New approaches towards the synthesis 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 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 sp²–sp² 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...
chosen, which significantly reduces the number of steps in the preparation of the conjugated system as compared to previous routes.\textsuperscript{13} 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.\textsuperscript{18} 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).\textsuperscript{13} Horner–Wadsworth–Emmons reaction of 5b with diethyl (3-trimethylsilyl-2-propynyl) phosphonate (\textit{a} methyl hydroxyl moieties at the 4- and 6-positions need to be reduced and C5–OH epimerized. L-rhamnose requires reduction at the 4-position and epimerization which were separated by column chromatography (Scheme 1). (18% isolated yield) and the desired 5b (47% isolated yield), which were separated by column chromatography (Scheme 1).

**Synthesis of conjugated system (3)**

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\textsubscript{1}(OAc), CH\textsubscript{2}Cl\textsubscript{2}, EDA\textsuperscript{a}, 15 h; (b) L\textsubscript{1}, CH\textsubscript{2}Cl\textsubscript{2}, 12 h (5a 18%, 5b 47%); (c) NaHMDS, HPO(OEt)\textsubscript{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%). \textsuperscript{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 \(\alpha\)-d-glucopyranoside or methyl \(\alpha\)-L-rhamnopyranoside. In the case of \(\alpha\)-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).

**Scheme 2** Synthesis of 4a from methyl \(\alpha\)-d-glucopyranoside; (a) SO\textsubscript{2}Cl\textsubscript{2}, pyridine, CHCl\textsubscript{3}, −78 to 50 °C, 7 h (56%); (b) Bu\textsubscript{3}SnH, AIBN\textsuperscript{a}, toluene, reflux, 12 h (89%); (c) 1,3-propanedithiol, 37% HCl, 12 h (87%); (d) acetone, CuSO\textsubscript{4}, H\textsubscript{2}SO\textsubscript{4}, 12 h (95%); (e) PPh\textsubscript{3}, BrOH, DEAD\textsuperscript{a}, THF, 1.5 h (82%); (f) MeI, acetone, H\textsubscript{2}O, 2,4,6-collidine, reflux, 12 h (87%); (g) PPh\textsubscript{3}, CBr\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1.5 h (72%); (h) LDA\textsuperscript{c}, THF, −78 °C, 2 h (88%); (i) LDA\textsuperscript{c}, HMPPA\textsuperscript{c}, MeI, THF, −78 to −10 °C, 2 h (88%); (j) PdCl\textsubscript{2}(PPh\textsubscript{3}), Bu\textsubscript{3}SnH, pentane (63%); (k) CH\textsubscript{2}Cl\textsubscript{2}, I\textsubscript{2}, 0 °C, 20 min (99%). \textsuperscript{a} AIBN = 2,2'-azobisisobutyronitrile, \textsuperscript{b} DEAD = diethyl azodicarboxylate, \textsuperscript{c} LDA = lithium diisopropylamide, \textsuperscript{d} HMPPA = hexamethylene phosphoramide.

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 and low yields were obtained with NBS\textsuperscript{16} in acetone and water. Eventually, treatment with Mel 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.\textsuperscript{17} Reaction of 14 with CBr\textsubscript{3} and PPh\textsubscript{3} under Corey–Fuchs conditions.

![Fig. 3](image-url) Target chiral building block from \(\alpha\)-glucopyranoside and \(\alpha\)-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.
conditions gave dibromo-olefin 15 in 72% yield over 2 steps.\textsuperscript{19,20} Elimination of HBr by treatment with LDA followed by a protic work-up resulted in the terminal alkyne 16 (88%),\textsuperscript{21} which was converted into the methylated alkyne 17 (88%) by reaction with LDA and Mel in the presence of HMPA.\textsuperscript{22} The direct synthesis of 17 from 15 by treatment with Mel and n-BuLi or i-BuLi was unsuccessful due to the intolerance of the benzyl group to these conditions.

Palladium-catalyzed hydrostannation of the internal alkyne was troublesome, due to palladium-black formation.\textsuperscript{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%.\textsuperscript{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 (2-D H-NMR). The synthesis of the chiral moiety was completed by exchange of the tributyltin moiety with iodine to give 4a (99%).\textsuperscript{25}

An alternative synthesis from methyl o-\textsuperscript{1}-rhamnopyranoside (19; Scheme 3) started with regioselective protection of the C2- and C3-hydroxy moieties as their acetonide by reaction with acetone under acidic conditions leading to 20 (90%).\textsuperscript{26} 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.\textsuperscript{27} Radical reduction of 21 gave the deoxygenated product 22.\textsuperscript{28} 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 the diol 23 in 71% over 2 steps.\textsuperscript{29} 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%).\textsuperscript{30} 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.

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\textsubscript{N}2 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.\textsuperscript{29,30} Comparison of the \textsuperscript{1}H- and \textsuperscript{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. Acetone-protection of two hydroxyl moieties by an acid catalysed reaction with acetone gave the two regioisomers 30 (80%) and the desired 31 (78%), which could be separated by column chromatography.\textsuperscript{14} After protection of the remaining C5-OH of 31 with TBDMSCl (84%, 32),\textsuperscript{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 benzyl 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 iodide 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.\textsuperscript{13,32}

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 \textit{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.\textsuperscript{13,14} 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. 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. Ni-catalysed reduction with NaBH₄ 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 sp²–sp² coupling. In our hands, however, compound 3a was unreactive towards stannylation (Bu₃SnH, CuCN, n-BuLi),38 and hydrozirconation (Schwartz reagent),39 while palladium catalyzed hydrostannation resulted exclusively in the undesired internal regiosomer.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,21,41 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 BrCH₂PPh₃Br (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%),43 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 alkyne 37 and the starting material 35 suggesting that at least the initial hydrozirconation was successful.44 Hydrostannation of 36 using a stannyllcuprate gave 38 in low yield (16%),45 but Stille coupling to 34 was unsuccessful once again.46

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.

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

R₁O(CO₂), (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, 5.52 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 I₂. The resulting black solution was washed with Na₂S₂O₃ (10% aq.) and brine, dried (Na₂SO₄) and concentrated. The product was purified by column chromatography (hexane–EtOAc 9 : 1) to give 5a (0.17 g, 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 I₂ in dichloromethane, a mixture of 5a and 5b in the same ratio as before was formed.

1-H-NMR

5a (CDCl₃, 300 MHz) δ = 1.30 (t, 3H, CH₂CH₂O, J = 7.2 Hz), 2.01 (s, 3H, CH₃), 2.25 (s, 3H, C–H₃), 2.43 (q, 2H, CH₂CH₂O, J = 7.2 Hz), 6.17 (d, 1H, C₂–H₂, J = 15.9 Hz), 6.27 (s, 1H, C₅–H₅), 8.39 (d, 1H, C₃–H₃, J = 16.2 Hz) ppm.

1-H-NMR 5b (CDCl₃, 300 MHz) δ = 1.30 (t, 3H, CH₂CH₂O, J = 7.2 Hz), 2.22 (s, 3H, CH₃), 2.26 (s, 3H, C–H₃), 4.23 (q, 2H, CH₂CH₂O, J = 7.2 Hz), 6.24 (d, 1H, C₂–H₂, J = 15.6 Hz), 6.36 (s, 1H, C₅–H₅), 7.24 (d, 1H, C₃–H₃, J = 16.6 Hz) ppm.

13C-NMR

5a (CDCl₃, 300 MHz) δ = 13.6 (q), 14.1 (q), 32.0 (q), 60.7 (t), 76.9. Carbon types were determined from APT-13C experiments.

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, TCL: silica gel 60, Merck, 0.25 mm. Components were visualized by staining with (a) KMnO₄ or (b) a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL). Optical rotations were measured on a Perkin-Elmer 241 or 241 MC polarimeter. Mass spectra (HRMS) were recorded on an AEL MS-902. 1H and 13C NMR spectra were recorded on a Varian Gemini-200 (50.32 MHz), a Varian VXR300 (75.48 MHz) or an Astra-AMX400 (100.59 MHz) spectrometer in CDCl₃. Chemical shift values are denoted in δ values (ppm) relative to residual solvent peaks (CHCl₃, 1H δ = 7.26, 13C δ = 76.9). Carbon types were determined from APT-13C experiments.
To a solution of NaHMDS (1.0 M in THF, 26 mL, 26 mmol) at 0 °C in vacuo, the color slowly changed to brown. The reaction mixture was stirred for 45 min and then quenched with NH4Cl (sat.), dried (Na2SO4) and concentrated. The product was purified by column chromatography (pentane–EtOAc 4:1 to 1:1) giving pure 5, found: 204.115, 182 [M+], HRMS calcd for C13H16O2: 204.115, found: 204.116.

**Methyl 4,6-di-O-dioxo-4,6-dideoxy-D-xylo-hexose-trimethylen-dithioacetal (10)**

Bu3SnH (30 mL, 32 g, 0.11 mol) was added dropwise to a solution of 9 (3.3 g, 23 mmol) in refluxing dry toluene (180 mL) under argon and AIBN (catalytic) was added. The resulting solution was stirred overnight. The solution was diluted with MeOH and water, neutralized with Na2CO3 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 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 (281 g, 122 mmol, 55.8%). 1H-NMR (CDCl3, 300 MHz) δ = 2.20 (br s, 4H, C2-OH, C3-OH), 3.48 (s, 4H, C3-H, C5-H), 3.68 (d, 2H, C6-H, J = 0.6 Hz), 3.85 (dd, 1H, C1-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. 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.

**4,6-Dimethyl-9-trimethylsilyl-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 NH4Cl (sat.). The aqueous layer was extracted with Et2O (× 3) and the combined organic layers were washed with brine (sat.), dried (Na2SO4) and concentrated. 7 (336 mg, 1.22 mmol, 61%, mixture of 6:1 major to minor 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), and purified by crystallization from dichloromethane–MeOH 19:1 to 9:1 to give pure 11 (3.3 g, 20 mmol, 89%). When the reaction was performed on larger scale, purification was done by crystallization from chloroform and pentane. 13C-NMR (CDCl3, 300 MHz) δ = 2.10 (dd, 1H, C6-H, J = 1.6 Hz), 3.07 (d, 1H, C3-H, J = 10.2 Hz), 2.46 (d, 1H, OH, J = 10.2 Hz), 1.34 (t, 6H, CH3), 1.27 (d, 3H, C6-H, J = 10.2 Hz), 2.03 (d, 1H, OH, J = 10.2 Hz), 2.46 (d, 1H, OH, J = 1.0 Hz), 3.33–3.44 (m, 1H, C2-H, C3-H), 3.77–3.95 (m, 2H, C5-H, C6-H), 4.75 (d, 2H, C2-OH, C3-OH), 4.06 (s, 1H, C4-CH3), 7.39 (d, 1H, C3-H, J = 15.5 Hz) ppm. MS(EI) for C13H16O2Si: m/z = 276 [M+], HRMS calcd for C13H16O2Si: 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, 0.4 eq) was stirred for 30 min under argon in the presence of EtOAc (47 μL, 0.4 mmol–toluol). 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 NH4Cl (sat.), dried (Na2SO4) 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. 1H-NMR major isomer (CDCl3, 200 MHz) δ = 1.29 (t, 3H, CH3, CH2, J = 7.0 Hz), 1.99 (d, 1H, C6-CH3, J = 0.8 Hz), 2.13 (s, 3H, C4-CH3), 3.38 (d, 1H, C9-H, J = 2.4 Hz), 4.21 (q, 2H, CH2, CH2, O), 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. 1H-NMR minor isomer (CDCl3, 200 MHz) δ = 1.30 (t, 3H, CH3, CH2, CH2, O, J = 7.0 Hz), 1.95 (d, 3H, C6-CH3, J = 1.0 Hz), 2.04 (s, 3H, C4-CH3), 3.22 (d, 1H, C9-H, J = 2.4 Hz), 4.21 (q, 2H, CH2, CH2, O), 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 C13H16O2Si: m/z = 276 [M+], HRMS calcd for C13H16O2Si: 276.155, found: 276.155.

**Methyl 4,6-di-O-dioxo-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 stirring was overnight. The solution was washed with 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. [α]D −30.3 (c 1.09 in MeOH), lit. [α]D29 −29.5 (c 1.00 in MeOH).

1H-NMR (CDCl3, 300 MHz) δ = 1.27 (d, 3H, C6-H, J = 6.3 Hz), 1.60 (dd, 1H, C4-H), 1.89 (dd, 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 Hz), 3.33–3.44 (m, 1H, C2-H, C3-H), 3.77–3.95 (m, 2H, C5-H, C6-H), 4.75 (d, 2H, C2-OH, C3-OH), 4.06 (s, 1H, C4-CH3), 7.39 (d, 1H, C3-H, J = 15.5 Hz) 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), 99.9 (d) ppm.
for CH₂O₃S₂; m/z = 238 [M⁺]. HRMS calc for C₁₇H₂₀O₄S₂: 282.127, found: 282.126.

4,6-Dideoxy-2,3-O-isopropylidene-D-xilo-hexose-trimethylen-dithioacetal (12)

11 (2.2 g, 9.2 mmol) was dissolved in dry acetone and CuSO₄ (2.9 g, 18.5 mmol, 2 eq) and a drop of H₂SO₄ were added. The resulted 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 (30 mL) was added over 20 min. The resulting mixture was stirred for 1 h and then quenched with MeOH and concentrated in vacuo. The reaction was quenched with water, with Et₂O (x 2), dried (MgSO₄), filtered and concentrated. The product was purified by column chromatography (hexane-EtOAc 9:1) to give 15 (5.7 g, 13 mmol, 72%) as a colorless oil. 1H-NMR (CDCl₃, 200 MHz) δ = 1.39–1.45 (m, 9H, C7-H, CMe₂, 1.82–2.20 (m, 4H, C₄-H, H′), 2.67–2.97 (m, 4H, dithian-H), 3.93 (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 (EI) for C₁₇H₂₀O₄S₂: m/z = 306 (M + NH₄)⁺.

5-O-benzyloxy-4,6-dideoxy-2,3-O-isopropylidene-D-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 (10 mL) was added to the resulting mixture and the product was extracted with Et₂O (x 3). The combined organic layers were washed with water and brine, dried (MgSO₄) and concentrated. The resulting brown solid was filtered and concentrated. The reaction was filtered with silica (CHCl₃) and then further purified by column chromatography (hexane-EtOAc 9:1) to give 15 (5.7 g, 13 mmol, 72%) as a colorless oil. 1H-NMR (CDCl₃, 200 MHz) δ = 1.36 (m, 6H, C₆-H, C₇-H'), 1.42 (d, 3H, CH₃, J = 6.3 Hz), 1.94 (ddd, 1H, C₄-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, C₇-H, J = 8.0, 8.0 Hz), 5.34 (m, 1H, C₅-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 = 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 C₁₂H₂₂O₃S₂: m/z = 278 [M⁺]. HRMS calc for C₁₂H₂₂O₃S₂: 278.101, found: 278.101.

6-O-benzoyloxy-1,1-dibromo-5,7-dideoxy-3,4-arabino-hept-1-ene (15)

13 (6.8 g, 18 mmol) was dissolved in aceton (140 mL) and water (35 mL) and 2,4,6-collidine (23.4 mL, 21.5 g, 178 mmol) and Mel (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 Mel (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 (x 3), NaHCO₃ (sat.) and brine, dried over MgSO₄ and concentrated. The crude 14 was used without purification in the next step after overnight drying in vacuo over P₂O₅. Triphenylphosphine (18.6 g, 71.1 mmol, 2 eq) was dissolved in freshly distilled dry dichloromethane (47 mL) and Cb (0.17 mL, 78.3% 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 NaHCO₃, the aqueous layer was extracted with dichloromethane (x 2), the combined organic layers were washed with water and brine, dried (MgSO₄) and concentrated. The resulting brown solid was then filtered over silica (CH₂Cl₂) and then further purified by column chromatography (hexane–EtOAc 1:9) to give 15 (5.7 g, 13 mmol, 72%) as a colorless oil. 1H-NMR (CDCl₃, 200 MHz) δ = 1.36 (m, 6H, C₆-H, C₇-H'), 1.42 (d, 3H, CH₃, J = 6.3 Hz), 1.94 (ddd, 1H, C₄-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, C₇-H, J = 8.0, 8.0 Hz), 5.34 (m, 1H, C₅-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. 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 (EI) for C₁₇H₂₀O₄S₂: m/z = 306 (M + NH₄)⁺.

To a solution of 15 (5.0 g, 6.7 mmol) in dry THF (77 mL), was added ADA (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 Et₂O (x 2), dried (MgSO₄), filtered and concentrated. The product was purified by column chromatography (hexane–EtOAc 9:1) to give 16 (1.7 g, 5.9 mmol, 88%) as a colorless oil. 1H-NMR (CDCl₃, 200 MHz) δ = 1.38–1.45 (m, 9H, C₇-H, CMe₂, 1.82–2.20 (m, 4H, C₄-H, H′), 2.67–2.97 (m, 4H, dithian-H), 3.93 (q), 27.0 (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 (EI) for C₁₇H₂₀O₄S₂: m/z = 306 (M + NH₄)⁺, HRMS calc for C₁₇H₂₀O₄S₂: m/z = 306.1237 (M + NH₄)⁺.
MS(Cl) for C₇H₆O₂Cl: m/z = 320 (M + NH₄)+, HRMS caleld for C₇H₆O₂Cl−: 287.128, found: 287.129.

**Benzoic acid 2-(2,2-dimethyl-5-(2-tributylstannanyl-propenyl)-1,3dioxolano-4-yl)-1-methyl-ethyl ester (18)**

\( \text{17 (230 mg, 761 mmol) was added to a suspension of PdCl}_2(\text{PPh}_3)_2 (27 mg, 38 mmol, 5 mol%) in pentane (6.9 mL) under argon and after stirring for 10 min, Bu₃SnH (0.83 mL, 3.1 mmol, 4 eq) was added over 2 min. After 45 min, TLC showed complete conversion and the mixture was concentrated. The product was purified by column chromatography (benzene-cyclohexane 9:1) giving 18 (282 mg, 475 mmol, 63%) and the internal hydrostannylation side product (45 mg, 76 mmol, 10%) both as colorless liquids.} \text{1H-NMR (CDCl}_3, 500 MHz) \delta = 0.70–1.03 (m, 15H, Bu-Sn), 1.19–1.60 (m, 21H, C₈-H, CMe₂, Bu-Sn), 1.31 (d, 3H, C₆-H), 1.35–1.42 (m, 9H, C₈-H, CMe₂), 1.77 (ddd, 1H, C₆-H), 2.06 (ddd, 1H, C₆-H), 2.49 (s, 3H, C₁-H), 3.84 (ddd, 1H, C₅-H), 4.33 (s, 1H, C₁-H) ppm. 13C-NMR (CDCl₃, 125 MHz) δ = 27.9 (t), 29.1 (t), 36.4 (t), 54.8 (q), 63.7 (d), 65.6 (d), 68.6 (d), 101.2 (d) ppm. \text{MS(CI) for C₃₀H₅₀O₄Sn: m/z = 593 [M]+.} \)

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

\( \text{18 (200 mg, 0.34 mmol) was dissolved in dichloromethane (2.7 mL) and 1L (114 mg, 0.45 mmol, 1.3 eq) in dichloromethane (0.7 mL) was added at −78 °C under argon. The resulting solution was stirred for 10 min at −78 °C and then warmed to rt.} \text{The solution was concentrated and 4a (144 mg, 0.33 mmol, 99%) was isolated as a yellow oil after column chromatography (hexane–EtOAc 9:1 to 4:1).} \)

\( \text{1H-NMR (CDCl}_3, 300 MHz) \delta = 1.35–1.42 (m, 9H, C₈-H, CMe₂), 1.84 (ddd, 1H, C₆-H), 2.06 (dd, 1H, C₆-H), 2.49 (s, 3H, C₁-H), 3.84 (ddd, 1H, C₅-H), 4.33 (s, 1H, C₁-H), 5.29 (d, 1H, C₃-H), 6.14 (d, 1H, C₃-H, J = 8.7 Hz), 7.41–7.58 (m, 3H, Bz-H), 8.02–8.06 (m, 2H, Bz-H) ppm. 13C-NMR (CDCl₃, 75 MHz) δ = 27.9 (t), 29.1 (t), 37.8 (t), 69.2 (d), 76.9 (d), 77.7 (d), 101.5 (s), 109.0 (s), 128.1 (d), 129.4 (d), 130.7 (s), 132.6 (d), 135.6 (d), 147.5 (s), 165.8 (s) ppm. MS(EI) for C₁₈H₂₂O₄: m/z = 287.128, found: 287.129.} \)

\( \text{A solution of } \text{Methyl-(2,3-isopropylidene)-2,3-dIDEOXO-4-L-lyxo-hexopyranoside (22):} \)

\( \text{21 (2.0 g, 6.1 mmol) was dissolved in toluene (27 mL) and AIBN (0.3 g, 1.8 mmol, 30 mol%) and tris(2-methylsilyl)silane (2.3 mL, 7.5 mmol, 1.2 eq) was added. The resulting solution was slowly heated to 110 °C and then refluxed for 30 min under argon, after which TLC showed complete conversion. After cooling to rt, NaHCO₃ (20% aq. solution) was added and the product was extracted with EtOAc (3 × 5). The combined organic layers were dried (MsO₄) and concentrated below 30 °C using MeOH to remove the toluene.} \text{22 was isolated as a yellow oil after column chromatography (hexane–EtOAc 9:2 to 9:5):} \)

\( \text{Due to volatility of the product, the yield was determined in the next step.} \)
Methyl-2,3-di-O-acetyl-4,6-dideoxy-α-t-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 NaHCO3 (20% aq.). The organic layer was washed with 1 M HCl, water and NaHCO3 (sat.), dried (Na2SO4) and concentrated to give 26. 1H-NMR (CDCl3, 300 MHz) δ = 1.28 (d, 3H, C6-H, J = 6.3 Hz), 1.29–2.13 (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. 13C-NMR (CDCl3, 75.4 MHz) δ = 20.8 (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. F-NMR (CDCl3) δ = 1.81 ppm.

A solution of the crude triﬂate 26 and tetrabutylammonium acetate (48.7 g, 162 mmol, 11 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%).

1H-NMR (CDCl3, 300 MHz) δ = 1.22 (d, 3H, C6-H, J = 6.5 Hz), 1.70 (m, 1H, C4-Hq, Jwax = 14.5, Jcax = 2.5 Hz, J = 1.81 J1d, 1H, C4-ax), 3.97 (s, 1H, C1-H), 4.74 (m, 1H, C2-H), 4.91 (m, 1H, C3-H) ppm. 13C-NMR (CDCl3, 75.4 MHz) δ = 20.4 (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 C12H22O3S2: m/z = 278 [M⁺]. HRMS calecd for C12H22O3S2: 278.101, found: 278.101.

1H-NMR (CDCl3, 300 MHz) δ = 1.20 (d, 3H, C6-H, J = 6.3 Hz), 1.40, 1.46 (2s, 6H, CMe3), 1.50 (m, 1H, C4-H), 1.92–2.14 (m, 3H, C4-H, C4-H', dithian-H), 2.74–2.96 (m, 5H, C6-H, C4-H), 3.64 (m, 1H, C7-H), 4.14 (d, 1H, C1-H, J = 7.0 Hz), 4.25 (m, 1H, C6-H) ppm.

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

3i (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 Et2O (∼2), dried (Na2SO4) and concentrated. Purification by column chromatography (hexane–EtOAc 9:5 to 9:1) gave 32 (593 mg, 1.51 mmol, 84%) as an oil. 1H-NMR (CDCl3, 300 MHz) δ = 0.06 (s, 6H, 2MeSi), 0.88 (s, 9H, BuSi), 1.20 (d, 3H, C6-H, J = 6.3 Hz), 1.40, 1.42 (2s, 6H, CMe2), 1.72–2.14 (m, 3H, 4H, C4-H, C4-H'), 2.74–2.97 (m, 4H, dithian-H), 3.99 (dd, 1H, C1-H, J = 5.1, 7.5 Hz), 4.01–4.15 (m, 3H, C1-H, C3-H, C5-H) ppm. 13C-NMR (CDCl3, 75.4 MHz) δ = −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 C16H26O8S2: m/z = 392 [M⁺], MS(1) for C16H26O8S2: m/z = 393 (M + H⁺), 410 (M + Na⁺), HRMS calecd for C16H26O8S2: 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. 1H-NMR (CDCl3, 200 MHz) δ = 0.06 (s, 6H, 2MeSi), 0.87 (s, 9H, BuSi), 1.19 (d, 3H, C6-H, J = 6.0 Hz), 1.42, 1.47 (2s, 6H, CMe2), 1.70–1.97 (m, 2H, C4-H, C4-H'), 4.18 (dd, 1H, C1-H, J = 5.0, 7.6, 7.6 Hz), 9.7 (d, 1H, O=CH, J = 2.4 Hz) 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) ppm.

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

4a (122 mg, 0.28 mmol, 1.2 eq) was dissolved in iPrNH2 (1.0 mL) and Pd(PPh3)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 Cul (0.9 mg, 4.6 μmol, 2 mol%) was added. After 5 min, 3a (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 NH4Cl (sat.) and brine, dried (Na2SO4) 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. 1H-NMR major tomer (CDCl3, 200 MHz) δ = 1.30 (3H, CH3), 2.47 (s, 3H, OCH3), 4.18 (d, 1H, C1-H, J = 7.0 Hz), 1.34–1.42 (m, 1H, C6-H, C7-H), 1.76–2.20 (m, 11H, CMe3) ppm.
7-Bromo-4,6-dimethyl-hepta-2,4,6-trienoic acid ethyl ester (34)

BrCH2PPh3Br (479 mg, 1.10 mmol, 2.0 eq) was suspended in dry THF (2.2 mL) and then CuI (1.8 mg, 9.3 \( \mu \)mol, 97%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 95 : 5) gave 34 (53 mg, 0.22 mmol, 40%) as a mixture of isomers. \( ^1 \)H-NMR (CDCl3, 300 MHz) major isomer \( \delta = 1.30 \) (t, 3H, CH2CH2O, J = 7.0 Hz), 1.91 (s, 3H, CH3-C), 1.94 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, 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, CH2CH2O, J = 7.0 Hz), 1.88 (s, 3H, CH3-C), 1.96 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, J = 15.6 Hz), 6.19 (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)

Ethynyl-trimethylsilane (99 \( \mu \)g, 0.45 mmol) was dissolved in dry THF (1.7 mL) and then CuI (1.8 mg, 9.3 \( \mu \)mol, 97%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 95 : 5) gave 35 (53 mg, 0.22 mmol, 40%) as a mixture of isomers. \( ^1 \)H-NMR (CDCl3, 300 MHz) major isomer \( \delta = 1.30 \) (t, 3H, CH2CH2O, J = 7.0 Hz), 1.91 (s, 3H, CH3-C), 1.94 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, 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, CH2CH2O, J = 7.0 Hz), 1.88 (s, 3H, CH3-C), 1.96 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, J = 15.6 Hz), 6.19 (s, 1H, C5-H), 6.35 (s, 1H, C7-H), 7.39 (d, 1H, C3-H, J = 15.9 Hz) ppm.

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

CuCN (5.1 mg, 57 \( \mu \)mol, 1.1 eq) was suspended in dry THF (2.2 mL) and then CuI (1.8 mg, 9.3 \( \mu \)mol, 97%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 95 : 5) gave 37 (45 mg, 0.22 mmol, 40%) as a mixture of isomers. \( ^1 \)H-NMR (CDCl3, 300 MHz) major isomer \( \delta = 1.30 \) (t, 3H, CH2CH2O, J = 7.0 Hz), 1.91 (s, 3H, CH3-C), 1.94 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, 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, CH2CH2O, J = 7.0 Hz), 1.88 (s, 3H, CH3-C), 1.96 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, J = 15.6 Hz), 6.19 (s, 1H, C5-H), 6.35 (s, 1H, C7-H), 7.39 (d, 1H, C3-H, J = 15.9 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 \( \mu \)mol, 1.1 eq) was suspended in dry THF (2.2 mL) and then CuI (1.8 mg, 9.3 \( \mu \)mol, 97%) was isolated as a colorless oil after purification by column chromatography (pentane–EtOAc 95 : 5) gave 38 (60 mg, 0.27 mmol, 67%) as a mixture of isomers. \( ^1 \)H-NMR (CDCl3, 300 MHz) major isomer \( \delta = 1.30 \) (t, 3H, CH2CH2O, J = 7.0 Hz), 1.91 (s, 3H, CH3-C), 1.94 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, 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, CH2CH2O, J = 7.0 Hz), 1.88 (s, 3H, CH3-C), 1.96 (s, 3H, C4-CH3), 4.21 (q, 2H, CH2CH3, J = 15.6 Hz), 6.19 (s, 1H, C5-H), 6.35 (s, 1H, C7-H), 7.39 (d, 1H, C3-H, J = 15.9 Hz) ppm.

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References

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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