone 93. In a 1-L two-necked flask equipped with a reflux-condenser and an argon bridge, hydroxy ester **92** (600 mg, 0.884 mmol) and distannoxane **67b** (1.96 g, 1.77 mmol) were dissolved in chlorobenzene (600 mL) and the resulting solution was stirred at reflux temperature for 89 h. The solvent was removed under reduced pressure to afford a yellow solid. Purification by flash chromatography on silica gel (15 − 40 μm particle size; *tert*-butyl methyl ether/hexanes, 1:4 → 1:3) afforded the title compound as a colourless foam (184 mg, 32% yield, 2.2:1.0 ratio of C9 epimers).
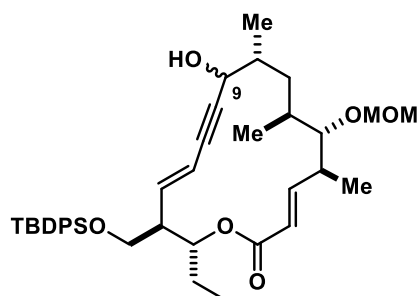
For analytical purposes, an aliquot was re-subjected to flash chromatography to give a pure sample of one of the C9 epimers. The signals of the second isomer had to be assigned from the NMR spectrum of the mixture containing both C9 epimers.

Spectral data of epimer 1: **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.68 – 7.59 (m, 4H), 7.49 – 7.34 (m, 6H), 6.77 (dd, *J* = 15.5, 9.7 Hz, 1H), 6.07 (dd, *J* = 15.8, 10.0 Hz, 1H), 5.81 (dd, *J* = 15.5, 0.7 Hz, 1H), 5.46 (dd, *J* = 15.8, 2.0 Hz, 1H), 5.02 (td, *J* = 9.6, 2.6 Hz, 1H), 4.72 – 4.65 (m, 2H), 4.58 (dd, *J* = 4.1, 2.3 Hz, 1H), 3.74 – 3.62 (m, 2H), 3.42 (s, 3H), 3.21 (dd, *J* = 9.9, 2.2 Hz, 1H), 2.66 – 2.50 (m, 1H), 2.29 (tt, *J* = 9.8, 4.5 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.76 – 1.57 (m, 2H), 1.45 – 1.35 (m, 1H), 1.34 – 1.28 (m, 2H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.90 – 0.84 (m, 3H). **^{13}C{^{1}H} NMR (epimer 1; 101 MHz, CDCl$_3$):** δ 166.7, 150.6, 143.6, 135.64, 135.59, 133.2, 133.1, 129.8, 129.7, 127.7, 121.7, 112.5, 99.4, 88.6, 86.3, 84.2, 73.9, 64.5, 63.2, 56.3, 52.1, 40.3, 35.1, 32.9, 31.1, 26.8, 25.3, 19.8, 19.2, 16.9, 15.2, 9.8.

Spectral data of epimer 2: **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.68 – 7.60 (m, 4H), 7.47 – 7.35 (m, 6H), 6.87 (dd, *J* = 15.6, 9.2 Hz, 1H), 6.02 (dd, *J* = 15.8, 9.8 Hz, 1H), 5.81 (d, *J* = 15.5 Hz, 1H), 5.46 (dd, *J* = 15.8, 2.1 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.72 – 4.65 (m, 2H), 4.14 (dd, *J* = 7.0, 1.8 Hz, 1H), 3.75 – 3.62 (m, 2H), 3.41 (s, 3H), 3.25 (dd, *J* = 8.5, 3.0 Hz, 1H), 2.70 – 2.53 (m, 1H), 2.38 – 2.23 (m, 1H), 2.01 – 1.86 (m, 1H), 1.75 – 1.58 (m, 2H), 1.46 – 1.34 (m, 1H), 1.34 – 1.26 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.07 (s, 9H), 1.04 – 0.98 (m, 6H), 0.89 – 0.83 (m, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.7, 151.4, 142.2, 135.64, 135.59, 133.20, 133.17, 133.13, 129.8, 129.7, 127.7, 121.2, 112.1, 97.9, 88.4, 86.3, 84.5, 74.1, 68.8, 63.5, 56.1, 51.7, 39.5, 35.0, 32.9, 31.1, 26.8, 25.5, 19.8, 19.0, 16.9, 15.2, 9.7. **IR (film):** 3468, 3071, 2959, 2929, 2873, 2857, 1717, 1651, 1461, 1428, 1240, 1222, 1176, 1147, 1104, 1030, 988,

858, 823, 792, 740, 702, 607, 504, 432 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{39}$H$_{54}$O$_6$SiNa 669.3582; found: 669.3583.

When the analogous cyclization was attempted with La(NO$_3$)$_3$ · H$_2$O by following a literature procedure,[103a] an epimeric mixture of a tetrahydropyran was obtained as the major product. The mixture displayed the following analytical and spectral data:
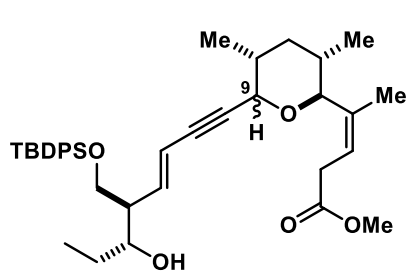
Signals of the (9R)-epimer: **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.66 – 7.63 (m, 4H), 7.41 -7.37 (m, 4H), 6.22 (dd, *J* = 16.2, 9.5 Hz, 1H), 5.59 (tq, *J* = 7.0, 1.2 Hz, 1H), 5.52 (ddd, *J* = 16.1, 1.8, 0.9 Hz, 1H), 3.85 – 3.76 (m, 4H), 3.67 (s, 3H), 3.34 (d, J = 9.9 Hz, 1H, 5-H), 3.15 – 3.02 (m, 2H, 2-H, 2'-H), 2.32 – 2.27 (m, 1H), 1.86 (dt, *J* = 13.4, 3.7 Hz, 1H), 1.76 – 1.71 (m, 1H), 1.69 – 1.67 (m, 1H), 1.66 (q, *J* = 1.0 Hz, 3H), 1.52 – 1.35 (m, 2H), 1.05 (s, 9H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.90 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 172.3, 140.8, 137.2, 135.7, 135.6, 132.8, 129.9, 129.9, 127.8, 127.8, 120.9, 112.7, 90.3, 87.2, 83.6, 74.8, 74.1, 66.4, 51.8, 49.5, 41.2, 37.0, 33.2, 32.4, 27.7, 26.9, 19.2, 17.9, 17.5, 11.9, 10.2. *Signals of the (9S)-epimer*: **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.68 – 7.65 (m, 4H), 7.46 – 7.41 (m, 2H), 7.41 – 7.37 (m, 4H), 6.25 (dd, *J* = 16.1, 9.3 Hz, 1H), 5.63 (tq, *J* = 6.8, 1.5 Hz, 1H), 5.57 (ddd, *J* = 16.1, 1.8, 0.9 Hz, 1H), 4.70 (d, *J* = 5.0 Hz, 1H), 3.83 – 3.80 (m, 4H), 3.66 (s, 3H), 3.15 – 3.02 (m, 2H), 2.37 – 2.32 (m, 1H), 2.00 – 1.92 (m, 1H), 1.63 (q, *J* = 1.1 Hz, 3H), 1.62 – 1.53 (m, 2H), 1.52 – 1.42 (m, 2H), 1.26 – 1.22 (m, 1H), 1.07 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 172.3, 140.6, 137.4 , 135.7, 135.6, 133.0, 129.9, 129.9, 127.8, 127.8), 120.8, 112.7, 86.5, 84.8,83.4, 74.2, 71.0, 66.5, 51.7, 49.5, 36.5, 34.6,33.2, 32.6, 27.8, 26.8, 19.2, 17.6, 17.6, 11.8, 10.3). **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{38}$H$_{52}$O$_5$SiNa 639.3476; found: 639.3486.

Dieneone 94. A solution of PhPCy$_2$ (52 mg, 0.19 mmol) in degassed THF (7 mL) was added to a stirred suspension of RuCp(MeCN)$_3$BF$_4$ (71 mg, 0.19 mmol) in degassed THF (20 mL). The resulting slightly turbid solution was stirred for 5 min before it was added to a solution of macrolide **93** (249 mg, 0.385 mmol) in degassed THF (23 mL). The resulting mixture was stirred at reflux temperature for 2.5 h. After cooling, the mixture was diluted with hexanes (50 mL) and filtered through a silica pad, which was rinsed with EtOAc/hexanes (1:1, 200 mL). The combined filtrates were evaporated to dryness, giving a yellow oil. Purification of this residue by automated column chromatography (Biotage® 50 g SNAP Ultra HP-Sphere™ 25μm cartridge, loading as a solution in hexanes, gradient of 2 – 50% EtOAc in hexanes over 20 column volumes) yielded the title compound as an off-white foam (162 mg, 65% yield). **mp** = 58 – 62 °C. **[α]$_D^{25}$** = +45.2 (*c* 0.80, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.68 – 7.60 (m, 4H), 7.47 – 7.34 (m, 6H), 7.19 – 7.09 (m, 1H), 6.60 (dd, *J* = 15.5, 9.9 Hz, 1H), 6.22 (d, *J* = 15.1 Hz, 1H), 6.17 – 6.03 (m, 2H), 5.76 (dd, *J* = 15.5, 0.7 Hz, 1H), 4.70 – 4.62 (m, 2H), 4.64 (d, *J* = 6.5 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.41 (s, 3H), 3.15 (dd, *J* = 10.3, 1.4 Hz, 1H), 2.65 – 2.52 (m, 2H), 2.39 – 2.29 (m, 1H), 1.72 – 1.58 (m, 1H), 1.54 – 1.47 (m, 2H), 1.47 – 1.36 (m, 1H), 1.35 – 1.27 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.83 (m, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 203.4, 166.1, 151.1, 142.3, 141.7, 135.62, 135.58, 133.2, 133.1, 132.8, 129.83, 129.80, 127.7, 122.9, 121.3, 99.3, 88.7, 73.8, 62.7, 56.3, 51.1, 44.7, 40.4, 34.1, 32.5, 26.8, 25.0, 19.5, 19.3, 17.7, 17.6, 9.7. **IR (film):** 2962, 2931, 2880, 2858, 1714, 1681, 1652, 1594, 1461, 1428, 1352, 1327, 1233, 1177, 1147, 1106, 1037, 983, 919, 823, 791, 735, 702, 648, 609, 504 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{39}$H$_{54}$O$_6$SiNa 669.3582; found: 669.3590.

Mycinolide IV (3). Aqueous HCl (3.0 M, 0.71 mL) was added to a solution of dienone **94** (14.3 mg, 22.1 μmol) in methanol (2.3 mL) and the resulting cloudy solution was stirred at 40 °C for 4.5 h. After reaching ambient temperature, the by then clear colourless solution was diluted with water (10 mL) and ethyl acetate (10 mL), and vigorously stirred for 2 min. The layers were separated and the aqueous phase was extracted with ethyl acetate (4 × 4 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 mL) and filtered through a pad of anhydrous sodium sulfate. The filtrate was concentrated under reduced pressure, furnishing a colourless solid. Purification by automated column chromatography (Biotage® 10 g SNAP Ultra HP-Sphere™ 25μm cartridge, loading immobilized on silica, gradient of 16 – 100% EtOAc in hexanes over 15 column volumes) afforded the title compound as a colourless solid (6.0 mg, 16 μmol, 74% yield). Trace impurities were removed by preparative HPLC for
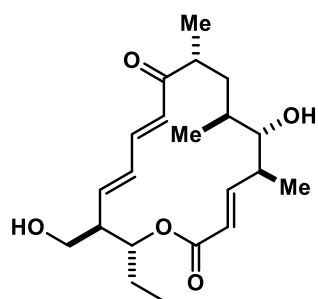
analytical purposes: Agilent 1260 Infinity pump, 150 mm length × 10 mm diameter YMC Triart C18 5 μm column, methanol/water (60:40 v/v, 4.7 mL/min, 12.6 MPa, 299 K) eluent, UV-detection at 220 nm. **mp** = 220 – 222 °C, lit.: 222 – 223 °C. $[\alpha]_D^{25}$ = +26.5 (c 0.28, MeOH), lit.: $[\alpha]_D^{27}$ = +24.3 (c 0.50, MeOH).

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.12 (dd, J = 15.0, 11.0 Hz, 1H, 11-H), 6.61 (dd, J = 15.5, 9.9 Hz, 1H, 3-H), 6.25 (d, J = 15.0 Hz, 1H, 10-H), 6.18 (dd, J = 15.2, 11.0 Hz, 1H, 12-H), 5.93 (dd, J = 15.2, 9.4 Hz, 1H, 13-H), 5.78 (d, J = 15.5 Hz, 1H, 2-H), 4.87 (ddd, J = 9.7, 9.0, 2.9 Hz, 1H, 15-H), 3.80 (dd, J = 10.8, 4.0 Hz, 1H, 21-H^A), 3.74 (dd, J = 10.8, 7.0 Hz, 1H, 21-H^B), 3.29 (dd, J = 10.3, 1.5 Hz, 1H, 5-H), 2.63 – 2.39 (m, 3H, 4-H, 8-H, 14-H), 1.83 (dqd, J = 14.7, 7.4, 2.9 Hz, 1H, 16-H^A), 1.58 (dquint, J = 14.7, 9.0, 7.4 Hz, 1H, 16-H^B), 1.52 – 1.42 (m, 2H, 7-H^{A,B}), 1.28 (dquintd, J = 11.0, 6.8, 6.0, 1.5 Hz, 1H, 6-H), 1.18 (d, J = 7.0 Hz, 3H, 20-H$_3$), 1.12 (d, J = 6.7 Hz, 3H, 18-H$_3$), 1.00 (d, J = 6.8 Hz, 3H, 19-H$_3$), 0.96 (t, J = 7.4 Hz, 3H, 17-H$_3$).

^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$): δ 203.2 (C-9), 166.1 (C-1), 151.3 (C-3), 141.7 (C-11), 140.6 (C-13), 134.1 (C-12), 123.4 (C-10), 121.1 (C-2), 80.2 (C-5), 73.5 (C-15), 62.2 (C-21), 51.6 (C-14), 44.7 (C-8), 40.4 (C-4), 33.8 (C-6), 31.6 (C-7), 25.4 (C-16), 19.3 (C-18), 17.7 (C-20), 17.3 (C-19), 9.7 (C-17). **^{1}H NMR (600 MHz, [D$_6$]-acetone):** δ 7.01 (ddd, J = 15.0, 11.1, 0.7 Hz, 1H, 11-H), 6.55 (dd, J = 15.5, 10.1 Hz, 1H, 3-H), 6.48 (dt, J = 15.0, 0.7 Hz, 1H, 10-H), 6.24 (ddt, J = 15.3, 11.1, 0.7 Hz, 1H, 12-H), 6.03 (ddt, J = 15.3, 9.4, 0.8 Hz, 1H, 13-H), 5.91 (dd, J = 15.5, 0.7 Hz, 1H, 2-H), 4.93 (td, J = 10.2, 9.0, 2.8 Hz, 1H, 15-H), 3.90 (t, J = 5.3 Hz, 1H, 23-H), 3.81 (d, J = 6.0 Hz, 1H, 22-H), 3.76 (dt, J = 10.9, 5.3 Hz, 1H, 21-H^A), 3.72 (ddd, J = 10.9, 5.3, 3.6 Hz, 1H, 21-H^B), 3.26 (ddd, J = 10.4, 6.0, 1.5 Hz, 1H, 5-H), 2.57 (tqd, J = 10.1, 6.7, 0.7 Hz, 1H, 4-H), 2.45 (dqd, J = 12.2, 6.9, 4.4 Hz, 1H, 8-H), 2.38 (ddddd, J = 10.0, 9.4, 5.3, 3.6, 0.8 Hz, 1H, 14-H), 1.90 (dqd, J = 14.5, 7.4, 2.8 Hz, 1H, 16-H^A), 1.65 (ddd, J = 13.9, 12.2, 3.4 Hz, 1H, 7-H^A), 1.57 (ddq, J = 14.5, 9.0, 7.4 Hz, 1H, 16-H^B), 1.49 (ddd, J = 13.9, 12.4, 4.4 Hz, 1H, 7-H^B), 1.18 (dqdd, J = 12.4, 6.8, 3.4, 1.5 Hz, 1H, 6-H), 1.15 (d, J = 6.9 Hz, 3H, 20-H$_3$), 1.08 (d, J = 6.7 Hz, 3H, 18-H$_3$), 0.95 (d, J = 6.8 Hz, 3H, 19-H$_3$), 0.91 (t, J = 7.3 Hz, 3H, 17-H$_3$). **^{13}C{^{1}H} NMR (151 MHz, [D$_6$]-acetone):** δ 201.1 (C-9), 164.7 (C-1), 150.6 (C-3), 140.3 (C-13), 140.1 (C-11), 132.1 (C-12), 122.7 (C-10), 120.3 (C-2), 78.1 (C-5), 72.5 (C-15), 59.9 (C-21), 50.2 (C-14), 43.9 (C-8), 39.5 (C-4), 33.1 (C-6), 30.3 (C-7), 23.8 (C-16), 17.9 (C-18), 15.9 (C-20), 15.9 (C-19), 8.2 (C-17). **IR (film):** 3419, 2964, 292, 1704, 1670, 1650, 1588, 1348, 1279, 1228, 1174, 1152, 1057, 1005, 988, 847. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{21}$H$_{32}$O$_5$Na 387.2142; found: 387.2143.

NMR Spectroscopic Comparison of Natural and Synthetic Mycinolide IV

Figure 4.6 shows a visual comparison of the recorded ^{13}C NMR spectrum (CDCl$_3$) of synthetic mycinolide IV (in black) and a simulated spectrum created in MestReNova (in red) based on the ^{13}C NMR shifts (CDCl$_3$) of authentic mycinolide IV reported in the literature.[38c] This comparison confirms the excellent agreement of the numeric data (Δppm $\leq$ 0.1 ppm).
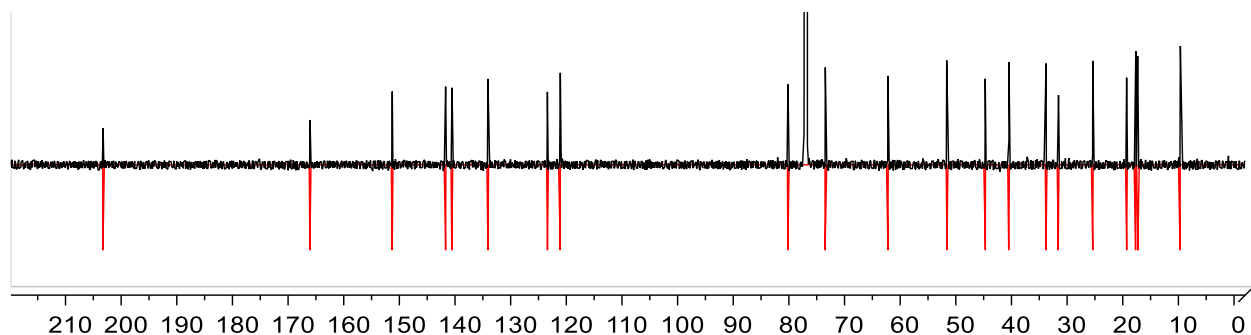
Figure 4.6: ^{13}C NMR shifts (CDCl$_3$, ppm) of synthetic (black) and authentic[38c] (red) mycinolide IV.

Figure 4.7 shows a visual comparison of a "virtual" 100 MHz ^{1}H NMR spectrum (red) of mycinolide IV simulated on the basis of the experimental NMR data recorded at 600 MHz ([D$_6$]-acetone) with the ^{1}H NMR spectrum ([D$_6$]-acetone/D$_2$O) reported in the literature (black).[38c] Since the latter spectrum was only graphically depicted, and no numeric values of chemical shifts and coupling constants were reported, this comparison is limited to this purely graphical and qualitative assessment. The frequency of the spectrum reported in the literature was not specified; it is assumed to be 100 MHz based on spectra of several mycinamicins reported by the same groups two years later. Since no NMR spectrometer was available to record a ^{1}H NMR spectrum of the synthesized material at 100 MHz, a spectrum was recorded at 600 MHz, and all proton chemical shifts were assigned and coupling constants were extracted. This information was then used for a simulation of the ^{1}H NMR spectrum at 100 MHz using the DAISY module in TOPSPIN. Additionally, OH signals of the recorded spectrum and their couplings to neighbouring protons were removed to account for their invisibility in the literature spectrum due to the presence of an undefined amount of D$_2$O.
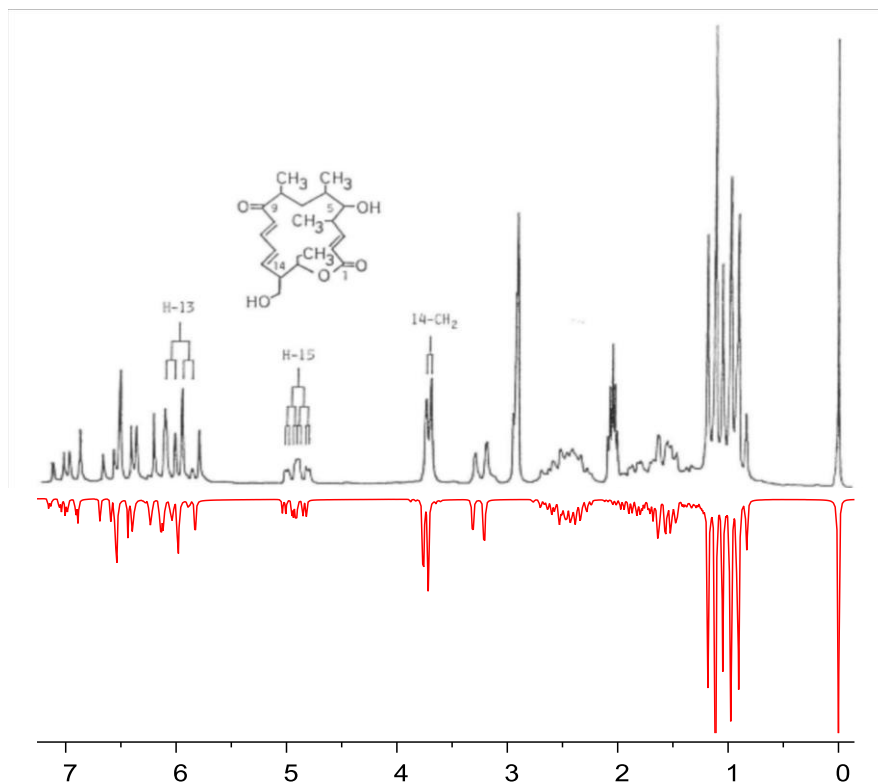
Figure 4.7: Comparision of a virtual ^{1}H NMR spectrum ([D$_6$]-acetone, ppm) of synthetic mycinolide IV with the literature spectrum ([D$_6$]-acetone/D$_2$O).[38c]

Attachment of the Carbohydrates to Complete the Total Synthesis of Mycinamicin IV

Compound 180. Aqueous HCl (1.5 M, 0.20 mL, 0.30 mmol) was added to a solution of compound **94** (5.2 mg, 8.0 µmol) in methanol (0.84 mL) at ambient temperature. After stirring for 8 h, the solution was diluted with water (3 mL) and ethyl acetate (3 mL), and vigorously stirred for 2 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with saturated aqueous sodium chloride (2 mL), filtered through a pad of anhydrous sodium sulfate, and the filtrate was evaporated. Purification of the crude product by flash chromatography on silica (15 – 40 µm particle size; hexanes/EtOAc, 2:1 → 1:1) afforded the title compound as a colorless solid (1.7 mg, 52% yield).). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.12 (ddd, J = 15.1, 11.0, 0.8 Hz, 1H), 6.61 (dd, J = 15.5, 9.9 Hz, 1H), 6.27 – 6.14 (m, 2H), 5.93 (dd, J = 15.2, 9.5 Hz, 1H), 5.77 (dd, J = 15.5, 0.7 Hz, 1H), 4.87 (ddd, J = 10.1, 9.0, 2.8 Hz, 1H), 4.68 (d, J = 6.6 Hz, 1H), 4.64 (d, J = 6.5 Hz, 1H), 3.80 (dd, J = 10.8, 4.1 Hz, 1H), 3.74 (dd, J = 10.8, 6.9 Hz, 1H), 3.41 (s, 3H), 3.15 (dd, J = 10.3, 1.5 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.47 (tdd, J = 10.1, 6.8, 4.1 Hz, 1H), 1.83 (dqd, J = 14.7, 7.4, 2.8 Hz, 1H), 1.62 – 1.46 (m, 3H), 1.34 – 1.27 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H),
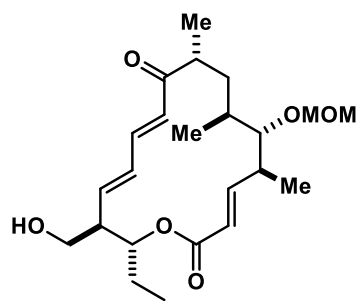
119

0.99 (d, $J = 6.8$ Hz, 3H), 0.96 (t, $J = 7.6$ Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 203.3, 166.1, 151.4, 141.7, 140.6, 134.1, 123.5, 121.2, 99.3, 88.6, 73.5, 62.2, 56.3, 51.6, 44.6, 40.4, 34.2, 32.5, 25.4, 19.5, 17.6, 17.6, 9.6. HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{23}$H$_{36}$O$_6$Na 431.2404; found 431.2402.

Glycosyl Acceptor 181. In a 10-mL Schlenk tube, a solution of dimethylboron bromide in dichloromethane (0.80 M, 0.19 mL, 0.15 mmol) was added dropwise to a solution of MOM ether **94** (32.7 mg, 50.5 µmol) in dichloromethane (1.0 mL) at −78 °C. After 1 h, a mixture of tetrahydrofuran (4 mL) and an aqueous solution of sodium carbonate (5% w/w, 4 mL) was introduced at that temperature. The mixture was warmed to room temperature by immersing the tube into a warm water bath, and vigorous stirring was continued for another 2 h. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with ethyl acetate (4 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 5:2) furnished the title compound as a colorless foam (24.4 mg, 80% yield). $[\alpha]_D^{20} = +47.6$ (c 0.45, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.69 – 7.59 (m, 4H), 7.48 – 7.35 (m, 6H), 7.18 – 7.10 (m, 1H), 6.60 (dd, $J = 15.5$, 9.9 Hz, 1H), 6.23 (d, $J = 15.1$ Hz, 1H), 6.15 – 6.04 (m, 2H), 5.77 (dd, $J = 15.6$, 0.7 Hz, 1H), 4.99 (ddd, $J = 10.1$, 9.0, 2.7 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.29 (d, $J = 10.3$ Hz, 1H), 2.62 – 2.45 (m, 2H), 2.39 – 2.29 (m, 1H), 1.73 – 1.61 (m, 1H), 1.58 – 1.35 (m, 4H), 1.34 – 1.24 (m, 1H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.07 (s, 9H), 1.00 (d, $J = 6.7$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 203.6, 166.3, 151.2, 142.5, 141.8, 135.8, 135.8, 133.33, 133.31, 132.95, 130.01, 129.98, 127.9, 123.0, 121.4, 80.4, 73.9, 62.9, 51.3, 45.0, 40.6, 33.9, 31.8, 27.0, 25.2, 19.5, 19.4, 17.9, 17.5, 9.88. IR (film): 3487, 3071, 2962, 2932, 2877, 2858, 1715, 1679, 1652, 1632, 1594, 1460, 1428, 1380, 1351, 1327, 1264, 1225, 1174, 1149, 1111, 988, 929, 8823, 790, 743, 703, 609, 504 cm^{-1}. HRMS-ESI m/z: [M+Na]$^+$ calcd for C$_{37}$H$_{50}$O$_5$SiNa 625.3320; found 625.3323.
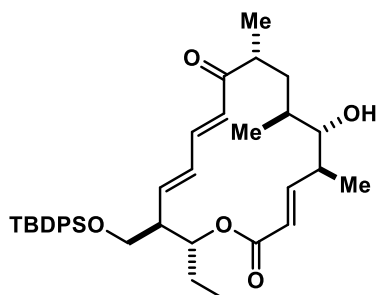
Glycosyl Acceptor 184. In a 10-mL Schlenk tube, a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate in dichloromethane (0.088 M, 0.46 mL, 41 μmol) was added dropwise to a solution of alcohol **181** (24.4 mg, 40.5 μmol) and trichloroacetimidate **139d** (129 mg, 0.304 mmol) in dichloromethane (1.3 mL) at room temperature. After stirring for 1.5 h, an additional amount of the silyl triflate stock solution (0.69 mL, 61 μmol) was added; the silyl triflate addition (0.23 mL, 20 μmol) was repeated one more time after stirring for another 2.5 h. After stirring for 1.5 h after the last addition, saturated aqueous sodium bicarbonate solution (10 mL) was introduced and the mixture was diluted with ethyl acetate (10 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/acetone, 5:1; 0.1% *v/v* of triethylamine added) furnished the intermediate glycosylation product admixed with trichloroacetamide (a byproduct from glycosyl donor activation) as a light yellowish gum.
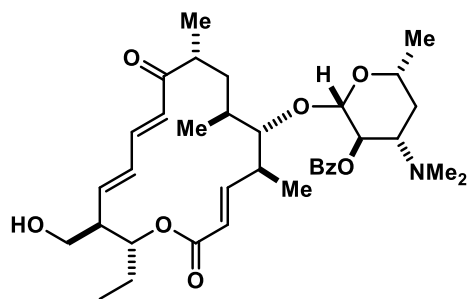
In a 10-mL Schlenk tube, a solution of TBAF in THF (0.50 M, 0.17 mL, 85 μmol) was added to a solution of this material in THF (0.63 mL) at room temperature. After stirring for 1 h, the mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/acetone, 2:1; 0.1% *v/v* of triethylamine added) furnished the title compound as a white, amorphous solid (21.4 mg, 84% yield). $[\alpha]_D^{20}$ = +38.3 (*c* 0.41, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.11 – 8.04 (m, 2H), 7.67 – 7.58 (m, 1H), 7.53 – 7.44 (m, 2H), 7.06 (dd. *J* = 15.1, 10.9 Hz, 1H), 6.48 (dd, *J* = 15.5, 9.9 Hz, 1H), 6.15 (d, *J* = 15.1 Hz, 1H), 6.09 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.91 (dd, *J* = 15.3, 9.3 Hz, 1H), 5.59 (d, *J* = 15.5 Hz, 1H), 5.32 – 5.20 (br m, 1H), 4.85 (td, *J* = 9.6, 2.8 Hz, 1H), 4.57 (d, *J* = 7.2 Hz, 1H), 3.81 – 3.55 (m, 4H), 3.26 (d, *J* = 10.1 Hz, 1H), 2.83 – 2.48 (br m, 7H), 2.44 – 2.33 (m, 2H), 1.87 – 1.72 (m, 2H), 1.64 – 1.36 (m, 4H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.25 – 1.19 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 – 0.83 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 203.7, 166.2, 165.3, 150.9, 141.7, 140.8, 134.0, 130.15, 130.06, 128.8, 123.8, 121.3, 101.8, 87.5, 73.8, 69.7, 68.6, 64.1, 62.1, 51.6, 44.8, 40.7, 34.2, 32.3, 31.9, 25.4, 20.8, 19.4, 17.8, 17.5, 9.8. **IR (film):** 3343, 2968, 2933, 2878, 1716, 1678, 1653, 1593, 1453, 1375, 1353, 1323, 1265, 1178, 1112, 1066, 1029, 999, 1066, 937, 755, 712 cm^{-1}. **HRMS-ESI *m/z*:** [M+H]$^+$ calcd for C$_{36}$H$_{52}$NO$_8$ 626.3687; found 626.3688.

When the glycosylation procedure described above was conducted with trimethyl- or triethylsilyl triflate as activator *added at or below 0 °C,* followed by warming to room temperature, an unstable product was formed that could be isolated in ca. 30% yield (with TMSOTf, addition at −30 °C). By comparison to the literature precedence,[58b] structure **183** could be assigned to this side product. The compound decomposed upon attempted re-purification of a small sample by flash chromatography. Moreover, the compound was not stable enough in CDCl₃ to deliver a satisfying $^{13}C\{^1H\}$ NMR spectrum by routine measurement overnight.

183
R$_f$ = 0.27 (hexanes/EtOAc, 25:1)

H-5
dd, 3.60 ppm
(J = 9.8, 3.1 Hz)

different
signal pattern
(^{1}H, δ: 7.3 – 5.6 ppm)

181
R$_f$ = 0.24 (hexanes/EtOAc, 5:2)

H-5
d, 3.29 ppm
(J = 10.3 Hz)
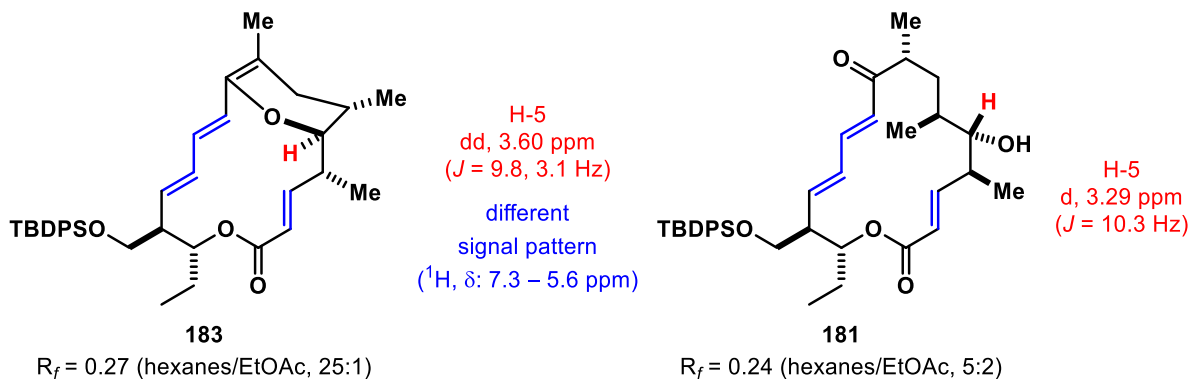
Following the same glycosylation procedure with either trimethyl- or triethylsilyl triflate as activator *added at room temperature*, the major product resulted from silylation of the acceptor alcohol (44% yield of **182** (R = Me) for addition of TMSOTf; 2 × 0.75 equiv used, 3.5 h stirring).

*Data of Compound **182** (R = Me)*: R$_f$ = 0.18 (hexanes/EtOAc, 20:1). ^{1}H NMR (400 MHz, CDCl₃): δ 7.68 – 7.60 (m, 4H), 7.48 – 7.36 (m, 6H), 7.18 – 7.09 (m, 1H), 6.60 (dd, J = 15.5, 10.0 Hz, 1H), 6.22 (d, J = 15.1 Hz, 1H), 6.16 – 6.02 (m, 2H), 5.74 (dd, J = 15.5, 0.7 Hz, 1H), 4.98 (ddd, J = 10.1, 9.0, 2.7 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.32 (dd, J = 10.1, 1.3 Hz, 1H), 2.59 – 2.43 (m, 2H), 2.39 – 2.28 (m, 1H), 1.73 – 1.60 (m, 1H), 1.54 – 1.35 (m, 2H), 1.18 (d, J = 6.9 Hz, 3H), 1.06 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.90 – 0.82 (m, 5H), 0.13 (s, 9H).

*Data of Compound **182** (R = Et)*: R$_f$ = 0.20 (hexanes/EtOAc, 20:1). ^{1}H NMR (400 MHz, CDCl₃): δ 7.68 – 7.58 (m, 4H), 7.48 – 7.35 (m, 6H), 7.17 – 7.08 (m, 1H), 6.60 (dd, J = 15.5, 10.0 Hz, 1H), 6.21 (d, J = 15.1 Hz, 1H), 6.15 – 6.01 (m, 2H), 5.72 (d, J = 15.5 Hz, 1H), 5.02 – 4.94 (m, 1H), 3.79 – 3.68 (m, 2H), 3.36 (d, J = 9.8 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.39 – 2.28 (m, 1H), 1.72 – 1.59 (m, 1H), 1.54 – 1.35 (m, 2H), 1.17 (d, J = 6.9 Hz, 3H), 1.06 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.93 (d, J = 6.8 Hz, 3H), 0.90 – 0.84 (m, 5H), 0.69 – 0.58 (m, 6H).

Macrolide 185. In a 10-mL Schlenk tube, a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate in dichloromethane (0.088 M, 0.20 mL, 18 µmol) was added dropwise to a solution of alcohol **184** (20.9 mg, 33.4 µmol) and trichloroacetimidate **21c** (39.0 mg, 103 µmol) in a mixture of dichloromethane (1.5 mL) and acetonitrile (1.5 mL) at room temperature. After stirring for 1 h, an additional amount of the silyl triflate stock solution (0.57 mL, 50 µmol) was added, and stirring was continued for another 2 h. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/acetone, 4:1 → 3:1 → 2:1; 0.1% *v/v* of triethylamine added) furnished title compound as a colorless gum (9.2 mg, 33% yield).
$[\alpha]_D^{20}$ = +28.5 (*c* 0.20, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.16 – 8.01 (m, 2H), 7.71 – 7.62 (m, 1H), 7.57 – 7.47 (m, 2H), 7.06 (dd, *J* = 15.1, 10.3 Hz, 1H), 6.46 (dd, *J* = 15.6, 9.8 Hz, 1H), 6.11 (d, *J* = 15.0 Hz, 1H), 6.06 – 5.89 (m, 2H), 5.57 (d, *J* = 15.5 Hz, 1H), 5.39 – 5.29 (br m, 1H), 4.84 (td, *J* = 9.9, 2.6 Hz, 1H), 4.61 (d, *J* = 8.0 Hz, 1H), 4.59 – 4.52 (br m, 1H), 4.43 (dd, *J* = 9.9, 2.6 Hz, 1H), 4.00 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.95 – 3.85 (m, 2H), 3.80 – 3.61 (br m, 2H), 3.55 – 3.45 (m, 7H), 3.26 (d, *J* = 10.0 Hz, 1H), 3.02 (dd, *J* = 8.0, 2.8 Hz, 1H), 2.81 (br s, 6H), 2.59 – 2.42 (m, 2H), 2.40 – 2.29 (m, 1H), 2.11 (s, 3H), 1.88 – 1.63 (m, 4H), 1.58 – 1.44 (m, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 – 0.84 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 203.6, 170.3, 166.0, 165.2, 150.5, 142.0, 141.6, 134.4, 133.1, 130.2, 129.1, 128.6, 123.4, 121.4, 101.5, 101.1, 87.3, 80.7, 77.9, 74.9, 74.0, 69.7, 68.8, 68.4, 67.5, 64.4, 61.7, 59.8, 49.3, 44.8, 44.5, 40.8, 37.2, 34.4, 34.1, 32.3, 25.3, 21.1, 20.6, 19.5, 17.9, 17.5, 17.4, 9.8. **IR (film):** 3373, 2968, 2933, 2880, 1726, 1679, 1653, 1595, 1453, 1373, 1325, 1262, 1236, 1170, 1090, 1067, 1001, 984, 754, 713 cm^{-1}. **HRMS-ESI** *m/z***:** [M+H]$^+$ calcd for C$_{46}$H$_{68}$NO$_{13}$ 842.4685; found 842.4684.

*Analytical and spectral data of the corresponding α-anomer isolated in an experiment using fluoride **21b** as the glycosyl donor*: $[\alpha]_D^{20}$ = +75.9 (*c* 0.27, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.10 – 8.03 (m, 2H), 7.62 – 7.55 (m, 1H), 7.51 – 7.42 (m, 2H), 7.10 (dd, *J* = 15.0, 10.9 Hz, 1H), 6.49 (dd, *J* = 15.5, 10.0 Hz, 1H), 6.15 (d, *J* = 15.1 Hz, 1H), 6.06 (dd, *J* = 15.3, 10.9 Hz, 1H), 5.92 (dd, *J* = 15.3, 9.1 Hz, 1H), 5.60 (d, *J* = 15.5 Hz, 1H), 5.25 – 5.10 (br m, 1H), 4.87 – 4.79 (m, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.49 (d, *J* = 7.4 Hz, 1H), 4.45 (dd, *J* = 10.0, 2.7 Hz, 1H), 4.19 – 4.09 (m, 1H), 3.94 (t, *J* = 2.8 Hz, 1H), 3.77 (dd, *J* = 9.6, 7.0 Hz,

1H), 3.62 – 3.48 (m, 2H), 3.48 (s, 3H), 3.40 (s, 3H), 3.30 (dd, J = 4.2, 2.9 Hz, 1H), 3.24 (d, J = 9.9 Hz, 1H), 3.19 – 3.01 (br m, 1H), 2.65 – 2.34 (m, 9H), 2.12 (s, 3H), 1.87 – 1.74 (m, 1H), 1.73 – 1.38 (m, 3H), 1.32 – 1.19 (m, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 204.0, 170.5, 166.1, 165.4, 150.9 (br), 142.2, 141.8, 133.5, 133.2, 130.0, 128.7, 123.2, 121.3, 102.4 (br), 97.1, 87.6, 78.7, 75.2, 74.5, 74.1, 71.3 (br), 68.9 (br), 68.3, 64.1, 61.8, 61.0, 57.4, 48.8, 44.9, 40.9, 34.2, 32.3, 25.4, 21.2, 20.9, 19.4, 17.9, 17.5, 17.1, 9.8.. **IR (film):** 3407, 2971, 2934, 2879, 1723, 1680, 1652, 1632, 1594, 1454, 1375, 1354, 1323, 1266, 1236, 1177, 1108, 1051, 1001, 984, 752, 712, 665 cm^{-1}. **HRMS-ESI m/z:** [M+H]$^+$ calcd for C$_{46}$H$_{68}$NO$_{13}$ 842.4685; found 842.4684.

Mycinamicin IV (2). In a 10-mL Schlenk tube equipped with a cooling finger under argon, macrolide **185** (9.2 mg, 11 µmol) was treated with a mixture of methanol, triethylamine and water (5:1:1 $v/v/v$, 0.80 mL) and the resulting mixture was stirred at 70 °C (bath temperature) for 6.5 h. For work-up, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium carbonate solution (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (dichloromethane/methanol, 9:1; 0.1% v/v of triethylamine added) furnished the title compound as a white, amorphous solid containing trace impurities (5.4 mg, 71% yield). Analytically pure mycinamicin IV was obtained by preparative HPLC: Agilent 1260 Infinity pump, 150 mm length × 10 mm diameter YMC Triart C18 5 µm column, methanol/aq. 20 mM NH$_4$HCO$_3$ pH 9.0 (70:30 v/v, 4.7 mL/min, 10.5 MPa, 300 K) eluent, UV-detection at 210 nm.
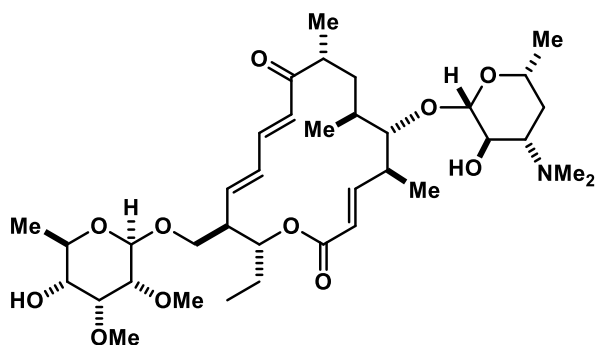
Analytical and spectral data of synthetic Mycinamicin IV (**2**): [α]$_D^{25}$ = +7.5 (c 0.3, CHCl$_3$). **^{1}H NMR (400 MHz, C$_6$D$_6$):** δ 7.44 – 7.34 (m, 1H, 11-H), 6.85 (dd, J = 15.5, 10.0 Hz, 1H, 3-H), 6.13 (d, J = 15.0 Hz, 1H, 10-H), 6.01 – 5.94 (m, 2H, 12-H, 13-H), 5.62 (d, J = 15.5 Hz, 1H, 2-H), 5.17 – 5.09 (m, 1H, 15-H), 4.66 (d, J = 7.8 Hz, 1H, 1''-H), 4.14 (d, J = 7.2 Hz, 1H, 1'-H), 3.92 (dd, J = 9.5, 3.7 Hz, 1H, 21a-H), 3.60 – 3.49 (m, 1H, 5''-H), 3.41 – 3.32 (m, 8H, 7''-H$_3$, 8''-H$_3$, 2'-H, 3''-H), 3.17 (dd, J = 9.5, 6.1 Hz, 1H, 21b-H), 3.11 (d, J = 10.3 Hz, 1H, 5-H), 3.07 – 2.98 (m, 2H, 5'-H, 4''-H), 2.84 (dd, J = 7.9, 2.8 Hz, 1H, 2''-H), 2.84 – 2.66 (m, 2H, 8-H, 4-H), 2.43 – 2.32 (m, 1H, 14-H), 2.24 – 2.15 (m, 1H, 3'-H), 1.86 (s, 6H, 7'-H$_6$), 1.85 – 1.75 (m, 1H, 7a-H), 1.72 – 1.59 (m, 2H, 7b-H, 16a-H), 1.52 – 1.43 (m, 1H, 6-H), 1.41 – 1.34 (m, 7H, 6''-H$_3$, 16b-H, 18-H$_3$), 1.28 (d, J = 6.8 Hz, 3H, 19-H$_3$), 1.13 – 1.00 (m, 7H, 4'a-H, 6'-H$_3$,

20-H$_3$), 0.94 (t, J = 7.3 Hz, 3H, 17-H$_3$), 0.93 – 0.80 (m, 1H, 4'b-H). **^{13}C{^{1}H} NMR (101 MHz, C$_6$D$_6$):** δ 201.9 (9-C), 166.1 (1-C), 152.1 (3-C), 141.6 (11-C), 141.3 (13-C), 133.6 (12-C), 124.1 (10-C), 121.6 (2-C), 105.4 (1'-C), 101.7 (1"-C), 88.0 (5-C), 82.6 (2"-C), 80.7 (3"-C), 73.7 (15-C), 73.0 (4"-C), 70.9 (5"-C), 70.6 (2'-C), 69.2 (5'-C), 68.6 (21-C), 66.4 (3'-C), 61.6 (8"-C), 59.7 (7"-C), 49.5 (14-C), 45.3 (8-C), 41.6 (4-C), 39.9 (7'-C), 34.7 (6-C), 33.1 (7-C), 28.5 (4'-C), 25.5 (16-C), 21.3 (6'-C), 19.7 (18-C), 18.3 (6"-C), 17.9 (19-C), 17.8 (20-C), 10.0 (17-C). **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.11 (ddd, J = 15.1, 11.0, 0.7 Hz, 1H, 11-H), 6.61 (dd, J = 15.5, 9.9 Hz, 1H, 3-H), 6.21 (d, J = 15.0 Hz, 1H, 10-H), 6.12 (ddd, J = 15.3, 11.0, 0.7 Hz, 1H, 12-H), 5.99 (dd, J = 15.3, 9.2 Hz, 1H, 13-H), 5.76 (dd, J = 15.4, 0.7 Hz, 1H, 2-H), 4.89 (ddd, J = 10.2, 9.0, 2.7 Hz, 1H, 15-H), 4.57 (d, J = 7.8 Hz, 1H, 1"-H), 4.24 (d, J = 7.3 Hz, 1H, 1'-H), 4.04 (dd, J = 9.5, 3.8 Hz, 1H, 21a-H), 3.75 (t, J = 3.1 Hz, 1H, 3"-H), 3.62 (s, 3H, 8"-H$_3$), 3.54 (dd, J = 9.5, 6.7 Hz, 1H, 21b-H), 3.53 – 3.40 (m, 7H, 5"-H, 7"-H$_3$, 5'-H, 2'-OH, 4"-OH), 3.28 (d, J = 10.5 Hz, 1H, 5-H), 3.24 (dd, J = 10.2, 7.3 Hz, 1H, 2'-H), 3.21 – 3.15 (br m, 1H, 4"-H), 3.03 (dd, J = 7.8, 2.8 Hz, 1H, 2"-H), 2.79 – 2.71 (m, 1H, 4-H), 2.59 – 2.50 (m, 2H, 8-H, 14-H), 2.47 (ddd, J = 12.3, 10.2, 3.9 Hz, 1H, 3'-H), 2.27 (s, 6H, 7'-H$_6$), 1.88 – 1.80 (m, 1H, 16a-H), 1.67 – 1.52 (m, 4H, 4'a-H, 16b-H, 7-H$_2$), 1.29 – 1.22 (m, 2H, 4'b-H, 6-H), 1.27 (d, J = 6.3 Hz, 3H, 6"-H$_3$), 1.24 (d, J = 6.8 Hz, 3H, 18-H$_3$), 1.23 (d, J = 6.1 Hz, 3H, 6'-H$_3$), 1.13 (d, J = 6.9 Hz, 3H, 20-H$_3$), 0.99 (d, J = 6.9 Hz, 3H, 19-H$_3$), 0.94 (t, J = 7.3 Hz, 3H, 17-H$_3$). **^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$):** δ 203.8 (9-C), 166.2 (1-C), 151.8 (3-C), 141.8 (11-C), 141.4 (13-C), 133.1 (12-C), 123.2 (10-C), 120.9 (2-C), 105.0 (1'-C), 101.1 (1"-C), 87.9 (5-C), 81.9 (2"-C), 79.9 (3"-C), 73.7 (15-C), 72.7 (4"-C), 70.6 (5"-C), 70.4 (2'-C), 69.5 (5'-C), 68.6 (21-C), 65.9 (3'-C), 61.8 (8"-C), 59.9 (7"-C), 49.2 (14-C), 44.9 (8-C), 41.4 (4-C), 40.3 (7'-C), 34.1 (6-C), 32.6 (7-C), 28.2 (4'-C), 25.3 (16-C), 21.2 (6'-C), 19.4 (18-C), 17.8 (6"-C), 17.7 (20-C), 17.4 (19-C), 9.7 (17-C). **IR (film):** 3453, 2968, 2932, 2878, 1714, 1679, 1651, 1593, 1458, 1379, 1353, 1324, 1277, 1233, 1167, 1073, 984, 963, 936, 835, 713, 546 cm^{-1}. **HRMS-ESI *m/z*:** [M+H]$^+$ calcd for C$_{37}$H$_{62}$NO$_{11}$ 696.4317; found 696.4310.

NMR Spectroscopic Comparison of Natural and Synthetic Mycinamicin IV
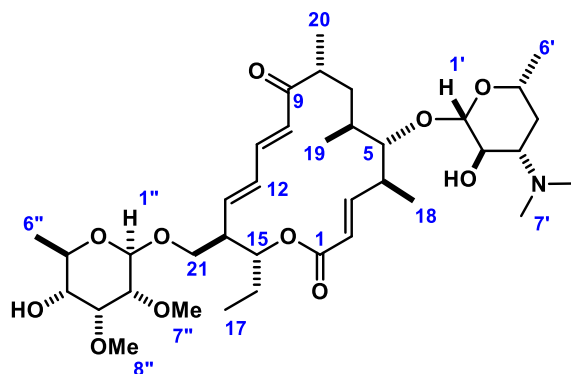
Table 4.5: Comparison of the NMR Data of Natural[38b] and Synthetic Mycinamicin IV: Signals of the Aglycon (numbering as shown in the Insert; indiscernible signals reported without designating any multiplicity)

Position	δ_C natural	δ_C synthetic	Deviation $\Delta\delta_C$	δ_H (*J*/Hz) synthetic
1	166.1	166.2	+0.1	-
2	120.9	120.9	0.0	5.76 dd (15.4, 0.7)
3	151.6	151.8	+0.2	6.61 dd (15.5, 9.9)
4	41.3	41.4	+0.1	2.75
5	87.9	87.9	0.0	3.28 d (10.5)
6	34.1	34.1	0.0	1.26
7	32.6	32.6	0.0	1.63
				1.56
8	44.9	44.9	0.0	2.56
9	203.4	203.8	+0.4	-
10	123.2	123.2	0.0	6.21 d (15.0)
11	141.7	141.8	+0.1	7.11 ddd (15.1, 11.0, 0.7)
12	133.0	133.1	+0.1	6.12 ddd (15.3, 11.0, 0.7)
13	141.3	141.4	+0.1	5.99 dd (15.3, 9.2)
14	49.2	49.2	0.0	2.53
15	72.7	73.7	+1.0	4.89 ddd (10.2, 9.0, 2.7)
16	25.3	25.3	0.0	1.84
				1.56
17	9.6	9.7	+0.1	0.94 t (7.3)
18	19.4	19.4	0.0	1.24 d (6.8)
19	17.4	17.4	0.0	0.99 d (6.9)
20	17.8	17.7	-0.1	1.13 d (6.9)
21	68.6	68.6	0.0	4.04 dd (9.5, 3.8)
				3.54 dd (9.5, 6.7)

Table 4.6: Comparison of the NMR Data of Natural[38b] and Synthetic Mycinamicin IV: Signals of the Carbohydrates (numbering as shown in the Insert; indiscernible signals reported without designating any multiplicity)

Position	δ_C natural	δ_C synthetic	Deviation $\Delta\delta_C$	δ_H (*J*/Hz) synthetic
1'	104.9	105.0	+0.1	4.24 d (7.3)
2'	70.4	70.4	0.0	3.24 dd (10.2, 7.3)
3'	65.8	65.9	+0.1	2.47 ddd (12.3, 10.2, 3.9)
4'	28.3	28.2	-0.1	1.65
				1.26
5'	69.5	69.5	0.0	3.49
6'	21.2	21.2	0.0	1.23 d (6.1)
7'	40.2	40.3	+0.1	2.27
1"	101.0	101.1	+0.1	4.57 d (7.8)
2"	81.9	81.9	0.0	3.03 dd (7.8, 2.8)
3"	79.9	79.9	0.0	3.75 t (3.1)
4"	72.7	72.7	0.0	3.18
5"	70.5	70.6	+0.1	3.52
6"	17.8	17.8	0.0	1.27 d (6.3)
7"	59.7	59.9	+0.2	3.51
8"	61.7	61.8	+0.1	3.62
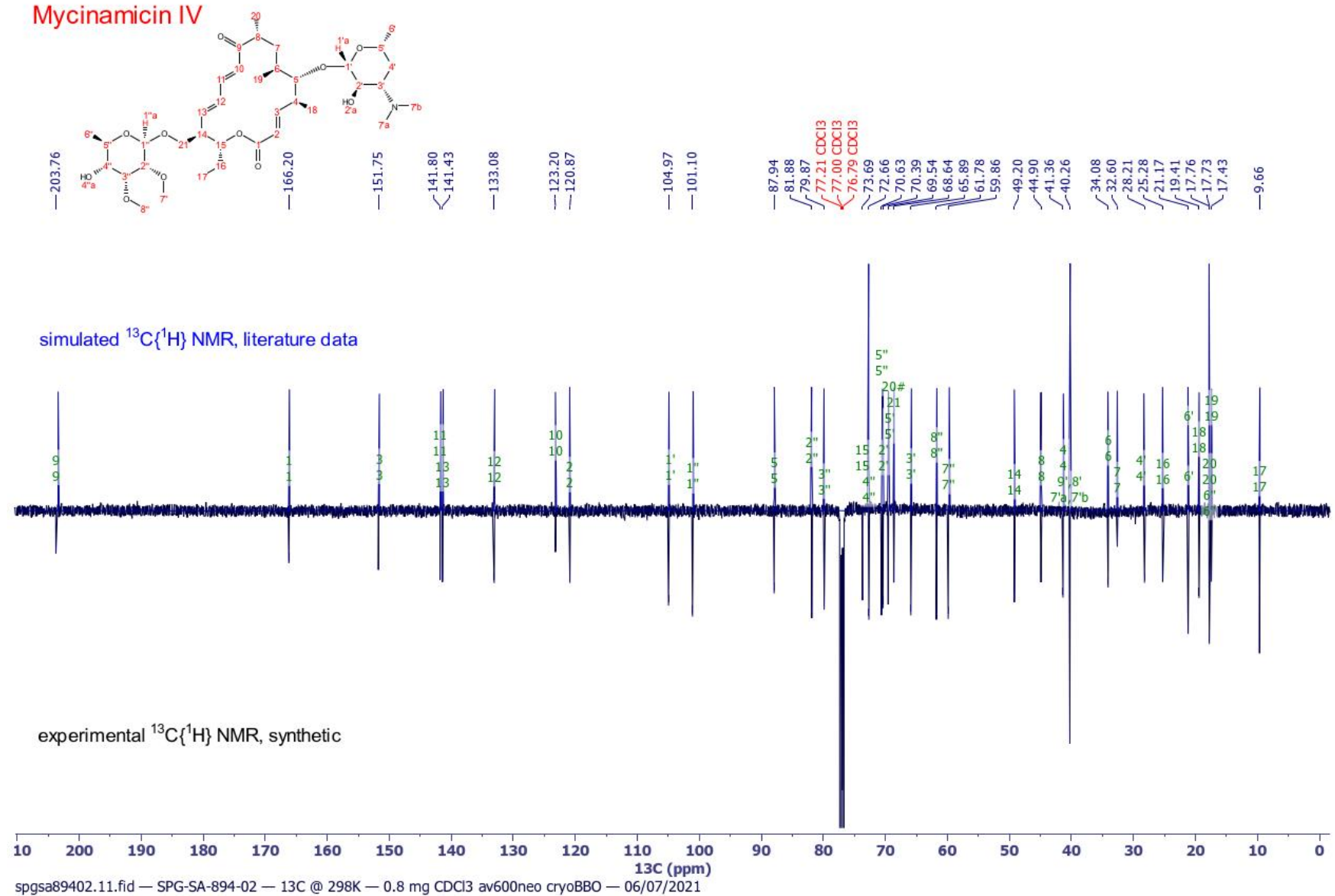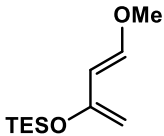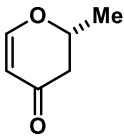
Figure 4.8: Comparison of ^{13}C NMR data in CDCl₃ of natural (top, generated from tabulated data[38b]) and synthetic Mycinamicin IV (bottom)

4.6 Syntheses of the Deoxy Sugars

Enantioselective Synthesis of Dihydropyranone 107

(*E*)-Triethyl((4-methoxybuta-1,3-dien-2-yl)oxy)silane (113b). In a 250-mL two-necked flask, triethylsilyl trifluromethanesulfonate (13 mL, 57 mmol) was added over 12 min to (*E*)-4-methoxybut-3-en-2-one (5.2 mL, 51 mmol) and triethylamine (17 mL, 100 mmol) in diethyl ether (90 mL) at −20 °C. After complete addition, the mixture was stirred for further 10 min at −20 °C and for another 2 h at 0 °C. The mixture was diluted with hexanes (80 mL) and quickly washed with ice-cold saturated aqueous solutions of sodium bicarbonate and sodium chloride (50 mL each). The organic layer was dried over anhydrous sodium sulfate, the drying agent was filtered off, and volatile material was removed under reduced pressure (38 °C, 20 mbar). The dark brown, oily liquid was purified by bulb-to-bulb distillation under reduced pressure (75 – 80 °C bath temperature, 10^{-3} mbar, receiving flask cooled in dry ice/acetone bath) to give the title compound as a colorless liquid (10.7 g, 97% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 6.89 (d, *J* = 12.3 Hz, 1H), 5.35 (d, *J* = 12.3 Hz, 1H), 4.09 – 4.04 (m, 2H), 3.59 (s, 3H), 1.03 – 0.97 (m, 9H), 0.76 – 0.68 (m, 6H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 154.3, 150.4, 103.3, 90.6, 56.6, 6.89, 5.12. The analytical data are in agreement with those reported in the literature.[115]

(*R*)-2-Methyl-2,3-dihydro-4H-pyran-4-one (107). A 25-mL Young tube was charged with pre-mixed powdered 4 Å molecular sieves (3.7 g) and chromium complex **114b** (260 mg, 0.534 mmol). The tube was immersed into a cooling bath (−20 °C) before acetaldehyde (10 mL, 178 mmol) was added, which had briefly been cooled on dry ice to facilitate the transfer. Siloxy diene **113b** (7.73 g, 36.1 mmol) was then added in one portion at −20 °C. The resulting mixture was vigorously stirred in the sealed tube for 15 h while allowing the cooling bath to gradually warm to ambient temperature. The mixture was directly loaded onto a solvent-packed silica column (hexanes/EtOAc, 25:1; 0.5% *v/v* of triethylamine added), eluting with the same solvent mixture to give the primary hetero-Diels-Alder adduct as an amber liquid (7.04 g).

A solution of trifluoroacetic acid in dichloromethane (10% *v/v*, 3.3 mL) was added to a solution of this material in dichloromethane (35 mL) at 0 °C (ice bath). The cooling bath was removed and the mixture was stirred for 3 h at room temperature. The acid was quenched with triethylamine (0.65 mL) and the solvent was removed under reduced pressure. Flash chromatography (pentane/*tert*-butyl methyl ether, 2:1 → 1:1) furnished the title compound as a volatile, light amber liquid (2.45 g, 61% yield, 93% *ee*). **bp** = 66 – 68 °C (13 mbar). $[\alpha]_D^{20}$ = +187.2 (*c* 1.5, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.34 (dd, *J* = 6.0, 0.7 Hz, 1H), 5.40 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.55 (dqdd, *J* = 12.7, 6.4, 4.5, 0.7 Hz, 1H), 2.51 (dd, *J* = 16.8, 12.6 Hz, 1H), 2.44 (ddd, *J* = 16.8, 4.5, 1.1 Hz, 1H), 1.46 (d, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR**

(101 MHz, CDCl₃): δ 192.8, 163.4, 107.0, 76.1, 43.6, 20.5. The enantiomeric purity was determined by GC (see below). The racemic sample was obtained following a literature procedure.[167] The analytical data are in agreement with those reported in the literature.[114, 168]
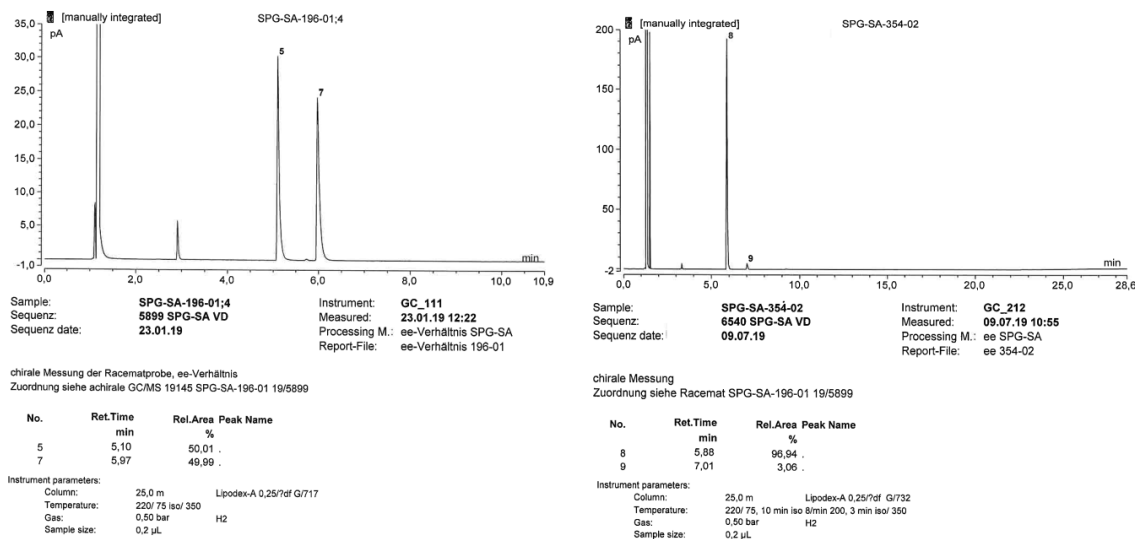
De Novo Synthesis of D-Aldgarose and the derived Glycosyl Donors

(2R,3R,4S,6R)-2-Methoxy-6-methyl-3-((triisopropylsilyl)oxy)-4-vinyltetrahydro-2H-pyran-
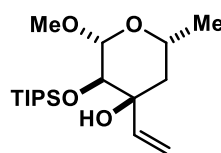
4-ol (118). In a 100-mL two-necked flask, aqueous hydrogen peroxide solution (35% *w/w*, 2.5 mL) and aqueous sodium hydroxide solution (2 M, 0.55 mL) were sequentially added to a solution of dihydropyrone **107** (1.24 g, 11.1 mmol) in methanol (52 mL) at −45 °C. Stirring was continued at that temperature for 2 h before the mixture was neutralized with acetic acid (0.07 mL) at −45 °C. Trimethyl phosphite (4.0 mL) was carefully added at this temperature and the reaction mixture was allowed to warm to −20 °C over 30 min. At this point, the same amount of trimethyl phosphite was added again. After stirring for 30 min at −20 °C, a peroxide test (Merck test strip) was negative. The mixture was warmed to ambient temperature and volatile material was removed under reduced pressure (10⁻² mbar, 30 °C). The residue was dissolved in ethyl acetate (40 mL) and the resulting solution was dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) furnished a colorless gum (1.31 g), which was used in the next step without further characterization.

In a round-bottom flask, triisopropylsilyl chloride (3.4 mL, 16 mmol) and imidazole (1.28 g, 18.8 mmol) were added to a solution of this material in DMF (7.0 mL) and the resulting mixture was stirred for 15 h at room temperature. The mixture was diluted with *tert*-butyl methyl ether (40 mL) and washed with saturated

aqueous sodium bicarbonate solution (40 mL). The aqeous phase was extracted with *tert*-butyl methyl ether (4 × 15 mL) and the combined organic layers were washed with aqueous HCl (1 M, 30 mL), saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure to give crude **116b** a colorless oil (3.83 g).

Vinylmagnesium bromide (1.0 M in THF, 40 mL, 40 mmol) was added to a solution of this material in diethyl ether (45 mL) at −78 °C. After stirring for 7 h at this temperature, reaction monitoring (^{1}H NMR) indicated full consumption of the starting material. The reaction was quenched with half-saturated aqueous ammonium chloride solution (75 mL) and the mixture was warmed to room temperature with vigorous stirring until a clear biphasic mixture was obtained. The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 25 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 90:1 → 70:1 → 60:1 → 50:1) furnished the title compound as a colorless oil (1.77 g, 46% yield). $[\alpha]_D^{20}$ = −42.9 (*c* 1.7, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.82 (dd, *J* = 17.1, 10.6 Hz, 1H), 5.35 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.12 (dd, *J* = 10.6, 1.3 Hz, 1H), 4.38 (d, *J* = 7.5 Hz, 1H), 3.96 (dddd, *J* = 12.5, 11.0, 6.3, 2.0 Hz, 1H), 3.50 (d, *J* = 7.5 Hz, 1H), 3.46 (s, 3H), 2.84 (d, *J* = 2.6 Hz, 1H), 1.70 (dd, *J* = 14.2, 2.1 Hz, 1H), 1.49 (ddd, *J* = 14.0, 11.1, 2.7 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.17 – 1.01 (m, 21H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 143.5, 114.1, 102.9, 75.6, 74.7, 66.7, 56.3, 43.5, 20.7, 18.4, 13.0. **IR (film):** 3551, 2944, 2894, 2867, 1465, 1383, 1347, 1326, 1310, 1293, 1246, 1214, 1164, 1114, 1095, 1069, 1052, 1015, 923, 883, 836, 811, 681, 600, 564 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{18}$H$_{36}$O$_4$SiNa 367.2275; found 367.2274.

(2*R*,3*R*,4*S*,6*R*)-2-Methoxy-6-methyl-3-((triisopropylsilyl)oxy)-4-vinyltetrahydro-2*H*-pyran-4-ol (119). 3-Chloro-perbenzoic acid (77 w-%, 2.47 g, 11.0 mmol) was added in one portion to a solution of allylic alcohol **118** (1.52 g, 4.41 mmol) in dichloromethane (40 mL) at 0 °C (ice bath). After stirring for 20 min at this temperature, the ice bath was removed and stirring was continued for 94 h. For work-up, the flask was again immersed into an ice bath before aqueous sodium sulfite solution (10% *w/w*, 20 mL) was carefully added, and the mixture was stirred for additional 15 min. Half-saturated aqueous sodium carbonate solution (50 mL) was introduced and the mixture was warmed to room temperature under vigorous stirring. It was diluted with dichloromethane (20 mL), the layers were separated, and the organic layer was washed with half-saturated aqueous sodium carbonate solution (50 mL) and brine (20 mL). The aqueous phases were extracted with *tert*-butyl methyl ether (5 × 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 20:1 → 10:1) furnished the
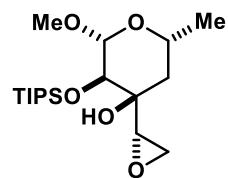
title compound as a colorless gum (1.28 g, 81% yield). $[\alpha]_D^{20}$ = −42.7 (*c* 1.2, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.36 (d, *J* = 7.5 Hz, 1H), 3.92 (dqd, *J* = 12.6, 6.3, 2.1 Hz, 1H), 3.65 (d, *J* = 7.6 Hz, 1H), 3.46 (s, 3H), 2.98 (dd, *J* = 3.9 Hz, 2.7 Hz, 1H), 2.81 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.79 (br d, *J* = 2.4 Hz, 1H), 2.74 (dd, *J* = 4.9, 3.9 Hz, 1H), 1.70 (dd, *J* = 14.0, 2.1 Hz, 1H), 1.38 (ddd, *J* = 13.7, 11.2, 2.0 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.23 – 1.12 (m, 3H), 1.11 – 1.06 (m, 18H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 102.5, 74.3, 72.1, 66.4, 56.2, 56.1, 44.3, 38.4, 20.8, 18.4, 13.1. **IR (film):** 3545, 2943, 2893, 2866, 1465, 1383, 1327, 1314, 1297, 1246, 1215, 1164, 1103, 1070, 1054, 1017, 999, 967, 919, 886, 842, 816, 795, 681, 654, 547, 484, 464 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{18}$H$_{36}$O$_5$SiNa 383.2224; found 383.2224.

(2*R*,3*R*,4*S*,6*R*)-2-Methoxy-6-methyl-3-((triisopropylsilyl)oxy)-4-vinyltetrahydro-2*H*-pyran-
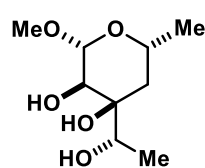
4-ol (120). In a 250-mL two-necked flask, a solution of epoxide **119** (1.36 g, 3.77 mmol) in diethyl ether (20 mL) was slowly added to a suspension of lithium aluminum hydride (345 mg, 9.09 mmol) in diethyl ether (60 mL) at 0 °C (ice bath). Once the addition was complete, the cooling bath was removed and stirring was continued for 2 h at room temperature. The mixture was cooled on ice and quenched with ethyl acetate (5 mL). Saturated aqueous Rochelle's salt solution (80 mL) was introduced and stirring continued for 14 h at room temperature to give a clear biphasic mixture. The aqueous phase was extracted with ethyl acetate (10 × 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (dichloromethane/methanol, 15:1) furnished the title compound as a colorless oil (710 mg, 91% yield), which crystallized upon standing at −20 °C. $[\alpha]_D^{20}$ = −43.3 (*c* 0.58, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.52 (d, *J* = 7.7 Hz, 1H), 4.02 (dqd, *J* = 12.6, 6.3, 2.3 Hz, 1H), 3.65 (q, *J* = 6.6 Hz, 1H), 3.59 (d, *J* = 7.7 Hz, 1H), 3.55 (s, 3H), 3.22 – 1.92 (br s, 3H), 1.55 (dd, *J* = 13.8, 2.3 Hz, 1H), 1.38 (dd, *J* = 13.7, 11.1 Hz, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 102.2, 73.8, 73.6, 72.0, 67.2, 57.1, 39.4, 21.0, 18.2. **IR (film):** 3416, 2973, 2934, 2845, 1641, 1447, 1384, 1327, 1277, 1210, 1162, 1125, 1072, 1048, 1030, 969, 930, 893, 865, 802, 730, 674, 528, 491 cm^{-1}. **HRMS-ESI m/z:** [M-H]$^-$ calcd for C$_9$H$_{17}$O$_5$ 205.1082; found 205.1082.

Methyl β-D-aldgaropyranoside (121a). A solution of phosgene (20% *w/w* in toluene, 2.6 mL, 4.9 mmol) was added over 5 min to a vigorously stirred solution of triol **120** (823 mg, 3.99 mmol) in dichloromethane (10 mL) and pyridine (10 mL) at 0 °C (ice bath). The white suspension was vigorously stirred for 2 h at this temperature before it was diluted with dichlormethane (25 mL) and washed with aqueous HCl (2 M, 1 × 20 mL, 2 × 10 mL). The aqueous phases were extracted with chloroform (5 × 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Remaining pyridine was largely removed by co-evaporation with toluene. Purification of the residue by flash chromatography (hexanes/EtOAc, 3:2 → 1:1 → 1:2) furnished the title compound as colorless crystals (737 mg, 80% yield). Single crystals suitable for X-ray diffraction were obtained by recrystallization from diethyl ether/dichloromethane (4:1). **mp** = 175 – 176 °C. $[\alpha]_D^{23}$ = −38.1 (*c* 1.0, MeOH). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.51 (d, *J* = 7.8 Hz, 1H), 4.38 (q, *J* = 6.6 Hz, 1H), 3.95 (dqd, *J* = 12.6, 6.3, 2.2 Hz, 1H), 3.56 (s, 3H), 3.45 (d, *J* = 7.1 Hz, 1H), 2.42 (br s, 1H), 1.86 (dd, *J* = 14.3, 2.2 Hz, 1H), 1.59 – 1.51 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 154.1, 101.8, 84.6, 81.4, 71.2, 67.4, 57.4, 41.0, 20.7, 13.7. **IR (film):** 3459, 2977, 2937, 2849, 1788, 1448, 1385, 1360, 1332, 1286, 1227, 1206, 1160, 1120, 1070, 1049, 1021, 955, 936, 817, 773, 731, 680, 620, 608, 569, 544, 516, 475 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{10}$H$_{16}$O$_6$Na 255.0839; found 255.0834. The analytical data are in agreement with those reported in the literature.[107b]

D-Aldgaropyranose (SI-8). Methyl glycoside **121a** (419 mg, 1.80 mmol) was dissolved in trifluoroacetic acid and tetrahydrofuran (1:2 *v/v*, 8.5 mL) and the resulting solution was stirred for 4 h at 100 °C. The mixture was cooled to room temperature and volatile material was removed under reduced pressure (10^{-3} mbar, 30 – 40 °C). The resulting yellowish gum was dissolved in ethyl acetate (30 mL), the solution dried over anhydrous sodium sulfate, and the drying agent was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (dichloromethane/methanol, 25:1 → 20:1) to furnish the title compound as a white solid (263 mg, 67% yield; α:β = 1:8). **mp** 169 – 170 °C. $[\alpha]_D^{20}$ = −7.3 (*c* 0.82, MeOH). **^{1}H NMR (400 MHz, [D$_4$]-methanol):** δ 4.72 (d, *J* = 7.8 Hz, 1H), 4.49 (q, *J* = 6.6 Hz, 1H), 3.90 (dqd, *J* = 12.5, 6.2, 2.1 Hz, 1H), 3.35 (d, *J* = 7.7 Hz, 1H), 1.92 (dd, *J* = 14.5, 2.2 Hz, 1H), 1.61 (dd, *J* = 14.5, 11.3 Hz, 1H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 156.5, 96.3, 87.3, 83.1, 72.4, 68.3, 41.9, 21.0, 13.7. **IR (film):** 3417, 2979, 2917, 1777, 1550, 1449, 1384, 1324, 1289, 1219, 1157, 1140, 1114, 1072, 1023, 960, 936, 902, 824, 774, 681, 629, 594 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_9$H$_{14}$O$_6$Na 241.0683; found 241.0680.

Methyl 2-O-acetyl-β-D-aldgaropyranoside (122a). A solution of phosgene (20% *w/w* in toluene, 2.4 mL, 4.5 mmol) was added over 5 min to a vigorously stirred solution of triol **120** (617 mg, 2.99 mmol) in dichloromethane (7.5 mL) and pyridine (7.5 mL) at 0 °C (ice bath). The white suspension was vigorously stirred for 2 h at this temperature before it was diluted with dichlormethane (25 mL) and washed with aqueous HCl (2 M, 2 × 15 mL). The aqueous phases were extracted with dichloromethane (4 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Remaining pyridine was largely removed by co-evaporation with toluene (8 mL).
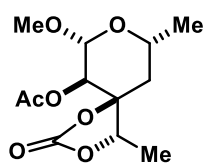
Triethylamine (1.3 mL, 9.3 mmol), 4-(dimethylamino)pyridine (73.6 mg, 0.602 mmol) and acetic anhydride (1.5 mL, 16 mmol) were added to a solution of this material in dichloromethane (30 mL) at 0 °C (ice bath). The resulting mixture was stirred for 3 h at room temperature before it was diluted with dichloromethane (15 mL) and washed with saturated aqueous sodium bicarbonate solution (25 mL). The aqueous phase was extracted with dichloromethane (5 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 3:1 → 2:1) furnished the title compound as a white, crystalline solid (482 mg, 59% yield) after co-evaporation with toluene to completely remove remaining pyridine. **mp** 112 – 113 °C. $[\alpha]_D^{20} = -74.8$ (*c* 1.2, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.91 (d, *J* = 7.9 Hz, 1H), 4.57 (d, *J* = 7.9 Hz, 1H), 4.39 (q, *J* = 6.8 Hz, 1H), 3.97 (dqd, *J* = 12.4, 6.2, 2.2 Hz, 1H), 3.48 (s, 3H), 2.12 (s, 3H), 1.91 (dd, *J* = 14.3, 2.2 Hz, 1H), 1.63 (dd, *J* = 14.3, 11.2 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 169.4, 153.7, 100.8, 85.4, 81.3, 70.0, 67.0, 57.2, 41.3, 21.1, 20.6, 13.3. **IR (film):** 2975, 2939, 2915, 2881, 2849, 1830, 1803, 1753, 1448, 1396, 1378, 1331, 1308, 1281, 1234, 1218, 1205, 1179, 1161, 1145, 1119, 1084, 1070, 1053, 1018, 1007, 956, 938, 914, 824, 773, 687, 615, 563, 548 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{12}$H$_{18}$O$_7$Na 297.0945; found 297.0939.

1,2-Di-O-acetyl-D-aldgaropyranose (122b). In a 10-mL round-bottom flask, a solution of concentrated sulfuric acid in acetic anhydride (1:99 v/v, 6.0 mL) was added to a solution of methyl glycoside **122a** (482 mg, 1.76 mmol) in acetic anhydride (6.0 mL) at 0 °C (ice bath). After 5 min, the cooling bath was removed and the mixture stirred for 1 h at room temperature. For work-up, the mixture was diluted with ethyl acetate (30 mL) and poured into ice-cold water (25 mL) in a separatory funnel. After careful shaking of the two layers, saturated aqueous sodium bicarbonate solution was slowly added until all acid was destroyed (ca. 40 mL). After the gas formation had ceased, the layers were separated and the aqueous phase was extracted with ethyl acetate (6 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying
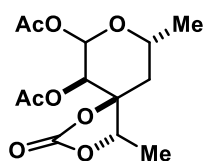
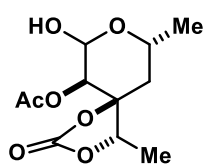agent was filtered off, and the filtrate was concentrated under reduced pressure. Remaining acetic anhydride was largely destroyed by co-evaporation with ethanol (2 × 2 mL) followed by azeotropic removal with toluene (2 mL). Purification of the residue by flash chromatography (hexanes/EtOAc, 3:1 → 2:1) furnished the title compound as a colorless foam after another co-evaporation with toluene/ethanol (2 × 10 mL) and drying at 10^{-3} mbar (517 mg, 98% yield; α:β = 2:3). $[\alpha]_D^{20}$ = +11.4 (*c* 0.79, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** *α*-anomer: δ 6.30 (d, *J* = 4.0 Hz, 1H), 5.00 (d, *J* = 4.0 Hz, 1H), 4.45 – 4.35 (m, 1H), 4.35 (q, *J* = 6.8 Hz, 1H), 2.16 (s, 3H), 2.068 (s, 3H), 2.03 – 1.90 (m, 1H), 1.72 – 1.62 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H). *β*-anomer: δ 5.87 (d, *J* = 8.1 Hz, 1H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.41 (q, *J* = 6.8 Hz, 1H), 4.17 – 4.07 (m, 1H), 2.10 (s, 3H), 2.074 (s, 3H), 2.03 – 1.92 (m, 1H), 1.72 – 1.62 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 170.0, 169.5, 169.2, 169.1, 153.5, 153.3, 91.7, 88.8, 85.0, 82.4, 81.7, 81.1, 69.1, 68.1, 67.2, 63.5, 40.9, 40.5, 21.2, 21.0, 20.9, 20.6, 20.5, 13.6, 13.4. **IR (film):** 2983, 2936, 1805, 1755, 1432, 1377, 1309, 1283, 1217, 1158, 1144, 1120, 1078, 1063, 1015, 917, 850, 811, 772, 689, 606, 559, 534 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{13}$H$_{18}$O$_8$Na 325.0894; found 325.0889.

2-O-Acetyl-D-aldgaropyranose (SI-9). Benzylamine (0.91 mL, 8.3 mmol) was added to a solution of acetate **122b** (503 mg, 1.66 mmol) in THF (14 mL). The resulting mixture was stirred for 17 h at room temperature before it was diluted with ethyl acetate (25 mL) and washed with aqueous HCl (1 M, 25 mL). The aqueous phase was extracted with ethyl acetate (4 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 1:1) furnished the title compound as a white solid (303 mg, 70% yield; α:β = 1:15). **mp** 144 – 146 °C. $[\alpha]_D^{20}$ = −39.3 (*c* 0.75, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** signals of the β-anomer only, δ 4.92 (dd, *J* = 9.1, 7.9 Hz, 1H), 4.79 (d, *J* = 7.9 Hz, 1H), 4.41 (q, *J* = 6.7 Hz, 1H), 4.03 (dqd, *J* = 12.5, 6.2, 2.2 Hz, 1H), 3.08 (d, *J* = 9.1 Hz, 1H), 2.17 (s, 3H), 1.93 (dd, *J* = 14.4, 2.2 Hz, 1H), 1.66 (dd, *J* = 14.4, 11.3 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** signals of the β-anomer only, δ 170.9, 153.4, 94.3, 85.0, 81.0, 72.3, 67.5, 41.3, 21.1, 20.7, 13.4. **IR (film):** 3416, 2978, 2924, 2855, 1790, 1750, 1639, 1448, 1431, 1378, 1326, 1284, 1228, 1157, 1115, 1069, 1051, 1013, 961, 938, 914, 871, 828, 774, 733, 688, 645, 616, 602, 561, 535, 508, 488, 460, 430 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{11}$H$_{16}$O$_7$Na 283.0788; found 283.0786.

2-O-Acetyl-D-aldgaropyranosyl fluoride (122c). In a 10-mL Schlenk tube, a solution of diethylaminosulfur trifluoride (0.13 M in dichloromethane, 3.1 mL, 0.40 mmol) was added to a solution of lactol **SI-9** (51.0 mg, 0.196 mmol) in dichloromethane (1.3 mL) at −15 °C. After stirring for 1.5 h at this temperature, the reaction mixture was diluted with *tert*-butyl methyl ether (10 mL) and washed with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (4 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to furnish the title compound as a colorless gum (40.3 mg, 78% yield; α:β = 1:2), which formed a white wax upon standing. For analytical purposes, an aliquot was re-subjected to flash chromatography to give a pure sample of the β-anomer. The signals of the α-anomer were then assigned from the NMR spectrum of the mixture containing both anomers. *Spectral data of the α-anomer*: **¹H NMR (400 MHz, CDCl₃):** δ 5.71 (dd, *J* = 53.2, 3.3 Hz, 1H), 4.82 (dd, *J* = 23.4, 3.3 Hz, 1H), 4.52 – 4.40 (m, 1H), 4.36 (q, *J* = 6.7 Hz, 1H), 2.19 (s, 3H), 2.02 (dd, *J* = 14.2, 2.4 Hz, 1H), 1.70 (dd, *J* = 14.4, 11.5 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.2 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 169.7, 153.3, 103.0 (d, *J* = 232 Hz), 82.1, 81.4, 68.0 (d, *J* = 25.1 Hz), 63.3 (d, *J* = 3.5 Hz), 40.2, 20.8, 20.3, 13.7. **¹⁹F{¹H} NMR (282 MHz, CDCl₃):** δ −147.2. *Spectral data of the β-anomer*: **¹H NMR (400 MHz, CDCl₃):** δ 5.40 (dd, *J* = 52.6, 7.2 Hz, 1H), 5.03 (dd, *J* = 11.3, 7.2 Hz, 1H), 4.43 (qd, *J* = 6.8, 1.7 Hz, 1H), 4.16 – 4.05 (m, 1H), 2.16 (s, 3H), 1.95 (dt, 14.5, 2.4 Hz, 1H), 1.71 (dd, *J* = 14.5, 11.3 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.35 (d, *J* = 6.2 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 169.1, 153.2, 107.0 (d, *J* = 214 Hz), 81.1 (d, *J* = 8.7 Hz), 81.0, 69.8 (d, *J* = 24.1 Hz), 68.0 (d, *J* = 4.2 Hz), 40.7, 20.9, 20.4, 13.6. **¹⁹F{¹H} NMR (282 MHz, CDCl₃):** δ −147.3. **IR (film):** 2983, 2924, 2851, 1803, 1756, 1450, 1374, 1285, 1228, 1180, 1158, 1147, 1079, 1064, 1022, 943, 919, 828, 803, 773, 691 cm⁻¹. **HRMS-ESI *m/z*:** [M+Na]⁺ calcd for C₁₁H₁₅FO₆Na 285.0745; found 285.0743.

1-Deoxy-1-(phenylthio)-2-O-acetyl-D-aldgaropyranoside (122d). In a 10-mL Schlenk tube, tin(IV) chloride (1 M in dichloromethane, 0.25 mL, 0.25 mmol) was added to a solution of acetate **122b** (83.8 mg, 0.277 mmol) and thiophenol (50 µL, 0.49 mmol) in dichloromethane (3.0 mL) at 0 °C (ice bath). After stirring for 1.5 h at this temperature, the reaction mixture was diluted with *tert*-butyl methyl ether (10 mL) and washed with saturated aqueous sodium carbonate solution (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 2:1) to furnish the title compound as yellowish gum (90.0 mg, 83% yield; α:β ≈ 2:3). *Characteristic data*: **¹H NMR (400 MHz, CDCl₃):** δ 7.49 – 7.41 (m, 2H),
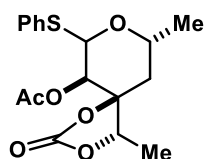
7.34 – 7.23 (m, 3H), 5.84 (d, J = 6.1 Hz, 1H, *single anomer*), 5.05 – 4.95 (m, 1H), 4.75 – 4.65 (m, 1H, *single anomer*), 4.43 – 4.33 (m, 1H), 4.03 – 3.93 (m, 1H, *single anomer*), 2.18 (s, 3H, *single anomer*), 2.16 (s, 3H, *single anomer*), 2.02 – 1.92 (m, 1H), 1.74 – 1.63 (m, 1H), 1.40 (d, J = 6.7 Hz, 3H, *single anomer*), 1.38 (d, J = 6.8 Hz, 3H, *single anomer*). 1.30 (d, J = 6.3 Hz, 3H, *single anomer*), 1.27 (d, J = 6.3 Hz, 3H, *single anomer*). **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for $C_{17}H_{20}O_6SNa$ 375.0873; found 375.0870.

1-Deoxy-1-(pyrimidin-2-ylthio)-2-O-acetyl-β-ᴅ-aldgaropyranoside (122e). In a 25-mL Schlenk tube, triethylphosphine (0.38 mL, 2.6 mmol) was added to a mixture of lactol **SI-8** (286 mg, 1.31 mmol) and bis(pyrimidin-2-yl) disulfide (350 mg, 1.57 mmol) in acetonitrile (4.5 mL) at 0 °C (ice bath). The mixture immediately turned yellow with formation of a precipitate. After stirring for 2 h at 0 °C, the mixture was diluted with chloroform (25 mL) and washed with saturated aqueous solutions of sodium chloride and sodium carbonate (25 mL each). The aqueous phases were combined and extracted with chloroform (4 × 10 mL). The organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/acetone, 3:2) to furnish a yellow syrup (316 mg, 77% yield), which was used in the next step without full characterization.
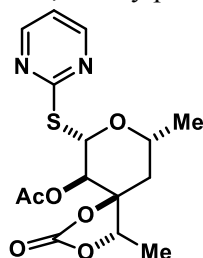
Triethylamine (0.38 mL, 2.7 mmol), 4-(dimethylamino)pyridine (31 mg, 0.25 mmol) and acetic anhydride (0.19 mL, 2.0 mmol) were added to a solution of this material in dichloromethane (9.5 mL) at room temperature. After stirring for 1 h, the mixture was diluted with chloroform (15 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL). The aqueous phase was extracted with chloroform (5 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 1:1 → 2:3) to furnish the title compound as a pale yellowish solid (255 mg, 71% yield). **mp** 179 – 180 °C. $[\alpha]_D^{20}$ = +169.7 (*c* 1.0, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 8.56 (d, J = 4.8 Hz, 2H), 7.01 (t, J = 4.9 Hz, 1H), 6.93 (d, J = 6.3 Hz, 1H), 5.19 (d, J = 6.3 Hz, 1H), 4.53 – 4.42 (m, 1H), 4.39 (q, J = 6.7 Hz, 1H), 2.09 (s, 3H), 1.99 (dd, J = 14.4, 2.2 Hz, 1H), 1.71 (dd, J = 14.4, 11.4 Hz, 1H), 1.42 (d, J = 6.7 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 170.8, 169.4, 157.7, 152.9, 117.4, 82.8, 81.3, 80.1, 68.6, 63.7, 40.8, 21.0, 20.6, 13.6. **IR (film):** 2979, 2937, 1804, 1752, 1565, 1551, 1384, 1285, 1226, 1203, 1181, 1144, 1072, 1015, 917, 811, 772, 751, 639, 605, 532 cm⁻¹. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for $C_{15}H_{18}N_2O_6SNa$ 377.0778; found 377.0774.

1-Deoxy-1-(phenylsulfoxyl)-2-O-acetyl-D-aldgaropyranoside (122f). In a 10-mL Schlenk tube, 3-chloroperbenzoic acid (6.0 mg, 0.024 mmol) was added to a solution of thioglycoside **122d** (7.0 mg, 0.020 mmol) in dichloromethane (0.2 mL) at −70 °C. The reaction mixture was gradually warmed to −40 °C over 1.5 h and then directly subjected to flash chromatography (hexanes/EtOAc, 2:1 → 1:2) to give three fractions containing separate isomers of the title compound. While the first fraction predominantly contained the byproduct 3-chlorobenzoic acid, washing of the remaining two fractions with saturated aqueous sodium carbonate solution furnished clean samples of single diastereomers of the title compound, which showed the following spectra data. Isomer with R_f = 0.19 (hexanes/EtOAc, 1:1), colorless gum (2.0 mg, 27% yield): **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.74 – 7.66 (m, 2H), 7.58 – 7.50 (m, 3H), 5.30 (d, J = 6.0 Hz, 1H), 4.63 (d, J = 6.1 Hz, 1H), 4.46 (q, J = 6.7 Hz, 1H), 4.00 – 3.91 (m, 1H), 2.24 (s, 3H), 2.00 (dd, J = 14.3, 2.1 Hz, 1H), 1.68 (dd, J = 14.3, 11.3 Hz, 1H), 1.44 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H). Isomer with R_f = 0.12 (hexanes/EtOAc, 1:1), white solid (1.7 mg, 23% yield): **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.67 – 7.61 (m, 2H), 7.55 – 7.50 (m, 3H), 5.50 (d, J = 9.7 Hz, 1H), 4.43 (q, J = 6.8 Hz, 1H), 4.16 (d, J = 9.7 Hz, 1H), 3.78 (dqd, J = 12.4, 6.2, 2.2 Hz, 1H), 2.23 (s, 3H), 1.91 (dd, J = 14.4, 2.2 Hz, 1H), 1.75 (dd, J = 14.4, 11.2 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H).
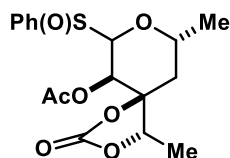
2-O-Acetyl-D-aldgaropyranosyl trichloroacetimidate (122g). Trichloroacetonitrile (0.56 mL, 5.6 mmol) and DBU (42 µL, 0.28 mmol) were sequentiall added to a solution of lactol **SI-9** (292 mg, 1.12 mmol) in dichloromethane (8.0 mL) at 0 °C (ice bath). The originally colorless solution turned slightly brown upon the addition of DBU and the color intensified over the course of the reaction. After 1 h, the mixture was warmed to room temperature and concentrated under reduced pressure. The residue was immediately subjected to flash chromatography (hexanes/EtOAc, 3:1; 0.1% v/v of triethylamine added) to give the title compound as a pale yellowish/white solid (416 mg, 92% yield; α:β = 1:3). **mp** = 123 – 124 °C. **$[\alpha]_D^{20}$** = +12.2 (c 0.97, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** α-anomer: δ 8.49 (s, 1H), 6.55 (d, J = 4.1 Hz, 1H), 5.04 (d, J = 4.1 Hz, 1H), 4.55 – 4.45 (m, 1H), 4.36 (q, J = 6.6, 6.1 Hz, 1H), 2.07 (s, 3H), 2.04 (dd, 14.4, 2.2 Hz, 1H), 1.73 (dd, J = 14.4, 11.8 Hz, 1H), 1.38 (d, J = 6.7 Hz, 3H), 1.28 (d, J = 6.3 Hz, 3H). β-anomer: δ 8.70 (s, 1H), 6.00 (d, J = 8.2 Hz, 1H), 5.26 (d, J = 8.2 Hz, 1H), 4.44 (q, J = 6.8 Hz, 1H), 4.18 (dqd, J = 12.4, 6.2, 2.2 Hz, 1H), 2.08 (s, 3H), 1.98 (dd, J = 14.4, 2.2 Hz, 1H), 1.74 (dd, J = 14.4, 11.3 Hz, 1H), 1.41 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 168.9, 161.1, 153.4, 95.5, 92.5, 85.3, 81.8, 81.4, 81.2, 68.9, 68.3, 67.6, 63.8, 41.0, 40.4, 21.0, 20.62, 20.57, 20.52, 13.6, 13.4. **IR (film):** 3336, 2982, 2936, 1805, 1757, 1676, 1447, 1427, 1380, 1336, 1286, 1223, 1158, 1084, 1062, 1012, 968, 935, 914, 836, 797, 771, 757, 688, 646, 610, 543 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{13}$H$_{16}$NO$_7$Cl$_3$Na 425.9885; found 425.9885.
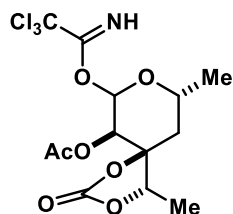
De Novo Synthesis of D-Desosamine and the derived Glycosyl Donors

(2R,3S,6R)-2-Methoxy-6-methyl-4-oxotetrahydro-2H-pyran-3-yl benzoate (116d). In a 25-mL round-bottom flask, benzoic acid anhydride (90% *w/w*, 686 mg, 2.73 mmol) and 4-(dimethylamino)pyridine (47.7 mg, 0.390 mmol) were added to a solution of ketol **116a** (288 mg, 1.80 mmol; as a mixture with its dimer **117**) and pyridine (0.36 mL, 4.5 mmol) in dichloromethane (10 mL) at 0 °C (ice bath). The cooling bath was removed and the reaction mixture was stirred for 6 h at room temperature. The mixture was diluted with dichloromethane (15 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 7:1) furnished the title compound as a white solid (466 mg, 98% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.15 – 8.04 (m, 2H), 7.65 – 7.55 (m, 1H), 7.51 – 7.42 (m, 2H), 5.30 (dd, J = 8.1, 1.0 Hz, 1H), 4.72 (d, J = 8.1 Hz, 1H), 3.85 (dqd, J = 10.5, 6.1, 3.4 Hz, 1H), 3.59 (s, 3H), 2.64 – 2.50 (m, 2H), 1.44 (d, J = 6.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 199.3, 165.4, 133.5, 130.2, 129.4, 128.5, 102.6, 78.5, 68.4, 57.2, 48.6, 21.4.
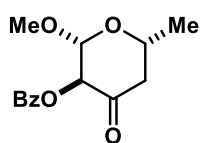
(2R,3R,4S,6R)-4-Hydroxy-2-methoxy-6-methyltetrahydro-2H-pyran-3-yl benzoate (24). In a 10-mL Schlenk tube, L-Selectride® (1.0 M in THF, 0.15 mL, 0.15 mmol) was added dropwise to a solution of benzoyl ketol **116d** (37.1 mg, 0.140 mmol) in THF (1.2 mL) at −78 °C. After stirring for 40 min at this temperature, ethyl acetate (3 mL) and saturated aqueous ammonium chloride solution (3 mL) were introduced, and the mixture was vigorously stirred for 30 min in a warm water bath (~30 °C). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 3:1 → 2:1) furnished the title compound as a colorless syrup, which formed a white solid upon standing (27.8 mg, 75% yield). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.10 – 8.01 (m, 2H), 7.62 – 7.55 (m, 1H), 7.50 – 7.40 (m, 2H), 4.83 (dd, J = 9.2, 7.8 Hz, 1H), 4.43 (d, J = 7.7 Hz, 1H), 3.91 (ddd, J = 11.5, 9.2, 5.3 Hz, 1H), 3.66 (dqd, J = 12.8, 6.4, 2.2 Hz, 1H), 3.51 (s, 3H), 2.12 (ddd, J = 13.1, 5.3, 2.0 Hz, 1H), 1.57 (dt, J = 13.1, 11.4 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H).
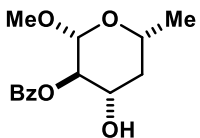
Oxime 132 and Hydrogenative Methylation Thereof.
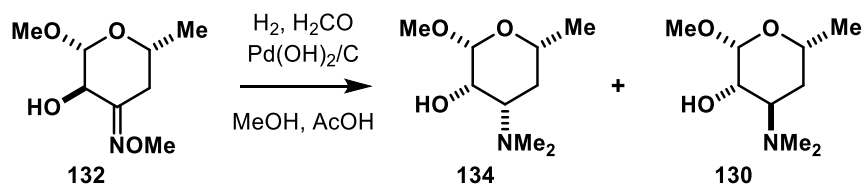
Methoxyamine hydrochloride (320 mg, 3.84 mmol) was added to a solution of ketol **116a** (123 mg, 0.768 mmol; as a mixture with its dimer **117**) in methanol (1.0 mL) and pyridine (0.37 mL), and the obtained mixture was stirred at 45 °C (bath temperature) for 15 h. The reaction mixture was then allowed to reach room temperature before it was diluted with ethyl acetate (10 mL). The resulting white suspension was washed with saturated aqueous sodium bicarbonate solution (10 mL) and brine (10 mL). The aqueous phases were extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Remaining pyridine was azeotropically removed twice with toluene, and the residue was purified by flash chromatography (hexane/EtOAc, 2:1) to furnish oxime **132** as a white solid (128 mg, 88% yield), which characterized as follows. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.18 (d, J = 7.7 Hz, 1H), 3.97 (d, J = 7.7 Hz, 1H), 3.90 (s, 3H), 3.62 – 3.53 (m, 1H), 3.59 (s, 3H), 3.21 (ddd, J = 14.8, 2.6, 0.6 Hz, 1H), 1.76 (ddd, J = 14.8, 11.4, 0.6 Hz, 1H), 1.33 (d, J = 6.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 153.9, 105.9, 71.3, 69.3, 62.3, 57.0, 32.7, 21.3. **IR (film):** 3460, 2972, 2938, 2903, 1644, 1446, 1384, 1324, 1273, 1242, 1205, 1160, 1115, 1046, 1000, 965, 937, 885, 841, 683, 660 cm^{-1}.

In a 10-mL two-necked flask under hydrogen atmosphere (balloon), a solution of oxime **132** (127 mg, 0.671 mmol) in methanol (2.0 mL) and acetic acid (0.30 mL) were sequentially added to a suspension of Pd(OH)$_2$/C (20% w/w, 48 mg, 68 μmol) in methanol (0.9 mL) at room temperature. After vigorous stirring for 30 h, TLC analysis (hexanes/EtOAc, 2:1) indicated only a small amount of remaining oxime. At this point, aqueous formaldehyde (37% w/w, 0.12 mL, 1.6 mmol) was introduced, and stirring was continued for another 16 h under the hydrogen atmosphere at room temperature. The reaction mixture was filtered through a short pad of Celite®, rinsing with methanol. The solvent and residual acetic acid were removed under reduced pressure (10^{-3} mbar), and the residue was subjected to flash chromatography (dichloromethane/methanol, 10:1; 0.3% v/v of triethylamine added). The fractions containing the product exhibited a single spot by TLC analysis (R$_f$ = 0.13 with same solvent mixture) and furnished a light yellowish oil (122 mg). ^{1}H NMR analysis of this sample revealed a mixture of two compounds (ca. 3:1 ratio by integration), the major one of which was assigned as the isomerization product **134** (see table 4.7).

*Spectral data of the minor component, assigned as **130** from the mixture with **134**:* **^{1}H NMR (400 MHz, CDCl$_3$):** δ 4.18 (d, J = 7.3 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.56 (s, 3H), 3.26 (d, J = 10.3, 7.3 Hz, 1H),

2.60 – 2.49 (m, 1H), 2.30 (s, 6H), 1.72 (ddd, J = 12.7, 4.0, 2.0 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H), 1.26 – 1.20 (m, 1H). $^{13}C\{^1H\}$ **NMR (101 MHz, CDCl$_3$):** δ 105.1, 70.1, 69.8, 65.5, 56.8, 40.5, 28.8, 21.4.

Table 4.7: Assignment of the major isomer **134** obtained from hydrogenation and reductive methylation of oxime **132** by NMR spectroscopy (^{1}H: 400 MHz, $^{13}C\{^1H\}$: 101 MHz, CDCl$_3$). The decreased vicinal coupling between H1 and H2 and the small ^4J coupling ("W-shaped coupling") between H2 and H4-eq are particularly indicative of the stereo-inversion at C2.
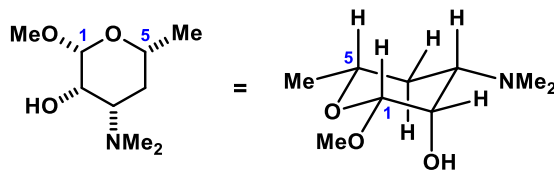
position	δ$_H$	multiplicity (J/Hz)	δ$_C$
1	4.69	d (3.4)	102.1
1-OMe	3.45	s	55.8
2	3.77	td (3.6, 0.9)	66.6
3	2.70	ddd (10.0, 4.9, 3.8)	57.2
3-NMe$_2$	2.35	s	42.8
4	ax, 2.00	ddd (13.6, 10.0, 5.6)	29.2
	eq, 1.54	dddd (13.4, 4.5, 4.1, 0.9)	
5	4.15	m	68.6
5-Me	1.34	d (6.8)	22.1

(2*R*,3*R*,4*R*,6*R*)-2-Methoxy-6-methyltetrahydro-2*H*-pyran-3,4-diol (136). In a 250-mL two-

necked flask, aqueous hydrogen peroxide solution (35% *w/w*, 4.2 mL, 43 mmol) and aqueous sodium hydroxide solution (2 M, 0.90 mL) were sequentially added to a solution of compound **107** (2.07 g, 18.5 mmol) in methanol (85 mL) at −45 °C. Stirring was continued at that temperature for 2 h before the mixture was neutralized with acetic acid (0.12 mL) at −45 °C. Trimethyl phosphite (8.0 mL) was carefully added at this temperature and the mixture was allowed to warm to −20 °C over the course of 30 min. At this point, the same amount of trimethyl phosphite was added again. After stirring for another 30 min at −20 °C, a peroxide test (Merck test strip) was negative. The mixture was warmed to ambient temperature and volatile components were removed under reduced pressure (10^{-2} mbar, 30 °C). The residue was dissolved in ethyl acetate (40 mL) and the resulting solution was dried over anhydrous sodium sulfate. The drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc, 2:1) furnished a colorless gum (2.07 g), which was used in the next step without further characterization.
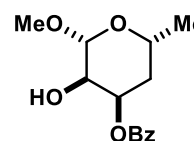
In a 500-mL two-necked flask, diisobutylaluminum hydride (25% *w/w* in toluene, 30 mL, 42 mmol) was added over 30 min to a solution of this material in tetrahydrofuran (70 mL) at −78 °C. The mixture was allowed to warm to room temperature over the course of 21 h. For work-up, the mixture was cooled in an ice bath, and the reaction was carefully quenched by the introduction of ethyl acetate (150 mL). Saturated aqueous Rochelle's salt solution (250 mL) was added, and the mixture was vigorously stirred at room temperature for 24 h to give a clear biphasic mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (7 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography with hexanes/acetone (5:2) furnished the title compound as a colorless oil, which solidified upon standing at −20 °C (1.73 g, 58% yield). **mp** = 50 – 53 °C. $[\mathbf{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = −82.3 (*c* 0.53, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 4.51 (d, *J* = 8.0 Hz, 1H), 4.16 (q, *J* = 3.2 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.54 (s, 3H), 3.38 (dd, *J* = 8.0 Hz, 3.3 Hz, 1H), 2.53 (br s, 2H), 1.89 (ddd, *J* = 14.3, 3.3, 2.2 Hz, 1H), 1.52 (ddd, *J* = 14.3, 11.4, 2.8 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 101.5, 71.9, 67.6, 66.8, 57.0, 38.7, 20.8. **IR (film):** 3434, 2971, 2919, 2889, 2842, 1447, 1384, 1343, 1285, 1204, 1159, 1128, 1073, 1042, 922, 897, 828, 720, 646 cm⁻¹. **HRMS-ESI *m/z*:** [M+Na]⁺ calcd for C₇H₁₄O₄Na 185.0784; found 185.0787.

(2*R*,3*R*,4*R*,6*R*)-4-Hydroxy-2-methoxy-6-methyltetrahydro-2*H*-pyran-3-yl benzoate (137).
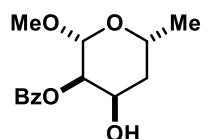
In a 100-mL two-necked flask, benzoyl chloride (1.24 mL, 10.7 mmol) was added to a solution of diol **136** (1.73 g, 10.7 mmol), 4-(dimethylamino)pyridine (261 mg, 2.14 mmol) and pyridine (1.8 mL, 22 mmol) in dichloromethane (56 mL) at 0 °C (ice bath). The mixture was stirred for 24 h while allowing the cooling bath to warm to room temperature. For work-up, the mixture was diluted with dichloromethane (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate (30 mL). The aqueous phase was extracted with dichloromethane (4 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography with hexanes/EtOAc (3:1) furnished the title compound as a colorless syrup (2.79 g, 92% yield). $[\mathbf{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = −47.5 (*c* 1.8, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 8.10 – 8.00 (m, 2H), 7.62 – 7.55 (m, 1H), 7.50 – 7.42 (m, 2H), 4.94 (dd, *J* = 8.1, 3.0 Hz, 1H), 4.87 (d, *J* = 8.1 Hz, 1H), 4.36 (q, *J* = 3.2 Hz, 1H), 4.19 – 4.08 (m, 1H), 3.51 (s, 3H), 2.13 (br s, 1H), 1.93 (ddd, *J* = 14.2, 3.7, 2.2 Hz, 1H), 1.69 (ddd, *J* = 14.1, 11.2, 2.7 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 165.5, 133.5, 129.9, 128.6, 99.4, 73.8, 67.2, 66.5, 56.8, 39.0, 20.9. **IR (film):** 2972, 2933, 2847, 1720, 1602, 1584, 1451, 1372, 1348, 1318, 1272, 1206, 1162, 1140, 1113, 1077, 1030, 1001, 905, 851, 712, 542 cm⁻¹. **HRMS-ESI *m/z*:** [M+H]⁺ calcd for C₁₄H₁₉O₅ 267.1227; found 267.1225.

(2*R*,3*R*,4*R*,6*R*)-3-Hydroxy-2-methoxy-6-methyltetrahydro-2*H*-pyran-4-yl benzoate (140). In a 50-mL round-bottom flask equipped with a Dean-Stark trap, a mixture of diol **136** (204 mg, 1.26 mmol) and dibutyltin oxide (339 mg, 1.36 mmol) in toluene (30 mL) was stirred at reflux temperature for 20 h, with azeotropic removal of water. The resulting light amber, clear solution was then cooled to room temperature, and concentrated to a volume of 5 – 10 mL under reduced pressure. Benzoyl chloride (0.17 mL, 1.5 mmol) was added, and the mixture was stirred for 20 min. Volatile components were evaporated under reduced pressure, and the residue was purified by flash chromatography with hexanes/EtOAc (4:1 → 3:1 → 2:1) to furnish the title compound as a colorless syrup (269 mg, 80% yield). $[\alpha]_D^{20}$ = −64.3 (*c* 1.1, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.09 – 8.03 (m, 2H), 7.61 – 7.55 (m, 1H), 7.49 – 7.42 (m, 2H), 5.60 (q, *J* = 3.2 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 1H), 4.08 – 3.98 (m, 1H), 3.61 (dt, *J* = 8.0, 3.4 Hz, 1H), 3.59 (s, 3H), 2.41 (d, *J* = 3.5 Hz, 1H), 2.03 (ddd, *J* = 14.7, 3.5, 2.1 Hz, 1H), 1.70 (ddd, *J* = 14.4, 11.4, 2.6 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.2, 133.4, 130.2, 129.8, 128.6, 102.0, 71.0, 67.2, 56.9, 37.5, 20.9. **IR (film):** 3485, 2973, 2932, 2874, 2844, 1717, 1602, 1584, 1451, 1383, 1354, 1315, 1275, 1206, 1160, 1117, 1068, 1040, 1028, 984, 715, 519 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{14}$H$_{18}$O$_5$Na 289.1046; found 289.1047.

Tosylation of Diol 136 via a Stannylene Acetal.
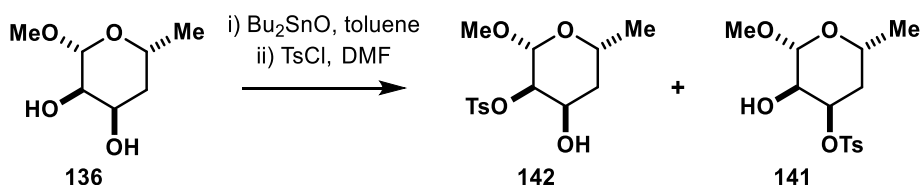
In a 50-mL round-bottom flask equipped with a Dean-Stark trap, a mixture of diol **136** (145 mg, 0.894 mmol) and dibutyltin oxide (240 mg, 0.964 mmol) in toluene (21 mL) was stirred at reflux temperature for 19 h, with azeotropic removal of water. The resulting light amber, clear solution was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DMF (4 mL), 4-toluenesulfonyl chloride (196 mg, 1.03 mmol) was added, and the mixture was stirred for 1 h. For work-up, the reaction mixture was diluted with *tert*-butyl methyl ether (30 mL) and washed with water (3 × 20 mL) and brine (20 mL). The aqueous layers were extracted with *tert*-butyl methyl ether (3 × 10 mL), the combined organic phases were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography with hexanes/EtOAc (3:1 → 2:1 → 1:1), first eluting the equatorial tosylate **142** (104 mg, 37% yield), followed by the axial tosylate **141** (154 mg, 55% yield).

Data of the equatorial tosylate 142: colorless gum; R_f (hexanes/EtOAc, 1:1) = 0.62. **¹H NMR (400 MHz, CDCl₃):** δ 7.83 – 7.76 (m, 2H), 7.36 – 7.29 (m, 2H), 4.57 (d, J = 7.9 Hz, 1H), 4.38 (br q, J = 3.1 Hz, 1H), 4.17 (dd, J = 7.9, 3.1 Hz, 1H), 4.06 – 3.95 (m, 1H), 3.19 (s, 3H), 2.44 (s, 3H), 1.91 (ddd, J = 14.3, 3.7, 2.1 Hz, 1H), 1.56 (ddd, J = 14.1, 11.3, 2.7 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H).

Data of the axial tosylate 141: colorless gum; R_f (hexanes/EtOAc, 1:1) = 0.36. **¹H NMR (400 MHz, CDCl₃):** δ 7.86 – 7.81 (m, 2H), 7.37 – 7.32 (m, 2H), 4.95 (td, J = 3.5, 2.3 Hz, 1H), 4.48 (d, J = 8.0 Hz, 1H), 3.98 (dqd, J = 12.6, 6.3, 1.9 Hz, 1H), 3.51 (s, 3H), 3.42 – 3.36 (m, 1H), 2.45 (s, 3H), 2.13 (d, J = 4.4 Hz, 1H), 2.05 (ddd, J = 14.7, 3.7, 2.2 Hz, 1H), 1.61 – 1.51 (m, 1H), 1.21 (d, J = 6.3 Hz, 3H).

(2R,3R,4R,6R)-2-Methoxy-6-methyl-4-((methylsulfonyl)oxy)tetrahydro-2H-pyran-3-yl
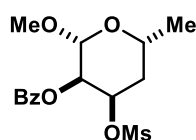
benzoate (SI-10). In a 100-mL two-necked flask, methanesulfonyl chloride (1.1 mL, 14 mmol) and triethylamine (3.7 mL, 27 mmol) were sequentially added to a solution of alcohol **137** (2.79 g, 10.5 mmol) and 4-(dimethylamino)pyridine (960 mg, 7.86 mmol) in dichloromethane (36 mL) at 0 °C (ice bath). After stirring for 10 min, the cooling bath was removed and stirring was continued for another hour at room termperature. For work-up, saturated aqueous sodium bicarbonate solution (40 mL) was added, and the resulting mixture was stirred for another hour at room temperature to destroy the excess of methanesulfonyl chloride. The mixture was diluted with ethyl acetate (40 mL), and the two layers were separated. The aqueous phase was extracted with ethyl acetate (4 × 15 mL), the combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography with hexanes/*tert*-butyl methyl ether (6:5) to furnish the title compound as a colorless foam (3.56 g, 99% yield). $[\alpha]_D^{20}$ = −57.5 (*c* 1.3, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 8.09 – 8.03 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.43 (m, 2H), 5.27 (td, J = 3.5, 2.3 Hz, 1H), 4.94 (dd, J = 8.2, 3.2 Hz, 1H), 4.85 (d, J = 8.2 Hz, 1H), 4.18 – 4.07 (m, 1H), 3.53 (s, 3H), 2.89 (s, 3H), 2.18 (ddd, J = 14.8, 3.8, 2.1 Hz, 1H), 1.84 (ddd, J = 14.8, 11.1, 2.3 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 165.7, 133.7, 130.0, 129.5, 128.7, 99.2, 77.9, 71.1, 66.6, 56.9, 38.5, 38.3, 20.4. **IR (film):** 3069, 3029, 2973, 2937, 2881, 2849, 1723, 1602, 1585, 1451, 1404, 1353, 1317, 1274, 1207, 1177, 1163, 1132, 1110, 1070, 1030, 1002, 971, 909, 860, 814, 762, 713, 694, 665, 528, 514 cm⁻¹. **HRMS-ESI *m/z*:** [M+Na]⁺ calcd for C₁₅H₂₀O₇SNa 367.0822; found 367.0822.

(2R,3R,4S,6R)-4-Azido-2-methoxy-6-methyltetrahydro-2H-pyran-3-yl benzoate (138).
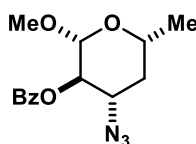
In a 100-mL round-bottom flask, a mixture of mesylate **SI-10** (3.56 g, 10.3 mmol) and sodium azide (874 mg, 13.4 mmol) in DMF (50 mL) was stirred at 90 °C (bath temperature) for 15 h. For work-up, the mixture was diluted with *tert*-butyl methyl ether (200 mL) and washed with water (1 × 50 mL, 2 × 30 mL) and brine (30 mL). The

combined water layers were extracted with *tert*-butyl methyl ether (1 × 50 mL, 2 × 30 mL), the organic phases were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography with hexanes/EtOAc (11:2) furnished the title compound as a white, crystalline solid (2.47 g, 82% yield). **mp** = 102 – 103 °C. $[\alpha]_D^{20}$ = +47.6 (*c* 0.37, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 8.09 – 8.05 (m, 2H), 7.62 – 7.55 (m, 1H), 7.49 – 7.43 (m, 2H), 5.03 (dd, *J* = 10.0, 7.8 Hz, 1H), 4.42 (d, *J* = 7.8 Hz, 1H), 3.76 – 3.66 (m, 2H), 3.46 (s, 3H), 2.09 (ddd, *J* = 13.1, 5.0, 1.9 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.34 (d, *J* = 6.2 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 165.5, 133.4, 130.0, 129.9, 128.5, 102.2, 73.7, 68.8, 60.6, 56.8, 37.9, 20.9. **IR (film):** 2977, 2934, 2872, 2844, 2106, 1728, 1450, 1391, 1370, 1338, 1314, 1305, 1275, 1215, 1190, 1164, 1143, 1106, 1071, 1028, 994, 705 cm⁻¹. **HRMS-ESI *m/z*:** [M+Na]⁺ calcd for C$_{14}$H$_{17}$O$_4$Na 314.1111; found 314.1108.

1-O-Methyl-2-O-benzoyl *β*-D-desosaminopyranoside (139a).

In a 250-mL two-necked flask under hydrogen atmosphere (balloon), a solution of azide **138** (2.47 g, 8.48 mmol) in a mixture of ethyl acetate/ethanol (8.0 mL/10 mL; syringe and flask rinsed with ethanol, 2 × 10 mL) was added to a suspension of Pd(OH)$_2$/C (20% *w/w*, 595 mg, 0.168 mmol) in ethanol (10 mL) at ambient temperature. After vigorous stirring for 1.5 h, TLC analysis (hexanes/EtOAc, 4:1) indicated full consumption of the azide. At this point, aqueous formaldehyde (37% *w/w*, 1.4 mL, 19 mmol) was added, and the mixture was stirred for further 17 h under hydrogen atmosphere at room temperature. The reaction mixture was filtered through a short pad of Celite®, rinsing with dichloromethane. The solvent was removed under reduced pressure and the residue was purified by flash chromatography with dichloromethane/methanol (25:1; 0.2% *v/v* of triethylamine added) to furnish the title compound as a colorless gum (2.44 g, 98% yield). $[\alpha]_D^{20}$ = −1.9 (*c* 1.1, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 8.10 – 8.02 (m, 2H), 7.59 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 5.10 (dd, *J* = 10.5, 7.5 Hz, 1H), 4.39 (d, *J* = 7.5 Hz, 1H), 3.65 (dqd, *J* = 10.9, 6.1, 2.0 Hz, 1H), 3.45 (s, 3H), 3.03 – 2.91 (m, 1H), 2.33 (s, 6H), 1.95 – 1.81 (m, 1H), 1.54 – 1.42 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 165.8, 133.0, 130.6, 130.0, 128.4, 103.4, 71.3, 69.5, 63.5, 56.8, 40.9, 32.1, 21.3. **IR (film):** 2971, 2937, 2866, 2833, 2782, 1721, 1602, 1584, 1451, 1389, 1342, 1314, 1294, 1271, 1228, 1164, 1124, 1108, 1068, 1053, 997, 975, 937, 888, 869, 840, 802, 710, 636, 549 cm⁻¹. **HRMS-ESI *m/z*:** [M+H]⁺ calcd for C$_{16}$H$_{24}$NO$_4$ 294.1700; found 294.1705.

1-O-Acetyl-2-O-benzoyl D-desosaminopyranose (139b).

In a round-bottom flask, a solution of concentrated sulfuric acid in acetic anhydride (1:33 *v/v*, 1.6 mL) was added to methyl glycoside **139a** (213 mg, 0.726 mmol), and the resulting mixture was stirred for 24 h at room temperature. For work up, the mixture was diluted with ethyl acetate (15 mL) and

carefully poured into saturated aqueous sodium bicarbonate solution (15 mL) in a separatory funnel. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated under reduced pressure. Most of the remaining acetic anhydride was evaporated under high vacuum. Purification of the residue by flash chromatography (dichloromethane/methanol, 35:1; 0.2% *v/v* of triethylamine added) furnished the title compound as a colorless gum (203 mg, 87% yield; α:β ≈ 6:1). $[\alpha]_D^{20}$ = +91.3 (*c* 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** signals of the α-anomer: δ 8.03 – 7.96 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.39 (m, 2H), 6.34 (d, *J* = 3.7 Hz, 1H), 5.31 (dd, *J* = 11.0, 3.7 Hz, 1H), 4.10 (dqd, *J* = 12.2, 6.2, 2.2 Hz, 1H), 3.42 – 3.25 (m, 1H), 2.37 (br s, 6H), 2.13 (s, 3H), 2.02 – 1.91 (m, 1H), 1.60 – 1.48 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H); signals of the β-anomer: δ 8.03 – 7.96 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.39 (m, 2H), 5.77 (d, *J* = 8.0 Hz, 1H), 5.20 (dd, *J* = 10.5, 8.0 Hz, 1H), 3.80 (dqd, *J* = 12.4, 6.2, 2.1 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.32 (br s, 6H), 1.98 (s, 3H), 1.92 – 1.83 (m, 1H), 1.55 – 1.45 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** signals of both anomers: δ 169.7, 169.5, 165.7, 165.6, 133.4, 133.2, 130.1, 129.93, 129.87, 128.58, 128.55, 93.84, 90.85, 70.8, 70.5, 69.4, 67.4, 63.5, 58.4, 40.9, 33.1, 31.4, 21.21, 21.16, 21.1. **IR (film):** 2974, 2939, 2870, 2833, 2782, 1750, 1721, 1602, 1584, 1452, 1373, 1316, 1272, 1228, 1161, 1138, 1113, 1080, 1070, 1044, 1011, 980, 943, 924, 873, 857, 803, 712, 600, 564, 507 cm^{-1}. **HRMS-ESI *m/z*:** [M+H]$^+$ calcd for C$_{17}$H$_{24}$NO$_5$ 322.1649; found 322.1645.

D-Desosamine (128). In a round-bottom flask, anhydrous potassium carbonate (34.0 mg, 0.246 mmol) was added to a solution of compound **139b** (38.6 mg, 0.120 mmol) in methanol (1.2 mL), and the mixture was stirred vigorously for 1 h at room temperature. The reaction mixture was filtered through a short plug of silica gel (3 cm × 2.5 cm), rinsing with dichloromethane/methanol (20:1, 20 mL) followed by methanol (90 mL) to elute the product. The combined filtrates were concentrated under reduced pressure to furnish the title compound as a pale yellowish oil (20.2 mg, 96% yield; α:β = 1:2). $[\alpha]_D^{25}$ = +57.9 (*c* 1.4, CHCl$_3$, after equilibration for ~90 min at 25 °C). **^{1}H NMR (400 MHz, [D$_4$]-methanol):** signals of the α-anomer: δ 5.09 (d, *J* = 3.6 Hz, 1H), 4.17 – 4.07 (m, 1H), 3.53 (dd, *J* = 10.6, 3.6 Hz, 1H), 2.96 (ddd, *J* = 12.3, 10.6, 4.0 Hz, 1H), 2.34 (s, 6H), 1.80 – 1.72 (m, 1H), 1.33 – 1.22 (m, 1H), 1.14 (d, *J* = 6.2 Hz, 3H); signals of the β-anomer: δ 4.42 (d, *J* = 7.4 Hz, 1H), 3.61 (dqd, *J* = 12.4, 6.2, 2.0 Hz, 1H), 3.20 (dd, *J* = 10.2, 7.4 Hz, 1H), 2.61 (ddd, *J* = 12.3, 10.2, 4.2 Hz, 1H), 2.33 (s, 6H), 1.80 – 1.72 (m, 1H), 1.31 – 1.17 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, [D$_4$]-methanol):** signals of the α-anomer: δ 94.4, 70.8, 65.3, 60.8, 40.7, 33.1, 21.5; signals of the β-anomer: δ 99.4, 72.9, 70.5, 65.7, 40.9, 32.1, 21.5. **IR (film):** 3366, 2970, 2935, 2871, 2835, 2786, 1654, 1457, 1382, 1321, 1279, 1163, 1096, 1042, 990, 975, 937, 867, 854, 833, 806, 752, 723, 634, 569, 421 cm^{-1}. **HRMS-ESI *m/z*:** [M+H]$^+$ calcd for C$_8$H$_{18}$NO$_3$ 176.1281; found 176.1281.
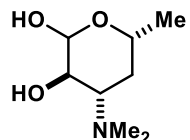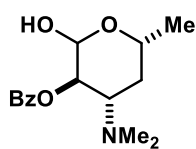
2-O-Benzoyl D-desosaminopyranose (SI-11). In a round-bottom flask, a solution of concentrated sulfuric acid in acetic anhydride (1:33 *v/v*, 15 mL) was added to methyl glycoside **139a** (2.44 g, 8.32 mmol), and the mixture was stirred for 24 h at room temperature. For work up, the mixture was diluted with ethyl acetate (30 mL) and carefully poured onto saturated aqueous sodium bicarbonate solution (50 mL) in a separatory funnel. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 20 mL) and brine (20 mL). The combined aqueous layers were extracted with ethyl acetate (5 × 25 mL). The organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated under reduced pressure. Most of the remaining acetic anhydride was evaporated under high vacuum. Purification of the residue by flash chromatography (dichloromethane/methanol, 35:1; 0.2% *v/v* of triethylamine added) furnished the intermediate glycosyl acetate admixed with a small amount of the remaining methyl glycoside (2.77 g, light yellowish gum).

In a round-bottom flask, a solution of ammonia in methanol (7 M, 59 mL) was added to a solution of this material in THF (12 mL) at 0 °C (ice bath), and the reaction mixture was stirred at this temperature for 5 h. The mixture was then concentrated under reduced pressure to give a light yellowish gum. Purification of the residue by flash chromatography (hexanes/acetone, 2:1; 0.1% *v/v* of triethylamine added) furnished the pure title compound as a colorless foam (1.96 g, 85% yield; α:β ≈ 1:1). $[\alpha]_D^{20}$ = +43.1 (*c* 0.71, MeOH). **¹H NMR (400 MHz, CDCl₃):** signals of the α-anomer: δ 8.11 – 8.03 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 – 7.41 (m, 2H), 5.43 (d, *J* = 3.6 Hz, 1H), 5.18 (dd, *J* = 11.0, 3.6 Hz, 1H), 4.24 (dqd, *J* = 12.5, 6.3, 2.3 Hz, 1H), 3.62 – 3.45 (m, 1H), 2.44 (br s, 6H), 2.14 – 2.00 (m, 1H), 1.55 – 1.43 (m, 1H), 1.22 (d, *J* = 6.2 Hz, 3H); signals of the β-anomer: δ 8.11 – 8.03 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 – 7.41 (m, 2H), 5.00 (dd, *J* = 10.4, 7.6 Hz, 1H), 4.68 (d, *J* = 7.6 Hz, 1H), 3.68 (dqd, *J* = 10.9, 6.1, 2.0 Hz, 1H), 3.10 – 2.98 (m, 1H), 2.35 (br s, 6H), 1.96 – 1.85 (m, 1H), 1.55 – 1.43 (m, 1H), 1.30 (d, *J* = 6.2 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** signals of both anomers: δ 167.2, 166.0, 133.4, 130.1, 130.0, 128.6, 128.5, 97.1, 91.3, 74.0, 71.5, 69.8, 64.6, 62.8, 57.6, 41.1, 40.9, 33.8, 33.0, 21.3, 21.2. **IR (film):** 3249, 2971, 2933, 2782, 1716, 1602, 1584, 1451, 138, 1368, 1315, 1269, 1160, 1121, 1057, 1028, 997, 937, 886, 839, 804, 711, 688, 634, 588 cm⁻¹. **HRMS-ESI *m/z*:** [M+H]⁺ calcd for $C_{15}H_{22}NO_4$ 280.1543; found 280.1543.

2-O-Benzoyl *α*-D-desosaminopyranosyl fluoride (139c). In a 60-mL Nalgene™ screw-capped reaction vessel, hydrogen fluoride pyridine complex (70% HF *w/w*, 1.5 mL) was added to a solution of acetate **139b** (185 mg, 0.576 mmol) in dichloromethane (6.0 mL) at 0 °C (ice bath). The reaction mixture, which turned pale yellowish upon the addition, was stirred for 3 h at 0 °C. For work-up, the cold reaction mixture was carefully poured into a saturated aqueous solution of sodium bicarbonate (30 mL). The layers were separated and the aqueous phase was extracted

with dichloromethane (4 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/acetone, 7:1; 0.1% *v/v* of triethylamine added) to furnish the title compound as a colorless oil (108 mg, 67% yield). $[\alpha]_D^{20}$ = +108.6 (*c* 1.0, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.12 – 8.07 (m, 2H), 7.62 – 7.55 (m, 1H), 7.50 – 7.43 (m, 2H), 5.74 (dd, *J* = 54.5, 2.7 Hz, 1H), 5.19 (ddd, *J* = 23.9, 11.0, 2.8 Hz, 1H), 4.21 (dqd, *J* = 12.3, 6.3, 2.3 Hz, 1H), 3.46 – 3.29 (br m, 1H), 2.37 (br s, 6H), 2.09 – 1.90 (br m, 1H), 1.55 (q, *J* = 12.4 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 166.0, 133.5, 130.1, 129.8, 128.6, 105.8 (d, *J* = 224 Hz), 70.3 (d, *J* = 25.6 Hz), 67.7 (d, *J* = 4.0 Hz), 57.9, 40.9, 33.0, 21.0. **^{19}F NMR (282 MHz, CDCl$_3$):** δ −147.2 (dd, *J* = 54.6, 24.1 Hz). **IR (film):** 2976, 2941, 2867, 2834, 2781, 1721, 1602, 1452, 1390, 1332, 1271, 1221, 1197, 1168, 1116, 1070, 1050, 1035, 982, 924, 875, 797, 711, 579 cm^{-1}. **HRMS-EI *m/z*:** [M]$^+$ calcd for C$_{15}$H$_{20}$NO$_3$F 281.1422; found 281.1420.

2-O-Benzoyl β-D-desosaminopyranosyl trichloroacetimidate (139d). Trichloroacetonitrile (0.34 mL, 3.4 mmol) and DBU (25 µL, 0.17 mmol) were sequentially added to a solution of lactol **SI-11** (234 mg, 0.838 mmol) in dichloromethane (4.0 mL) at room temperature. The originally colorless solution turned light brown upon the addition of DBU and the color intensified over the course of the reaction. After 1 h, the mixture was concentrated under reduced pressure. The residue was immediately subjected to flash chromatographic purification (hexanes/acetone 5:1 → 4:1; 0.2% *v/v* of triethylamine added) to furnish the title compound as a pale yellowish gum (283 mg, 80% yield). $[\alpha]_D^{20}$ = +36.2 (*c* 0.40, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 8.53 (s, 1H), 8.02 – 7.97 (m, 2H), 7.55 – 7.50 (m, 1H), 7.44 – 7.37 (m, 2H), 5.89 (d, *J* = 7.7 Hz, 1H), 5.39 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.87 (dqd, *J* = 12.4, 6.1, 2.1 Hz, 1H), 3.04 (ddd, *J* = 12.3, 10.3, 4.3 Hz, 1H), 2.34 (s, 6H), 1.93 – 1.84 (m, 1H), 1.66 – 1.55 (m, 1H), 1.36 (d, *J* = 6.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 165.5, 161.8, 133.0, 130.4, 129.8, 128.4, 98.1, 90.9, 71.0, 70.5, 63.4, 40.9, 31.5, 21.3. **^{1}H NMR (400 MHz, C$_6$D$_6$):** δ 8.54 (s, 1H), 8.21 – 8.15 (m, 2H), 7.08 – 6.94 (m, 3H), 6.21 (d, *J* = 7.9 Hz, 1H), 5.63 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.40 (dqd, *J* = 12.3, 6.1, 2.2 Hz, 1H), 2.72 (ddd, *J* = 12.2, 10.5, 4.3 Hz, 1H), 2.10 (s, 6H), 1.28 (ddd, *J* = 13.1, 4.4, 2.2 Hz, 1H), 1.19 – 1.11 (m, 1H), 1.07 (d, *J* = 6.1 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, C$_6$D$_6$):** δ 165.5, 162.0, 132.8, 131.1, 130.0, 128.5, 128.4, 98.4, 91.5, 70.8, 63.8, 40.7, 30.7, 21.1. **IR (film):** 3340, 2975, 2936, 2868, 2833, 2783, 1726, 1674, 1602, 1584, 1452, 1375, 1343, 1292, 1268, 1198, 1164, 1124, 1106, 1062, 1025, 934, 828, 796, 710, 646, 631, 579, 564 cm^{-1}. **HRMS-ESI *m/z*:** [M+H]$^+$ calcd for C$_{17}$H$_{22}$N$_2$O$_4$Cl$_3$ 423.0640; found 423.0638.

Synthesis of D-Mycinose and the derived Glycosyl Donors from D-Isoascorbic Acid

6-Bromo-6-deoxy-D-isoascorbic acid (SI-12). In a round-bottom flask, D-isoascorbic acid **164** (15.8 g, 89.6 mmol) was added to hydrogen bromide in acetic acid (33 w-%, 70 mL) at room temperature. The flask was covered with aluminum foil and the mixture stirred for 16 h before it was carefully poured into ice-cold water (350 mL). Stirring was continued for 78 h at room temperature. Volatile components were removed under high vacuum at 40 °C to give a very dark brown residue, which was subjected to flash chromatography (dichloromethane/methanol, 10:1). A second purification by flash chromatography (hexanes/acetone, 2:1) was necessary to give the title compound as a dark orange wax (18.1 g, 84% yield). $[\alpha]_D^{25}$ = −20.3 (*c* 0.92, MeOH). **¹H NMR (400 MHz, methanol-d⁴):** δ 4.86 (d, *J* = 3.3 Hz, 1H), 4.12 (ddd, *J* = 8.0, 4.8, 3.3 Hz, 1H), 3.59 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.47 (dd, *J* = 10.6, 7.7 Hz, 1H). **¹³C{¹H} NMR (101 MHz, methanol-d⁴):** δ 172.8, 154.5, 120.2, 77.9, 72.5, 32.9. **IR (film):** 3224, 1756, 1668, 1341, 1295, 1204, 1134, 1092, 1009, 844, 819, 759, 615, 517 cm⁻¹. **HRMS-ESI m/z:** [M+H]⁺ calcd for $C_6H_8O_5Br$ 238.9550; found 238.9550.
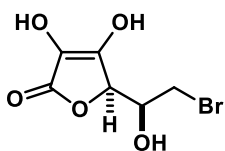
6-Bromo-6-deoxy-2,3-di-O-methyl-D-isoascorbic acid (165). In a round-bottom flask, a solution of trimethylsilyl diazomethane in diethyl ether (2 M, 100 mL, 200 mmol) was added via a dropping funnel over 30 min to a solution of enediol **SI-12** (11.5 g, 48.0 mmol) in toluene/methanol (7:2, 495 mL) at 0 °C (ice bath). After 10 min, the cooling bath was removed and stirring continued for 4.5 d at room temperature. The reaction was quenched by the sequential, dropwise addition of acetic acid and methanol (both 18 mL) at 0 °C. After stirring for 2 h at room temperature, the mixture was concentrated under reduced pressure and the residue was subjected to flash chromatography (hexanes/EtOAc, 3:1 → 1:1) to give the title compound as a yellowish syrup (10.0 g, 78% yield). $[\alpha]_D^{20}$ = −17.1 (*c* 1.1, CHCl₃). **¹H NMR (400 MHz, CDCl₃):** δ 4.79 (br d, *J* = 4.5 Hz, 1H), 4.17 (s, 3H), 4.14 – 4.08 (m, 1H), 3.85 (s, 3H), 3.59 – 3.48 (m, 2H). **¹³C{¹H} NMR (101 MHz, CDCl₃):** δ 168.6, 157.5, 123.3, 75.3, 71.6, 60.5, 59.9, 32.8. **IR (film):** 3428, 2956, 1765, 1673, 1463, 1434, 1330, 1233, 1213, 1136, 1099, 1052, 984, 956, 768 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for $C_8H_{11}O_5BrNa$ 288.9682; found 288.9682.

6-Deoxy-2,3-di-O-methyl-D-isoascorbic acid (SI-13). In a 100-mL two-necked flask under hydrogen atmosphere (two balloons), triethylamine (2.8 mL, 20 mmol) and a solution of bromide **165** (2.66 g, 9.96 mmol) in methanol (20 mL) were added to a vigorously stirred suspension of Pd/C (10% *w/w*, 211 mg, 0.198 mmol) in methanol (20 mL). After vigorous stirring for 3 h at room temperature, the mixture was filtered through a short plug of Celite®, which was rinsed with dichloromethane (5 × 10 mL). The combined filtrates were
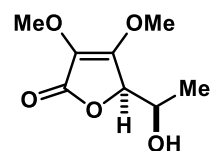
concentrated and the residue was loaded onto Celite®. Purification by flash chromatography (hexanes/EtOAc, 1:1) furnished the title compound as a colorless syrup (1.67 g, 89% yield). $[\alpha]_D^{20}$ = +15.6 (*c* 1.2, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 4.60 (d, *J* = 3.9 Hz, 1H), 4.15 (s, 3H), 4.07 (qd, *J* = 6.5, 3.8 Hz, 1H), 3.85 (s, 3H), 2.08 (br s, 1H), 1.22 (d, *J* = 6.6 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 169.2, 158.0, 123.2, 78.3, 68.0, 60.6, 59.7, 17.0. **IR (film):** 3418, 2979, 2942, 2841, 1758, 1673, 1463, 1380, 1346, 1332, 1231, 1214, 1183, 1132, 1093, 1049, 1022, 1005, 985, 955, 936, 849, 803, 769, 722, 671 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C$_8$H$_{12}$O$_5$Na 211.0577; found 211.0578.

(3R,4R,5R)-5-((R)-1-hydroxyethyl)-3,4-dimethoxydihydrofuran-2(3H)-one (166). A 100-mL steel autoclave with glass inlay and magnetic stirring bar was charged with solutions of alkene **SI-13** (1.05 g, 5.58 mmol) and [Rh(dppb)(cod)]BF$_4$ (426 mg, 0.588 mmol) in dichloromethane (35 mL and 20 mL) under an argon atmosphere. Then, a hydrogen atmosphere was applied (100 bar total pressure) and the mixture was stirred for 24 h at room temperature. For work-up, the pressure was released and the mixture was concentrated under reduced pressure. The residue was loaded onto Celite® and subjected to flash chromatography (hexanes/acetone, 5:2) to furnish the title compound as a white, crystalline solid (1.00 g, 94% yield). **mp** = 129 – 130 °C. $[\alpha]_D^{20}$ = +17.3 (*c* 1.1, CHCl$_3$). **¹H NMR (400 MHz, CDCl$_3$):** δ 4.29 (dd, *J* = 3.3, 2.4 Hz, 1H), 4.21 (d, *J* = 5.8 Hz, 1H), 4.17 – 4.09 (m, 2H), 3.65 (s, 3H), 3.47 (s, 3H), 1.94 (br s, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). **¹³C{¹H} NMR (101 MHz, CDCl$_3$):** δ 173.2, 85.4, 76.4, 75.4, 66.8, 59.4, 58.0, 18.9. **IR (film):** 3496, 2997, 2977, 2941, 2904, 2884, 2840, 1760, 1463, 1449, 1393, 1258, 1199, 1155, 1142, 1110, 1066, 1041, 1011, 993, 983, 955, 933, 866, 841, 787, 758, 644, 564, 478 cm⁻¹. **HRMS-ESI m/z:** [M+Na]⁺ calcd for C$_8$H$_{14}$O$_5$Na 190.0836; found 190.0837.
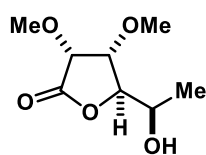
1,4-Di-O-acetyl-β-D-mycinopyranose (21a). In a 250-mL Schlenk flask with cooling jacket, a solution of diisobutylaluminum hydride in hexanes (1.0 M, 16.5 mL, 23 mmol) was added over 10 min to a suspension of lactone **166** (876 mg, 4.61 mmol) in toluene (50 mL) at −78 °C. After complete addition, the mixture was stirred for 5 min at −78 °C and for another 4 h at −55 °C. The reaction was quenched by slow addition of ethyl acetate (10 mL) at −55 °C. Saturated aqueous Rochelle's salt solution (80 mL) and ethyl acetate (50 mL) were introduced and the resulting mixture was vigorously stirred for 14 h at room temperature until a clean separation of the layers was reached. The aqueous phase was extracted with ethyl acetate (10 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure to give a thick colorless gum.

A solution of concentrated sulfuric acid in acetic anhydride (1:99 v/v, 5 mL) was added to a solution of this material in acetic anhydride (10 mL) at 0 °C (ice bath). The ice bath was removed and stirring continued at ambient temperature for 40 min. The dark amber solution was diluted with ethyl acetate (20 mL) and poured into ice-cold water (20 mL) in a separatory funnel. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate solution (20 mL). The combined aqueous phases were extracted with ethyl acetate (6 × 10 mL), the organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the filtrate was concentrated under reduced pressure. Remaining acetic anhydride was largely removed under high vacuum (10^{-2} mbar, warm water bath, ca. 3 h). Purification of the resulting amber oil by flash chromatography (hexanes/ethyl acetate, 4:1 → 3:1 → 5:2) furnished the title compound as a colorless, crystalline solid (606 mg, 48% yield). **mp** 99 – 101 °C. $[\mathbf{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +28.0 (c 0.64, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.89 (d, J = 8.3 Hz, 1H), 4.45 (dd, J = 9.9, 2.6 Hz, 1H), 4.10 (dq, J = 10.0, 6.3 Hz, 1H), 4.00 (t, J = 2.6 Hz, 1H), 3.54 (s, 3H), 3.47 (s, 3H), 3.22 (dd, J = 8.3, 2.7 Hz, 1H), 2.134 (s, 3H), 2.126 (s, 3H), 1.18 (d, J = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 170.4, 169.4, 92.0, 80.0, 76.5, 74.6, 68.5, 61.5, 58.7, 21.3, 21.1, 17.5. **IR (film):** 2983, 2940, 2834, 1755, 1451, 1370, 1224, 1173, 1139, 1100, 1060, 1000, 966, 935, 909, 886, 709, 562 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{12}$H$_{20}$O$_7$Na 299.1101; found 299.1101.

4-O-Acetyl-D-mycinopyranose (SI-14). Benzylamine (0.55 mL, 5.0 mmol) was added to a solution of acetate **21a** (276 mg, 0.999 mmol) in THF (8.5 mL). The resulting mixture was stirred for 15 h at room temperature before it was diluted with ethyl acetate (20 mL) and washed with aqueous HCl (1 M, 20 mL). The aqueous phase was extracted with ethyl acetate (4 × 10 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was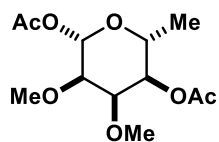 concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc, 3:1 → 1:1) furnished the title compound as a colorless gum (114 mg, 49% yield; α/β ≈ 3:4). $[\mathbf{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = +58.5 (c 1.2, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** signals of the α-anomer: δ 5.23 – 5.14 (m, 1H), 4.47 (dt, J = 10.1, 2.2 Hz, 1H), 4.18 (dq, J = 10.1, 6.2 Hz, 1H), 4.06 – 4.03 (m, 1H), 3.57 (s, 3H), 3.47 (s, 3H), 3.30 (t, J = 2.8 Hz, 1H), 2.13 (s, 3H), 1.20 (t, J = 6.2 Hz, 3H). signals of the β-anomer: δ 5.01 (d, J = 7.8 Hz, 1H), 4.47 (dt, J = 10.2, 2.3 Hz, 1H), 4.00 (m, 1H), 3.98 (t, J = 2.8 Hz, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 3.05 (dd, J = 7.9, 2.7 Hz, 1H), 2.13 (s, 3H), 1.19 (d, J = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** signals of the α-anomer: δ 170.3, 92.2, 78.9, 76.8, 74.1, 62.2, 60.9, 60.0, 21.1, 17.4. signals of the β-anomer: δ 170.3, 94.3, 82.1, 76.5, 74.1, 67.8, 61.6, 58.6, 21.1, 17.4. **IR (film):** 3464, 2982, 2937, 2835, 1740, 1453, 1375, 1236, 1199, 1158, 1131, 1097, 1081, 1047, 1003, 963, 921, 834, 796, 712, 603, 561, 528, 495 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{10}$H$_{18}$O$_6$Na 257.0996; found 257.0997.
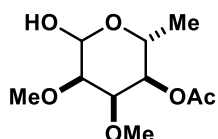
4-O-Acetyl-D-mycinopyranosyl fluoride (21b). In a 60-mL Nalgene™ screw-capped reaction vessel, hydrogen fluoride pyridine complex (70% HF *w/w*, 1.7 mL) was added to a solution of acetate **X** (316 mg, 1.14 mmol) in dichloromethane (12 mL) at 0 °C (ice bath). The reaction mixture, which turned pale yellowish upon the addition, was stirred for 2 h at 0 °C. For work-up, the cold reaction mixture was carefully poured into a saturated aqueous solution of sodium bicarbonate (30 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, the drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc, 4:1 → 3:1) to furnish the anomers of the title compound in separate fractions.
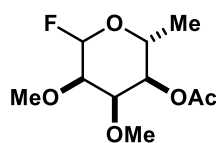
Analytical and spectroscopic data of the *α-anomer*: colorless oil, giving a white solid upon standing (184 mg, 68% yield); R_f = 0.20 (hexanes/EtOAc, 3:1). $[\alpha]_D^{20}$ = +122.0 (*c* 0.59, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.60 (ddt, *J* = 53.7, 3.2, 0.9 Hz, 1H), 4.54 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.38 (dq, *J* = 10.3, 6.3 Hz, 1H), 4.04 – 4.01 (m, 1H), 3.56 (s, 3H), 3.49 (s, 3H), 3.31 (dt, *J* = 26.7, 3.2 Hz, 1H), 2.14 (s, 3H), 1.20 (d, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 170.3, 104.3 (d, *J* = 234 Hz), 77.7 (d, *J* = 23.1 Hz), 75.4 (d, *J* = 1.7 Hz), 73.8, 63.7 (d, *J* = 2.5 Hz), 61.7, 57.5, 21.1, 17.0. **^{19}F{^{1}H} NMR (282 MHz, CDCl$_3$):** δ −144.9. **IR (film):** 2982, 2939, 2834, 1738, 1453, 1376, 1328, 1234, 1204, 1180, 1138, 1120, 1088, 1049, 992, 937, 891, 867, 832, 786, 713, 660, 549 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{10}$H$_{17}$FO$_5$Na 259.0952; found 259.0952.

Analytical and spectroscopic data of the β-anomer: colorless oil (48.9 mg, 18% yield); R_f = 0.41 (hexanes/EtOAc, 3:1). $[\alpha]_D^{20}$ = +39.4 (*c* 0.70, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 5.46 (dd, *J* = 54.1, 7.2 Hz, 1H), 4.52 (dd, *J* = 9.6, 2.6 Hz, 1H), 4.09 (dq, *J* = 9.5, 6.3 Hz, 1H), 3.96 (dt, *J* = 4.0, 2.8 Hz, 1H), 3.54 – 3.52 (m, 6H), 3.21 (ddd, *J* = 11.6, 7.2, 2.9 Hz, 1H), 2.13 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 170.3, 108.4 (d, *J* = 212 Hz), 80.5 (d, *J* = 20.6 Hz), 77.0 (d, *J* = 9.5 Hz), 74.05, 68.6 (d, *J* = 5.0 Hz), 61.5, 59.1 (d, *J* = 2.0 Hz), 21.1, 17.6. **^{19}F{^{1}H} NMR (282 MHz, CDCl$_3$):** δ −145.9. **IR (film):** 2984, 2937, 2835, 1743, 1453, 1373, 1313, 1234, 1202, 1138, 1100, 1074, 1051, 999, 966, 907, 709, 563, 485 cm^{-1}. **HRMS-ESI *m/z*:** [M+Na]$^+$ calcd for C$_{10}$H$_{17}$FO$_5$Na 259.0952; found 259.0951.

4-O-Acetyl-D-mycinopyranosyl trichloroacetimidate (21c). Trichloroacetonitrile (0.17 mL, 1.7 mmol) and DBU (12 µL, 80 µmol) were sequentially added to a solution of lactol **SI-14** (78.0 mg, 0.333 mmol) in dichloromethane (2.2 mL) at room temperature. The originally colorless solution turned slightly brown upon the addition of DBU and the color intensified over the course of the reaction. After 2 h, the mixture was concentrated under reduced pressure and the residue was immediately purified by flash chromatography (hexanes/EtOAc, 4:1; 0.2% *v/v* of triethylamine added). The title compound was obtained as a colorless syrup (75.1 mg, 60% yield; α/β ≈ 1:12). $[\alpha]_D^{20}$ = +12.2 (*c* 0.97, CHCl$_3$). **^{1}H NMR (400 MHz, CDCl$_3$):** signals of the β-anomer only, δ 8.64 (s, 1H), 6.04 (d, *J* = 8.1 Hz, 1H), 4.53 (dd, *J* = 9.8, 2.6 Hz, 1H), 4.14 (dq, *J* = 9.7, 6.3 Hz, 1H), 4.01 (t, *J* = 2.7 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 3.37 (dd, *J* = 8.2, 2.8 Hz, 1H), 2.13 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H). **^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$):** δ 170.4, 161.4, 96.6, 91.2 (br), 80.2, 77.2, 74.4, 68.8, 61.6, 59.5, 21.1, 17.5. **IR (film):** 3339, 2983, 2936, 2835, 1732, 1673, 1451, 1373, 1294, 1232, 1199, 1172, 1140, 1099, 1045, 1001, 966, 906, 836, 795, 734, 713, 645, 603, 574, 507, 475, 432 cm^{-1}. **HRMS-ESI m/z:** [M+Na]$^+$ calcd for C$_{12}$H$_{18}$NO$_6$Cl$_3$Na 400.0092; found 400.0092.
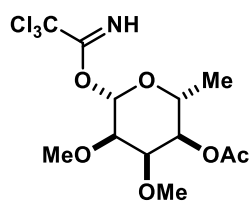
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APPENDIX A – Supporting Chrystallographic Information
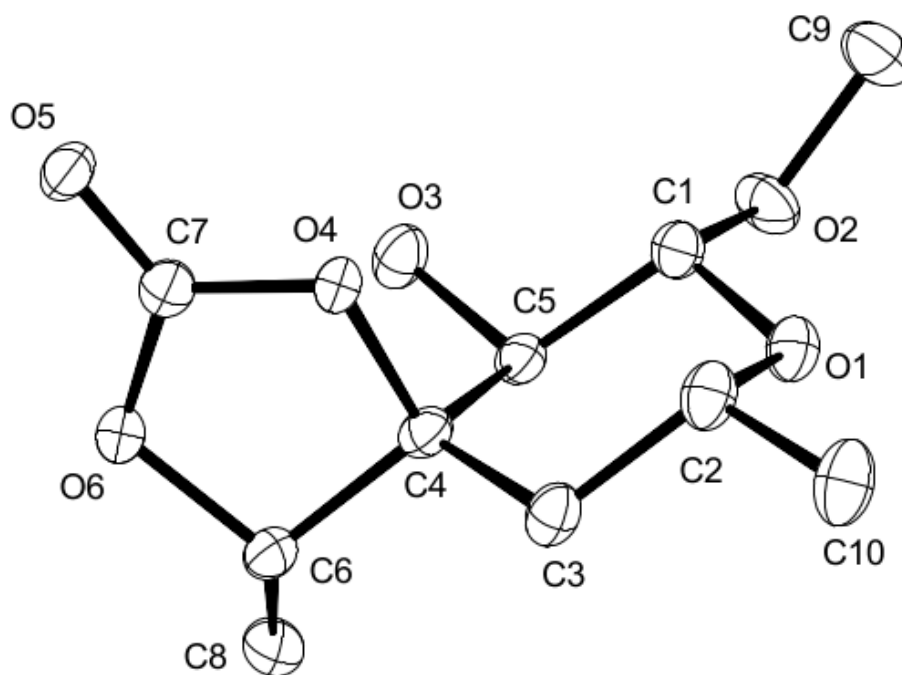
Figure S1: Structure of methyl β-D-aldgaropyranoside (**121a**) in the solid state; arbitrary numbering scheme (differing from numbering in main chapters).

X-ray Crystal Structure Analysis of Compound 121a. $C_{10}H_{16}O_6$, $M_r = 232.23$ g · mol^{-1}, colorless plate, crystal size $0.781 \times 0.236 \times 0.228$ mm^3, monoclinic, space group $P2_1$[4], $a = 5.9006(2)$ Å, $b = 10.7626(4)$ Å, $c = 8.9193(3)$ Å, $\beta = 93.5490(10)°$, $V = 565.34(3)$ Å^3, $T = 100(2)$ K, $Z = 2$, $D_{calc} = 1.364$ g · cm^3, $\lambda = 1.54178$ Å, $\mu(Cu\text{-}K_\alpha) = 0.967$ mm^{-1}, analytical absorption correction ($T_{min} = 0.68$, $T_{max} = 0.85$), Bruker AXS Enraf-Nonius KappaCCD diffractometer with a FR591 rotating Cu-anode X-ray source, $7.521 < \theta < 72.359°$, 19774 measured reflections, 2155 independent reflections, 2129 reflections with $I > 2\sigma(I)$, $R_{int} = 0.0281$. $S = 1.194$, 168 parameters, absolute structure parameter $= -0.02(7)$, residual electron densitry +0.2 (0.25 Å from H3B) / −0.2 (0.81 Å from C10) e · Å^{-3}. The hydrogens at C1, C2, C4, C5 and C6 were found and refined, all other hydrogens were placed in calculated positions.

The structure was solved by *SHELXT* and refined by full-matrix least-squares (*SHELXL*) against F^2 to $R_1 = 0.032$ [$I > 2\sigma(I)$], $wR_2 = 0.076$. **CCDC-2047121**.

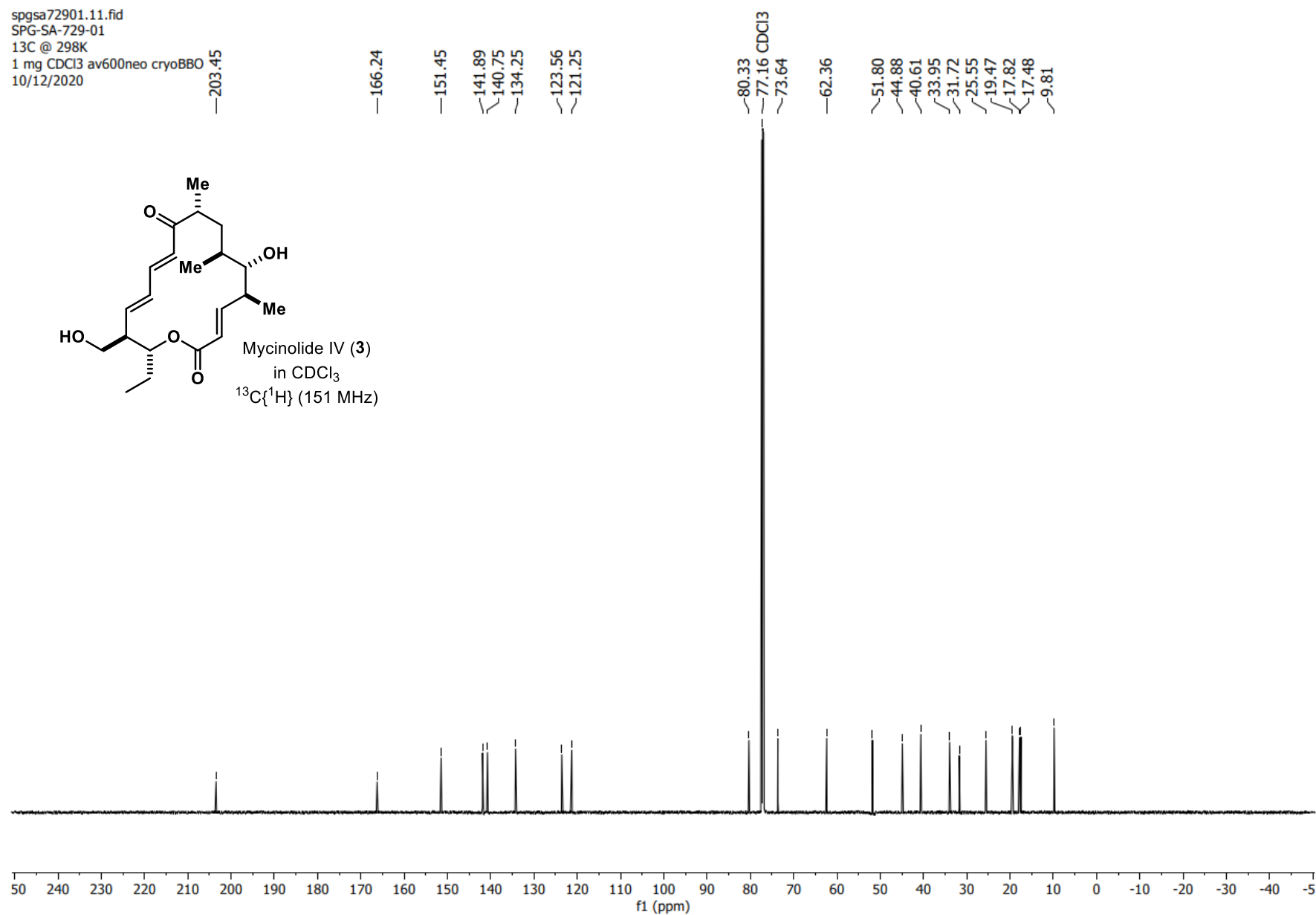# APPENDIX B – Spectra Copies of Selected Key Compounds and Natural Products

fr25049-SPG-SA-544-01.10.fid
SPG-SA-544-01

68 in CDCl$_3$
^{1}H (400 MHz)
^{13}C{^{1}H} (101 MHz)

−7.26 CDCl3

fr25049-SPG-SA-544-01.13.fid
SPG-SA-544-01

spgsa72901.10.fid
SPG-SA-729-01
1H @ 298K
1 mg CDCl3 av600neo cryoBBO
10/12/2020

—7.26 CDCl3

Mycinolide IV (**3**)
in CDCl$_3$
^{1}H (600 MHz)

spgsa72901.11.fid
SPG-SA-729-01
13C @ 298K
1 mg CDCl3 av600neo cryoBBO
10/12/2020

203.45

166.24

151.45

141.89
140.75
134.25

123.56
121.25

80.33
77.16 CDCl3
73.64

62.36

51.80
44.88
40.61
33.95
31.72
25.55
19.47
17.82
17.48
9.81

Mycinolide IV (**3**)
in CDCl₃
¹³C{¹H} (151 MHz)

50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
f1 (ppm)

my06046-SPG-SA-293-02.10.fid
SPG-SA-293-02

—7.26 CDCl3

MeO,,, O ,,Me

HO

O

O

O,,,, Me

121a in CDCl$_3$
^{1}H (400 MHz)
^{13}C{^{1}H} (101 MHz)

1.00
1.04
1.04
3.03
1.08
0.95
1.08
4.30
3.18

f1 (ppm)
2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

my06046-SPG-SA-293-02.12.fid
SPG-SA-293-02

77.16 CDCl3

f1 (ppm)
270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40

mz04056-SPG-SA-794-02.10.fid
SPG-SA-794-02

—7.26 CDCl3

MeO,,,,''''O'''''Me

BzO''''

NMe2

139a in CDCl3
^{1}H (400 MHz)
^{13}C{^{1}H} (101 MHz)

2.07
1.05
2.13
1.00
1.07
1.11
3.06
1.04
6.08
1.02
1.09
3.23

f1 (ppm)

mz04056-SPG-SA-794-02.12.fid
SPG-SA-794-02

—77.16 CDCl3

f1 (ppm)

my05043-SPG-SA-594-02.10.fid
SPG-SA-594-02

21a in CDCl$_3$
^{1}H (400 MHz)
^{13}C{^{1}H} (101 MHz)

my06005-SPG-SA-594-02.11.fid
SPG-SA-594-02

Aldgamycin N (**1**)
in CDCl₃
¹H (600 MHz)

spgsa69603.11.fid
SPG-SA-696-03
13C @ 298K
4 mg CDCl3 av600neo cryoBBO
29/10/2020

Aldgamycin N (**1**)
in CDCl$_3$
^{13}C{^{1}H} (151 MHz)

spgsa89402.10.fid
SPG-SA-894-02
1H @ 298K
0.8 mg CDCl3 av600neo cryoBBO
06/07/2021

7.26 CDCl3

Mycinamicin IV (**2**)
in CDCl₃
$^{13}C\{^1H\}$ (151 MHz)

(H₂O)

f1 (ppm)

spgsa89402.11.fid
SPG-SA-894-02
13C @ 298K
0.8 mg CDCl3 av600neo cryoBBO
06/07/2021

203.76

166.20

151.75

141.80
141.43

133.08

123.20
120.87

104.97
101.10
87.94
81.88
79.87
73.69
72.66
70.63
70.39
69.54
68.64
65.89
61.78
59.86
49.20
44.90
41.36
40.26
34.08
32.60
28.21
25.28
21.18
19.41
17.77
17.73
17.43
9.66

Mycinamicin IV (**2**)
in CDCl₃
$^{13}C\{^{1}H\}$ (151 MHz)

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)