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New approaches towards the synthesis of the side-chain of mycolactones A and B

Ruben P. van Summeren, Ben L. Feringa* and Adriaan J. Minnaard*

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands. E-mail: B.L.Feringa@rug.nl, A.J.Minnaard@rug.nl; Fax: +31-503634296

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New approaches towards the synthesis of the C1′–C16′ side-chain of mycolactones A and B from *Mycobacterium ulcerans* are reported. Chiral building block **4** (Fig. 2) with the correct stereochemistry was obtained starting from naturally occurring monosaccharides, *i.e.* D-glucose or L-rhamnose. The polyunsaturated moiety **3** was synthesized in only 3 steps from 2,4-dimethylfuran. The building blocks were connected through a Sonogashira coupling resulting in the fast and convergent assembly of an 8,9-dehydro analogue **2** of the side-chain of mycolactones A and B. The synthesis of **1** is at this stage hampered by the lack of a selective partial hydrogenation protocol for alkynes embedded in a conjugated system. Alternative strategies involving palladium catalyzed sp^2–sp^2 coupling between C7′ and C8′ or C9′ and C10′ (Fig. 1) were also explored.

Introduction

Buruli Ulcer is a severe skin disease, caused by *Mycobacterium ulcerans*, occurring primarily in tropical countries. Infection by *M. ulcerans* results in the formation of large, painless necrotic ulcers in the absence of an acute inflammatory response.[1,2] Small and co-workers showed that the bacterium uses a heterogeneous mixture of polyketide toxins known as mycolactones A, B, C and D for tissue destruction and immune suppression.[3,4,5,6] In 2002, Kishi and co-workers reported the first total synthesis of mycolactones A and B (Fig. 1), confirming the relative and absolute stereochemistry.[7,8] Further research into the (biological) properties of mycolactones A and B and analogues thereof has been impeded by the difficulty of obtaining the compounds in sufficient quantities. A general and efficient synthetic route which would allow easy access to the target compound as well as analogues is therefore highly desirable. In our efforts to achieve this goal, we initially restricted our target to the unsaturated side-chain **1** (C1′–C16′; Fig. 1) of the molecule.

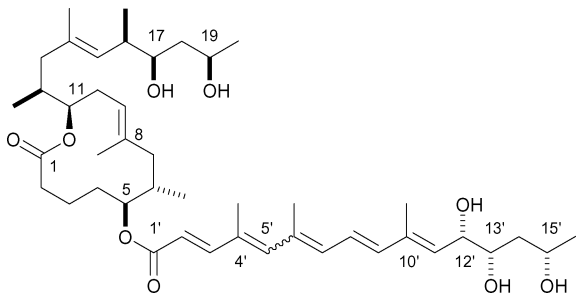

Fig. 1 Mycolactones A and B are related to each other through *cis–trans* isomerisation at the C4′–C5′ double bond.

Retrosynthesis

Until today, the synthesis of the C1′–C16′ fragment of mycolactones A and B has only been reported by Kishi *et al.* in 2002.[7] Prior to that, when the stereochemistry was still unknown, the synthesis of a C15′-epimer was published by Gurjar and Cherian.[9] Both syntheses are based on the coupling of a chiral moiety to a conjugated chain, which is assembled by a series of Horner–Wadsworth–Emmons chain-elongation reactions. Kishi's approach towards the chiral part (C8′–C16′) relied on a Sharpless asymmetric dihydroxylation reaction to introduce the stereogenic centers on C12′ and C13′ (α : β ratio of 3.8 : 1), while Gurjar and Cherian started from D-glucose. At first glance, the choice to use a chiral catalyst instead of a compound from the natural pool can be appreciated, as the naturally occurring sugars with the correct stereochemistry are rare and expensive L-sugars (D-sugars result in C15′-epimers). Nonetheless, we believe that using monosaccharides is preferable, because it provides absolute stereocontrol and the correct stereochemistry can be installed in a straightforward manner by epimerization of a single stereocenter. Moreover, sugars offer an easy method to make analogues due to the wide variety of monosaccharides available.

As outlined in the retrosynthetic analysis (Fig. 2), we planned to synthesize the C1′–C16′ side-chain of mycolactone A and B (**1**) by partial hydrogenation of an 8,9-dehydro analogue **2**. The assembly of **2** was envisioned by connection of conjugated unit **3** (C1′–C9′) to chiral moiety **4** (C10′–C16′) *via* Sonogashira coupling. For the synthesis of fragment **3** a new strategy was

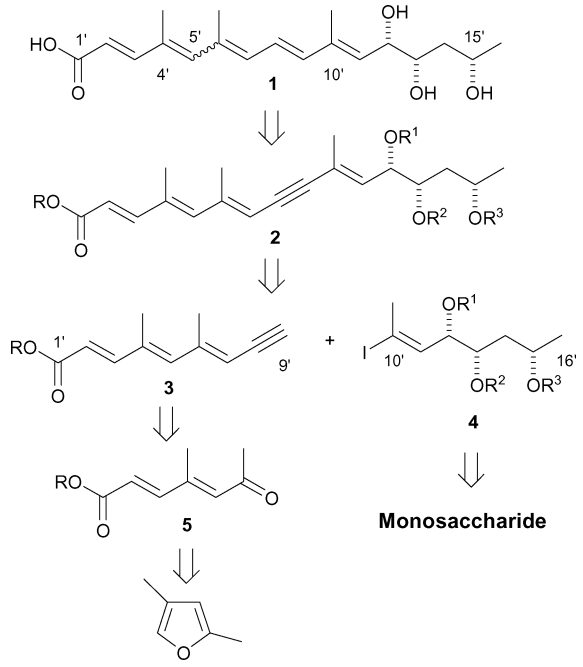

Fig. 2 Retrosynthetic analysis.

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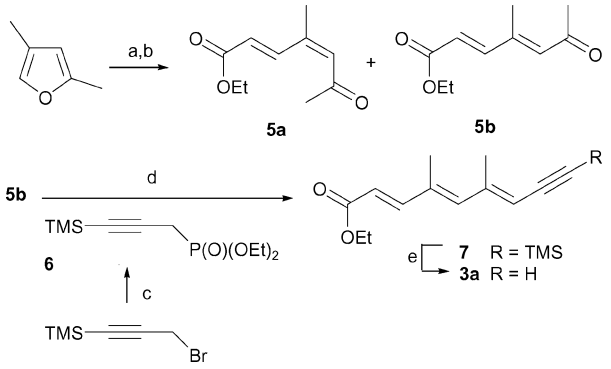
chosen, which significantly reduces the number of steps in the preparation of the conjugated system as compared to previous routes.[7,9] For the assembly of **4**, two routes starting from different monosaccharides were explored.

Results and discussion

Synthesis of the conjugated building block (3)

2,4-Dimethylfuran was synthesized according to the procedure of Morel and Verkade in two steps starting from mesityl oxide.[10] It was subsequently submitted to a rhodium-catalyzed reaction with ethyl diazoacetate to give a mixture of **5a** (18% isolated yield) and the desired **5b** (47% isolated yield), which were separated by column chromatography (Scheme 1).[11] Horner–Wadsworth–Emmons reaction of **5b** with diethyl (3-trimethylsilyl-2-propynyl) phosphonate (**6**),[12] gave **7** in 61% yield as a mixture of *cis–trans*-isomers which could not be separated at this stage.[13] The preparation of the conjugated building block was concluded by cleavage of the TMS-group with TBAF resulting in the unstable terminal alkyne **3a** (80%).



Scheme 1 Synthesis of conjugated system **3a**; (a) 0.4 mol% $Rh_2(OAc)_4$, CH_2Cl_2, EDA[a], 15 h; (b) I_2, CH_2Cl_2, 12 h (**5a** 18%, **5b** 47%); (c) NaHMDS, $HPO(OEt)_2$, THF, −10 °C, 1 h (78%); (d) *n*-BuLi, THF, 0 °C to rt, 3.5 h (61%); (e) TBAF, THF, EtOAc, 0 °C, 45 min (80%). [a] EDA = ethyl diazoacetate.

Synthesis of the chiral building block (4)

In order to obtain chiral building block **4** with the required stereochemistry, two routes were explored starting from either cheap and readily available methyl α-D-glucopyranoside or methyl α-L-rhamnopyranoside. In the case of D-glucose, the hydroxyl moieties at the 4- and 6-positions need to be reduced and the stereocenter at the 5-position needs to be epimerized. L-rhamnose requires reduction at the 4-position and epimerization at the 3-position (see Fig. 3).

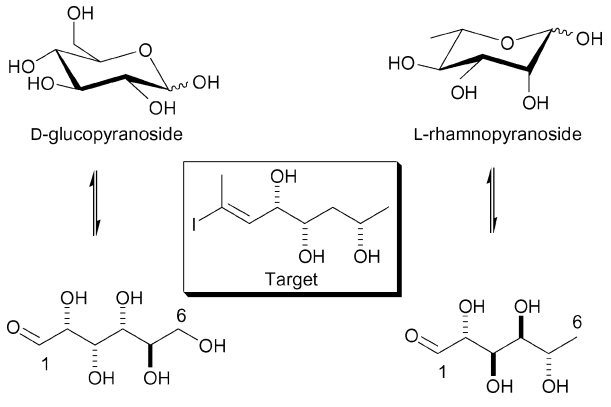
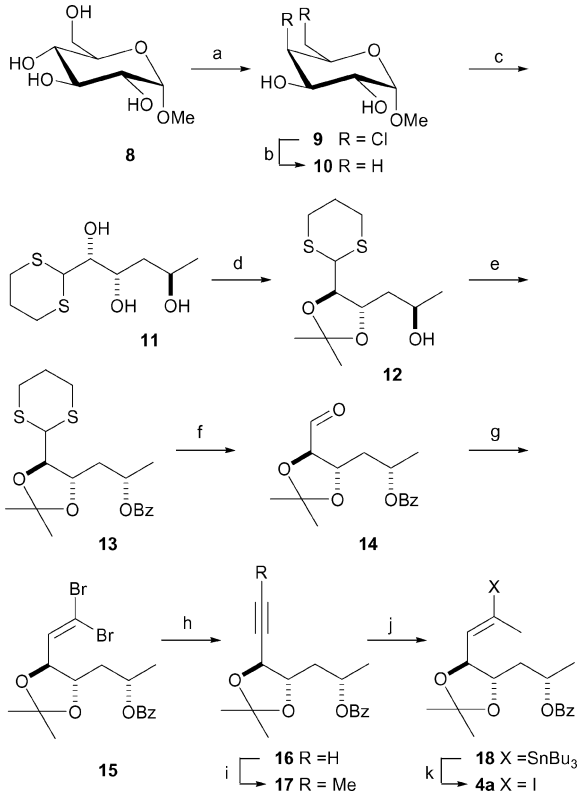


Fig. 3 Target chiral building block from D-glucopyranoside and L-rhamnopyranoside; in the case of glucose, C4–OH and C6–OH have to be reduced and C5–OH epimerized. In the case of rhamnose, C4–OH has to be reduced and C3–OH epimerized.

A building block with the correct stereochemistry (**13**) was synthesized in only six steps from D-glucose according to the procedure of Redlich *et al.* (Scheme 2).[14] First, the reduction of the 4- and 6-hydroxyl moieties was realized in two steps without protecting the 2- and 3-hydroxyl functions; methyl α-D-glucopyranoside (**8**) was reacted with sulfuryl chloride resulting in dichloro compound **9** (56%) with exclusively the galacto-configuration as described by Jones *et al.*[15] Subsequent radical reduction with tributyltin hydride and a catalytic amount of AIBN gave the reduced product **10** in 89% isolated yield. Ring-opening and protection of the aldehyde were achieved in one pot by stirring in 37% HCl in the presence of 1,3-propanedithiol leading to dithioacetal **11** (87%). The 2- and 3-hydroxyl functions were regioselectively protected as their acetonide by reaction with acetone under acidic conditions (**12**; 95%), after which the 5-hydroxyl group was epimerized in a Mitsunobu reaction with benzoic acid resulting in **13** (82%) and a dehydrated side product (16%).[14] Comparison of the ^{13}C-NMR spectra of **13** with its epimer obtained from the reaction of **12** with benzoyl chloride showed that there was only one diastereoisomer present.



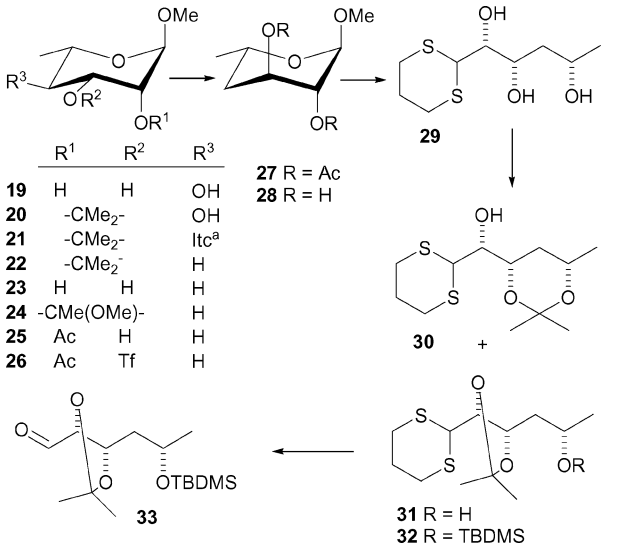
Scheme 2 Synthesis of **4a** from methyl α-D-glucopyranoside; (a) SO_2Cl_2, pyridine, $CHCl_3$, −78 to 50 °C, 7 h (56%); (b) Bu_3SnH, AIBN[a], toluene, reflux, 12 h (89%); (c) 1,3-propanedithiol, 37% HCl, 12 h (87%); (d) acetone, $CuSO_4$, H_2SO_4, 12 h (95%); (e) PPh_3, BzOH, DEAD[b], THF, 1.5 h (82%); (f) MeI, acetone, H_2O, 2,4,6-collidine, reflux, 12 h; (g) PPh_3, CBr_4, CH_2Cl_2, 0 °C to rt, 1.5 h (72%); (h) LDA[c], THF, −78 °C, 2 h (88%); (i) LDA[c], HMPA[d], MeI, THF, −78 to −10 °C, 2 h (88%); (j) $PdCl_2(PPh_3)_2$, Bu_3SnH, pentane (63%); (k) CH_2Cl_2, I_2, −78 °C to rt, 20 min (99%). [a] AIBN = 2,2′-azobis(2-methylpropionitrile), [b] DEAD = diethyl azodicarboxylate, [c] LDA = lithium diisopropylamide, [d] HMPA = hexamethylphosphoramide.

With the stereochemistry in place, the next objective was to elongate the chain of **13** 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[16] and low yields were obtained with NBS[17] in acetone and water. Eventually, treatment with MeI and 2,4,6-collidine in a refluxing mixture of acetone and water gave the aldehyde (**14**; no epimerization at C2 observed), which was used without further purification.[18] Reaction of **14** with CBr_4 and PPh_3 under Corey–Fuchs

conditions gave dibromo-olefin **15** in 72% yield over 2 steps.[19,20] Elimination of HBr by treatment with LDA followed by a protic work-up resulted in the terminal alkyne **16** (88%),[21] which was converted into the methylated alkyne **17** (88%) by reaction with LDA and MeI in the presence of HMPA.[22] The direct synthesis of **17** from **15** by treatment with MeI and *n*-BuLi or *t*-BuLi was unsuccessful, due to the intolerance of the benzoyl-group to these conditions.

Palladium-catalyzed hydrostannation of the internal alkyne was troublesome, due to palladium-black formation.[23] Increasing the catalyst-loading resulted in additional side-product formation. Fortunately, changing the solvent from THF to pentane prevented Pd-black formation improving the yield of **18** from 45% to 63%.[24] Moreover, the regioselectivity of the reaction was superior in pentane enhancing the ratio of terminal to internal hydrostannation product from 2.6 : 1 in THF to 6.3 : 1 in pentane (2D-^{1}H-NMR). The synthesis of the chiral moiety was completed by exchange of the tributyltin moiety with iodine to give **4a** (99%).[23]

An alternative synthesis from methyl α-L-rhamnopyranoside (**19**; Scheme 3) started with regioselective protection of the C2- and C3-hydroxyl moieties as their acetonide by reaction with acetone under acidic conditions leading to **20** (90%).[25] The remaining free C4–OH was then reacted with 1,1′-thiocarbonyldiimidazole to give the activated precursor **21** for a Barton–McCombie reduction in quantitative yield.[26] Radical reduction of **21** gave the deoxygenated product **22**.[21,27] Cleavage of the acetonide was first attempted with trifluoroacetic acid (55% over 2 steps), but the results with the milder amberlite H^+-resin proved to be superior giving the diol **23** in 71% over 2 steps.[28] Selective protection of the C2–OH was then achieved by reaction of **23** with trimethyl orthoacetate followed by partial hydrolysis of the resulting orthoester **24** leading to the formation of monoacetate **25** (80%).[26] It should be noted that the regioselectivity in the hydrolysis step strongly depended 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.



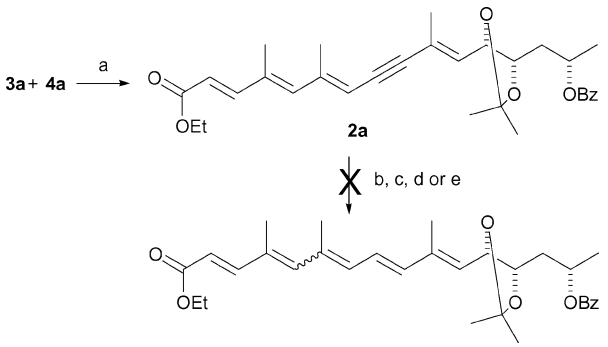
Scheme 3 Synthesis of **33** from methyl α-L-rhamnopyranoside; (**19** → **20**) acetone, $CuSO_4$, H_2SO_4, 12 h (90%); (**20** → **21**) 1,2-dichloroethane, 1,1′-thiocarbonyldiimidazole, reflux, 2 h (quant.); (**21** → **22**) toluene, AIBN[b], tris(trimethylsilyl)silane, reflux, 30 min; (**22** → **23**) water, 1,4-dioxane, amberlite(120)H^+, 12 h (71% from **21**); (**23** → **25**) (i) *p*-toluenesulfonic acid·H_2O, acetonitrile, trimethyl orthoacetate, 10 min, (ii) CH_2Cl_2, 90% CF_3COOH, 5 min (80%); (**25** → **26**) CH_2Cl_2, pyridine, Tf_2O, −10 °C to rt, 1.5 h; (**26** → **27**) toluene, Bu_4NOAc, 12 h (71% from **25**); (**27** → **28**) THF, MeOH, NaOMe (pH 9) 2 h; (**28** → **29**) 1,3-propanedithiol, 37% aq. HCl, 0 °C, 2 h (89% from **27**); (**29** → **30** + **31**) acetone, $CuSO_4$, H_2SO_4, 12 h (**30** in 8% and **31** in 78%); (**31** → **32**) DMF, TBDMSCl, imidazole, 70 °C, 12 h (84%); (**32** → **33**) MeI, acetone, H_2O, 2,4,6-collidine, reflux, 12 h (89%). [a] Itc = imidazolylthiocarbonyl, [b] AIBN = 2,2′-azobis(2-methylpropionitrile).

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 trifluoromethylsulfonate **26** followed by an S_N2 substitution with tetraethylammonium acetate gave no conversion at all. However, changing to tetrabutylammonium acetate showed a remarkable improvement leading to the formation of **27** in 71% yield.[29,30] Comparison of the ^{1}H- and ^{13}C-NMR spectra of **27** with the acetylated product of **23** 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 **27** in HCl (37% aq.) in the presence of 1,3-propanedithiol, but only 21% of **29** was isolated. The acetyl-groups were therefore first removed under mildly basic conditions (pH 9) giving **28**, after which ring opening proceeded very well providing **29** in 89% yield over two steps. Acetonide-protection of two hydroxyl moieties by an acid catalysed reaction with acetone gave the two regioisomers **30** (8%) and the desired **31** (78%), which could be separated by column chromatography.[14] After protection of the remaining C5–OH of **31** with TBDMSCl (84%, **32**),[31] the dithioacetal was deprotected as before to give aldehyde **33** in 89% yield. Unfortunately, the TBDMS–ether was not stable under Corey–Fuchs conditions giving a complex mixture of products. Obviously, the target molecule **4a** can be synthesized from **31** as described above for D-glucose when a benzoyl ester is chosen as a protecting group.

Overall, the route from D-glucose was preferred as it is more cost-effective and concise; less steps are required and the overall yield is higher.

Coupling of the building blocks and partial hydrogenation

Sonogashira coupling of terminal alkyne **3a** to vinyl iodine **4a** proceeded quantitatively resulting in the isolation of **2a** in an excellent 94% yield (Scheme 4). We anticipated that partial *cis*-hydrogenation of the internal alkyne of 8,9-dehydro analogue **2a** would lead to **1** after deprotection and isomerization to its all *trans* configuration.[13,32]



Scheme 4 Coupling of the building blocks and subsequent partial hydrogenation; (a) $Pd(PPh_3)_4$, CuI, iPr–NH_2, 2 h (94%); (b) H_2, Lindlar catalyst, hexanes, EtOAc, quinoline, 12 h; (c) Zn, $Cu(OAc)_2·H_2O$, $AgNO_3$, H_2O, MeOH, 12 h; (d) H_2, THF, Elsevier catalyst, 3 h; (e) $Ni(OAc)_2·4H_2O$, EtOH, hydrazine, $NaBH_4$, H_2; see text for details.

Disappointingly, to date, partial hydrogenation of the internal alkyne to the alkene has not shown sufficient selectivity to be useful on a preparative scale. Lindlar catalyst was typically unreactive regardless of the solvent, temperature, catalyst loading, and/or hydrogen pressure. Only at 65 bar of hydrogen some conversion was observed, but with a lack of selectivity leading to overreduction. The Zn(Cu/Ag)-reduction method in aqueous MeOH as developed by Boland *et al.*, is known to selectively hydrogenate triple bonds which are embedded in a conjugated system and has been successfully used on systems similar to **2a**.[33,34] However, 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 at this stage.

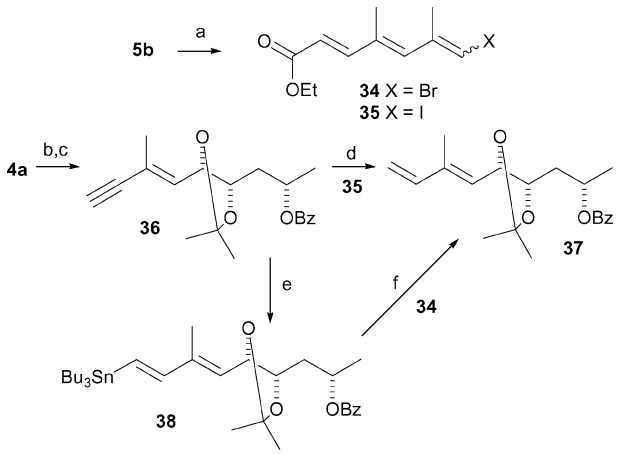
To the best of our knowledge, the partial reduction of alkynes in conjugation with an ester using Zn(Cu/Ag) is not known in literature.[35] Moreover, free hydroxyl moieties are known to occasionally aid the selectivity of Zn(Cu/Ag)-reductions. We therefore decided to attempt the partial reduction of the internal alkyne on the analogue of **2a** having a terminal alcohol instead of an ethyl ester. This approach did not lead to a significant improvement of selectivity. Removal of the isopropylidene-moiety of **2a** was not beneficial either. An effort was made with a homogeneous palladium catalyst developed by Elsevier for selective alkyne hydrogenation, but no conversion was seen in this case.[36] Ni-catalysed reduction with $NaBH_4$ on the other hand proved to be too active and gave only overreduced product.[37]

Alternative strategies

As an alternative approach, we tried to functionalize terminal alkyne **3a** to obtain an olefin suitable for palladium catalyzed sp^2–sp^2 coupling. In our hands, however, compound **3a** was unreactive towards stannylcupration (Bu_3SnH, CuCN, *n*-BuLi),[38] and hydrozirconation (Schwartz reagent),[39] while palladium catalyzed hydrostannation resulted exclusively in the undesired internal regioisomer.[40] Even though it is known that palladium catalyzed hydrostannation on terminal alkynes in direct conjugation with an ester predominately gives the α-addition product,[23,41] we were surprised to find that this also holds true when the ester and terminal alkyne are separated by three double bonds.

In a final attempt, the point of connection of the building blocks was changed from C9′–C10′ to C7′–C8′ (see Fig. 2). This new strategy implied that the conjugated building block needed to be one double bond shorter (*i.e.* **34** and **35**), while the chiral building block required elongation by two carbon atoms (*i.e.* **36**).

The first objective was met by reacting **5b** in a Wittig reaction with $BrCH_2PPh_3Br$ (**34**, 40% isolated yield) or its iodine analogue (**35**, 13% isolated yield; Scheme 5).[42] The second goal was realized by Sonogashira coupling of **4a** with trimethylsilylacetylene (97%),[32] giving the free alkyne **36** (86%) after deprotection with TBAF. Compound **36** was then used in a Negishi coupling to **35** resulting in the isolation of the terminal alkene **37** and the starting material **35** suggesting that at least the initial hydrozirconation was successful.[43] Hydrostannation of **36** using a stannylcuprate gave **38** in low yield (16%),[38a] but Stille coupling to **34** was unsuccessful once again.[44]



Scheme 5 Alternative coupling strategies; (a) *n*-BuLi, piperidine, XCH_2PPh_3X, THF, 8 h (40% for **34** and 13% for **35**); (b) $Pd(PPh_3)_4$, CuI, i-$PrNH_2$, TMS–acetylene 1 h (97%); (c) TBAF, THF, 0 °C, 1 h (86%); (d) (i) **36**, THF, $ZrHClCp_2$, 5 h; (ii) $PdCl_2(PPh_3)_2$, DIBAL-H, **35**, 15 min; (iii) solution of **35** added to solution of **36**, $ZnCl_2$, 12 h; (e) CuCN, *n*-BuLi, Bu_3SnH, THF, −30 °C (16%); (f) $Pd(PhCN)_2Cl_2$, DMF, THF, $(i\text{-}Pr)_2NEt$.

Conclusions

From the above results it is concluded that the application of monosaccharides is a viable alternative to asymmetric catalysis for the synthesis of the chiral part of the side-chain of mycolactones A and B and analogues thereof. Furthermore, it has been demonstrated that an efficient route is available to rapidly assemble a conjugated building block **3a** from 2,4-dimethylfuran. The Pd-catalyzed coupling of the conjugated **3a** and the chiral building block **4a** constitutes a concise and efficient synthesis of an 8,9-dehydro analogue **2a** of the side-chain of mycolactones A and B. Although Zn(Cu/Ag)-reduction of **2a** seems to give small quantities of the desired product, the lack of selectivity in this reaction still obstructs the synthesis of **1** on a synthetically useful scale at this stage.

Experimental

General experimental 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. Chromatography: silica gel, Merck type 9385 230–400 mesh, TLC: silica gel 60, Merck, 0.25 mm. Components were visualized by staining with (a) $KMnO_4$ or (b) a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H_2O (500 mL) and H_2SO_4 (25 mL). Optical rotations were measured on a Perkin-Elmer 241 or 241 MC polarimeter. Mass spectra (HRMS) were recorded on an AEI MS-902. ^1H 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 δ values (ppm) relative to residual solvent peaks ($CHCl_3$, ^1H $\delta = 7.26$, ^{13}C $\delta = 76.9$). Carbon types were determined from APT ^{13}C experiments.

4-Methyl-6-oxo-hepta-2,4-dienoic acid ethyl ester (5a and 5b)

$Rh_2(OAc)_4$ (10 mg, 23 μmol) and 2,4-dimethylfuran (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 $Na_2S_2O_3$ (10% aq.) and brine, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (hexane–EtOAc 9 : 1) to give **5a** (0.17 g, 0.93 mmol, 18%) and the all-*trans*-isomer **5b** (0.44 g, 2.4 mmol, 47%). The latter was a yellow liquid which became crystalline upon standing at 4 °C. When **5a** was treated with I_2 in dichloromethane, a mixture of **5a** and **5b** in the same ratio as before was formed. ^{1}H-NMR **5a** ($CDCl_3$, 300 MHz) $\delta = 1.30$ (t, 3H, CH_3CH_2O, $J = 7.2$ Hz), 2.01 (s, 3H, CH_3), 2.25 (s, 3H, C7-H), 4.23 (q, 2H, CH_3CH_2O, $J = 7.2$ Hz), 6.17 (d, 1H, C2-H, $J = 15.9$ Hz), 6.27 (s, 1H, C5-H), 8.39 (d, 1H, C3-H, $J = 16.2$ Hz) ppm.

^{1}H-NMR **5b** ($CDCl_3$, 300 MHz) $\delta = 1.30$ (t, 3H, CH_3CH_2O, $J = 7.2$ Hz), 2.22 (s, 3H, CH_3), 2.26 (s, 3H, C7-H), 4.23 (q, 2H, CH_3CH_2O, $J = 7.2$ Hz), 6.24 (d, 1H, C2-H, $J = 15.6$ Hz), 6.36 (s, 1H, C5-H), 7.24 (d, 1H, C3-H, $J = 15.6$ Hz) ppm. ^{13}C-NMR **5b** ($CDCl_3$, 50.3 MHz) $\delta = 13.6$ (q), 14.1 (q), 32.0 (q), 60.7 (t),

124.2 (d), 131.8 (d), 146.7 (s), 147.3 (d), 166.2 (s), 198.9 (s) ppm. MS(EI) for $C_{10}H_{14}O_3$: $m/z = 182$ [M$^+$], HRMS calcd for $C_{10}H_{14}O_3$: 182.094, found: 182.095.

(3-Trimethylsilanyl-prop-2-ynyl)-phosphonic acid diethyl ester (6)

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 was quenched with water and the aqueous layer was extracted with EtOAc (× 2). The combined organic layers were washed with HCl (2 M) and water, dried (Na_2SO_4) and concentrated. The product was purified by column chromatography (pentane–EtOAc 4 : 1 to 1 : 1) giving **6** (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_3CH_2O, $J =$ 7.2 Hz), 2.80 (d, 2H, CH_2, $J = 22.2$ Hz), 4.18 (q, 4H, CH_3CH_2O) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = -0.3$ (q), 16.2 (q), 16.3 (q), 17.8 (t), 20.6 (t), 62.9 (t), 63.0 (t) ppm.

4,6-Dimethyl-9-trimethylsilanyl-nona-2,4,6-trien-8-ynoic acid ethyl ester (7)

6 (1.0 g, 4.0 mmol, 2.0 eq) was dissolved in THF (20 mL) and *n*-BuLi (1.6 M in hexane, 2.5 mL, 4.0 mmol) was added at 0 °C under argon. After stirring for 30 min of which the last 10 were at rt, the solution had turned dark red. At this point, a solution of **5b** (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 NH_4Cl (sat). The aqueous layer was extracted with Et_2O (× 3) and the combined organic layers were washed with brine (sat.), dried (Na_2SO_4) and concentrated. **7** (336 mg, 1.22 mmol, 61%, mixture of **2** *cis–trans* isomers with a ratio of approximately 4 : 1) was isolated as a yellow solid after column chromatography (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, 3H, CH_3CH_2O, $J = 7.0$ Hz), 2.00 (s, 3H, C6-CH_3), 2.14 (s, 3H, C4-CH_3), 4.21 (q, 2H, CH_3CH_2O), 5.59 (s, 1H, C7-H), 5.91 (d, 1H, C2-H, $J = 15.5$ Hz), 6.28 (s, 1H, C5-H), 7.32 (d, 1H, C3-H, $J = 15.5$ Hz) 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, CH_3CH_2O), 1.95 (s, 3H, C6-CH_3), 2.04 (s, 3H, C4-CH_3), 4.21 (q, 2H, CH_3CH_2O), 5.53 (s, 1H, C7-H), 5.94 (d, 1H, C2-H, $J = 14.5$ Hz), 6.68 (s, 1H, C5-H), 7.39 (d, 1H, C3-H, $J = 15.5$ Hz) ppm. MS(EI) for $C_{16}H_{24}O_2Si$: $m/z = 276$ [M$^+$], HRMS calcd for $C_{16}H_{24}O_2Si$: 276.155, found: 276.155.

4,6-Dimethyl-nona-2,4,6-trien-8-ynoic acid ethyl ester (3a)

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 µl, 0.48 mmol). The solution was cooled to 0 °C and **7** (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 NH_4Cl (sat.), dried (Na_2SO_4) and concentrated. **3a** (59 mg, 0.29 mmol, 80%) was isolated after column chromatography (pentane–EtOAc 95 : 5) as a colorless oil, which turned brown within 15 min. The product was therefore immediately used in the next step. ^{1}H-NMR *major isomer* ($CDCl_3$, 200 MHz) $\delta = 1.29$ (t, 3H, CH_3CH_2O, $J =$ 7.0 Hz), 1.99 (d, 3H, C6-CH_3, $J = 0.8$ Hz), 2.13 (s, 3H, C4-CH_3), 3.38 (d, 1H, C9-H, $J = 2.4$ Hz), 4.21 (q, 2H, CH_3CH_2O), 5.54 (s, 1H, C7-H), 5.91 (d, 1H, C2-H, $J = 15.6$ Hz), 6.28 (s, 1H, C5-H), 7.31 (d, 1H, C3-H, $J = 15.6$ Hz) ppm.

^{1}H-NMR *minor isomer* ($CDCl_3$, 200 MHz) $\delta = 1.30$ (t, 3H, CH_3CH_2O, $J = 7.0$ Hz), 1.95 (d, 3H, C6-CH_3, $J = 1.0$ Hz), 2.04 (s, 3H, C4-CH_3), 3.22 (d, 1H, C9-H, $J = 2.4$ Hz), 4.21 (q, 2H, CH_3CH_2O), 5.49 (s, 1H, C7-H), 5.94 (d, 1H, C2-H, $J =$ 15.6 Hz), 6.71 (s, 1H, C5-H), 7.39 (d, 1H, C3-H, $J = 16.0$ Hz) ppm. MS(EI) for $C_{13}H_{16}O_2$: $m/z = 204$ [M$^+$], HRMS calcd for $C_{13}H_{16}O_2$: 204.115, found: 204.116.

Methyl 4,6-dideoxy-4,6-dichloro-α-D-galactopyranoside (9)

Methyl α-D-glucopyranoside (**8**) (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, 8 eq.) was added dropwise at −78 °C under argon. The resulting yellow solution was stirred for 2 h while slowly warming to rt. Subsequently, the solution was heated to 50 °C and stirred for another 5 h. After cooling to rt, the solution was diluted with MeOH and water, neutralized with $Na_2CO_3 \cdot 10H_2O$ 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%). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 2.20$ (br s, 2H, C2-OH, C3-OH), 3.48 (s, 3H, C1-OCH_3), 3.68 (d, 2H, C6-H, $J = 6.6$ Hz), 3.85 (dd, 1H, C2-H, $J = 3.6$, 9.6 Hz), 3.99 (dd, 1H, C3-H, $J = 3.6$, 9.6 Hz), 4.14 (t, 1H, C5-H, $J = 6.6$ Hz), 4.53 (d, 1H, C4-H, $J = 3.3$ Hz), 4.86 (d, 1H, C1-H, $J = 3.6$ Hz) ppm. ^{13}C-NMR (DMSO, 50.3 MHz) $\delta = 44.4$ (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 (10)

Bu_3SnH (30 mL, 32 g, 0.11 mol) was added dropwise to a solution of **9** (5.3 g, 23 mmol) in refluxing dry toluene (180 mL) under argon and AIBN (catalytic) was added. The resulting solution was refluxed overnight and then cooled to rt and concentrated *in vacuo*. The obtained oil was diluted with CH_3CN and washed with hexanes (× 2). Concentration gave a solid which was dissolved in water and washed with Et_2O (× 3). Concentration of the aqueous layer gave a white solid which was further purified by column chromatography (dichloromethane–MeOH 19 : 1 to 9 : 1) to give pure **10** (3.3 g, 20 mmol, 89%). When the reaction was performed on larger scale, purification was done by crystallization from chloroform and pentane. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.21$ (d, 3H, C6-H, $J = 6.3$ Hz), 1.36 (q, 1H, C4-H), 1.98 (ddd, 1H, C4-H′, $J = 2.4$, 5.1, 12.9 Hz), 2.05 (d, 1H, OH, $J = 10.2$ Hz), 2.46 (d, 1H, OH, $J = 2.1$), 3.33–3.44 (m, 1H, C2-H), 3.41 (s, 3H, C1-OCH_3), 3.77–3.95 (m, 2H, C3-H, C5-H), 4.75 (d, 1H, C1-H, $J = 3.6$ Hz) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 20.7$ (q), 39.6 (t), 55.1 (q), 64.0 (d), 68.9 (d), 74.3 (d), 99.7 (d) ppm.

4,6-Dideoxy-D-xylo-hexose-trimethylen-dithioacetal (11)

1,3-Propanedithiol (6.8 mL, 7.1 g, 65 mmol) was added to a solution of **10** (6.0 g, 37 mmol) in 37% HCl (68 mL) and stirred overnight. The solution was then neutralized with 25% 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 9 : 1) gave **11** (7.7 g, 32 mmol, 87%) as a white solid. Alternatively, **11** could be purified by crystallization from dichloromethane–MeOH. $[\alpha]_D$ −30.3 (*c* 1.09 in MeOH), (lit.,[9] $[\alpha]_D^{20}$ −29.5 (*c* 1.00 in MeOH)). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.27$ (d, 3H, C6-H, $J = 6.3$ Hz), 1.60 (ddd, 1H, C4-H), 1.89 (ddd, 1H, C4-H′), 2.03 (m, 2H, dithian-H), 2.70 (m, 2H, dithian-H), 2.92 (m, 2H, dithian-H), 3.74 (d, 1H, C2-H, $J = 8.1$ Hz), 4.03 (d, 1H, C3-H, $J = 8.1$ Hz), 4.17 (m, 1H, C5-H), 4.31 (d, 1H, C1-H, $J = 9.6$) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 23.6$ (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(EI)

for $C_9H_{18}O_3S_2$: m/z = 238 [M^+], HRMS calcd for $C_9H_{18}O_3S_2$: 238.070, found: 238.069.

4,6-Dideoxy-2,3-*O*-isopropyliden-D-xylo-hexose-trimethylen-dithioacetal (12)

11 (2.2 g, 9.2 mmol) was dissolved in dry acetone and $CuSO_4$ (2.9 g, 18.5 mmol, 2 eq) and a drop of H_2SO_4 were added. The resulting green suspension was stirred overnight and then filtered. The filtrate was neutralized with 25% ammonia and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine and extracted with dichloromethane (× 3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (hexane–EtOAc 4 : 1) gave **12** (2.4 g, 8.7 mmol, 95%) as a colorless oil. $[\alpha]_D$ −55.0 (*c* 1.04 in MeOH), (lit.,[9] $[\alpha]_D^{20}$ −64.8 (*c* 1.17 in MeOH)). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.24 (d, 3H, C6-H, J = 6 Hz), 1.44 (m, 6H, CMe_2), 1.71–2.17 (m, 4H, C4-H, H′, dithian-H), 2.31 (br s, 1H, OH), 2.77–2.96 (m, 4H, dithian-H), 3.95 (dd, 1H, C2-H, J = 5.7, 7.8 Hz), 4.08 (m, 1H, C5-H), 4.13 (d, 1H, C1-H, J = 5.4 Hz), 4.34 (ddd, 1H, C3-H, J = 3.3, 7.8, 7.8 Hz) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ = 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 $C_{12}H_{22}O_3S_2$: m/z = 278 [M^+], HRMS calcd for $C_{12}H_{22}O_3S_2$: 278.101, found: 278.101.

5-*O*-benzoyl-4,6-dideoxy-2,3-*O*-isopropyliden-L-arabino-hexose-trimethylen-dithioacetal (13)

Triphenylphosphine (13 g, 50 mmol) and benzoic acid (5.8 g, 48 mmol) were added to a solution of **12** (6.2 g, 22 mmol) in dry THF (115 mL) at rt. 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_2O (× 3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. **13** (7.0 g, 18 mmol, 82%) was obtained as a yellow oil after purification by column chromatography (hexane–EtOAc 9 : 1 to 4 : 1). The remaining 18% was isolated as the dehydrated side product. ^{1}H-NMR **13** ($CDCl_3$, 200 MHz) δ = 1.39–1.44 (m, 9H, C6-H, CMe_2), 1.82–2.20 (m, 4H, C4-H, H′, dithian-H), 2.67–2.97 (m, 4H, dithian-H), 3.96 (dd, 1H, C2-H, J = 5.2, 7.6), 4.12 (d, 1H, C1-H, J = 5.2 Hz), 4.26 (ddd, 1H, C3-H, J = 4.4, 7.6, 7.6 Hz), 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) δ = 19.8 (q), 25.6 (t), 26.7 (q), 27.3 (q), 29.1 (t), 29.5 (t), 39.5 (t), 48.2 (d), 69.0 (d), 75.5 (d), 82.6 (d), 109.6 (s), 128.1 (d), 129.5 (d), 130.6 (s), 132.6 (d), 165.9 (s) ppm. MS(EI) for $C_{19}H_{26}O_4S_2$: m/z = 282 [M^+], HRMS calcd for $C_{19}H_{26}O_4S_2$: 282.127, found: 282.126.

The C5-epimer of **13** was synthesized by reaction of **12** with benzoyl chloride in pyridine. ^{1}H-NMR C5-epimer of **13** ($CDCl_3$, 300 MHz) δ = 1.39–1.43 (m, 9H, C6-H, CMe_2), 1.82–2.25 (m, 4H, C4-H, H′, dithian-H), 2.74–2.98 (m, 4H, dithian-H), 3.93 (dd, 1H, C2-H, J = 5.7, 7.5), 4.11 (d, 1H, C1-H, J = 5.4 Hz), 4.24 (ddd, 1H, C3-H, J = 2.1, 8.3, 8.3 Hz), 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) δ = 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.

6-*O*-benzoyl-1,1-dibromo-5,7-dideoxy-3,4-*O*-isopropyliden-L-arabino-hept-1-ene (15)

13 (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 rt and the acetone was removed *in vacuo*. The remaining solution was diluted with dichloromethane, washed with 2 M HCl (× 3), $NaHCO_3$ (sat.) and brine, dried over $MgSO_4$ and concentrated. The crude **14** was used without purification in the next step after overnight drying *in vacuo* over P_2O_5. Triphenylphosphine (18.6 g, 71.1 mmol, 4eq) was dissolved in freshly distilled dry dichloromethane (47 mL) and CBr_4 (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 rt and was stirred until TLC showed the reaction to be complete (approximately 1 h, hexane–EtOAc 4 : 1 to see the product and dichloromethane–MeOH 98 : 2 to see the aldehyde). The reaction was quenched with sat. $NaHCO_3$, the aqueous layer was extracted with dichloromethane (× 2), the combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The resulting brown solid was first filtered over silica ($CHCl_3$) and then further purified by column chromatography (hexane–EtOAc 9 : 1) to give **15** (5.7 g, 13 mmol, 72%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ = 1.36 (m, 6H, CMe_2), 1.42 (d, 3H, C7-H, J = 6.3 Hz), 1.94 (ddd, 1H, C5-H, J = 4.2, 6.2, 14.2 Hz), 2.14 (ddd, 1H, C5-H′, J = 14.2 Hz), 3.92 (ddd, 1H, C4-H, J = 4.2, 8.0, 8.0 Hz), 4.34 (dd, 1H, C3-H, J = 8.0, 8.0 Hz), 5.34 (m, 1H, C6-H), 6.42 (d, 1H, C2-H, J = 8.6 Hz), 7.39–7.60 (m, 3H, Bz-H), 8.02–8.07 (m, 2H, Bz-H) ppm. ^{13}C-NMR ($CDCl_3$, 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 $C_{17}H_{20}O_4Br_2$: m/z = 466 $(M + NH_4)^+$.

Benzoic acid 2-(2,2-dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-1-methyl-ethyl ester (17)

To a solution of **15** (3.0 g, 6.7 mmol) in dry THF (77 mL), was added LDA (0.43 M in THF–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 Et_2O (× 2), dried ($MgSO_4$), filtered and concentrated. The product was purified by column chromatography (hexane–EtOAc 9 : 1) to give the free alkyne (**16**, 1.7 g, 5.9 mmol, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ = 1.38–1.45 (m, 9H, C7-H, CMe_2, J = 6.2 Hz), 1.97 (ddd, 1H, C5-H), 2.16 (ddd, 1H, C5-H′), 2.48 (d, 1H, C1-H, J = 1.8 Hz), 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. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ = 20.0 (q), 26.0 (q), 26.9 (q), 38.0 (t), 68.7 (d), 70.1 (d), 74.9 (s), 78.4 (d), 110.1 (s), 128.2 (d), 129.4 (d), 130.5 (s), 132.7 (d), 165.8 (s) ppm. MS(CI) for $C_{17}H_{20}O_4$: m/z = 306 $(M + NH_4)^+$, HRMS calcd for $C_{17}H_{20}O_4$–CH_3: 273.113, found: 273.114.

16 (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–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 5 more min, MeI (0.28 mL, 0.63 g, 4.4 mmol, 3.0 eq) was added. The resulting solution was warmed to −10 °C over 2 h, after which GC-MS showed the reaction to be complete. The reaction was quenched with 1 M HCl, extracted with Et_2O (× 2), dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (pentane–EtOAc 95 : 5 to 9 : 1) gave **17** (392 mg, 1.30 mmol, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 1.36–1.44 (m, 9H, C8-H, CMe_2), 1.75 (s, 3H, C1-H), 1.93 (ddd, 1H, C6-H), 2.16 (ddd, 1H, C6-H′), 4.11 (ddd, 1H, C5-H), 4.24 (d, 1H, C4-H, J = 8.1 Hz), 5.35 (m, 1H, C7-H), 7.41–7.57 (m, 3H, Bz-H), 8.04–8.06 (d, 2H, Bz-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) δ = 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 $C_{18}H_{22}O_4$: $m/z = 320$ $(M + NH_4)^+$, HRMS calcd for $C_{18}H_{22}O_4$–CH_3: 287.128, found: 287.129.

Benzoic acid 2-(2,2-dimethyl-5-(2-tributylstannanyl-propenyl)-[1,3]dioxolan-4-yl)-1-methyl-ethyl ester (18)

17 (230 mg, 761 μmol) was added to a suspension of $PdCl_2(PPh_3)_2$ (27 mg, 38 μmol, 5 mol%) in pentane (6.9 mL) under argon and after stirring for 10 min, Bu_3SnH (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 **18** (282 mg, 475 μmol, 63%) and the internal hydrostannylation side product (45 mg, 76 μmol, 10%) both as colorless liquids. ^{1}H-NMR ($CDCl_3$, 500 MHz) $\delta = 0.70$–1.03 (m, 15H, Bu-Sn), 1.19–1.60 (m, 21H, C8-H, CMe_2, Bu-Sn), 1.77 (ddd, 1H, C6-H), 1.96 (d, 3H, C1-H, $J = 1.6$ Hz), 2.06 (ddd, 1H, C6-H′), 3.75 (ddd, 1H, C5-H), 4.54 (m, 1H, C4-H), 5.31 (m, 1H, C7-H), 5.47 (dd, 1H, C3-H, $J = 1.9$, 8.6 Hz), 7.41–7.56 (m, 3H, Bz-H), 8.02–8.06 (m, 2H, Bz-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 9.0$ (t), 13.6 (q), 19.9 (q), 27.0 (q), 27.2 (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(EI) for $C_{30}H_{50}O_4Sn$: $m/z = 593$ $[M^+]$.

Benzoic acid 2-[5-(2-iodo-propenyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-1-methyl-ethyl ester (4a)

18 (200 mg, 0.34 mmol) was dissolved in dichloromethane (2.7 mL) and I_2 (114 mg, 0.45 mmol, 1.3 eq) in dichloromethane (0.7 mL) was added at −78 °C under argon. The resulting solution was stirred for 10 min at −78 °C and then warmed to rt. The solution was concentrated and **4a** (144 mg, 0.33 mmol, 99%) was isolated as a yellow oil after column chromatography (hexane–EtOAc 39 : 1; 2.5 volume-% Et_3N was used during the preparation of the column). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta =$ 1.35–1.42 (m, 9H, C8-H, CMe_2), 1.84 (ddd, 1H, C6-H), 2.06 (ddd, 1H, C6-H′), 2.49 (s, 3H, C1-H), 3.84 (ddd, 1H, C5-H), 4.29 (m, 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), 132.6 (d), 137.0 (d), 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-(2,3-*O*-isopropylidene-α-L-rhamnopyranoside) (20)

19 (21.5 g, 110 mmol) was dissolved in dry acetone and $CuSO_4$ (34 g, 220 mmol, 2 eq) and H_2SO_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% ammonia and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine and extracted with dichloromethane (× 3). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (hexane–EtOAc 9 : 1 to 4 : 1) gave **20** as an oil (23.3 g, 98.6 mmol, 90%). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.31$ (d, 3H, C6-H, $J = 6.3$ Hz), 1.35, 1.53 (2s, 6H, CMe_2), 2.16 (d, 1H, OH), 3.39 (s, 3H, OMe), 3.39 (m, 1H, C4-H), 3.65 (m, 1H, C5-H), 4.07 (t, 1H, C3-H, $J = 6.6$ Hz), 4.13 (d, 1H, C2-H, $J = 6.0$ Hz), 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(CI) 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 (21)

A solution of **20** (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 rt, the solvent was removed and the product was purified by crystallization from ether–hexane and/or by column chromatography (hexane–EtOAc 4 : 1 to 1 : 1) giving a white solid (19.0 g, 54.8 mmol, 99.7%). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.28$ (d, 3H, C6-H, $J = 6.3$ Hz), 1.36, 1.61 (2s, 6H, CMe_2), 3.43 (s, 3H, OMe), 3.95 (dq, 1H, C5-H, $J_{5,6} = 6.3$ Hz), 4.22 (d, 1H, C2-H, $J = 5.4$ Hz), 4.37 (dd, 1H, C3-H), 4.95 (s, 1H, C1-H), 5.74 (dd, 1H, C4-H, $J = 7.8$, 9.9 Hz), 7.07, 7.65, 8.40 (3s, 3H, imidazole) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 17.0$ (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 $C_{14}H_{20}N_2O_5S$: $m/z = 329$ $(M + H)^+$.

Methyl-4,6-dideoxy-2,3-*O*-isopropylidene-α-L-lyxo-hexapyranoside (22)

21 (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 rt, $NaHCO_3$ (20% aq. solution) was added and the product was extracted with EtOAc (× 3). The combined organic layers were dried ($MgSO_4$) and concentrated below 30 °C using MeOH to remove the toluene. **22** was isolated as a yellow oil after column chromatography (hexane–EtOAc 98 : 2 to 95 : 5). Due to volatility of the product, the yield was determined in the next step. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.22$ (d, 3H, C6-H, $J =$ 6.3 Hz), 1.34, 1.52 (2s, 6H, CMe_2), 1.47 (m, 1H, C4-H), 1.86 (m, 1H, C4-H′), 3.38 (s, 3H, OMe), 3.77 (m, 1H, C5-H), 3.92 (d, 1H, C2-H, $J = 5.4$ Hz), 4.30 (m, 1H, C3-H), 4.91 (s, 1H, C1-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 21.1$ (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 (23)

Amberlite-120-(Na^+)-resin was stirred in 2 M HCl-solution for 1.5 h and then filtered off and flushed with 2 M HCl-solution twice. 4.0 g of the thus obtained resin was added to a solution of **22** (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 1 M NaOH (aq) and then concentrated. After column chromatography ($CHCl_3$–EtOH 9 : 1), **23** (703 mg, 4.33 mmol, 71% from **21**) was isolated as a white foam. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.23$ (d, 3H, C6-H, $J = 6.0$ Hz), 1.47 (m, 1H, C4-H), 1.74–1.87 (m, 3H, C4-H′, 2-OH), 3.37 (s, 3H, OMe), 3.72 (s, 1H, C2-H), 3.84 (m, 1H, C3-H), 3.96 (m, 1H, C5-H), 4.73 (s, 1H, C1-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 21.0$ (q), 36.3 (t), 54.8 (q), 63.7 (d), 65.6 (d), 68.6 (d), 101.2 (d) ppm. MS(CI) for $C_7H_{14}O_4$: $m/z = 180$ $(M + NH_4)^+$.

Methyl-2-*O*-acetyl-4,6-dideoxy-α-L-lyxo-hexapyranoside (25)

23 (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 (hexane–EtOAc 4 : 1) showed complete conversion. After concentration, the residue was taken up in dichloromethane, washed with $NaHCO_3$ (5% aq.) and water, dried (Na_2SO_4) and concentrated to give **25** (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, 3H, C6-H, $J = 6.3$ Hz), 1.56 (m, 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-α-L-arabino-hexopyranoside (27)

Trifluoromethanesulfonic anhydride (7.45 mL, 44.1 mmol, 3.0 eq) was slowly added to a solution of **25** (3.0 g, 14.7 mmol) and pyridine (7.2 mL, 88.2 mmol, 6.0 eq) in dichloromethane (70 mL) at −10 °C under argon. The mixture was slowly warmed to rt and after stirring for an additional 1.5 h, the solution was diluted with dichloromethane and poured into ice-cold $NaHCO_3$ (20% aq.). The organic layer was washed with 1 M HCl, water and $NaHCO_3$ (sat.), dried (Na_2SO_4) and concentrated to give **26**. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.28$ (d, 3H, C6-H, $J = 6.3$ Hz), 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 (s, 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), 98.8 (d), 121.4 (s), 169.6 (s) ppm. ^{19}F-NMR ($CDCl_3$) $\delta = 1.81$ ppm.

A solution of the crude triflate **26** and tetrabutylammonium 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 (hexane–EtOAc 4 : 1) to give **27** (2.6 g, 10.4 mmol, 71% from **25**) as an oil and a side product resulting from dehydration (0.2 g, 1.2 mmol, 8%). ^{1}H-NMR **27** ($CDCl_3$, 500 MHz) $\delta = 1.22$ (d, 3H, C6-H, $J = 6.5$ Hz), 1.70 (m, 1H, C4-Heq, $J_{4eq,4ax} = 14.5$, $J_{4eq,5} = 2.5$ Hz), 1.81 (ddd, 1H, C4-ax, $J_{3,4ax} = 3.5$, $J_{4ax,5} = 11.0$ Hz), 2.08, 2.09 (2s, 6H, 2OAc), 3.38 (s, 3H, OMe), 4.14 (m, 1H, C5-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(CI) = 264 $(M + NH_4)^+$.

^{1}H-NMR of the C3-epimer of **27** obtained from acetylation of **23**: ($CDCl_3$, 300 MHz) $\delta = 1.24$ (d, 3H, C6-H, $J = 6.3$ Hz), 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 (29)

27 (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% 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% ammonia. Subsequently the aqueous layer was washed with petroleum–ether (40–60; × 5) 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 **29** (87 mg, 0.36 mmol, 87%) as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 1.24$ (d, 3H, C6-H, $J = 6.3$ Hz), 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, 1H, C2-H, $J = 8.1$ Hz), 4.05 (d, 1H, C3-H, $J = 8.4$ Hz), 4.15 (m, 1H, C5-H), 4.31 (d, 1H, C1-H, $J = 9.6$) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 23.9$ (q), 25.3 (t), 27.0 (t), 27.6 (t), 42.2 (t), 47.7 (d), 67.9 (d), 70.9 (d), 73.5 (d) ppm. MS(EI) for $C_9H_{18}O_3S_2$: $m/z = 238$ $[M^+]$, HRMS calcd for $C_9H_{18}O_3S_2$: 238.070, found: 238.071.

4,6-Dideoxy-2,3-*O*-isopropyliden-L-arabino-hexose-trimethylen-dithioacetal (31)

29 (600 mg, 2.52 mmol) was dissolved in dry acetone and $CuSO_4$ (778 mg, 3.06 mmol, 1.2 eq) and a drop of H_2SO_4 were added. The resulting green suspension was stirred overnight and then filtered. The filtrate was neutralized with 25% NH_3 and the resulting blue suspension was filtered again. The filtrate was concentrated, suspended in brine and extracted with dichloromethane (× 3). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (hexane–EtOAc 95 : 5 to 4 : 1) gave **31** (549 mg, 1.97 mmol, 78%) and **30** (55 mg, 0.20 mmol, 8%) as colorless oils. ^{1}H-NMR **31** ($CDCl_3$, 200 MHz) $\delta = 1.21$ (d, 3H, C6-H, $J = 6$ Hz), 1.43, 1.45 (2s, 6H, CMe_2), 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 (br s, 1H, OH), 3.93 (dd, 1H, C2-H, $J = 5.8$, 8.0 Hz), 4.05 (m, 1H, C5-H), 4.11 (d, 1H, C1-H, $J = 5.2$ Hz), 4.21 (ddd, 1H, C3-H, $J = 2.6$, 7.6, Hz) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 23.2$ (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(EI) for $C_{12}H_{22}O_3S_2$: $m/z = 278$ $[M^+]$, HRMS calcd for $C_{12}H_{22}O_3S_2$: 278.101, found: 278.101.

^{1}H-NMR **30** ($CDCl_3$, 300 MHz) $\delta = 1.20$ (d, 3H, C6-H, $J = 6.3$ Hz), 1.40, 1.46 (2s, 6H, CMe_2), 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, C-H), 4.03 (m, 1H, C-H), 4.14 (d, 1H, C1-H, $J = 7.0$ Hz), 4.25 (m, 1H, C-H) ppm.

5-*O*-*tert*-butyl-dimethyl-silyl-4,6-dideoxy-2,3-*O*-isopropyliden-L-arabino-hexose-trimethylen-dithioacetal (32)

31 (500 mg, 1.80 mmol) was dissolved in DMF 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 rt, the reaction mixture was diluted with water, extracted with Et_2O (× 2), dried (Na_2SO_4) and concentrated. Purification by column chromatography (hexane–EtOAc 95 : 5 to 9 : 1) gave **32** (593 mg, 1.51 mmol, 84%) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta = 0.06$ (s, 6H, 2 MeSi), 0.88 (s, 9H, *t*BuSi), 1.20 (d, 3H, C6-H, $J = 6.3$ Hz), 1.40, 1.42 (2s, 6H, CMe_2), 1.72–2.14 (m, 4H, C4-H, H′, dithian-H), 2.74–2.97 (m, 4H, dithian-H), 3.90 (dd, 1H, C2-H, $J = 5.1$, 7.5 Hz), 4.01–4.15 (m, 3H, C1-H, C3-H, C5-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = -4.9$ (q), −4.7 (q), 18.0 (s), 22.8 (q), 25.7 (t), 25.8 (q), 26.8 (q), 27.3 (q), 29.1 (t), 29.5 (t), 43.6 (t), 47.9 (d), 66.1 (d), 75.9 (d), 83.2 (d), 109.3 (s) ppm. MS(EI) for $C_{18}H_{36}O_3S_2Si$: $m/z = 392$ $[M^+]$, MS(CI) for $C_{18}H_{36}O_3S_2Si$: $m/z = 393$ $(M + H)^+$, 410 $(M + NH_4)^+$, HRMS calcd for $C_{18}H_{36}O_3SiS_2$: 392.188, found: 392.188.

5-*O*-*tert*-butyl-dimethyl-silyl-4,6-dideoxy-2,3-*O*-isopropyliden-L-arabino-hexanal (33)

32 (137 mg, 0.35 mmol) was converted into **33** (94 mg, 0.31 mmol, 89%) using a procedure analogous to the synthesis of **14**. ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 0.06$ (s, 6H, 2 MeSi), 0.87 (s, 9H, *t*BuSi), 1.19 (d, 3H, C6-H, $J = 6.0$ Hz), 1.42, 1.47 (2s, 6H, CMe_2), 1.70–1.97 (m, 2H, C4-H, H′), 3.97–4.06 (m, 2H, C2-H, C5-H), 4.18 (ddd, 1H, C3-H, $J = 5.0$, 7.6, 7.6 Hz), 9.72 (d, 1H, O=CH, $J = 2.4$ Hz) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = -5.0$ (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.

Benzoic acid-2-[5-(10-ethoxycarbonyl-2,6,8-trimethyl-deca-1,5,7,9-tetren-3-ynyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-1-methyl-ethyl ester (2a)

4a (122 mg, 0.28 mmol, 1.2 eq) was dissolved in $iPrNH_2$ (1.0 mL) and $Pd(PPh_3)_4$ (5.3 mg, 4.6 μmol, 2 mol%) was added. The solution was stirred under argon at ambient temperature for 5 min, after which CuI (0.9 mg, 4.6 μmol, 2 mol%) was added. After 5 min, **3a** (47 mg, 0.23 mmol) in $iPrNH_2$ (0.85 mL) was added and the mixture was stirred for 2 h and then concentrated. The residue was dissolved in Et_2O, washed with NH_4Cl (sat.) and brine, dried (Na_2SO_4) and concentrated. **2a** (109 mg, 0.22 mmol, 94%) was isolated as a yellow oil after purification by column chromatography (hexane–EtOAc 19 : 1 to 9 : 1) and what was left of **4a** (20 mg, 0.05 mmol, 20%) was recovered. ^{1}H-NMR *major isomer* ($CDCl_3$, 200 MHz) $\delta = 1.30$ (t, 3H, CH_3CH_2O, $J = 7.0$ Hz), 1.34–1.42 (m, 9H, C16-H, CMe_2), 1.76–2.20 (m, 11H,

C4-, C6-, C10-CH_3, C14-H_2), 3.85 (ddd, 1H, C13-H), 4.22 (q, 2H, CH_3CH_2O), 4.39 (m, 1H, C12-H), 5.31 (m, 1H, C15-H), 5.67 (s, 1H, C7-H), 5.74 (dd, 1H, C11-H, $J = 1.6$, 9.0 Hz), 5.91 (d, 1H, C2-H, $J = 15.6$ Hz), 6.31 (s, 1H, C5-H), 7.30–7.59 (m, 5H, Bz-H, C2-H), 8.03 (m, 2H, Bz-H) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 13.9$ (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), 132.6 (d), 134.2 (s), 140.5 (d), 146.1 (s), 149.7 (d), 165.7 (s), 167.0 (s) ppm. MS(EI) for $C_{31}H_{38}O_6$: $m/z =$ 506 [M^+], HRMS calcd for $C_{31}H_{38}O_6$: 506.267, found: 506.268.

7-Bromo-4,6-dimethyl-hepta-2,4,6-trienoic acid ethyl ester (34)

$BrCH_2PPh_3Br$ (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 hexane, 0.69 mL, 1.10 mmol, 2.0 eq) were added upon which the solution turned brown–red. After stirring for 15 min, **5b** (100 mg, 0.55 mmol) in THF (2.2 mL) was added and the reaction was stirred for 6 h. The reaction was quenched with NH_4Cl (sat.), the aqueous layer was extracted with Et_2O (× 3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography (pentane–EtOAc 95 : 5) gave **34** (57 mg, 0.22 mmol, 40%) as a mixture of isomers. ^{1}H-NMR ($CDCl_3$, 300 MHz) *major isomer* $\delta =$ 1.30 (t, 3H, CH_3CH_2O, $J =$ 7.0 Hz), 1.91 (s, 3H, C6-CH_3), 1.94 (s, 3H, C4-CH_3), 4.21 (q, 2H, CH_3CH_2O), 5.92 (d, 1H, C2-H, $J = 15.6$ Hz), 6.17 (s, 1H, C5-H), 6.24 (s, 1H, C7-H), 7.31 (d, 1H, C3-H, $J = 15.3$ Hz) ppm. *Minor isomer* $\delta = 1.31$ (t, 3H, CH_3CH_2O, $J = 7.0$ Hz), 1.88 (s, 3H, C6-CH_3), 1.96 (s, 3H, C4-CH_3), 4.21 (q, 2H, CH_3CH_2O), 5.95 (d, 1H, C2-H, $J = 15.6$ Hz), 6.14 (s, 1H, C5-H), 6.35 (s, 1H, C7-H), 7.39 (d, 1H, C3-H, $J = 15.9$ Hz) ppm.

7-Iodo-4,6-dimethyl-hepta-2,4,6-trienoic acid ethyl ester (35)

Preparation as described for **34**. **35** (70 mg, 0.23 mmol, 13%) was isolated as a single isomer from **5b** (321 mg, 1.76 mmol) using 1.91 g of ICH_2PPh_3I (3.53 mmol, 2.0 eq). ^{1}H-NMR ($CDCl_3$, 400 MHz) $\delta = 1.30$ (t, 3H, CH_3CH_2O, $J = 7.2$ Hz), 1.89 (s, 3H, C6-CH_3), 1.99 (s, 3H, C4-CH_3), 4.21 (q, 2H, CH_3CH_2O), 5.93 (d, 1H, C2-H, $J =$ 16.0 Hz), 6.21 (s, 1H, C5-H), 6.31 (s, 1H, C7-H), 7.30 (d, 1H, C3-H, $J = 16.0$ Hz) ppm.

Benzoic acid 2-[2,2-dimethyl-5-(2-methyl-but-1-en-3-ynyl)-[1,3]dioxolan-4-yl]-1-methyl-ethyl ester (36)

Ethynyl-trimethylsilane (99 µl, 0.70 mmol, 1.5 eq) was dissolved in $iPrNH_2$ (1.7 mL) and $Pd(PPh_3)_4$ (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, **4a** (200 mg, 0.46 mmol) in $iPrNH_2$ (1.4 mL) was added and the mixture was stirred for 1 h and then concentrated. The residue was dissolved in Et_2O and washed with NH_4Cl (sat.). The aqueous layer was extracted with Et_2O (× 3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The product (180 mg, 0.45 mmol, 97%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 19 : 1). ^{1}H-NMR ($CDCl_3$, 200 MHz) $\delta = 0.16$ (s, 9H, TMS), 1.38 (m, 9H, C9-H, CMe_2), 1.74–1.87 (m, 4H, C7-H, C3-CH_3), 2.03 (ddd, 1H, C7-H′), 3.82 (ddd, 1H, C6-H), 4.34 (t, 1H, C5-H, $J = 8.6$ Hz), 5.32 (m, 1H, C8-H), 5.78 (dd, 1H, C4-H, $J = 1.6$, 9.0 Hz), 7.41–7.58 (m, 3H, Bz-H), 8.04 (m, 2H, Bz-H) ppm.

The TMS–alkyne (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 NH_4Cl (sat.). The aqueous layer was extracted with Et_2O (× 3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. **36** (127 mg, 0.39 mmol, 86%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 97 : 3 to 95 : 5). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta =$ 1.39 (m, 9H, C9-H, CMe_2), 1.78–1.89 (m, 4H, C7-H, C3-CH_3), 2.05 (ddd, 1H, C7-H′), 2.86 (s, 1H, C1-H), 3.84 (ddd, 1H, C6-H), 4.36 (t, 1H, C5-H, $J = 8.7$ Hz), 5.32 (m, 1H, C8-H), 5.82 (d, 1H, C4-H, $J = 9.0$ Hz), 7.40–7.57 (m, 3H, Bz-H), 8.03 (d, 2H, Bz-H, $J = 7.2$ Hz) ppm. ^{13}C-NMR ($CDCl_3$, 50.3 MHz) $\delta = 17.8$ (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 (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 calcd for $C_{20}H_{24}O_4$: 328.167, found: 328.167.

Benzoic acid 2-[2,2-dimethyl-5-(2-methyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-1-methyl-ethyl ester (37)

^{1}H-NMR ($CDCl_3$, 400 MHz) $\delta =$ 1.39 (m, 9H, C9-H, CMe_2), 1.78–1.89 (m, 4H, C7-H, C3-CH_3), 2.08 (ddd, 1H, C7-H′), 3.83 (ddd, 1H, C6-H), 4.47 (t, 1H, C5-H, $J = 8.8$ Hz), 5.08 (d, 1H, C1-H, $J = 10.4$ Hz), 5.23 (d, 1H, C1-H′, $J = 17.6$ Hz), 5.30 (m, 1H, C8-H), 5.38 (d, 1H, C4-H, $J = 8.8$ Hz), 6.32 (dd, 1H, C2-H, $J =$ 10.8, 17.2 Hz), 7.43 (t, 2H, Bz-H, $J = 7.6$ Hz), 7.55 (t, 1H, Bz-H, $J = 7.6$ Hz), 8.03 (d, 2H, Bz-H, $J = 7.6$ Hz) ppm.

Benzoic acid 2-[2,2-dimethyl-5-(2-methyl-4-tributylstannanyl-buta-1,3-dienyl)-[1,3]dioxolan-4-yl]-1-methyl-ethyl ester (38)

CuCN (5.1 mg, 57 µmol, 1.1 eq) was suspended in dry THF (0.27 mL) under argon and *n*-BuLi (1.6 M in hexane, 71 µl, 114 µmol, 2.2 eq) was added at −40 °C giving a colorless solution after 20 min. The solution was then warmed to −30 °C and Bu_3SnH (31 µl, 114 µmol, 2.2 eq) was added resulting in a yellow solution. **36** (17 mg, 52 µmol) 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 firstly MeOH and then NH_4Cl (sat.)–NH_3 (12.5%) 4 : 1 (v/v). The aqueous layer was extracted with Et_2O (× 3) and the combined organic layers were dried (Na_2SO_4) and concentrated. Even though GC-MS showed only 1 product apart from starting material, **38** (5 mg, 8.1 µmol, 16%) was isolated in low yield after performing column chromatography twice (AlOx basic, pentane–EtOAc 39 : 1). ^{1}H-NMR ($CDCl_3$, 300 MHz) $\delta =$ 0.89 (m, 15H, Bu-Sn), 1.19–1.54 (m, 21H, Bu-Sn, C9-H, CMe_2), 1.83 (m, 4H, C7-H, C3-CH_3), 2.05 (m, 1H, C7-H′), 3.84 (m, 1H, C6-H), 4.48 (m, 1H, C5-H), 5.32 (m, 3H, C1-H, C4-H, C8-H), 6.39 (dd, 1H, C2-H, $J = 19.2$, J ^{1}H–^{117}Sn = J^1H–^{119}Sn = 72.3 Hz), 7.43 (m, 2H, Bz-H), 7.55 (m, 1H, Bz-H), 8.03 (d, 2H, Bz-H, $J = 8.1$ Hz) ppm.

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8 During the course of our research, it was brought to our attention by Prof. Dr J. Lugtenburg, that 1,3-steric interactions between the methyl substituents on C4′ and C6′ of the side-chain of mycolactones A and B will force the side-chain into the 5′-s-*cis* conformation rather than the 5′-s-*trans* conformation which is depicted in Figs. 1 and 2 and Scheme 4. However, for ease of presentation and to avoid unnecessary confusion, we have chosen to follow the literature precedents.
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