Chapter 2
Total Synthesis of Mycolactones

2.1 Introduction
Buruli ulcer (BU) is a severe necrotizing skin disease, characterized by the formation of large, painless necrotic ulcers in the absence of an acute inflammatory response. It is caused by Mycobacterium ulcerans, the third most common mycobacterial pathogen of humans after its more infamous family members M. tuberculosis and M. leprae. Recently, it has been reported, that M. ulcerans secretes a heterogeneous mixture of polyketide toxins known as mycolactones. Clinical evidence shows, that these mycolactone toxins are indeed responsible for tissue destruction and immune suppression.\(^1\)

2.2 Biological context
BU was first reported in 1948 by MacCallum and colleagues,\(^2\) even though large ulcers almost certainly caused by M. ulcerans had been described by Sir Albert Cook as early as 1897.\(^3\) The disease primarily occurs in sub-Saharan Africa, but is also known in tropical areas of Papua New Guinea, Malaysia, China, French Guiana, Mexico and Australia among others.\(^4\) BU affects all age groups, but about 50% of the cases concerns children. Unfortunately, the disease has long been neglected, possibly because foci of infection are located in local communities with little economic or political influence.\(^4\) Recently however, the World Health Organization (WHO) has declared the emergence of BU an immediate and serious health hazard. In 1998, this resulted in the Global Buruli Ulcer Initiative (GBUI) aiming to mobilize and coordinate international research as was formulated in the Yamoussoukro Declaration.\(^5\) In 2004, this was followed by the adoption of a resolution on Buruli ulcer calling for additional (scientific) efforts.\(^6\)
Chapter 2

2.2.1 Infection

Proximity to marshes and wetlands is a risk factor for infection, but the exact mode of transmission remains unclear. Current evidence indicates that the infection is transmitted through mild traumatic injuries or skin abrasions, after contact with contaminated water, soil or vegetation. The isolation of *M. ulcerans* from the salivary glands of *Naucoris* sp. has incriminated aquatic insects as possible passive hosts serving as the key reservoir species. In support of this hypothesis, mice were infected in the laboratory after insect bites. The involvement of slowly moving or stagnant water for the proliferation of *M. ulcerans* combined with the increased agricultural activities involving irrigation in some of the endemic regions is almost certainly responsible for the steep rise in reported infections over the last decade.

2.2.2 Treatment

At present, complete surgical removal of infected tissue is the only way to effectively treat BU, leaving the patient with extensive scarring or even complete loss of limbs. To date, drug treatment has proven to be ineffective. Even though a number of antibiotics seem to be effective *in vitro*, the results obtained in *in vivo* studies are disappointing. In 2002 however, Dega *et al*. reported an *in vivo* study on mice disclosing that *M. ulcerans* is sensitive to a combination of amikacin and rifampicin. WHO guidelines now recommend the use of these anti-mycobacterial drugs in combination with surgery. Ideally, the development of a vaccine to prevent infection would offer the best structural solution, but attempts in this area have met with limited success so far.

2.2.3 Structure of mycolactones

The increased research activity toward BU led to a first major breakthrough when Small and co-workers isolated and identified mycolactones A and B (Figure 2.1) as the polyketide toxins secreted by *M. ulcerans*. Since then, several other mycolactones have been identified (C, D, E and F; Figure 1) all of which show conservation of the lactone core, but modifications in the side chain. Even though the biological effects of mycolactones have been extensively studied and documented as being cytotoxic, apoptotic and immunosuppressive, the mechanisms by which they act remain an enigma. Biological evaluation shows that the lactone core in itself is sufficient for cytopathicity, but that the
side chain greatly enhances its virulence factor probably by facilitating entrance into the cell or by interaction with an intracellular target molecule. The mode of action of all mycolactone analogues seems therefore identical, but the potency varies with the composition of the side chain (mycolactones A and B being the most potent). This suggests, that the differences in virulence that are observed between geographical strains of *M. ulcerans* can be directly correlated to their differences in mycolactone profile.¹⁴ᵇ

![Figure 2.1 Molecular structures of natural mycolactones.](image)

### 2.2.4 Biosynthesis of mycolactones A and B

From the onset of the joint effort against BU, the determination of the complete genome sequence of *M. ulcerans* received high priority. A fundamental understanding of the molecular machinery of the bacterium provides opportunities for rational drug targeting and vaccine design. The sequencing of the entire genome has recently been achieved by Stinear and co-workers.¹⁵ Previously, the genes encoding for the biosynthesis of mycolactones had already been identified.¹⁶ To this end, the DNA from *M. ulcerans* was compared to the DNA from *M. marinum*; a closely related species which does not produce mycolactones.

---

¹ During the course of my research, it was brought to my attention by Prof. Dr. J. Lugtenburg, that 1,3-steric interactions between the methyl substituents on C4’ and C6’ of the side chain of mycolactone B (E-configuration) will force the side chain into the 5’-s-cis conformation rather than the 5’-s-trans conformation which is depicted in figure 2.1. However, for ease of presentation and to avoid unnecessary confusion, I have chosen to follow the literature precedent for the remainder of this chapter.
This approach resulted in the identification of a giant plasmid called pMUM001, most of which consists of six genes coding for proteins involved in mycolactone synthesis. Two polyketide synthases (PKS MLSA1 and MLSA2) are responsible for the synthesis of the mycolactone core, while a third PKS (MLSB) constructs the side chain. The arrangement of the three PKS resembles an ‘assembly-line’ of enzymes. For the formation of the lactone core by MLSA1 and MLSA2, the growing polyketide chain is extended nine times by a ketosynthase and an acyltransferase adding either a C2- (malonate) or a C3-unit (methylmalonate). The added unit is subsequently reduced to the appropriate degree by enzymes immediately following the acyltransferase in the assembly-line (Figure 2.2). The saturated parts in the chain are obtained by the consecutive action of a ketoreductase, a dehydratase and an enoylreductase (Scheme 2.1). When the enoylreductase is missing an olefin is formed, while a hydroxyl moiety is produced if only a ketoreductase is present.

After completion of the chain, a terminal thioesterase/cyclase releases the product as the 12-membered lactone ring. In a similar fashion, MLSB produces the side chain by seven chain extensions. In this case a polyketide-modifying enzyme denoted P450 monooxygenase (also encoded by pMUM001) is believed to introduce the additional hydroxyl moiety at carbon 12. The function of the other two genes on pMUM001 is still unclear, but it is speculated that the protein encoded by one of them catalyzes ester bond formation between the mycolactone core and the side chain.

Figure 2.2 Organization of the mycolactone PKS genes.
Interestingly, the three PKS genes contain a high degree of identical nucleotide sequences. In fact, the entire 105-kb mycolactone locus contains only 9.5 kb of unique DNA sequence and this has important implications. First of all, the relative simplicity of the genome suggests that mycolactones evolved only very recently. Moreover, the enormous size of the plasmid is believed to make it genetically unstable and therefore sensitive to mutation. This hypothesis is supported by the fact that in the absence of purifying selection, deletion of plasmid sequences readily proceeds resulting in loss of mycolactone production. The instability of the plasmid may partly explain why different geographical strains of *M. ulcerans* show a different mycolactone profile (*vide supra*). For example, it has been proven that the extra methyl group in the side chain of mycolactone F (Figure 2.1) arises from the substitution of an acyltransferase 1 domain (malonate) by an acyltransferase 3 domain (methylmalonate) in module 7 of MSLB (Figure 2.2). Similarly, a mutation in the gene coding for P450 monooxygenase that renders the enzyme inactive would result in the production of mycolactone C instead of A/B. It seems that the circumstances are ideal for the creation of a large family of mycolactones and that the structural diversity that can be found in nature may therefore be much larger than first anticipated.

### 2.2.5 Production of mycolactones

Access to a wide variety of natural and non-natural mycolactones is essential for a better understanding of the biological mechanisms by which they act and ultimately for the
development of better drugs and vaccines. Unfortunately, initial research was hampered by the lack of sufficient material. The bacterium produces its toxins in minute amounts and cultivation of *M. ulcerans* is problematic due to slow growth and formation of aggregates. In 2001, a large scale suspension cultivation process for the isolation of useful amounts of mycolactones was described, but the procedure remained cumbersome and the overall yield was still low. Synthetic organic chemists were therefore called upon to supply larger quantities. In 2002, Kishi and co-workers met this challenge by completion of the total synthesis of mycolactones A and B and more recently they reported the construction of mycolactone C (see also § 2.3). An additional advantage of a (general) synthetic approach is, that it is currently the only method to access non-natural mycolactones as well.

The recent discovery, that pMUM001 encodes all the genes required for the biosynthesis of mycolactones (*vide supra*), may make transformation of this plasmid a possible alternative for the production of natural mycolactones in the future.

### 2.3 Previous total syntheses of mycolactones

Until today, only Kishi and co-workers have reported a total synthesis of mycolactones. Prior to that, before the elucidation of the stereochemistry by Small and co-workers, Gurjar *et al.* synthesized the side chain, but with the wrong stereochemistry at C15′ as appeared later.

#### 2.3.1 Synthesis of the mycolactone core by Kishi

The mycolactone core was assembled by connection of three chiral building blocks (2.4, 2.7 and 2.10; Scheme 2.2). For the preparation of fragment 2.4 enantiopure olefin 2.1 was converted into the epoxide, which was opened with propyne to give alcohol 2.2 as a mixture of diastereomers. After protective group manipulations, cyclic acetal 2.3 was obtained, which could be separated from its diastereoisomer. The building block was completed by hydrozirconation with Schwartz reagent followed by halogen metal exchange.

The two stereocenters of fragment 2.7 were installed in a single step by application of the Brown crotylboration protocol to aldehyde 2.5 resulting in terminal olefin 2.6. Subsequently, 2.7 was obtained in three straightforward steps.
Total Synthesis of Mycolactones

For the introduction of the stereogenic centers of building block 2.10, the Brown protocol was employed in the key step once again, this time resulting in terminal olefin 2.9. Appropriate functionalization to obtain vinyl iodine 2.10 was achieved in six additional steps.

Scheme 2.2 Synthesis of chiral building blocks for the mycolactone core.\(^{13a}\)

The assembly of the mycolactone core from the enantiopure building blocks commenced with the cross-coupling of fragments 2.4 and 2.7 using a modified Negishi coupling protocol (Scheme 2.3).\(^{13b}\) Product 2.11 was subsequently subjected to a five-step sequence to generate primary iodide 2.12 suitable for connection to 2.10 in a second Negishi coupling. Selective removal of the TES-group and the primary TBS-group of 2.13 was achieved in one pot by treatment with buffered HF-pyridine. Oxidation of the primary alcohol to the corresponding carboxylic acid in two steps then set the stage for a Yamaguchi macrolactonization to form the 12-membered ring. The synthesis of the mycolactone core was completed by deprotection of the remaining hydroxyl moieties to give 2.15.
An important aspect of the synthesis of the mycolactone core as described above, is that it constitutes a general method for the preparation of any desired diastereoisomer. In addition, the convergent approach avoids long linear sequences, which makes the synthesis of analogues relatively straightforward. Nevertheless, there is still room for improvement, for example in the yields of the cross-coupling steps and in reducing the overall number of steps (for instance in the preparation of 2.10). With regard to the introduction of new chiral centers (i.e. formation of 2.2, 2.6 and 2.9), the authors unfortunately fail to mention the obtained levels of diastereoselectivity and/or enantioselectivity. The Brown crotylboration protocol usually gives excellent diastereoselectivity (de > 99%) and high enantioselectivity (ee 90% ± 5%). An indication for the enantiopurity of 2.6 is the preparation of its enantiomer by others in 86% ee using the same method. A definite improvement should be possible in the synthesis of fragment 2.4 where a stereocenter is introduced with low/no
selectivity resulting in the loss of a substantial amount of compound two steps later. Alternatively, the stereocenters of this building block can be formed via asymmetric Sharpless epoxidation followed by hydroxyl-directed dimethyl cuprate opening of the epoxide as reported by Forsyth et al. (Scheme 2.4).  

![Scheme 2.4 Alternative preparation of 2.4.](image)

2.3.2 Synthesis of a side chain epimer

Gurjar and Cherian synthesized a C15'-epimer of the side chain of mycolactones A and B by cross-coupling of a conjugated building block (2.19: C1'-C8') and a chiral building block (2.23: C9'-C16'; Scheme 2.5). The construction of the conjugated fragment started with the reduction of ester 2.16 (available in 3 steps from allyl alcohol) to the corresponding alcohol. Subsequent oxidation to the aldehyde followed by Wittig olefination yielded ester 2.17. A second reduction-oxidation-Wittig chain elongation sequence resulted in the formation of ester 2.18. To make the building block suitable for cross-coupling, the allylic alcohol was deprotected and converted into phosphonate 2.19 in two steps.

For the preparation of the chiral fragment, the methyl glycoside bond of 4,6-dideoxy-D-xylo-hexopyranoside 2.20 was hydrolyzed and the resulting hemiacetal reduced to give diol 2.21. By adopting a protection-deprotection protocol, the secondary alcohol was selectively shielded in three steps (2.22), after which the primary alcohol was oxidized to the aldehyde. The synthesis of the chiral building block was concluded via a Wittig-reduction-oxidation sequence similar to the ones described above. Horner-Wadsworth-Emmons (HWE) coupling of the thus obtained aldehyde 2.23 to phosphonate 2.19 proceeded readily to give the protected side chain 2.24 in 65% yield.
Section 2.3.3 Synthesis of the side chain of mycolactones A, B and C

In their synthesis of the side chains of mycolactones A, B and C, Kishi and co-workers adopted the strategy of Gurjar et al. to couple a conjugated C1’-C8’ fragment to a chiral C9’-C16’ fragment. To this end, the methyl ester analogue of conjugated building block 2.19 (Scheme 2.6) was prepared employing similar procedures as described in Scheme 2.5. The synthesis of the chiral building block started from aldehyde 2.25, which was available from ethyl (S)-3-hydroxy-n-butyrate in two steps. HWE chain elongation afforded olefin 2.26, which was subjected to a catalytic asymmetric dihydroxylation to give a 3.8:1 mixture of diol 2.27 and its diastereomer. Protection of the hydroxyl groups followed by a reduction-oxidation-Wittig chain elongation sequence resulted in olefin 2.28.
Allylic alcohol 2.29 was subsequently obtained by reduction of the ester, at which stage the diastereomers could be separated. Finally, oxidation to the aldehyde afforded conjugated building block 2.30, which was coupled to phosphonate 2.31 to give carboxylic acid 2.32 after base-mediated hydrolysis.

Scheme 2.6 Synthesis of the side chain of mycolactones A and B.\(^{20a}\)

For the synthesis of the side chain of mycolactone C, aldehyde 2.25 was subjected to a Brown allylation protocol to give olefin 2.33 as a single diastereomer.\(^{20b}\) Protection of the hydroxyl moiety followed by ozonolysis afforded the aldehyde, which was used in a Wittig reaction to obtain ester 2.34 (Scheme 2.7). Beyond this stage, the route established for the side chain of mycolactone A/B was followed (Scheme 2.6).
Chapter 2

Scheme 2.7 Synthesis of the side chain of mycolactone C.20b

The total synthesis of mycolactones A and B was completed via a Yamaguchi esterification of the side chain 2.32 with a suitably protected mycolactone core followed by removal of the protecting groups (Scheme 2.8). Because hydrolysis of the cyclopentylidene acetal was accompanied by side reactions on the unsaturated fatty acid moiety, the C17- and C19 hydroxyl groups were protected as TBS-ethers in the total synthesis of mycolactone C.

Scheme 2.8 Coupling of the side chain and the core unit.20a

2.4 New approaches towards the side chain of mycolactones A and B25

The total synthesis of mycolactones A, B and C (vide supra) offers new opportunities in the biological and medical field with regard to Buruli ulcer disease (see § 2.2.5). However, even though the synthesis as described in paragraph 2.3 constitutes a general method capable of producing a range of (non-natural) mycolactones, alternative (more efficient) approaches remain a continuing area of research.
2.4.1 Retrosynthesis

For the assembly of the conjugated system, both Kishi and Gurjar employed reduction-oxidation-Wittig sequences that elongate the chain with one double bond at the time (§ 2.3.2). The construction of 2.19 or 2.32 takes nine linear steps from 2.16, which leaves ample room for improvement. We envisioned the synthesis of a conjugated C1’-C9’ system (2.37 in Figure 2.3) in only 3 steps from 2,4-dimethylfuran. We subsequently planned to connect terminal alkyne 2.37 to chiral C10’-C16’ fragment 2.38 via a Sonogashira coupling to obtain 8,9-dehydro analogue 2.36. Finally, partial hydrogenation of the alkyne followed by deprotection should complete the synthesis of the side chain 2.35.

![Figure 2.3 Retrosynthetic analysis.](image)

With regard to the preparation of the chiral building block, the choice of Kishi to use an asymmetric catalyst in combination with ethyl (S)-3-hydroxy-n-butyrate (enantiomer also available) can be appreciated, as it gives access to all diastereomers (Scheme 2.6). In contrast, the use of readily available D-monosaccharides admittedly allows variation at C12’ and C13’, but restricts the configuration at C15’ to the non-natural epimer. Preparation of natural C15’-epimers requires the use of L-sugars, which are often rare and expensive.
(Figure 2.4). On the other hand, monosaccharides have the advantage that they offer absolute stereocontrol as opposed to the 58% d.e. obtained during the Sharpless dihydroxylation reaction.\textsuperscript{20a} Besides, in principle, sugars also provide access to regioisomers with hydroxyl moieties at C14' or C16'.

![Figure 2.4 Correlation of stereochemistry between sugars and chiral building blocks.](image)

In order to benefit from the advantages that monosaccharides offer, while avoiding limitations in the configuration at C15', we attempted to synthesize a chiral building block with the correct stereochemistry starting from cheap monosaccharides by epimerization of a single stereocenter. To this end two routes were explored starting from either D-glucose or L-rhamnose. In case of D-glucose, the C5-position needs to be epimerized and the hydroxyl groups at C4 and C6 need to be removed. L-Rhamnose requires epimerization at C3 and removal of C4-OH (Figure 2.4). After installation of the correct stereochemistry, chain elongation with two carbon atoms and suitable functionalization to obtain vinyl iodine 2.38 was planned to proceed in five steps.

### 2.4.2 Synthesis of the conjugated building block (2.37)

The preparation of conjugated building block 2.37a started with the formation of δ-sultone 2.40 (39%) via subjection of mesityl oxide to a mixture of acetic anhydride and
sulfuric acid (Scheme 2.9). Subsequent pyrolysis in the presence of activated CaO and quinoline afforded 2,4-dimethylfuran (2.41) in 40% yield under expulsion of sulfur dioxide.\textsuperscript{26}

\[ \text{mesityl oxide} \xrightarrow{\text{Ac}_2\text{O}, \text{H}_2\text{SO}_4, -10^\circ\text{C to rt, 20h}} \text{2.40} \xrightarrow{\text{CaO, quinoline, 230}^\circ\text{C}} \text{2.41} \]

1) \( \text{N}_2 \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{CH}_2\text{Cl}_2, 10^\circ\text{C}} \text{2.39a, 18\%} + \text{2.39b, 47\%} \)
2) \( \text{I}_2, \text{CH}_2\text{Cl}_2 \)

\[ \text{TBAF, THF, EtOAc, } 0^\circ\text{C, 45 min, 80\%} \]

**Scheme 2.9 Synthesis of the conjugated building block.**

Furan 2.41 was then treated with ethyl diazoacetate (EDA) in the presence of catalytic \( \text{Rh}_2(\text{OAc})_4 \) as described by Wenkert \textit{et al.} to give elaborate conjugated system 2.39 as a mixture of \textit{cis/trans} isomers (2.39a and 2.39b) (Figure 2.5).\textsuperscript{27} When exposed to iodine, the system equilibrated to a mixture of 2.39a (18% isolated yield) and the desired all-\textit{trans} 2.39c (47% isolated yield), which could be separated by column chromatography. Re-exposure of pure 2.39a to iodine furnished a mixture of 2.39a and 2.39c in the same ratio as before.

\[ \text{EDA} \xrightarrow{[\text{Rh}]} \text{2.41} \xrightarrow{[\text{Rh}]} \text{2.39a, 18\%} + \text{2.39b, 47\%} \xrightarrow{\text{I}_2} \text{2.39a} \]

**Figure 2.5 Reaction of EDA with 2,4-dimethylfuran.**

Chapter2
Chapter 2

Chain elongation of 2.39c by a Horner-Wadsworth-Emmons reaction with diethyl (3-trimethylsilyl-2-propynyl) phosphonate (2.42)\textsuperscript{25} proceeded readily to give 2.43 in 61% yield as a mixture of cis/trans isomers that could not be separated.\textsuperscript{29} Finally, cleavage of the TMS-group with TBAF resulted in the unstable terminal alkyne 2.37a (80%).

2.4.3 Synthesis of the chiral building block from D-glucose (2.38)

As explained in paragraph 2.4.1, installation of the correct stereochemistry from D-glucose requires reduction of C4-OH and C6-OH and epimerization at C5 (Figure 2.4). To this end, a six step procedure developed by Redlich et al. for the synthesis of bicyclic acetals was adopted.\textsuperscript{30} In the event, D-glucose was converted into methyl α-D-glucopyranoside (2.44) by refluxing in anhydrous methanol in the presence of Dowex 50W (H\textsuperscript{+}).\textsuperscript{31} Reaction of 2.44 with sulfuryl chloride in pyridine followed by dechlorosulfation in the presence of sodium iodide resulted in dichloro compound 2.45 (56%) with exclusively the galacto-configuration as described by Jones et al. (Scheme 2.10)\textsuperscript{32} Alternatively, treatment of 2.44 with triphenylphosphine, tetrachloromethane and imidazole in acetonitrile/pyridine (1:1 v/v) at 50 °C gave 2.45 as well, but conversion was often incomplete and separation from side products was tedious.\textsuperscript{33} Radical reduction of 2.45 with tri-n-butyltin hydride in the presence of a catalytic amount of AIBN (α,α'-azoisobutyronitrile) afforded 4,6-dideoxy-hexopyranoside 2.46 in 89% yield. Subsequent deprotection of the anomeric center and opening of the resulting hemi-acetal was achieved in one pot by subjection to 1,3-propanedithiol in 37% HCl to give dithioacetal 2.47 in 87% yield. After regioselective protection of C2-OH and C3-OH as their acetonide by reaction with acetone under acidic conditions (2.48, 95%), epimerization at C5 was accomplished via a Mitsunobu reaction with benzoic acid (2.49, 82%). The mass balance in this reaction was completed by the C4-C5 olefin resulting from dehydration (16%). Comparison of the \textsuperscript{13}C-NMR-spectra of 2.49 (t, 39.5 ppm) with its C5-epimer (t, 40.5 ppm) obtained from the reaction of 2.48 with benzyol chloride showed that there was only one diastereoisomer present.
With the stereochemistry in place, the next objective was to elongate the chain of 2.49 in order to make it suitable for coupling. Deprotection of the aldehyde proved not to be straightforward as the dithioacetal was resistant to mercury salts and low yields were obtained with NBS in acetone and water. Eventually, treatment with MeI and 2,4,6-collidine in a refluxing mixture of acetone and water gave aldehyde 2.50 (no epimerization at C2 according to $^1$H-NMR), which was used without further purification after drying in vacuo over $\text{P}_2\text{O}_5$. Reaction of 2.50 with CBr$_4$ and PPh$_3$ under Corey-Fuchs conditions
gave dibromo-olefin 2.51 in 72% yield over 2 steps. Elimination of HBr by treatment with LDA followed by a protic work-up resulted in the terminal alkyne 2.52 (88%), which was converted into the methylated alkyne 2.53 (88%) by reaction with LDA and MeI in the presence of HMPA. The direct synthesis of 2.53 from 2.51 by treatment with MeI and n-BuLi or t-BuLi was unsuccessful, due to the intolerance of the benzoyl group to these conditions.

Figure 2.6 COSY-spectrum of 2.54b showing interaction between C3-H and C4-H.

Palladium-catalyzed hydrostannation of the internal alkyne did not go to completion, due to palladium-black formation. Increasing the catalyst loading resulted in full conversion, but was accompanied by additional side-product formation. Fortunately, changing the solvent from THF to n-pentane prevented Pd-black formation improving the yield of 2.54
from 63% to 73%. Moreover, the regioselectivity of the reaction was superior in n-pentane enhancing the ratio of the terminal (2.54b) to internal (2.54a) hydrostannation product from 2.6 : 1 in THF to 6.3 : 1 in n-pentane. Assignment of 2.54a and 2.54b was based on the difference in $^1J$-value of the vinylic CH$_3$ with the vinylic proton ($J = 6.6$ Hz for 2.54a and $J = 1.6$ Hz for 2.54b) and on the COSY-interaction between C3-H and C4-H in 2.54b (Figure 2.6). Proof that 2.54b was indeed the trans-isomer, was obtained by NOESY-NMR, which showed a clear interaction between C4-H and C1-H$_3$ (Figure 2.7). The synthesis of the chiral moiety was completed by exchange of the tri-n-butyltin moiety in 2.54b with iodine to give 2.38a (99%).

![Figure 2.7 NOESY-spectrum of 2.54b showing interaction between C1-H$_3$ and C4-H.](image)
Chapter 2

The route depicted in Scheme 2.10 constitutes a general procedure for making analogues of 2.38 with any desired stereochemistry starting from different 4,6-dideoxy-D-hexopyranosides (2.46-analogues). However, it should be noted, that the conversion of methyl α-D-glucopyranoside (2.44) into 4,6-dichloro-compound 2.45 without protection of the C2-OH and C3-OH is not generally applicable to monosaccharides of any configuration. This can be explained by looking at the mechanism in more detail (Figure 2.8).

![Figure 2.8 Formation of chlorodeoxy sugars.](image)

The process involves initial formation of a tetrachlorosulfate intermediate, followed by displacement of specific chlorosulfates by chloride ions liberated during the chlorosulfation. Whether the S_n2-displacement occurs at a particular center or not, depends on both steric and electronic factors. The primary chlorosulfate at the six-position is the least hindered and is therefore always the first to undergo substitution. The C2-chlorosulfate on the other hand has shown almost complete inertness in every case even when the steric environment is comparable to C4. This is usually explained by the proximity of two β-oxygen atoms (compared to one for C4), which are known to considerably retard the rate of nucleophilic substitution. The reactivity at the C3-position depends on the anomeric configuration and on neighboring substituents. In case of 2.44, the C3-position is unreactive because the axial anomeric methoxy group obstructs axial approach of a chloride ion at the C3-position. In concordance, methyl β-D-glucopyranoside gives indeed a mixture of the 3,6- (major) and 4,6-dichloro (minor) compounds. However, formation of the 3,4,6-trichloro-compound is not observed, possibly because a neighboring axial substituent leads to unfavorable interactions in the transition state due to the near-eclipsed conformation of the large substituents on C3 and C4. Analogously, substitution of an equatorial chlorosulfate at C4 is impaired by an axial substituent at C2 or C3, which precludes the synthesis of a C12'- or a C13'-epimer of the side chain employing this particular reduction strategy. This is supported by the
observation, that α-D-mannopyranoside gives in fact a 6-monochloro derivative.\textsuperscript{43} Alternative routes to obtain 4,6-dideoxy-D-hexopyranosides are therefore required to make the strategy in Scheme 2.10 completely general.

2.4.4 Synthesis of a chiral building block from L-rhamnose

In order to obtain a chiral fragment with the correct stereochemistry from L-rhamnose, reduction of C4-OH and epimerization at C3 is required (Figure 2.4). The synthesis started by protection of the anomeric center via acid-catalyzed reaction with methanol to give methyl α-L-rhamnopyranoside (2.55; Scheme 2.11). Subsequently, the C2- and C3-hydroxyl moieties were regioselectively protected as their acetonide by reaction with acetone under acidic conditions leading to 2.56 (90\%).\textsuperscript{46} The remaining free C4-OH was then reacted with 1,1’-thiocarbonyldiimidazole to give the activated precursor for a Barton-MacCombie deoxygenation (2.57) in quantitative yield.\textsuperscript{47,48} Subsequent radical reduction of 2.57 with tris(trimethylsilyl)silane in the presence of AIBN afforded 2.58 (not shown).\textsuperscript{39,49} Cleavage of the acetonide was first attempted with trifluoroacetic acid (55\% over 2 steps), but the results with the milder amberlite H\textsuperscript{+}-resin proved to be superior giving diol 2.59 in 71\% over 2 steps.\textsuperscript{50} Selective protection of the C2-OH was then achieved by reaction of 2.59 with trimethyl orthoacetate followed by partial hydrolysis of the resulting orthoester leading to the formation of monoacetate 2.60 (80\%).\textsuperscript{48} It should be noted that the regioselectivity in the hydrolysis step strongly depends on the choice of solvent. In acetonitrile a 3:1 mixture of C2:C3 O-acetylated regioisomers was obtained, while in dichloromethane only the desired C2 O-acetylated product was observed. Subsequent epimerization of the C3-center proved not to be straightforward. Mitsunobu conditions gave only very low conversions (<10\%) and the alternative procedure comprising formation of a triflate (2.61; not shown) followed by a S\textsubscript{N}2-displacement with tetraethylammonium acetate gave no conversion at all. However, changing to tetra-n-butylammonium acetate led to the isolation of 2.62 in a gratifying 71\% yield, with only a minor amount (8\%) of side product resulting from dehydration of the C3-C4 bond.\textsuperscript{51} This remarkable improvement is most likely due to the superior phase-transfer properties of the tetra-n-butyl salt, which can act as a co-solvent when used in large excess (11 eq. in our case). Comparison of the \textsuperscript{1}H- and \textsuperscript{13}C-NMR spectra of 2.62 with the acetylated product of 2.60 proved that epimerization had
indeed taken place. An attempt was made to deprotect the hydroxyl moieties and to form the dithioacetal in one pot by stirring 2.62 in HCl (37% aq.) in the presence of 1,3-propanedithiol, but only 21% of 2.63 was isolated. The acetyl groups were therefore first removed under mildly basic conditions (pH 9), after which ring opening proceeded very well, providing 2.63 in 89% yield over two steps. Acetonide protection of two hydroxyl moieties by acid-catalyzed reaction with acetone gave two regioisomers; 2.64a (8%) and the desired 2.64b (78%), which were separated by column chromatography. After protection of the remaining C5-OH of 2.64b with TBDMSCl (2.65, 84%), the dithioacetal was deprotected as before to give aldehyde 2.66 in 89% yield. Unfortunately, the TBDMS-ether was not stable under Corey-Fuchs conditions giving a complex mixture of products. Obviously, the target molecule 2.38a can be synthesized from 2.64b as described above for D-glucose if a benzoyl ester is chosen as a protecting group.

Scheme 2.11 Chiral building block from L-Rhamnose.
For the preparation of 2.38a, the route starting from D-glucose seems more attractive, because it is much more cost-effective and concise; less steps are required and the overall yield is higher. Nevertheless, in light of the fact that preparation of the C13'-epimer of the side chain from D-monosaccharides requires a different (more elaborate) reduction strategy (§ 2.4.3), the route from L-rhamnose may be useful, since the C13'-epimer can be easily accessed by omission of the epimerization steps.

### 2.4.5 Coupling and partial hydrogenation

Sonogashira coupling of terminal alkyne 2.37a to vinyl iodine 2.38a proceeded readily, resulting in the isolation of 2.36a in an excellent 94% yield (Scheme 2.12). It was anticipated that partial cis-hydrogenation of the internal alkyne of 8,9-dehydro analogue 2.36a would lead to 2.35a after isomerization to its all trans configuration.\(^{53,29}\)

Disappointingly, partial hydrogenation of the internal alkyne to the alkene did not show sufficient selectivity to be useful on a preparative scale. Lindlar catalyst (Pd/CaCO\(_3\)/Pb) was typically unreactive regardless of the solvent, temperature, catalyst loading, and/or hydrogen pressure.\(^{54,55}\) Only at 65 bar of hydrogen some conversion was observed, but with a complete lack of selectivity leading to overreduction. An effort was made with a homogeneous palladium catalyst developed by Elsevier for selective alkyne hydrogenation, but once again no conversion was seen at one bar of hydrogen pressure.\(^{56}\) Ni-catalyzed reduction with NaBH\(_4\) on the other hand proved to be too active and gave only overreduced products.\(^{57}\) Finally, we turned to the Zn(Cu/Ag)-reduction method in aqueous MeOH as developed by Boland and co-workers.\(^{58}\) This method is known to selectively cis-hydrogenate triple bonds which are embedded in a conjugated system and has been successfully used by Nakanishi among others.\(^{29,59}\) However, in our case Zn(Cu/Ag)-reduction resulted in a mixture of (over)reduced products containing only traces of a compound with the correct mass (as observed with GC-MS). Even though the desired product was likely to be in the mixture, this could not be confirmed by isolation and full characterization. In any case, the lack of selectivity in the partial reduction of the alkyne precludes this strategy as a viable synthetic pathway. As it is known that free hydroxyl moieties occasionally aid the selectivity of Boland-reductions, the isopropylidene-moiety of
2.36a was removed by treatment with acetic acid and water, but this did not have a beneficial effect on the outcome of the partial reduction step.

\[
2.37a + 2.38a \rightarrow \text{Scheme 2.12 Coupling of the building blocks and partial hydrogenation/reduction.}
\]

In light of the difficulties we have encountered in the semi-hydrogenation of 2.36a, I believe that there is currently no general method for the selective partial reduction of alkynes embedded in an alkene system while in conjugation with an electron withdrawing moiety. In this respect it should be noted, that for example in the elegant total synthesis of 6,7-dehydrostipiamide, the final reduction to stipiamide itself is also not reported (Figure 2.9).

\[
\text{Figure 2.9 Structure of 6,7-dehydrostipiamide.}
\]

Only the Lindlar catalyst has been used with varying success in the past, but the results are highly substrate-dependent. In some cases good selectivity is observed, but in other examples the catalyst is inactive or the reaction has to be stopped after consumption of a certain amount of hydrogen to avoid overreduction. To the best of my knowledge, the partial reduction of alkynes in conjugation with an ester using Zn(Cu/Ag) has not been
Total Synthesis of Mycolactones

reported. It was therefore decided to synthesize 2.69 having a primary alcohol instead of an ester (Scheme 2.13).

\[ \text{Scheme 2.13 Alternative approach: removing the conjugated electron withdrawing group.} \]

Unfortunately, Boland-reduction of 2.69 resulted in a complex mixture from which only a small amount of a compound with the correct mass (GC-MS and EI- and CI-MS) was isolated. Whether this was indeed the desired product 2.70 was unclear and in any event the yield of the reaction was too low to continue with this approach.

2.4.6 Alternative strategies

As an alternative approach, an attempt was made to functionalize terminal alkyne 2.37a to obtain an olefin suitable for palladium catalyzed sp\(^2\)-sp\(^2\) coupling. In my hands, however, 2.37a was unreactive towards stannylcupration (Bu\(_3\)SnH, CuCN, n-BuLi),\(^{62}\) and hydrozirconation (Schwartz reagent),\(^{63}\) while palladium-catalyzed hydrostannation resulted exclusively in the undesired internal regioisomer (2.71, Scheme 2.14).\(^{64}\) Even though it is known that palladium-catalyzed hydrostannation of terminal alkynes in direct conjugation with an ester predominately gives the α-addition product,\(^{41,65}\) it was surprising to find that this also holds true when the ester and terminal alkyne are separated by three double bonds.
In a second attempt, the point of connection of the building blocks was changed from C9’-C10’ to C7’-C8’ (see Figure 2.3). This strategy implied that the conjugated building block needed to be one double bond shorter (i.e. 2.72 and 2.73), while the chiral building block required elongation by two carbon atoms (i.e. 2.75; Scheme 2.15). The first objective was met by reacting 2.39c in a Wittig reaction with BrCH₂PPh₂Br (2.72, 40% isolated yield) or its iodine analogue (2.73, 13% isolated yield). The second goal was realized by Sonogashira coupling of 2.38a with trimethylsilylacetylene (97%), giving the free alkyne 2.75 (86%) after deprotection with TBAF. Subsequent Negishi coupling of 2.75 to 2.73 resulted in the isolation of terminal alkene 2.76 and starting material 2.73 suggesting that the initial hydrozirconation took place, but that either transmetallation with Zn was unsuccessful or that the catalytic cycle was blocked at some stage. Similarly, hydrostannation of 2.75 using a stannylcuprate gave 2.77 in low yield (16%), but Stille coupling to 2.72 afforded alkene 2.76 and the staring vinyl halide once again.

---

**Scheme 2.14 Hydrostannation of 2.37a.**

**Scheme 2.15 Alternative coupling strategies (1).**
Finally, an effort was made to couple the building blocks via formation of the C6'-C7'-bond using a Horner-Wadsworth-Emmons reaction on conjugated system 2.39c (Scheme 2.16). To this end, propargyl alcohol was subjected to a radical hydrostannylation resulting in a mixture of isomers from which the desired trans-isomer 2.78c could be isolated by column chromatography in 49% yield. Treatment of 2.78c with triphenylphosphine and carbon tetrabromide in the presence of 2,6-lutidine afforded the corresponding allylic bromide (2.79, 74%), which was converted into diethyl phosphonate 2.80 (58%) by reaction with diethylphosphite and NaH. Subsequent Stille coupling of 2.80 to 2.38a furnished phosphonate 2.81 in a moderate 65% yield. Regrettably, HWE-reaction with conjugated ketone 2.39c did not give the desired product, but only side product 2.82 resulting from reaction with acetone, which was most likely formed in situ by cleavage of part of the acetonide. The opposite approach to first do a HWE-coupling of 2.80 to ketone 2.39c followed by a Stille coupling to 2.38a gave no conversion in the first step.

\[
\begin{align*}
\text{HO} & \quad \text{Bu}_3\text{SnH}, \text{AlBN, 80}^\circ\text{C, 2 h} \\
\text{Bu}_3\text{SnH} & \quad \text{80}^\circ\text{C, 2 h} \\
\text{HO} & \quad \text{SnBu}_3 \\
\text{Bu}_3\text{SnH} & \quad \text{SnBu}_3 \\
\text{HO} & \quad \text{SnBu}_3 \\
\text{Bu}_3\text{SnH} & \quad \text{SnBu}_3 \\
\end{align*}
\]

\[
\begin{align*}
1) \text{PPh}_3, \text{CBr}_4, \text{CH}_3\text{CN}, \\
& \quad \text{2,6-lutidine 15 min, 74%} \\
2) \text{NaH, HP(O)(OEt)}_2, \\
& \quad \text{DMF, 3 h, 58%} \\
\text{THF, NaHMDS, -80}^\circ\text{C to -40}^\circ\text{C} \\
& \quad \text{then -80}^\circ\text{C, 2.39c in THF,} \\
& \quad \text{HMPA, warmed to rt, 3 h} \\
\end{align*}
\]

Scheme 2.16 Alternative coupling strategies (2).

2.5 Summary and concluding remarks

In this chapter, new approaches towards the synthesis of natural and non-natural mycolactones were described. In particular, the development of an alternative route to
construct the side chain of mycolactones A and B (and analogues thereof) was discussed. It was shown, that the application of monosaccharides is a viable alternative to asymmetric catalysis for the synthesis of the chiral part (2.38a and 2.66) of the side chain. Compound 2.38a was prepared in twelve steps from D-glucose in 12% yield and with complete stereocontrol (Scheme 2.10). In comparison, Kishi and co-workers synthesized a similar building block (2.30) in ten steps from (S)-3-hydroxy-n-butyrate in 18% yield (Scheme 2.6). In their case, the stereoselective introduction of the hydroxyl moieties at C12' and C13' was accomplished with moderate diastereoselectivity (58% de) using a Sharpless dihydroxylation reaction, after which the undesired diastereomer was removed at a later stage of the synthesis.

Due to the vast number of different, readily available, monosaccharides, the new route is in principle suitable for the synthesis of a wide range of analogues. However, manipulation of monosaccharides to obtain linear enantiopure building blocks containing the structural motif of the desired analogue is not always straightforward. More specifically, new ways have to be explored for the reductive removal of the appropriate hydroxyl moieties (depending on the target).

In addition, an efficient route for the rapid assembly of conjugated building block 2.37a from 2,4-dimethylfuran in 3 steps was described. Unfortunately, employment of 2.37a is currently obstructed by the lack of an efficient method for the partial reduction of the 8,9-dehydro analogue 2.36, which was obtained by Sonogashira coupling to 2.38a. Alternative cross-coupling methods for the direct synthesis of (protected) 2.35 failed so far to give the desired product.

### 2.6 Experimental section

General remarks: reagents were purchased from Aldrich, Acros Chimica, Merck or Fluka and were used as received unless otherwise stated. All solvents were reagent grade and were dried and distilled before use according to standard procedures, after which they were stored under argon. Chromatography: silica gel, Merck type 9385 230-400 mesh, TLC: silica gel 60, Merck, 0.25 mm. Components were visualized by staining with a) KMnO₄, b) a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL) or c) a mixture of p-methoxybenzaldehyde (2.1 mL), AcOH
(1.8 mL), H$_2$SO$_4$ (6.3 mL) and EtOH (170 mL). Optical rotations were measured on a Perkin-Elmer 241 or 241 MC polarimeter with a 10 cm cell (c given in g/100 mL). Mass spectra (HRMS) were recorded on an AEI MS-902. $^1$H- and $^{13}$C-NMR spectra were recorded on a Varian Gemini-200 (50.32 MHz), a Varian VXR300 (75.48 MHz) or a Varian AMX400 (100.59 MHz) spectrometer in CDCl$_3$. Chemical shift values are denoted in $\delta$ values (ppm) relative to residual solvent peaks (CHCl$_3$, $^1$H $\delta = 7.26$, $^{13}$C $\delta = 76.9$). Carbon assignments are based on APT $^{13}$C experiments.

**4,6-Dimethyl-[1,2]oxathiine 2,2-dioxide (2.40):**$^{26}$ Concentrated sulfuric acid (72.3 mL, 1.36 mmol) was added over 1 h at -10°C to acetic anhydride (300 mL, 3.19 mmol, 2.35 eq), after which mesityl oxide (156 mL, 1.36 mmol) was added over 1 h at the same temperature. The resulting dark red solution was stirred overnight at -5°C and then for 8 more h at room temperature. The mixture was then poured into ice-water upon which a solid precipitated. Filtration and drying in vacuo gave 2.40 (85 g, 0.53 mmol, 39%) as a sand-colored solid. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta = 2.04$ (s, 3H), 2.15 (s, 3H), 5.61 (s, 1H), 6.26 (s, 1H) ppm. Mp: 70°C, (lit.$^{26a}$ 70.5-71.0°C).

**2,4-Dimethylfuran (2.41):**$^{26}$ CaO was activated by heating it overnight at a 1000°C using a 'moffeloven'. Freshly ignited CaO (17.5 g, 312 mmol), quinoline (1.0 mL, 8.4 mmol) and 2.40 (17.5 g, 109 mmol) were thoroughly mixed in a three-necked flask. The flask was equipped with a distillation device, which was connected to an erlenmeyer containing aqueous KOH (3.3 M, 37 mL) at 0°C. Upon heating of the three-necked flask to 230°C a yellow liquid was transferred into the erlenmeyer. The organic layer was separated from the aqueous layer and washed with water, diluted aq. H$_2$SO$_4$ (1.0 M) and aq. NaHCO$_3$ (sat.), dried (MgSO$_4$), filtered and purified by distillation (bp 94°C, lit.$^{26b}$ 94.5-95.0) to give 2.41 (4.15 g, 43.2 mmol, 39.6%) as a colorless liquid. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta = 1.97$ (s, 3H), 2.24 (s, 3H), 5.83 (s, 1H), 7.03 (s, 1H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta = 9.6$ (q), 13.3 (q), 108.1 (d), 120.5 (s), 137.1 (d), 152.0 (s) ppm.

**Ethyl (2E,4Z)-4-methyl-6-oxohepta-2,4-dienoate (2.39a) and Ethyl (2E,4E)-4-methyl-6-oxohepta-2,4-dienoate (2.39c):**$^{27}$ Rh$_2$(OAc)$_4$ (10 mg, 23 µmol), and 2,4-dimethylfuran (2.41, 1.0 g, 10.4 mmol, 2.0 eq) were dissolved in dichloromethane (14.3 mL) under argon and a solution of ethyl diazoacetate (0.55 mL, 5.2 mmol) in dichloromethane (3.6 mL) was slowly added over 10 h employing a syringe pump. The resulting solution was stirred for another 5 h at which point the catalyst was removed by filtration over a Florisil column. The green solution was then concentrated and the residue was taken up in dichloromethane (14.3 mL) and stirred overnight under argon in the presence of a catalytic amount of I$_2$. The resulting black solution was washed with aq.
Na$_2$SO$_3$ (10% w/w) and brine (sat.), dried (Na$_2$SO$_4$) and concentrated. The product was purified by column chromatography (n-hexane-EtOAc 9:1) to give 2.39a (0.17 g, 0.93 mmol, 18%) and the all-trans-isomer 2.39c (0.44 g, 2.4 mmol, 47%). The latter was a yellow liquid which became crystalline upon standing at 4 °C. When 2.39a was treated with I$_2$ in dichloromethane, a mixture of 2.39a and 2.39c in the same ratio as before was formed. 

$^1$H-NMR 2.39a (CDCl$_3$, 300 MHz) $\delta$ = 1.30 (t, $J$ = 7.2 Hz, 3H, CH$_3$CH$_2$O), 2.01 (s, 3H, CH$_3$), 2.25 (s, 3H, C7-H), 4.23 (q, $J$ = 7.2 Hz, 2H, CH$_2$CH$_2$O), 6.17 (d, $J$ = 15.9 Hz, 1H, C2-H), 6.27 (d, $J$ = 16.2 Hz, 1H, C3-H) ppm. 

$^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$ = 14.1 (q), 14.2 (q), 32.0 (q), 60.7 (t), 124.2 (d), 131.8 (d), 146.7 (s), 147.3 (d), 147.7 (s), 166.2 (s), 198.9 (s) ppm. MS(EI) for C$_{10}$H$_{13}$O$_2$: m/z = 182 [M$^+$], HRMS calcd for C$_{10}$H$_{13}$O$_2$: 182.094, found: 182.095. 

(3-Trimethylsilyl-prop-2-ynyl)-phosphonic acid diethyl ester (2.42):$^{28}$ To a solution of NaHMDS (1.0 M in THF, 26 mL, 26 mmol) at -10 °C was added diethyl phosphonate (3.4 mL, 26 mmol) in THF (8.0 mL) under argon. This solution was stirred for 15 min and then treated with (3-bromo-prop-1-ynyl)-trimethylsilane (3.7 mL, 26 mmol) in THF (8.0 mL) maintaining the temperature at -10 °C. After stirring for 1 h, the reaction mixture was quenched with water and the aqueous layer extracted with EtOAc (2x). The combined organic layers were washed with aq. HCl (2.0 M) and water, dried (Na$_2$SO$_4$) and concentrated. The product was purified by column chromatography (n-pentane-EtOAc 4:1 to 1:1) giving 2.42 (5.1 g, 20 mmol, 78%) as a colorless liquid. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 0.14 (s, 9H, TMS), 1.34 (t, 6H, CH$_3$CH$_2$O, $J$ = 7.2 Hz), 2.80 (d, 2H, CH$_2$, $J$ = 22.2 Hz), 4.18 (q, 4H, CH$_2$CH$_2$O) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = -0.1 (q), 16.3 (q), 17.8 + 20.6 (t, $J_{C,P}$ = 145 Hz), 62.9 (t, $J_{C,P}$ = 6.9 Hz), 94.4 (s) ppm. 

Ethyl 4,6-dimethyl-9-trimethylsilyl-nona-2,4,6-trien-8-ynoate (2.43): 2.42 (1.0 g, 4.0 mmol, 2.0 eq) was dissolved in THF (20 mL) and n-BuLi (1.6 M in n-hexane, 2.5 mL, 4.0 mmol) was added at 0 °C under argon. After stirring for 30 min of which the last 10 min were at room temperature, the solution had turned dark red. At this point, a solution of 2.39c (367 mg, 2.01 mmol) in THF (8.0 mL) was added upon which the color slowly changed to brown. The reaction mixture was stirred for 3 h and then quenched with aq. NH$_4$Cl (sat.). The aqueous layer was extracted with Et$_2$O (3x) and the combined organic layers were washed with brine (sat.), dried (Na$_2$SO$_4$) and concentrated. 2.43 (336 mg, 1.22 mmol, 61%), mixture of cis/trans isomers with a ratio of approximately 4:1 was isolated as a yellow solid after column chromatography (n-hexane-EtOAc 98:2 to 95:5 to 4:1). $^1$H-NMR major isomer (CDCl$_3$, 500 MHz) $\delta$ = 0.22 (s, 9H, TMS), 1.30 (t, $J$ = 7.0 Hz, 3H, CH$_3$CH$_2$O), 2.00 (s, 3H, C6-CH$_3$), 2.14 (s, 3H, C4-CH$_3$), 4.21 (q, 2H, CH$_2$CH$_2$O), 5.59 (s, 1H, C7-H), 5.91 (d, $J$ = 15.5 Hz, 1H, C2-H), 6.28 (s, 1H, C5-H), 7.32 (d, $J$ = 15.5 Hz, 1H, C3-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = -0.1 (q), 13.9 (q), 14.2 (q), 19.7 (q), 60.2 (t), 103.0 (s), 103.5 (s), 113.2 (d), 117.8 (d), 134.5 (s), 140.3 (d), 147.3 (s), 149.7 (d), 167.1 (s) ppm. $^1$H-NMR minor isomer (CDCl$_3$, 500 MHz) $\delta$
= 0.18 (s, 9H, TMS), 1.31 (t, 3H, CH₃CH₂O), 1.95 (s, 3H, C6-CH₃), 2.04 (s, 3H, C4-CH₃), 4.21 (q, 2H, CH₃CH₂O), 5.53 (s, 1H, C7-H), 5.94 (d, J = 14.5 Hz, 1H, C2-H), 6.68 (s, 1H, C5-H), 7.39 (d, J = 15.5 Hz, 1H, C3-H) ppm. MS(EI) for C₁₆H₂₄O₂Si: m/z = 276 [M⁺], HRMS calcd for C₁₆H₂₄O₂Si: 276.155, found: 276.155.

Ethyl 4,6-dimethylnona-2,4,6-trien-8-ynoate (2.37a): TBAF (1.0 M in THF, 1.45 mL, 1.45 mmol, 4.0 eq) was stirred for 30 min under argon in the presence of EtOAc (47 mL, 0.48 mmol). The solution was cooled to 0 °C and 2.43 (100 mg, 0.36 mmol) in dry THF (1.8 mL) was added. The mixture was stirred for 45 min at 0 °C and then quenched with aq. NH₄Cl (sat.), dried (Na₂SO₄) and concentrated. 2.37a (59 mg, 0.29 mmol, 80%) was isolated after column chromatography (n-pentane-EtOAc 95:5) as a colorless oil, which turned brown within 15 min. The product was therefore immediately used in the next step. ¹H-NMR major isomer (CDCl₃, 200 MHz) δ = 1.29 (t, J = 7.0 Hz, 3H, CH₃CH₂O), 1.99 (d, J = 0.8 Hz, 3H, C6-CH₃), 2.13 (s, 3H, C4-CH₃), 3.38 (d, J = 2.4 Hz, 1H, C9-H), 4.21 (q, 2H, CH₃CH₂O), 5.54 (s, 1H, C7-H), 5.91 (d, J = 15.6 Hz, 1H, C2-H), 6.28 (s, 1H, C5-H), 7.31 (d, J = 15.6 Hz, 1H, C3-H) ppm.

¹H-NMR minor isomer (CDCl₃, 200 MHz) δ = 1.30 (t, J = 7.0 Hz, 3H, CH₃CH₂O), 1.95 (d, J = 1.0 Hz, 3H, C6-CH₃), 2.04 (s, 3H, C4-CH₃), 3.22 (d, J = 2.4 Hz, 1H, C9-H), 4.21 (q, 2H, CH₃CH₂O), 5.49 (s, 1H, C7-H), 5.91 (d, J = 15.6 Hz, 1H, C2-H), 6.71 (s, 1H, C5-H), 7.39 (d, J = 16.0 Hz, 1H, C3-H) ppm. MS(EI) for C₁₃H₁₆O₂: m/z = 204 [M⁺], HRMS calcd for C₁₃H₁₆O₂: 204.115, found: 204.116.

Methyl α-D-glucopyranoside (2.44):³¹ Dowex 50W (pTsOH) was stirred in HCl (2.0 M aq) for 2 h and then filtrated and washed with HCl (2.0 M aq), water and MeOH. A suspension of the thus obtained resin (38 g) and α-D-glucose (42.0 g, 233 mmol) in MeOH (600 mL) was heated under reflux overnight. After cooling to room temperature, the resin was filtered off and the filtrate concentrated to give methyl α-D-glucopyranoside (α:β = 62:38) in quantitative yield. Pure 2.44 (23.5 g, 122 mmol, 52.2%) was obtained as a white solid after crystallization from ethanol. ¹³C-NMR (DMSO, 50.3 MHz) δ = 54.3 (q), 61.0 (t), 70.3 (d), 72.0 (d), 72.6 (d), 73.4 (d), 99.7 (d) ppm.

Methyl 4,6-dideoxy-4,6-dichloro-α-D-galactopyranoside (2.45):³² Methyl α-D-glucopyranoside (2.44) (42.5 g, 218 mmol) was dissolved in pyridine-chloroform (430 mL, 1:1 v/v) and sulfuryl chloride (142 mL, 236 g, 1.75 mol, 8eq.) was added dropwise at -78 °C under argon. The resulting yellow solution was stirred for 2 h while slowly warming to room temperature. Subsequently the solution was heated to 50 °C and stirred for another 5 h. After cooling to room temperature the solution was diluted with MeOH and water, neutralized with Na₂CO₃·10H₂O and quenched with a NaI-solution (16 g in 40 mL water-MeOH, 1:1 v/v). The resulting solution was concentrated in vacuo by co-evaporation with toluene and purified by continuous liquid-liquid extraction from water with chloroform. Concentration in vacuo gave a brown/red solid which was further purified by crystallization from chloroform to give white crystals (28.1 g, 122 mmol, 55.8%). ¹H-NMR
Chapter 2

(CDCl₃, 300 MHz) δ = 2.20 (br s, 2H, C₂-OH, C₃-OH), 3.48 (s, 3H, C₁-OCH₃), 3.68 (d, J = 6.6 Hz, 2H, C₆-H), 3.85 (dd, J = 3.6, 9.6 Hz, 1H, C₂-H), 3.99 (dd, J = 3.6, 9.6 Hz, 1H, C₃-H), 4.14 (t, J = 6.6 Hz, 1H, C₅-H'), 4.53 (d, J = 3.3 Hz, 1H, C₄-H), 4.86 (d, J = 3.6 Hz, 1H, C₁-H) ppm. ¹³C-NMR (DMSO, 50.3 MHz) δ = 44.4 (t), 54.7 (q), 64.9 (d), 67.6 (d), 67.7 (d), 69.3 (d), 99.9 (d) ppm.

**Methyl 4,6-dideoxy-α-D-xylo-hexopyranoside (2.46):**³⁰ Bu₃SnH (30 mL, 32 g, 0.11 mol) was added dropwise to a solution of 2.45 (5.3 g, 23 mmol) in refluxing dry toluene (180 mL) under argon and AIBN (0.10 g, 0.61 mmol, 2.6 mol%) was added. The resulting solution was heated under reflux overnight and then cooled to room temperature and concentrated in vacuo. The obtained oil was diluted with CH₃CN and washed with n-hexanes (2x). Concentration gave a solid which was dissolved in water and washed with Et₂O (3x). Concentration of the aqueous layer afforded a white solid which was further purified by column chromatography (dichloromethane-MeOH 19:1 to 9:1) to give pure 2.46 (3.3 g, 20 mmol, 89%). When the reaction was performed on larger scale, purification was done by crystallization from chloroform and n-pentane.

**1H-NMR (CDCl₃, 300 MHz) δ =** 1.21 (d, J = 6.3 Hz, 3H, C₆-H), 1.36 (q, 1H, C₄-H), 1.98 (ddd, J = 2.4, 5.1, 12.9 Hz, 1H, C₄-H'), 2.03 (m, 2H, dithian-H), 2.70 (m, 2H, dithian-H), 2.92 (m, 2H, dithian-H), 3.33-3.44 (m, 1H, C₂-H), 3.77-3.95 (m, 2H, C₃-H, C₅-H), 4.75 (d, J = 3.6 Hz, 1H, C₁-H) ppm.

**13C-NMR (CDCl₃, 50.3 MHz) δ =** 20.7 (q), 39.6 (t), 55.1 (q), 64.0 (d), 68.9 (d), 74.3 (d), 99.7 (d) ppm.

4,6-Dideoxy-α-D-xylo-hexose-trimethylen-dithioacetal (2.47):³⁰ 1,3-propanedithiol (6.8 mL, 7.1 g, 65 mmol) was added to a solution of 2.46 (6.0 g, 37 mmol) in 37% aq. HCl (68 mL) and stirred overnight. The solution was then neutralized with 25% aq. ammonia and concentrated in vacuo. The resulting white solid was stirred in acetone for 1 h after which the suspension was filtered and the filtrate concentrated. Purification by column chromatography (dichloromethane-MeOH 19:1 to 9:1) gave pure 2.47 (7.7 g, 32 mmol, 87%) as a white solid. Alternatively 2.47 could be purified by crystallization from dichloromethane-MeOH. [α]D -30.3 (c 1.09 in MeOH), (lit., ³⁰ [α]D -29.5 (c 1.00 in MeOH)). ¹H-NMR (CDCl₃, 300 MHz) δ = 1.27 (d, J = 6.3 Hz, 3H, C₆-H), 1.60 (ddd, J = 3.3, 8.4, 14.7 Hz, 1H, C₄-H), 1.89 (m, 1H, C₄-H'), 2.03 (m, 2H, dithian-H), 2.70 (m, 2H, dithian-H), 2.92 (m, 2H, dithian-H), 3.74 (d, J = 8.1 Hz, 1H, C₂-H), 4.03 (d, J = 8.1 Hz, 1H, C₃-H), 4.17 (m, 1H, C₅-H), 4.31 (d, J = 9.6 Hz, 1H, C₁-H) ppm. ¹³C-NMR (CDCl₃, 50.3 MHz) δ = 23.6 (q), 25.3 (t), 26.8 (t), 27.4 (t), 42.3 (t), 47.6 (d), 65.3 (d), 67.7 (d), 73.3 (d) ppm. MS(El) for C₉H₁₈O₃S₂: m/z = 238 [M⁺], HRMS calcld for C₉H₁₈O₃S₂: 238.070, found: 238.069.

4,6-Dideoxy-2,3-O-isopropyliden-α-D-xylo-hexose-trimethylen-dithioacetal (2.48):³⁰ 2.47 (2.2 g, 9.2 mmol) was dissolved in dry acetone (30 mL) and CuSO₄ (2.9 g, 18.5 mmol, 2 eq) and H₂SO₄ (0.14 mL, 0.78 mmol, 8.4 mol%) were added. The resulting green suspension was stirred overnight and then filtered. The filtrate was neutralized with 25% aq. ammonia and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine (sat.) and extracted with dichloromethane (3x). The
combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. Purification by column chromatography (n-hexane-EtOAc 4:1) gave 2.48 (2.4 g, 8.7 mmol, 95%) as a colorless oil. [$\alpha$]$_D$ -55.0 (c 1.04 in MeOH), (lit., $^9$ $\alpha$]$_D$ -64.8 (c 1.17 in MeOH)). $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.24 (d, $J = 6.0$ Hz, 3H, C6-H3), 1.44 (m, 6H, CMe$_2$), 1.71-2.17 (m, 4H, C4-H, dithian-H), 2.31 (br s, 1H, OH), 2.77-2.96 (m, 4H, dithian-H), 3.95 (dd, $J = 5.7, 7.8$ Hz, 1H, C5-H), 4.13 (d, $J = 5.4$ Hz, 1H, C1-H), 4.34 (ddd, $J = 3.3, 7.8, 7.8$ Hz, 1H, C3-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 23.5 (q), 25.6 (t), 26.7 (q), 27.3 (q), 29.2 (t), 29.5 (t), 41.3 (t), 48.0 (d), 65.1 (d), 76.1 (d), 82.2 (d), 109.5 (s) ppm. MS(EI) for C$_{12}$H$_{22}$O$_3$S$_2$: m/z = 278 [M$^+$], HRMS calcd for C$_{12}$H$_{22}$O$_3$S$_2$: 278.101, found: 278.101.

5-O-Benzoyl-4,6-dideoxy-2,3-O-isopropyliden-L-arabino-hexose-trimethylene-dithioacetal (2.49): $^{30}$ Triphenylphosphine (13 g, 50 mmol) and benzoic acid (5.8 g, 48 mmol) were added to a solution of 2.48 (6.2 g, 22 mmol) in dry THF (115 mL) at room temperature. Subsequently, a solution of diethylazodicarboxylate (DEAD, 8.4 g, 48 mmol) in dry THF (30 mL) was added over 20 min. The resulting mixture was stirred for 1 h and then quenched with MeOH and concentrated in vacuo. Water was added to the resulting oil and the product was extracted with Et$_2$O (3x). The combined organic layers were dried (MgSO$_4$), filtered and concentrated. 2.49 (7.0 g, 18 mmol, 82%) was obtained as a yellow oil after purification by column chromatography (n-hexane-EtOAc 9:1 to 4:1). The remaining 18% was isolated as a yellow oil, which appeared to be the side product resulting from C4-C5 dehydration according to $^1$H-NMR. $^1$H-NMR 2.49 (CDCl$_3$, 200 MHz) $\delta$ = 1.39-1.44 (m, 9H, C6-H3, CMe$_2$), 1.82-2.00 (m, 4H, C4-H, dithian-H), 2.67-2.97 (m, 4H, dithian-H), 3.96 (dd, $J = 5.2, 7.6$ Hz, 1H, C2-H), 4.12 (d, $J = 5.2$ Hz, 1H, C1-H), 4.26 (ddd, $J = 4.4, 7.6, 7.6$ Hz, 1H, C3-H), 5.38 (m, 1H, C5-H) 7.38-7.60 (m, 3H, Bz-H), 8.03-8.09 (m, 2H, Bz-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 19.8 (q), 25.6 (t), 26.7 (q), 27.3 (q), 29.1 (t), 29.5 (t), 41.3 (t), 48.2 (d), 69.0 (d), 75.5 (d), 82.6 (d), 109.5 (s), 128.1 (d), 129.5 (d), 130.6 (s), 132.6 (d), 165.9 (s) ppm. MS(EI) for C$_{19}$H$_{26}$O$_4$S$_2$: m/z = 282 [M$^+$], HRMS calcd for C$_{19}$H$_{26}$O$_4$S$_2$: 282.127, found: 282.126.

$^1$H-NMR side product (CDCl$_3$, 300 MHz) $\delta$ = 1.39-1.43 (m, 9H, C6-H3, CMe$_2$), 1.74 (dd, $J = 1.8, 6.6$ Hz, 3H, C6-H3), 1.84-2.17 (m, 2H, dithian-H), 2.74-3.03 (m, 4H, dithian-H), 3.94 (dd, $J = 4.2, 8.0$ Hz, 1H, C2-H), 4.10 (d, $J = 4.2$ Hz, 1H, C1-H), 4.47 (t, $J = 8.0$ Hz, 1H, C3-H), 5.47 (m, 1H), 5.87 (m, 1H) ppm.

The C5-epimer of 2.49 was synthesized by reaction of 2.48 with benzoyl chloride in pyridine. $^1$H-NMR C5-epimer of 2.49 (CDCl$_3$, 300 MHz) $\delta$ = 1.39-1.43 (m, 9H, C6-H3, CMe$_2$), 1.82-2.25 (m, 4H, C4-H, dithian-H), 2.74-2.98 (m, 4H, dithian-H), 3.93 (dd, $J = 5.7, 7.5$ Hz, 1H, C2-H), 4.11 (d, $J = 5.4$ Hz, 1H, C1-H), 4.24 (ddd, $J = 2.1, 8.3, 8.3$ Hz, 1H, C3-H), 5.32 (m, 1H, C5-H) 7.41-7.71 (m, 3H, Bz-H), 8.06-8.18 (m, 2H, Bz-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 20.6 (q), 25.6 (t), 26.8 (q), 27.3 (q), 29.1 (t), 29.4 (t), 40.5 (t), 48.05 (d), 69.4 (d), 75.6 (d), 82.6 (d), 109.7 (s), 128.2 (d), 129.5 (d), 130.5 (s), 132.7 (d) ppm.
(1S)-2-[(4S,5R)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-methylethyl benzoate: 2.49

(6.8 g, 18 mmol) was dissolved in acetone (140 mL) and water (35 mL) and 2,4,6-collidine (23.4 mL, 21.5 g, 178 mmol) and MeI (11.1 mL, 25.2 g, 178 mmol) were added. The resulting solution was refluxed under argon for 3.5 h at which point another portion of MeI (11.1 mL) was added. After refluxing for another 4.5 h, the mixture was cooled to room temperature and the acetone was removed in vacuo. The remaining solution was diluted with dichloromethane, washed with aq. HCl (2 M, 3x), aq. NaHCO₃ (sat.) and brine (sat.), dried (MgSO₄) and concentrated. Crude 2.50 was used without purification in the next step after overnight drying in vacuo over P₂O₅.

(1S)-2-[(4S,5S)-5-(2,2-dibromovinyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-methylethyl benzoate (2.51): Triphenylphosphine (18.6 g, 71.1 mmol, 4 eq.) was dissolved in freshly distilled dry dichloromethane (47 mL) and CBr₄ (sublimed prior to use, 11.8 g, 35.6 mmol, 2 eq.) in dichloromethane (47 mL) was added at 0 °C under argon. The resulting yellow/red solution was stirred for 10 min, after which the crude aldehyde in dichloromethane (42 mL) was added dropwise. The solution was then allowed to reach room temperature and stirred until TLC showed the reaction to be complete (approximately 1 h, n-hexane-EtOAc 4:1 to detect the product and dichloromethane-MeOH 98:2 to detect the aldehyde). The reaction was quenched with aq. NaHCO₃ (sat.), the aqueous layer was extracted with dichloromethane (2x), the combined organic layers were washed with water and brine (sat.), dried (MgSO₄) and concentrated. The resulting brown solid was first filtered over silica (CHCl₃) and then further purified by column chromatography (n-hexane-EtOAc 9:1) to give 2.51 (5.7 g, 13 mmol, 72% from 2.49) as a colorless oil.

1H-NMR (CDCl₃, 200 MHz) δ = 1.36 (m, 6H, CMe₂), 1.42 (d, J = 6.3 Hz, 3H, C7-H₃), 1.94 (ddd, J = 4.2, 6.2, 14.2 Hz, 1H, C5-H), 2.14 (m, 1H, C5-H'), 3.92 (ddd, J = 4.2, 8.0, 8.0 Hz, 1H, C4-H), 4.34 (t, J = 8.0 Hz, 1H, C3-H), 5.34 (m, 1H, C6-H), 6.42 (d, J = 8.6 Hz, 1H, C2-H), 7.39-7.60 (m, 3H, Bz-H), 8.02-8.07 (m, 2H, Bz-H) ppm. 13C-NMR (CDCl₃, 50.3 MHz) δ = 20.0 (q), 26.5 (q), 27.0 (q), 38.0 (t), 68.9 (d), 76.8 (d), 80.7 (d), 94.5 (s), 109.6 (s), 128.1 (d), 129.4 (d), 130.6 (s), 132.7 (d), 135.0 (d), 165.8 (s) ppm. MS(CI) for C₁₇H₂₀O₄Br₂: m/z = 466 (M + NH₄)⁺.

(1S)-2-[(4S,5S)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-methylethyl benzoate (2.52): To a solution of 2.51 (3.0 g, 6.7 mmol) in dry THF (77 mL), was added LDA (0.43 M in THF/n-hexane, 34 mL, 14.6 mmol, 2.2 eq.) at -78 °C under argon. The resulting solution was stirred for 2 h, after which TLC showed complete conversion. The reaction was quenched with water, extracted with Et₂O (2x), dried (MgSO₄), filtered and concentrated. The product was purified by column chromatography (n-hexane-EtOAc 9:1) to give the free alkyne (2.52, 1.7 g, 5.9 mmol, 88%) as a colorless oil.

1H-NMR (CDCl₃, 200 MHz) δ = 1.38 (s, 3H, CMe₂), 1.43 (s, 3H, CMe₂), 1.43 (d, J = 6.2 Hz, 3H, C7-H₃), 1.97 (ddd, J = 4.6, 5.4, 14.0 Hz, 1H, C5-H), 2.16 (m, 1H, C5-H'), 2.48 (d, J = 1.8 Hz, 1H, C1-H), 4.22 (m, 2H, C3-H, C4-H), 5.36 (m, 1H, C6-H), 7.39-7.60 (m, 3H, Bz-H), 8.02-8.08 (m, 2H, Bz-H) ppm. 13C-NMR (CDCl₃, 50.3 MHz) δ = 20.0 (q), 26.0 (q), 26.9 (q), 38.0 (t), 68.7
(1S)-2-[(4S,5S)-2,2-dimethyl-5-prop-1-yn-1-yl-1,3-dioxolan-4-yl]-1-methylethyl benzoate (2.53): 2.52 (425 mg, 1.47 mmol) was dissolved in dry THF (3.7 mL) and added to a solution of LDA (0.43 M in THF/n-hexane, 10.2 mL, 4.4 mmol, 3.0 eq.) at -78 °C under argon. After 3 min HMPA (1.28 mL, 1.32 g, 7.37 mmol, 5.0 eq.) was added and after an additional 5 min MeI (0.28 mL, 0.63 g, 4.4 mmol, 3.0 eq.) was added. The resulting solution was allowed to warm to -10 °C over 2 h, after which GC-MS showed the reaction to be complete. The reaction was quenched with aq. HCl (1 M), extracted with Et₂O (2x), dried (MgSO₄), filtered and concentrated. Purification by column chromatography (n-pentane-EtOAc 95:5 to 9:1) gave 2.53 (392 mg, 1.30 mmol, 88%) as a colorless oil. ¹H-NMR (CDCl₃, 400 MHz) = 1.36-1.44 (m, 9H, C₈-H₃, CMe₂), 1.75 (s, J = 2.0 Hz, 3H, C₁-H), 1.94 (dt, J = 5.2, 14.0 Hz, 1H, C₆-H), 2.16 (ddd, J = 5.1, 5.7, 14.4 Hz, 1H, C₆-H'), 4.11 (ddd, J = 5.2, 6.8, 8.0 Hz, 1H, C₅-H), 4.24 (ddd, J = 2.0, 4.0, 8.0 Hz, 1H, C₄-H), 5.34 (m, 1H, C₇-H), 7.41-7.57 (m, 3H, Bz-H), 8.04-8.06 (m, 2H, Bz-H) ppm. ¹³C-NMR (CDCl₃, 50.3 MHz) = 3.5 (q), 20.1 (q), 26.3 (q), 27.0 (q), 38.0 (t), 68.9 (d), 70.7 (d), 74.7 (s), 78.3 (d), 83.5 (s), 109.3 (s), 128.2 (d), 129.4 (d) 130.6 (s), 132.7 (d), 165.8 (s) ppm. MS(CI) for C₁₇H₂₀O₄: m/z = 306 (M + NH₄)⁺, HRMS calcd for C₁₇H₂₀O₄: m/z = 306.1449, found: 306.1451.

(1S)-2-[(4S,5S)-2,2-dimethyl-5-(1E)-2-tri-n-butylstannanylprop-1-en-1-yl]-1,3-dioxolan-4-yl]-1-methylethyl benzoate (2.54b): 2.53 (230 mg, 761 µmol) was added to a suspension of PdCl₂(PPh₃)₂ (27 mg, 38 µmol, 5 mol%) in n-pentane (6.9 mL) under argon and after stirring for 10 min, Bu₃SnH (0.83 mL, 3.1 mmol, 4 eq.) was added over 2 min. After 45 min TLC showed complete conversion and the mixture was concentrated. The product was purified by column chromatography (benzene-cyclohexane 9:1) giving 2.54b (282 mg, 475 µmol, 63%) and the internal hydrostannylation side product 2.54a (45 mg, 76 µmol, 10%) both as colorless liquids. ¹H-NMR 2.54b (CDCl₃, 400 MHz) = 0.70-1.03 (m, 15H, Bu-Sn), 1.19-1.60 (m, 21H, C₈-H₃, CMe₂, Bu-Sn), 1.77 (ddd, J = 3.2, 6.4, 14.0 Hz, 1H, C₆-H), 1.96 (d, J = 1.6 Hz, 3H, C₁-H), 2.06 (ddd, J = 6.8, 8.8, 14.0 Hz, 1H, C₆-H'), 3.75 (ddd, J = 3.6, 8.4, 8.4 Hz, 1H, C₅-H), 4.54 (t, J = 8.4 Hz, 1H, C₄-H), 5.31 (m, 1H, C₇-H), 5.47 (dd, J = 2.0, 8.4 Hz, 1H, C₃-H), 7.41-7.56 (m, 3H, Bz-H), 8.02-8.06 (m, 2H, Bz-H) ppm. ¹³C-NMR (CDCl₃, 50.3 MHz) δ = 9.0 (t), 13.6 (q), 19.9 (q), 27.0 (q), 27.2 (t), 29.0 (t), 37.8 (t), 69.2 (d), 76.0 (d), 77.7 (d), 108.5 (s), 128.1 (d), 129.4 (d), 130.7 (s), 132.6 (d), 135.6 (d), 147.5 (s), 165.8 (s) ppm. MS(ESI) for C₆H₅O₂Sn: m/z = 593 [M⁺]. ¹H-NMR 2.54a (CDCl₃, 200 MHz) δ = 0.70-1.03 (m, 15H, Bu-Sn), 1.20-1.60 (m, 21H, C₈-H₃, CMe₂, Bu-Sn), 1.72-1.84 (m, 1H, C₆-H), 1.79 (d, J = 6.6 Hz, 3H, C₁-H), 2.04 (ddd, J = 5.6, 9.4, 13.6 Hz, 1H, C₆-H'), 3.57 (ddd, J = 3.4, 9.2, 9.2 Hz, 1H, C₅-H), 4.76 (dd, J = 1.2, 8.6 Hz, 1H, C₄-H), 5.32 (m, 1H, C₇-H), 5.84 (dd, J = 1.2, 6.6 Hz, 1H, C₂-H), 7.38-7.58 (m,
Chapter 2

3H, Bz-H), 8.01-8.07 (m, 2H, Bz-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 10.3 (t), 13.6 (q), 16.4 (q), 19.5 (q), 27.1 (q), 27.3 (t), 29.0 (t), 38.1 (t), 69.5 (d), 77.6 (d), 80.8 (d), 108.1 (s), 128.1 (d), 129.4 (d), 130.7 (s), 132.6 (d), 137.8 (d), 147.7 (s), 167.5 (s) ppm.

(1S)-2-{(4S,5S)-5-[(1E)-2-iodoprop-1-en-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.38a): 2.54b (200 mg, 0.34 mmol) was dissolved in dichloromethane (2.7 mL) and I$_2$ (114 mg, 0.45 mmol, 1.3eq) in dichloromethane (0.7 mL) was added at -78 $^\circ$C under argon. The resulting solution was stirred for 10 min at -78 $^\circ$C and then allowed to warm to room temperature. The solution was concentrated and 2.38a (144 mg, 0.33 mmol, 99%) was isolated as a yellow oil after column chromatography (n-hexane-EtOAc 39:1; 2.5 volume-% Et$_3$N was used during the preparation of the column).

$^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.35 (s, 3H, CMe$_2$), 1.38 (s, 3H, CMe$_2$), 1.41 (d, $J = 6.3$ Hz, 3H, C8-H), 2.06 (m, 1H, C6-H), 3.84 (dd, $J = 3.9, 8.1, 8.1$ Hz, 1H, C5-H), 4.29 (t, $J = 8.7$ Hz, 1H, C4-H), 5.31 (m, 1H, C7-H), 6.14 (d, 1H, C3-H, $J = 8.7$ Hz), 7.41-7.58 (m, 3H, Bz-H), 8.04 (m, 2H, Bz-H) ppm.

$^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 19.9 (q), 26.7 (q), 27.1 (q), 28.4 (q), 37.5 (t), 68.9 (d), 76.9 (d), 77.7 (d), 101.5 (s), 109.0 (s), 128.1 (d), 129.4 (d), 130.5 (s), 165.7 (s) ppm. MS(CI) for C$_{18}$H$_{23}$IO$_4$: m/z = 448 (M + NH$_4$)$^+$, HRMS calcd for C$_{20}$H$_{23}$IO$_4$: 430.064, found: 430.066.

Methyl $\alpha$-L-rhamnopyranoside (2.55): L-rhamnose (2.0 g, 11 mmol) was dissolved in MeOH (80 mL) and acetyl chloride (1.2 mL, 17 mmol) was added. The resulting solution was stirred under argon for 60 h and then neutralized with Na$_2$CO$_3$ (s) and filtered. The filtrate was concentrated and purified by column chromatography (EtOAc-MeOH 97.5 : 2.5) to give 2.55 (1.4 g, 6.9 mmol, 63%) as a white foam.

$^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.31 (d, $J = 6.3$ Hz, 3H, C6-H), 1.35, 1.53 (2s, 6H, CMe$_2$), 2.16 (d, $J = 4.5$ Hz, 1H, OH), 3.39 (s, 3H, OMe), 3.39 (m, 1H, C4-H), 4.07 (t, $J = 4.5$ Hz, 1H, C3-H), 4.13 (d, $J = 6.0$ Hz, 1H, C2-H), 4.85 (s, 1H, C1-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 17.3 (q), 54.6 (q), 67.9 (d), 70.7 (d), 71.5 (d), 72.5 (d), 101.5 (s), 109.0 (s), 128.1 (d), 129.4 (d), 130.5 (s), 132.6 (d), 137.0 (d) 167.5 (s) ppm. MS(Cl) for C$_{7}$H$_{14}$O$_5$: m/z = 196 (M + NH$_4$)$^+$. MS(Cl) for C$_{10}$H$_{18}$O$_5$: m/z = 236 (M + NH$_4$)$^+$.

Methyl-(2,3-O-isopropylidene-$\alpha$-L-rhamnopyranoside) (2.56): 2.55 (21.5 g, 110 mmol) was dissolved in dry acetone and CuSO$_4$ (34 g, 220 mmol, 2 eq) and H$_2$SO$_4$ (1.7 mL) were added. The resulting green suspension was stirred overnight under argon and then filtered. The filtrate was made basic (pH 9) with 25% aq. ammonia and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine (sat.) and extracted with dichloromethane (3x). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated. Purification by column chromatography (n-hexane-EtOAc 9:1 to 4:1) gave 2.56 as an oil (23.3 g, 98.6 mmol, 90%). $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.31 (d, $J = 6.3$ Hz, 3H, C6-H), 1.35, 1.53 (2s, 6H, CMe$_2$), 2.16 (d, $J = 4.5$ Hz, 1H, OH), 3.39 (s, 3H, OMe), 3.39 (m, 1H, C4-H), 3.65 (m, 1H, C5-H), 4.07 (t, $J = 6.6$ Hz, 1H, C3-H), 4.13 (d, $J = 6.0$ Hz, 1H, C2-H), 4.85 (s, 1H, C1-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 17.3 (q), 26.0 (q), 27.8 (q), 54.8 (q), 65.6 (d), 74.3 (d) 75.6 (d), 78.3 (d), 98.0 (d), 109.3 (s) ppm. MS(Cl) for C$_{10}$H$_{18}$O$_5$: m/z = 236 (M + NH$_4$)$^+$.
Methyl-4-O-(imidazol-1-ylthiocarbonyl)-2,3-O-isopropylidene-α-L-rhamnopyranoside (2.57): A solution of 2.56 (13.5 g, 57.1 mmol) and 1,1'-thiocarbonyldiimidazole (12.8 g, 71.5 mmol, 1.3 eq) in anhydrous 1,2-dichloroethane (200 mL) was refluxed for 2 h under argon. After cooling to room temperature, the solvent was removed and the product was purified by crystallization from ether/n-hexane and/or by column chromatography (n-hexane-EtOAc 4:1 to 1:1) giving a white solid (19.0 g, 54.8 mmol, 99.7%).

1H-NMR (CDCl$_3$, 300 MHz) δ = 1.28 (d, $J = 6.3$ Hz, 3H, C$_6$-H$_3$), 1.36, 1.61 (2s, 6H, CMe$_2$), 3.43 (s, 3H, OMe), 3.95 (dq, $J_{5,6} = 6.3$ Hz, 1H, C$_5$-H), 4.22 (d, $J = 5.4$ Hz, 1H, C$_2$-H), 4.37 (dd, $J = 5.7$, 7.5 Hz, 1H, C$_3$-H), 4.95 (s, 1H, C$_1$-H), 5.74 (dd, $J = 7.8$, 9.9 Hz, 1H, C$_4$-H), 7.07, 7.65, 8.40 (3s, 3H, imidazole) ppm.

13C-NMR (CDCl$_3$, 50.3 MHz) δ = 17.0 (q), 26.1 (q), 27.4 (q), 55.1 (q), 63.6 (d), 75.1 (d), 75.8 (d), 83.0 (d), 97.8 (d), 110.2 (s), 118.0 (d), 130.8 (d) 136.7 (d), 183.8 (s) ppm. MS(CI) for C$_{14}$H$_{20}$N$_2$O$_5$S: m/z = 329 (M + H)$^+$. 

Methyl-4,6-dideoxy-2,3-O-isopropylidene-α-L-lyxo-hexapyranoside (2.58): 2.57 (2.0 g, 6.1 mmol) was dissolved in toluene (27 mL) and AIBN (0.3 g, 1.8 mmol, 30 mol%) and tris(trimethylsilyl)silane (2.3 mL, 7.5 mmol, 1.2 eq) were added. The resulting solution was slowly heated to 110°C and then refluxed for 30 min under argon, after which TLC showed complete conversion. After cooling to room temperature, aq. NaHCO$_3$ (20% w/w) was added and the product was extracted with EtOAc (3x). The combined organic layers were dried (MgSO$_4$) and concentrated below 30°C using MeOH to remove the toluene. 2.58 was isolated as a yellow oil after column chromatography (n-hexane-EtOAc 98:2 to 95:5). Due to volatility of the product, the yield was determined in the next step.

1H-NMR (CDCl$_3$, 300 MHz) δ = 1.22 (d, $J = 6.0$ Hz, 3H, C$_6$-H$_3$), 1.47 (q, $J = 12.4$ Hz, 1H, C$_4$-H), 1.74-1.87 (m, 3H, C$_4$-H', 2-OH), 3.37 (s, 3H, OMe), 3.72 (s, 1H, C$_2$-H), 3.96 (m, 1H, C$_3$-H), 4.73 (s, 1H, C$_1$-H) ppm. 13C-NMR (CDCl$_3$, 50.3 MHz) δ = 21.0 (q), 26.2 (q), 28.1 (q), 36.0 (t), 54.7 (q), 61.9 (d), 70.9 (d), 72.6 (d), 98.7 (d), 108.6 (s) ppm. MS(CI) for C$_{10}$H$_{18}$O$_4$: m/z = 220 (M + NH$_4$)$^+$. 

Methyl-4,6-dideoxy-α-L-lyxo-hexapyranoside (2.59): Amberlite-120-(Na$^+$)-resin was stirred in an aq. HCl-solution (2 M) for 1.5 h and then filtered off and flushed with aq. HCl-solution (2 M) twice. 4.0 g of the thus obtained resin was added to a solution of 2.58 (1.23 g, 6.10 mmol) in water (37 mL) and 1,4-dioxane (37 mL). After stirring for 12 h, the resin was filtered off and the solution was neutralized with aq. NaOH (1 M) and then concentrated. After column chromatography (CHCl$_3$-EtOH 9:1) 2.59 (703 mg, 4.33 mmol, 71% from 2.57) was isolated as a white foam. NMR-data are as reported in literature. 1H-NMR (CDCl$_3$, 300 MHz) δ = 1.23 (d, $J = 6.0$ Hz, 3H, C$_6$-H$_3$), 1.47 (q, $J = 12.4$ Hz, 1H, C$_4$-H), 1.74-1.87 (m, 3H, C$_4$-H', 2-OH), 3.37 (s, 3H, OMe), 3.72 (s, 1H, C$_2$-H), 3.84 (s, 1H, C$_3$-H), 3.96 (m, 1H, C$_5$-H), 4.73 (s, 1H, C$_1$-H) ppm. 13C-NMR (CDCl$_3$, 50.3 MHz) δ = 21.0 (q), 36.3 (t), 54.8 (q), 63.7 (d), 65.6 (d), 68.6 (d), 101.2 (d) ppm. MS(CI) for C$_7$H$_{16}$O$_4$: m/z = 180 (M + NH$_4$)$_2^+$.
Methyl-2-O-acetyl-4,6-dideoxy-\(\alpha\-L\)-lyxo-hexapyranoside (2.60): 2.59 (670 mg, 4.13 mmol) was dissolved in acetonitrile (13 mL), and \(p\-toluenesulfonic acid\) monohydrate (41 mg) and trimethyl orthoacetate (0.95 mL, 7.43 mmol, 1.8 eq) were added. The resulting solution was stirred for 10 min and then concentrated. The residue was dissolved in dichloromethane (13 mL) and 90% aqueous trifluoroacetic acid (4.06 mL) was added. The thus obtained mixture was stirred for 5 min after which TLC (\(n\)-hexane-EtOAc 4:1) showed complete conversion. After concentration, the residue was taken up in dichloromethane, washed with \(aq\) NaHCO\(_3\) (5% w/w) and water, dried (Na\(_2\)SO\(_4\)) and concentrated to give 2.60 (675 mg, 3.30 mmol, 80%) as an oil, which was used in the next step without further purification. \(^1\)H-NMR of the crude product showed only 1 regioisomer present: (CDCl\(_3\), 300 MHz) \(\delta = 1.24\) (d, \(J = 6.3\) Hz, 3H, C6-H\(_3\)), 1.56 (q, \(J = 12.0\) Hz, 1H, C4-H), 1.77 (m, 2H, C4-H', OH), 2.14 (s, 1H, OAc), 3.35 (s, 3H, OMe), 3.87 (m, 1H, C5-H), 4.12 (m, 1H, C3-H), 4.71 (s, 1H, C1-H), 4.92 (br s, 1H, C2-H) ppm.

Methyl-2,3-di-O-acetyl-4,6-dideoxy-\(\alpha\-L\)-arabino-hexopyranoside (2.62): Trifluoromethanesulfonic anhydride (7.45 mL, 44.1 mmol, 3.0 eq) was slowly added to a solution of 2.60 (3.0 g, 14.7 mmol) and pyridine (7.2 mL, 88.2 mmol, 6.0 eq) in dichloromethane (70 mL) at -10 \(^\circ\)C under argon. The mixture was slowly warmed to room temperature and after stirring for an additional 1.5 h, the solution was diluted with dichloromethane and poured into ice-cold \(aq\) NaHCO\(_3\) (20% w/w). The organic layer was washed with \(aq\) HCl (1 M), water and \(aq\) NaHCO\(_3\) (sat.), dried (Na\(_2\)SO\(_4\)) and concentrated to give 2.61. \(^1\)H-NMR (CDCl\(_3\), 300 MHz) \(\delta = 1.28\) (d, \(J = 6.3\) Hz, 3H, C6-H), 1.98-2.13 (m, 5H, C4-H,H', OAc), 3.35 (s, 3H, OMe), 3.93 (m, 1H, C5-H), 4.72 (s, 1H, C1-H), 5.14 (brs, 1H, C2-H), 5.29 (m, 1H, C3-H) ppm. \(^13\)C-NMR (CDCl\(_3\), 50.3 MHz) \(\delta = 20.6\) (2q), 34.5 (t), 55.0 (q), 63.7 (d), 67.5 (d), 81.6 (d), 121.4 (s), 169.6 (s) ppm. \(^{19}\)F-NMR (CDCl\(_3\)) \(\delta = 1.81\) ppm.

A solution of the crude triflate 2.61 and tetra-\(n\)-butylammonium acetate (48.7 g, 162 mmol, 11.0 eq) in dry toluene (40 mL) was stirred overnight under argon. The mixture was concentrated and purified by column chromatography (\(n\)-hexane-EtOAc 4:1) to give 2.62 (2.6 g, 10.4 mmol, 71% from 2.60) as an oil and a side product resulting from dehydration (0.2 g, 1.2 mmol, 8%). \(^1\)H-NMR of the side product (CDCl\(_3\), 200 MHz) \(\delta = 1.32\) (d, \(J = 7.2\) Hz, 3H, C6-H\(_3\)), 1.70 (m, \(J_{ax,ax} = 14.5\), \(J_{eq,eq} = 2.5\) Hz, 1H, C4=Heq), 1.81 (d, \(J_{ax,ax} = 3.5\), \(J_{eq,eq} = 2.5\) Hz, 1H, C4-H), 2.08, 2.09 (2s, 6H, 2OAc), 3.38 (s, 3H, OMe), 4.14 (m, 1H, C3-H), 4.60 (s, 1H, C1-H), 4.74 (m, 1H, C2-H), 4.91 (m, 1H, C3-H) ppm. \(^13\)C-NMR (CDCl\(_3\), 50.3 MHz) \(\delta = 20.7\) (q), 20.8 (q), 21.0 (q), 32.6 (t), 55.1 (q), 59.7 (d), 66.5 (d), 67.2 (d), 98.7 (d), 169.3 (s), 170.0 (s) ppm. MS(EI) for C\(_{11}\)H\(_{18}\)O\(_6\): m/z = 215 [M + H – MeOH]”, MS(Cl) = 264 (M + NH\(_4\))”. \(^1\)H-NMR of the side product (CDCl\(_3\), 200 MHz) \(\delta = 1.32\) (d, \(J = 7.2\) Hz, 3H, C6-H\(_3\)), 2.09 (s, 3H, OAc), 3.47 (s, 3H, OMe), 4.30 (m, 1H, C5-H), 4.74 (brs, 1H, C1-H), 4.89 (m, 1H, C2-H), 5.78 + 5.83 (2 ddd, \(J = 1.2, 2.2, 4.8\) Hz and \(J = 1.2, 2.0, 5.0\) Hz, 1H, C3-H), 5.97 + 6.02 (2m, 1H, C4-H) ppm. MS(EI) for C\(_9\)H\(_{14}\)O\(_4\): m/z = 186 [M]”, MS(Cl) = 204 (M + NH\(_4\))”.
Total Synthesis of Mycolactones

1H-NMR of the C3-epimer of 2.62 obtained from acetylation of 2.59: (CDCl₃, 300 MHz) δ = 1.24 (d, J = 6.3 Hz, 3H, C6-H), 1.74 (m, 2H, 2C4-H), 1.99 (s, 3H, OAc), 2.12 (s, 3H, OAc), 3.35 (s, 3H, OMe), 3.94 (m, 1H, C5-H), 4.65 (s, 1H, C1-H), 5.05 (s, 1H, C2-H), 5.21 (m, 1H, C3-H) ppm.

4,6-Dideoxy-L-arabino-hexose-trimethylen-dithioacetal (2.63): 2.62 (100 mg, 0.41 mmol) was dissolved in MeOH-THF (2.0 mL, 1:1 v/v) and NaOMe was added until pH 9 was reached. The thus obtained reaction mixture was stirred for 2 h and then concentrated. The residue was dissolved in 37% aq. HCl (1.0 mL), after which 1,3-propanedithiol (85 µL, 0.82 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred for 24 h and then neutralized with 25% aq. ammonia. Subsequently the aqueous layer was washed with petroleum-ether (40-60; 5x) and concentrated to give a white solid which was suspended in acetone and stirred for 5 min. The solid was filtered off and the filtrate concentrated affording 2.63 (87 mg, 0.36 mmol, 87%) as a white solid. 1H-NMR (CDCl₃, 300 MHz) δ = 1.24 (d, J = 6.3 Hz, 3H, C6-H), 1.64 (m, 1H, C4-H), 1.81 (m, 1H, C4-H'), 2.05 (m, 2H, dithian-H), 2.67-2.97 (m, 4H, dithian-H), 3.70 (d, J = 8.1 Hz, 1H, C2-H), 4.05 (d, J = 8.4 Hz, 1H, C3-H), 4.31 (d, J = 9.6 Hz, 1H, C1-H) ppm. 13C-NMR (CDCl₃, 50.3 MHz) δ = 23.9 (q), 25.3 (t), 27.0 (t), 42.2 (t), 47.7 (d), 67.9 (d), 73.5 (d) ppm. MS(EI) for C₉H₁₈O₃S₂: m/z = 238 [M+], HRMS calcd for C₉H₁₈O₃S₂: 238.070, found: 238.071.

4,6-Dideoxy-2,3-O-isopropyliden-L-arabino-hexose-trimethylen-dithioacetal (2.64b): 2.63 (600 mg, 2.52 mmol) was dissolved in dry acetone and CuSO₄ (778 mg, 3.06 mmol, 1.2 eq.) and a drop of H₂SO₄ were added. The resulting green suspension was stirred overnight and then filtered. The filtrate was neutralized with 25% aq. NH₃ and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine (sat.) and extracted with dichloromethane (3x). The combined organic layers were dried (Na₂SO₄) and concentrated. Purification by column chromatography (n-hexane-EtOAc 95:5 to 4:1) gave 2.64b (549 mg, 1.97 mmol, 78%) and 2.64a (55 mg, 0.20 mmol, 8%) as colorless oils. 1H-NMR 2.64b (CDCl₃, 200 MHz) δ = 1.21 (d, J = 6.0 Hz, 3H, C6-H), 1.43, 1.45 (2s, 6H, CMe₂), 1.67 (m, 1H, C4-H), 1.86-2.17 (m, 3H, C4-H'), dithian-H), 2.74-3.01 (m, 4H, dithian-H), 3.09 (brs, 1H, OH), 3.93 (dd, J = 5.8, 8.0 Hz, 1H, C2-H), 4.05 (m, 1H, C5-H), 4.11 (d, J = 5.2 Hz, 1H, C1-H), 4.21 (ddd, J = 2.6, 7.6, 10.0 Hz, 1H, C3-H) ppm. 13C-NMR (CDCl₃, 50.3 MHz) δ = 23.2 (q), 25.6 (t), 26.8 (q), 27.2 (q), 29.2 (t), 29.4 (t), 42.3 (t), 47.9 (d), 67.2 (d), 78.8 (d), 82.9 (d), 110.0 (s) ppm. MS(ESI) for C₁₂H₂₂O₃S₂: m/z = 278 [M⁺], HRMS calcd for C₁₂H₂₂O₃S₂: m/z = 278.101, found: 278.101.

1H-NMR 2.64a (CDCl₃, 300 MHz) δ = 1.20 (d, J = 6.3 Hz, 3H, C6-H), 1.40, 1.46 (2s, 6H, CMe₂), 1.50 (m, 1H, C4-H), 1.92- 2.14 (m, 3H, C4-H'), dithian-H), 2.74-2.96 (m, 5H, dithian-H, OH), 3.64 (m, 1H), 4.03 (m, 1H), 4.14 (d, J = 7.0 Hz, 1H, C1-H), 4.25 (m, 1H, C3-H) ppm.
5-O-tert-Butyl-dimethyl-silyl-4,6-dideoxy-2,3-O-isopropyliden-1-arabino-hexose-trimethylen-dithiaoacetal (2.65): 2.64b (500 mg, 1.80 mmol) was dissolved in DMF (3.0 mL) and TBDMSCl (541 mg, 3.59 mmol, 2.0 eq.) and imidazole (245 mg, 3.59 mmol, 2.0 eq.) were added. The resulting solution was stirred for 12 h at 70 °C under argon. After cooling to room temperature, the reaction mixture was diluted with water, extracted with Et₂O (2x), dried (Na₂SO₄) and concentrated. Purification by column chromatography (n-hexane-EtOAc 95:5 to 9:1) gave 2.65 (593 mg, 1.51 mmol, 84%) as an oil.

1H-NMR (CDCl₃, 300 MHz) δ = 0.06 (s, 6H, 2MeSi), 0.88 (s, 9H, tBuSi), 1.20 (d, J = 6.3 Hz, 3H, C₆-H₃), 1.40, 1.42 (2s, 6H, CMe₂), 1.72-2.14 (m, 4H, C₄-H,H', dithian-H), 2.74-2.97 (m, 4H, dithian-H), 3.90 (dd, J = 5.1, 7.5 Hz, 1H, C₂-H), 4.01-4.15 (m, 3H, C₁-H, C₃-H, C₅-H) ppm.

13C-NMR (CDCl₃, 50.3 MHz) δ = -4.9 (q), -4.7 (q), 18.0 (s), 22.8 (q), 25.7 (q), 26.8 (q), 27.3 (q), 29.1 (t), 29.5 (t), 43.6 (q), 47.9 (d), 66.1 (q), 75.9 (d), 83.2 (q), 109.3 (s) ppm. MS(EI) for C₁₈H₃₆O₃S₂: m/z = 392 [M+H]+, MS(CI) for C₁₈H₃₆O₃S₂: m/z = 393 (M + H)+, 410 (M + NH₄)+, HRMS calcd for C₁₈H₃₆O₃SiS₂: 392.188, found: 392.188.

(4R,5S)-5-[(2S)-2-(tert-Butyl-dimethyl-silanyloxy)-propyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (2.66): 2.65 (137 mg, 0.35 mmol) was converted into 2.66 (94 mg, 0.31 mmol, 89%) using a procedure analogous to the synthesis of 2.50.

1H-NMR (CDCl₃, 200 MHz) δ = 0.06 (s, 6H, 2MeSi), 0.87 (s, 9H, tBuSi), 1.19 (d, J = 6.0 Hz, 3H, C₆-H₃), 1.42, 1.47 (2s, 6H, CMe₂), 1.70-1.97 (m, 2H, C₄-H,H'), 3.97-4.06 (m, 2H, C₂-H, C₅-H), 4.18 (ddd, J = 5.0, 7.6, 7.6 Hz, 1H, C₃-H), 9.72 (d, J = 2.4 Hz, 1H, O=CH) ppm.

13C-NMR (CDCl₃, 50.3 MHz) δ = -5.0 (q), -4.5 (q), 17.9 (s), 23.2 (q), 25.7 (q), 26.1 (q), 27.0 (q), 42.8 (t), 65.6 (d), 73.9 (d), 85.0 (d), 110.8 (s), 200.6 (d) ppm.

(1S)-2-{(4S,5S)-5-(11-ethoxy-2,6,8-trimethyl-11-oxoundeca-1,5,7,9-tetraen-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.36a): 2.38a (122 mg, 0.28 mmol, 1.2 eq) was dissolved in iPrNH₂ (1.0 mL) and Pd(PPh₃)₄ (5.3 mg, 4.6 mol, 2 mol%) was added. The solution was stirred under argon at ambient temperature for 5 min, after which CuI (0.9 mg, 4.6 mol, 2 mol%) was added. After 5 min, 2.37a (47 mg, 0.23 mmol) in iPrNH₂ (0.85 mL) was added and the mixture was stirred for 2 h and then concentrated. The residue was dissolved in Et₂O, washed with aq. NH₄Cl (sat.) and brine (sat.), dried (Na₂SO₄) and concentrated. 2.36a (109 mg, 0.22 mmol, 94%) was isolated as a yellow oil after purification by column chromatography (n-hexane-EtOAc 19:1 to 9:1) and remaining 2.38a (20 mg, 0.05 mmol, 20%) was recovered.

1H-NMR major isomer (CDCl₃, 200 MHz) δ = 1.30 (t, J = 7.0 Hz, 3H, CH₃CH₂O), 1.34-1.42 (m, 9H, C₁₆-H₆, CMe₂), 1.76-2.20 (m, 11H, C₄,-C₆,-C₁₀-CH₂, C₁₄-H₂), 3.85 (ddd, J = 3.8, 8.2, 8.2 Hz, 1H, C₁₃-H), 4.22 (q, J = 7.2 Hz, 2H, CH₃CH₂O), 4.39 (m, 1H, C₁₂-H), 5.31 (m, 1H, C₁₅-H), 5.67 (s, 1H, C₇-H), 5.74 (dd, J = 1.6, 9.0 Hz, 1H, C₁₁-H), 5.91 (d, J = 15.6 Hz, 1H, C₃-H), 6.31 (s, 1H, C₅-H), 7.30-7.59 (m, 5H, Bz-H, C₂-H), 8.03 (m, 2H, Bz-H) ppm. ¹³C-NMR (CDCl₃, 50.3 MHz) δ = 13.9 (q), 14.2 (q), 17.9 (q), 19.5 (q), 19.9 (q), 26.7 (q), 27.1 (q), 37.6 (t), 60.1 (t), 69.0 (d), 71.1 (d), 77.6 (d), 87.0
(s), 99.9 (s), 108.9 (s), 113.4 (d), 117.6 (d), 124.4 (s), 128.1 (d), 129.4 (d), 130.6 (s), 132.2 (d), 134.2 (s), 140.5 (d), 146.1 (s), 165.7 (s), 167.0 (s) ppm. MS(EI) for C₃₁H₃₈O₆: m/z = 506 [M⁺], HRMS calcd for C₃₁H₃₈O₆: 506.267, found: 506.268.

4,6-Dimethyl-9-trimethylsilanyl-nona-2,4,6-trien-8-yn-1-ol (2.67): 2.67 (398 mg, 1.44 mmol) was dissolved in dichloromethane (7.2 mL) and DiBAl-H (1.0 M in n-hexanes, 3.17 mL, 3.17 mmol, 2.2 eq) was added at -70 °C. The resulting mixture was stirred for 2 h under argon, while warming to -60 °C. The reaction was quenched with MeOH and the precipitate was dissolved with aq. NH₄Cl (sat.) and aq. HCl (1.0 M). The aqueous layer was extracted with dichloromethane (3x), after which the combined organic layers were washed with aq. NaHCO₃ (sat.) and brine (sat.), dried (MgSO₄), filtered and concentrated. 2.67 (336 mg, 1.44 mmol, quantitative) was isolated as a colorless oil (single isomer) after purification by column chromatography (n-pentane-EtOAc 85:15 to 4:1).

1H-NMR (CDCl₃, 200 MHz) δ = 0.20 (s, 9H, TMS), 1.96 (s, 3H, C6-CH₃), 2.09 (s, 3H, C4-CH₃), 4.23 (d, J = 6.0 Hz, 2H, CH₂OH), 5.47 (s, 1H, C7-H), 5.87 (dt, J = 6.0, 15.8 Hz, 1H, C2-H), 5.95 (s, 1H, C5-H), 7.32 (d, J = 15.8 Hz, 1H, C3-H) ppm.

4,6-Dimethylnona-2,4,6-trien-8-yn-1-ol (2.68): 2.67 (50 mg, 0.21 mmol) was converted into 2.68 (23 mg, 0.14 mmol, 67%) using a procedure analogous to the synthesis of 2.37a. Due to the instability of 2.68, it was immediately used in the next step without purification.

(1S)-2-{(4S,5S)-5-(11-hydroxy-2,6,8-trimethyl-undeca-1,5,7,9-tetraen-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.69): 2.68 (23 mg, 0.14 mmol) was coupled to 2.38a (88 mg, 0.20 mmol, 1.4 eq) to give 2.69 (51 mg, 0.11 mmol, 77%, single isomer) as described for the preparation of 2.36a. Column chromatography was performed with dichloromethane-MeOH 99:1 to 98:2. 1H-NMR (CDCl₃, 300 MHz) δ = 1.34-1.42 (m, 9H, C16-H₃, CMe₂), 1.79-2.20 (m, 11H, C4,- C6-, C10-CH₃, C14-H₂), 3.84 (ddd, J = 3.3, 8.1, 8.1 Hz, 1H, C13-H), 4.24 (brs, 2H, CH₂OH ), 4.39 (m, 1H, C12-H), 5.30 (m, 1H, C15-H), 5.52 (s, 1H, C7-H), 5.70 (d, J = 9.0 Hz, 1H, C11-H), 5.89 (dt, J = 6.0, 15.6 Hz, 1H, C2-H), 5.98 (s, 1H, C5-H), 6.30 (d, J = 15.9 Hz, 1H, C3-H), 7.42 (t, J = 7.5 Hz, 2H, Bz-H), 7.54 (t, J = 7.5 Hz, 1H, Bz-H), 8.03 (d, J = 7.5 Hz, 2H, Bz-H) ppm.

(1S)-2-{(4S,5S)-5-(11-hydroxy-2,6,8-trimethyl-undeca-1,3,5,7,9-pentaen-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.70): HCl (2.0 M aq, 30 mL) was added to a double schlenk containing zinc (5.0 g) and the resulting suspension was stirred under argon for 5 min. The HCl was then removed by filtration and the zinc was washed with HCl (2.0 M aq, 3x 30 mL) and water (10 x 30 mL). The zinc was suspended in water (40 mL) and argon was bubbled
through for 15 min, after which Cu(OAc)$_2$·H$_2$O (0.5 g) was added and stirring continued for another 15 min. Subsequently, AgNO$_3$ (0.5 g) was added, which resulted in an exothermic reaction and a change of color from light grey to black. After stirring for 30 min, the zinc-amalgam was filtered and washed with water (30 mL), MeOH, acetone and Et$_2$O. The zinc-amalgam was then suspended in MeOH (15 mL) and water (10 mL) and 3 mL of this suspension was added to 2.69 (25 mg, 54 µmol), after which the reaction mixture was stirred overnight under argon. The amalgam was removed by filtration over celite and the filtrate was partly concentrated in vacuo until all the MeOH was removed. The remaining aqueous solution was subsequently extracted with dichloromethane (3x) and the combined organic layers were washed with brine (sat.), dried (Na$_2$SO$_4$) and concentrated. Purification by column chromatography and/or preparative TLC (dichloromethane-MeOH 99:1 to 98:2) gave a small amount of product that could be 2.70. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.26-1.48 (m, 9H, C$_{16}$-H$_3$, CMe$_2$), 1.72-2.28 (m, 11H, C$_4$-C$_6$-, C$_{10}$-CH$_3$, C$_{14}$-H$_2$), 3.83 (ddd, $J$ = 3.3, 8.1, 8.1 Hz, 1H, C$_{13}$-H), 4.24 (m, 2H, CH$_2$OH ), 4.43 (m, 1H, C$_{12}$-H), 5.23-5.42 (m, 3H), 5.80-6.86 (m, 5H), 7.42 (m, 2H, Bz-H), 7.54 (m, 1H, Bz-H), 8.03 (d, $J$ = 7.5 Hz, 2H, Bz-H) ppm. MS(EI) for C$_{29}$H$_{38}$O$_5$: m/z = 466 [M$^+$]+, MS(CI) m/z = 484 (M + NH$_4$)$_4$+. 

Ethyl 4,6-Dimethyl-8-tri-$n$-butylstannanylnona-2,4,6,8-tetraenoate (2.71): A solution of 2.37a (55 mg, 0.27 mmol) in THF (1.0 mL) was added to a solution of PdCl$_2$(PPh$_3$)$_2$ (9.5 mg, 14 µmol, 5 mol%) in THF (1.5 mL) and the resulting mixture was stirred for 10 min under argon. Subsequently, Bu$_3$SnH (0.29 mL, 1.1 mmol, 4.0 eq.) was added over 2 min and stirring was continued for an additional 15 min. The reaction mixture was concentrated and 2.71 was isolated as a colorless oil after purification by column chromatography (n-hexane-EtOAc 99:1 to 9:1). $^1$H-NMR (CDCl$_3$, 200 MHz) $\delta$ = 0.91 (m, 15H), 1.30 (m, 9H), 1.50 (m, 6H), 1.92 (s, 3H, C$_6$-CH$_3$), 1.99 (s, 3H, C$_4$-CH$_3$), 4.21 (q, $J$ = 7.0 Hz, 2H, CH$_3$CH$_2$O), 5.41 (dd, $J$ = 1.2, 3.2 Hz, 1H, C$_9$-H), 5.71 (dd, $J$ = 2.0, 3.2 Hz, 1H, C$_9$-H'), 5.84 (d, $J$ = 15.4 Hz, 1H, C$_2$-H), 6.24 (s, 1H, C$_7$-H), 6.32 (s, 1H, C$_5$-H), 7.37 (d, $J$ = 15.4 Hz, 1H, C$_3$-H) ppm. $^{13}$C-NMR (CDCl$_3$, 50.3 MHz) $\delta$ = 9.9 (t), 13.6 (q), 13.7 (q), 14.2 (q), 17.5 (q), 27.2 (t), 28.9 (t), 60.0 (t), 115.7 (d), 127.7 (t), 130.8 (s), 131.1 (s), 140.4 (d), 143.9 (d), 150.8 (d), 151.4 (s), 167.5 (s) ppm. MS(EI) for C$_{25}$H$_{44}$O$_2$Sn: m/z = 496 [M$^+$]+, HRMS calcd for C$_{25}$H$_{44}$O$_2$Sn: 496.236, found: 496.235.

Ethyl (2E,4E)-7-bromo-4,6-dimethylhepta-2,4,6-trienoate (2.72): BrCH$_2$PPh$_3$Br (479 mg, 1.10 mmol, 2.0 eq) was suspended in dry THF (2.7 mL) under argon and piperidine (108 µl, 1.10 mmol, 2.0 eq) and n-BuLi (1.6 M in n-hexane, 0.69 mL, 1.10 mmol, 2.0 eq) were added upon which the solution turned brown/red. After stirring for 15 min, 2.39c (100 mg, 0.55 mmol) in THF (2.2 mL) was added and the reaction mixture was stirred for 6 h. The reaction was quenched with aq. NH$_4$Cl (sat.), the aqueous layer was extracted with Et$_2$O (3x) and the combined organic layers were washed with brine (sat.), dried (Na$_2$SO$_4$) and concentrated. Purification by column chromatography (n-pentane-EtOAc 95:5) gave 2.72 (57 mg, 0.22 mmol, 40%) as a mixture of isomers. $^1$H-NMR (CDCl$_3$, 300 MHz) major isomer $\delta$ = 1.30 (t, $J$ = 7.0 Hz, 3H, CH$_3$CH$_2$O), 1.91 (s, 3H, C$_6$-CH$_3$), 1.94 (s, 3H, C$_4$-CH$_3$), 4.21 (q, $J$ = 7.2 Hz, 2H, CH$_2$CH$_2$O), 5.92 (d, $J$ = 15.6 Hz, 1H,
Total Synthesis of Mycolactones

C2-H), 6.17 (s, 1H, C5-H), 6.24 (s, 1H, C7-H), 7.31 (d, J = 15.3 Hz, 1H, C3-H) ppm.

Minor isomer δ = 1.31 (t, J = 7.0 Hz, 3H, CH3CH2O), 1.88 (s, 3H, C6-CH3), 1.96 (s, 3H, C4-CH3), 4.21 (q, J = 7.2 Hz, 2H, CH3CH2O), 5.95 (d, J = 15.6 Hz, 1H, C2-H), 6.14 (s, 1H, C5-H), 6.35 (s, 1H, C7-H), 7.39 (d, J = 15.9 Hz, 1H, C3-H) ppm.

Ethyl (2E,4E)-7-iodo-4,6-dimethylhepta-2,4,6-trienoate (2.73): Preparation as described for 2.72. 2.73 (70 mg, 0.23 mmol, 13%) was isolated as a single isomer from 2.39c (321 mg, 1.76 mmol) using 1.91 g of ICH2PPh3I (3.53 mmol, 2.0 eq).

1H-NMR (CDCl3, 400 MHz) δ = 1.30 (t, J = 7.2 Hz, 3H, CH3CH2O), 1.89 (s, 3H, C6-CH3), 1.99 (s, 3H, C4-CH3), 4.21 (q, J = 7.2 Hz, 2H, CH3CH2O), 5.93 (d, J = 16.0 Hz, 1H, C2-H), 6.21 (s, 1H, C5-H), 6.31 (s, 1H, C7-H), 7.30 (d, J = 16.0 Hz, 1H, C3-H) ppm.

(1S)-2-{(4S,5S)-2,2-dimethyl-5-[(1E)-2-methyl-4-trimethylsilyl-but-1-en-3-yn-1-yl]-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.74): Ethynyltrimethylsilane (99 μL, 0.70 mmol, 1.5 eq) was dissolved in iPrNH2 (1.7 mL) and Pd(PPh3)4 (10.7 mg, 9.3 μmol, 2 mol%) was added. The solution was stirred under argon at ambient temperature for 5 min, after which CuI (1.8 mg, 9.3 μmol, 2 mol%) was added. After 5 min, 2.38a (200 mg, 0.46 mmol) in iPrNH2 (1.4 mL) was added and the mixture was stirred for 1 h and then concentrated. The residue was dissolved in Et2O and washed with aq. NH4Cl (sat.). The aqueous layer was extracted with Et2O (3x) and the combined organic layers were washed with brine (sat.), dried (Na2SO4) and concentrated. The product (2.74, 180 mg, 0.45 mmol, 97%) was isolated as a colorless oil after purification by column chromatography (n-pentane-EtOAc 19:1).

1H-NMR (CDCl3, 200 MHz) δ = 0.16 (s, 9H, TMS), 1.38 (m, 9H, C9-H3, CMe2), 1.74-1.87 (m, 4H, C7-H, C3-CH3), 2.03 (ddd, J = 6.6, 8.6, 14.0 Hz, 1H, C7-H'), 3.82 (ddd, J = 3.4, 8.4, 8.4 Hz, 1H, C6-H), 4.34 (t, J = 8.6 Hz, 1H, C5-H), 5.32 (m, 1H, C8-H), 5.78 (dd, J = 1.6, 9.0 Hz, 1H, C4-H), 7.41-7.58 (m, 3H, Bz-H), 8.04 (m, 2H, Bz-H) ppm.

13C-NMR (CDCl3, 50.3 MHz) δ = 17.8 (q), 19.9 (q), 26.7 (q), 27.1 (q), 37.6 (t), 69.0 (d), 77.0 (d), 77.6 (d), 85.2 (s), 109.1 (s), 123.2 (s), 128.1 ppm.

(1S)-2-{(4S,5S)-2,2-dimethyl-5-[(1E)-2-methylbut-1-en-3-yn-1-yl]-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.75): 2.74 (180 mg, 0.45 mmol) was dissolved in dry THF (2.2 mL) and TBAF (1.0 M in THF, 0.90 mL, 0.90 mmol, 2.0 eq) was added at 0°C. The resulting solution was stirred under argon for 1 h and then quenched with aq. NH4Cl (sat.). The aqueous layer was extracted with Et2O (3x) and the combined organic layers were washed with brine (sat.), dried (Na2SO4) and concentrated. The product (2.75, 127 mg, 0.39 mmol, 86%) was isolated as a colorless oil after purification by column chromatography (n-pentane-EtOAc 97:3 to 95:5).

1H-NMR (CDCl3, 400 MHz) δ = 1.35, 1.39 (2s, 6H, CMe2), 1.40 (d, J = 6.4 Hz, 3H, C9-H3), 1.81 (ddd, J = 3.6, 6.4, 14.0 Hz, 1H, C7-H), 1.89 (d, J = 1.2 Hz, 3H, C3-CH3), 2.06 (ddd, J = 6.4, 8.4, 14.0 Hz, 1H, C7-H'), 2.86 (s, 1H, C1-H), 3.84 (ddd, J = 3.6, 8.4, 8.4 Hz, 1H, C6-H), 4.36 (t, J = 8.4 Hz, 1H, C5-H), 5.32 (m, 1H, C8-H), 5.81 (dd, J = 1.2, 9.2 Hz, 1H, C4-H), 7.40-7.57 (m, 3H, Bz-H), 8.03 (m, 2H, Bz-H) ppm. 13C-NMR (CDCl3, 50.3 MHz) δ = 17.8 (q), 19.9 (q), 26.7 (q), 27.1 (q), 37.6 (t), 69.0 (d), 77.0 (d), 77.6 (d), 85.2 (s), 109.1 (s), 123.2 (s), 128.1 ppm.
(d), 129.4 (d), 130.7 (s), 132.6 (d), 134.0 (d), 165.8 (s) ppm. MS (EI) for C_{20}H_{24}O_{4}: m/z = 328 [M⁺]. HRMS calc'd for C_{20}H_{24}O_{4}: 328.167, found: 328.167.

(1S)-2-{(4S,5S)-2,2-dimethyl-5-[(1E)-2-methylbuta-1,3-dien-1-yl]-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.76): 1H-NMR (CDCl₃, 400 MHz) δ = 1.39 (m, 9H, C₉-H₃, CMe₂), 1.81 (ddd, J = 4.0, 6.4, 14.0 Hz, 1H, C₇-H), 1.84 (s, 3H, C₃-C₃H₃), 2.08 (m, 1H, C₇-H'), 3.83 (ddd, J = 3.6, 8.4, 8.4 Hz, 1H, C₆-H), 4.47 (t, J = 8.8 Hz, 1H, C₅-H), 5.08 (d, J = 10.4 Hz, 1H, C₁-H), 5.23 (d, J = 17.6 Hz, 1H, C₁-H'), 5.30 (m, 1H, C₈-H), 5.38 (d, J = 8.8 Hz, 1H, C₄-H), 6.32 (dd, J = 10.8, 17.2 Hz, 1H, C₂-H), 7.43 (t, J = 7.6 Hz, 2H, Bz-H), 7.55 (t, J = 7.6 Hz, 1H, Bz-H), 8.03 (d, J = 7.6 Hz, 2H, Bz-H) ppm.

(1S)-2-{(4S,5S)-2,2-dimethyl-5-[(1E,3E)-2-methyl-4-tri-ter-butylstannanyl-buta-1,3-dien-1-yl]-1,3-dioxolan-4-yl}-1-methylethyl benzoate (2.77): CuCN (5.1 mg, 0.057 mol, 1.1 eq) was suspended in dry THF (0.27 mL) under argon and n-BuLi (1.6 M in n-hexane, 71 l, 0.114 mol, 2.2 eq) was added at -40 °C giving a colorless solution after 20 min. The solution was then warmed to -30 °C and Bu₃SnH (31 l, 0.114 mol, 2.2 eq) was added resulting in a yellow solution. 2.75 (17 mg, 0.052 mol) in THF (0.11 mL) was added to the cuprate and the mixture was stirred for 75 min. Even though TLC showed that conversion was not complete, the reaction was quenched with first MeOH and then aq. NH₄Cl (sat.) - aq. NH₃ (12.5%) 4:1 (v/v). The aqueous layer was extracted with Et₂O (3x) and the combined organic layers were dried (Na₂SO₄) and concentrated. Even though GC-MS showed only 1 product apart from starting material, 2.77 (5 mg, 0.0081 mol, 16%) was isolated in low yield after performing column chromatography twice (AIOx basic, n-pentane-EtOAc 39:1).

(2E)-3-Tri-ter-butylstannanyprop-2-en-1-ol (2.78c): 71 Bu₃SnH (6.00 ml, 0.223 mmol, 1.3 eq) and AIBN (0.28 g, 1.7 mmol, 10 mol%) were added to propargyl alcohol (1.00 mL, 0.171 mmol) and the resulting solution was heated under reflux (80 °C) for 2 h. The reaction mixture was cooled to room temperature and the product was then purified by column chromatography (n-hexane-Et₂O 95:5 to 4:1) to give a mixture of 2.78a and 2.78b (1.25 g, 3.60 mmol, 21.0%, less polar) and pure 2.78c (2.90 g, 8.35 mmol, 48.9%, more polar) as colorless liquids. 1H-NMR 2.78c (CDCl₃, 300 MHz) δ = 0.78-1.00 (m, 15H), 1.24-1.60 (m, 12H), 4.17 (brs, 2H, CH₂OH), 6.08-6.31 (m, 2H) ppm.

(E)-3-bromo-1-tri-ter-butylstannanylp propane (2.79): 22 2.78c (2.15 g, 6.19 mmol) was dissolved in acetonitrile (57 mL) and PPh₃ (3.25 g, 12.4 mmol, 2.0 eq), CBr₄ (2.47 g, 7.45 mmol, 1.15 eq) and 2,6-lutidine (144 µl, 1.23 mmol, 0.20 eq) were added. The resulting solution was stirred for 15 min under argon, after which...
TLC (n-hexane-Et$_2$O 4:1) showed the reaction to be complete. The reaction mixture was poured into aq. NaHCO$_3$ (sat., 70 mL) and extracted with n-hexane (3 x 70 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated. Purification by column chromatography (n-hexane-Et$_2$O 99:1) gave 2.79 (1.88 g, 4.59 mmol, 74.2%) as a colorless liquid. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 0.80-1.02 (m, 15H), 1.22-1.60 (m, 12H), 3.96 (d, $J = 6.6$ Hz, 2H, CH$_2$Br), 6.12 (dt, $J = 6.6$, 18.9 Hz, 1H, C2-H), 6.29 (m, 1H, C1-H) ppm.

(3-Tri-n-butylstannanyl-allyl)-phosphonic acid diethyl ester (2.80): To a solution of 2.79 (0.26 g, 0.63 mmol) in DMF (4.2 mL) were added NaH (50% in oil, 152 mg, 3.17 mmol, 5.0 eq) and a solution of diethyl phosphite (0.40 mL, 3.10 mmol, 4.9 eq) in DMF (4.2 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred under argon for 3 h, after which it was poured into water (50 mL). The aqueous layer was extracted with Et$_2$O (3 x 50 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated. 2.80 (172 mg, 0.37 mmol, 58%) was isolated as a colorless oil after purification by column chromatography (n-hexane-EtOAc 4:1 to 1:1). $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 0.88 (t, $J = 7.5$ Hz, 15H), 1.30 (m, 12H), 1.48 (m, 6H), 3.96 (dd, $J = 6.6$, 21.6 Hz, 2H, CH$_2$P), 4.09 (m, 4H, CH$_3$CH$_2$OP), 5.90 (m, 1H, C2-H), 6.15 (dd, $J = 4.5$, 18.6 Hz, 1H, C3-H) ppm.

(1S)-2-[(4S,5S)-5-[(1E,3E)-5-(diethoxyphosphoryl)-2-methyl-penta-1,3-dien-1-yl]-2,2-dimethyl-1,3-dioxolan-4-yl]-1-methylethyl benzoate (2.81): Pd(CH$_3$CN)$_2$Cl$_2$ (9.0 mg, 10 mol%) was added to a solution of 2.38a (150 mg, 0.35 mmol) in DMF (2.3 mL) and stirred for 2 min, after which 2.80 (179 mg, 0.38 mmol, 1.1 eq) in DMF (0.80 mL) was added. The resulting solution was stirred overnight under argon and then quenched with brine (sat.). The product was extracted with Et$_2$O (3x) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated. 2.81 (110 mg, 0.23 mmol, 65%) was isolated as a colorless oil after column chromatography (n-pentane-EtOAc 4:1 to 1:2). $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$ = 1.30 (t, $J = 7.2$ Hz, 6H, CH$_3$CH$_2$), 1.37 (m, 9H, C10-H, CMe$_2$), 1.75-1.85 (m, 1H, C8-H), 1.82 (s, 3H, C4-CH$_3$), 2.06 (m, 1H, C8-H'), 2.62 (dd, $J = 7.2$, 22.2 Hz, 2H, CH$_3$P), 3.80 (ddd, $J = 3.9$, 8.1, 8.1 Hz, 1H, C7-H), 4.08 (m, 4H, CH$_3$CH$_2$), 4.44 (t, $J = 8.7$ Hz, C6-H), 5.29 (m, 2H, C5-H, C9-H), 5.64 (m, 1H, C2-H), 6.12 (dd, $J = 4.8$, 15.6 Hz, 1H, C3-H), 7.42 (t, $J = 7.5$ Hz, 2H, Bz-H), 7.54 (t, $J = 7.5$ Hz, 1H, Bz-H), 8.01 (d, $J = 7.8$ Hz, 2H, Bz-H) ppm.

(1S)-2-[(4S,5S)-5-[(1E,3E)-2,6-dimethyl-hepta-1,3,5-trien-1-yl]-1-methylethyl benzoate (2.82): 2.81 (37 mg, 76 $\mu$mol) was dissolved in THF (0.42 mmol) and NaHMDS (1.0 M in THF, 80 $\mu$L, 80 $\mu$mol, 1.05 eq) was added at -78 °C upon which the solution turned orange/brown. The mixture was warmed to -40 °C over 45 min and then cooled again to -78 °C, after which 2.39c (9.3 mg, 51 $\mu$mol) in THF (0.21 mL) was added. The reaction was allowed to warm to 0 °C over
2 h, at which point HMPA (14 µl) was added. The mixture was stirred for another h while warming to room temperature and was then quenched with brine (sat.). The aqueous layer was extracted with Et₂O (3x) and the combined organic layers were dried (MgSO₄), filtered and concentrated. Column chromatography (n-pentane-EtOAc-Et₃N 90:10:2) afforded starting material 2.39c and 2.82, but none of the desired cross-coupled product. ¹H-NMR 2.82 (CDCl₃, 300 MHz) δ = 1.39 (m, 9H, C1-H$_3$, CMe$_2$), 1.75-1.85 (m, 1H, C3-H), 1.80 (s, 3H, CH$_3$), 1.81 (s, 3H, CH$_3$), 1.88 (s, 3H, CH$_3$), 2.08 (m, 1H, C3-H'), 3.81 (ddd, J = 4.2, 8.4, 8.4 Hz, 1H, C4-H), 4.47 (t, J = 8.7 Hz, C5-H), 5.30 (m, 2H, C2-H, C6-H), 5.85 (d, J = 10.8 Hz, 1H, C10-H), 6.07 (d, J = 15.3 Hz, 1H, C8-H), 6.44 (dd, J = 10.8, 15.3 Hz, 1H, C9-H), 7.42 (t, J = 7.5 Hz, 2H, Bz-H), 7.54 (t, J = 7.8 Hz, 1H, Bz-H), 8.01 (d, J = 7.5 Hz, 2H, Bz-H) ppm.

2.7 References


15 Stinear, T. P. *Report of the 8th annual WHO advisory group meeting on Buruli ulcer, 2005*, in press.


Total Synthesis of Mycolactones
