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Total Synthesis of the Phenolic Glycolipid Mycoside B and the Glycosylated *p*-Hydroxybenzoic Acid Methyl Ester HBAD-I, Virulence Markers of *Mycobacterium tuberculosis*

Santiago Barroso,^[a] Danny Geerdink,^[a] Bjorn ter Horst,^[a] Eva Casas-Arce,^[a] and Adriaan J. Minnaard*^[a]

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The phenolic glycolipid mycoside B, present in *Mycobacterium bovis* and hypervirulent strains of *Mycobacterium tuberculosis*, has been synthesized for the first time. Multiple methyl groups were introduced by the extensive use of catalytic asymmetric 1,4-addition reactions, asymmetric hydrogenation of a β -keto ester afforded the basis for the central 1,3-diol moiety, and introduction of the 2-*O*-methyl- α -L-

rhamnoside unit was achieved by stereoselective glycosylation with *p*-iodophenol and subsequent Sonogashira coupling, providing a basis for the generation of analogues. In addition, the related monosaccharide HBAD-I, present in the same species, has been efficiently synthesized for the first time by selective methylation of the hydroxy group at C-2 of a rhamnoside.

Introduction

Tuberculosis (TB) is today still one of the most important infectious diseases. Although antibiotics and a vaccine (*Bacillus Calmette–Guérin*, BCG) are available, the number of cases reveals that the disease continues to be a global problem: 8 million casualties and 1.5 million deaths every year.^[1] The synergy with HIV and the advent of new multi-drug-resistant and hypervirulent strains poses additional threats.^[2] *Mycobacterium tuberculosis* (*M. tuberculosis*) is the most prominent cause of TB, but the related species, *Mycobacterium bovis* (*M. bovis*), can also cause the disease.

The disclosure of the full genome sequence of *M. tuberculosis* H37Rv^[3] has allowed scientists to identify the enzymes involved in the biosynthesis and transport of secondary metabolites that are important in host–pathogen interactions. Furthermore, knockout experiments have shed light on the specific role of a number of these compounds. The most prominent representatives are the complex methyl-branched lipids with long alkyl chains, often glycosylated.^[4] This is also the case in the phenolic glycolipids (PGLs), which are suspected of being involved in the hypervirulence of specific mycobacterial strains.^[5]

Monoglycosylated mycoside B (Figure 1, 1) is the major PGL in *M. bovis*.^[6] This compound is also found as a minor PGL in some specific strains of *M. tuberculosis*^[6c] in which triglycosyl PGL-tb1 is the predominant species.^[7] PGLs are

among the most specific virulence factors and permit the strain causing an infection to be deduced and discrimination between recent infection and vaccination. Furthermore, it has been shown that not all *Mycobacterium bovis* BCG strains used for vaccination are able to produce mycoside B and phthiocerol dimycocerosates (PDIMs), providing a correlation between the ability to produce these compounds and the risk of complications after vaccination observed in clinical studies.^[8] In this regard, an enzyme-linked immunosorbent assay (ELISA) based on PGLs has recently shown potential for the diagnosis of TB in HIV-infected patients.^[9] In addition, a lipidomic platform has been established for the chemotaxonomic analysis of *M. tuberculosis*.^[10]

The variation in the structures of the different mycobacterial PGLs mainly resides in the glycosyl terminus. Differences in occurrence are found between species of the genus, but also occur within strains of the same species. For example, minor PGLs, different to mycoside B and PGL-tb1, have been found in some strains of *M. tuberculosis*, which has biological implications.^[11] Because access to pure, chemically synthesized PGLs is crucial for reliable immunological studies, a synthetic strategy to readily obtain with minimal changes the different PGLs is desirable. We recently communicated the first total synthesis of trisaccharide PGL-tb.^[12] The key elements of the strategy are the modularity, the high control over the stereoselectivity, and the introduction of the glycosyl moiety (the most variable part of the PGLs) by a late-stage Sonogashira reaction. Here, a full account of this work is presented combined with a second application of this strategy to the synthesis of mycoside B.

[a] Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747 AG, Groningen, The Netherlands
E-mail: a.j.minnaard@rug.nl

Homepage: <http://www.rug.nl/fmns-research/stratingh>

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Figure 1. Related PDIM, PGLs, and *p*-HBAD found in *M. tuberculosis*. and *M. bovis*.

Aryl rhamnoside HBAD-I (**2**, Figure 1) is clearly closely related to mycoside B. The compound has been detected in the culture medium of all reference strains of *M. tuberculosis* and *M. bovis*.^[13] According to Daffé and co-workers, *p*-hydroxybenzoic acid is the precursor of both **1** and **2**. However, it is remarkable that **2** and its acid form are not precursors of **1**. Thus, compound **2** is a final metabolite of both mycobacteria. Concerning the biosynthesis of these compounds, Daffé and co-workers proposed that the Pks15/1 gene is responsible for the elongation of the *p*-hydroxybenzoic acid to form a *p*-hydroxyphenylalkanoate.^[13,14] The latter compound is transformed by the gene PpsA-E into the phenolphthiocerol unit. Daffé and co-workers disclosed that

mutations in pks15/1 are responsible for the lack of phenolic glycolipids in PGL-deficient *M. tuberculosis* strains. Glycosylation is achieved by the use of Rv2962c encoded enzymes in the final step of the biosynthesis of both **1** and **2**.

Note, the secretion of methyl benzoate **2** and its analogue triglycosyl methyl benzoate appears to be highly relevant. Studies with knockout bacteria have shown that the inhibited production of some or all *p*-HBADs is inter-related to an increased secretion of pro-inflammatory cytokines.^[15] In other words, *p*-HBADs seem to attenuate the immune response of the host. Given the immunological interest and the connection of **2** to mycoside B, we decided to synthesize **2** as well.

Results and Discussion

The dissimilar nature of the different parts of mycoside B calls for a strongly convergent synthetic strategy. The retrosynthesis we devised for mycoside B (**1**) parallels the one used in the synthesis of PGL-tb1 and divides this complex molecule into three main building blocks: rhamnoside **3**, mycocerosic acid (**4**), and diol **5**, as summarized in Scheme 1.

The first of these units, 2-*O*-methyl- α -L-rhamnoside **3**, appropriately benzylated (see above), is equipped with a *p*-iodophenol unit. This functionalization allows the carbohydrate to be installed through a Sonogashira coupling reaction instead of by glycosylation.^[16] In our view, this should simplify the connection of the carbohydrate to the lipid chain. No less important, the α configuration at the anomeric center could exclusively be ensured at an earlier stage of the synthesis.

The synthesis of building block **5** faces two main challenges. One is the selective generation of the different stereocenters, there being a significant distance between them. To solve this problem we relied on a one-pot 1,4-addition/alkylation reaction by using 2-cycloheptenone (**6**) as the starting material. The aforementioned approach provides the first two stereocenters on the right hand of the molecule and bridges the gap between these and the *anti*-1,3-diol unit, in turn prepared by asymmetric Ru^{II}-catalyzed hydrogenation of a β -keto ester followed by alkylation and subsequent reduction.

The other challenge encountered in **5** is the 16-carbon spacer that has to connect the 1,3-diol moiety with the aromatic ring in rhamnoside **3**. It was found that such an α,ω -difunctionalized alkyl chain suitable for a Sonogashira reaction was readily accessible from commercially available alkynol **7**.

The third main block, mycocerosic acid (**4**), is one of several methyl-branched fatty acids from *M. tuberculosis* that we have synthesized over the years by using an iterative protocol comprising catalytic asymmetric conjugate addition, reduction, and Horner–Wadsworth–Emmons olefination.^[17] Conveniently, esterification of the 1,3-diol moi-

ety was planned for the last-but-one step of our synthesis, due to the precious nature of the all-*R*-tetramethyl-branched acid **4**. Finally, concomitant reduction of the triple bond and hydrogenolysis of the benzyl protecting groups should deliver mycoside B.

In parallel with the synthesis of PDIM-A and PGL-tb1, the synthesis of mycoside B commenced with building block **6** (Scheme 2).^[12,18] Thus, 2-cycloheptenone (**6**) was transformed into **9** in a one-pot catalytic asymmetric 1,4-addition of Me₂Zn followed by in situ alkylation with iodothane. Use of a catalyst prepared in situ from Cu^{II} triflate and a chiral phosphoramidite ligand (Feringa's ligand) afforded **9** in an *er* of 97.5:2.5.^[19] The *dr* of the alkylation is >20:1, considerably higher than generally observed in the corresponding six-membered-ring systems.^[20] We have also noted these excellent diastereoselectivities previously in eight-membered-ring systems.^[21] A regioselective and stereospecific Baeyer–Villiger reaction served to insert the oxygen at the stereogenic center bearing the ethyl substituent. Despite extensive experimentation, the best result obtained with the Baeyer–Villiger reaction was a moderate 60% yield, achieved by using *m*CPBA. Undoubtly this outcome is due to the increase in ring strain incurred on progressing from a seven- to an eight-membered ring, which renders the C-to-O shift in the reaction unfavorable. Versatile solutions to this problem are scarce, and also enzymatic Baeyer–Villiger reactions are invariably carried out on six-membered-ring systems or substrates for which ring strain is relieved. An accompanying problem is that more reactive congeners of *m*CPBA raise safety concerns.^[22] After methanolysis of **10**, methyl ester **11** was *O*-methylated to give ester **12**, thereby completing the construction of the right-hand side of **5**.

The reduction of **12** with DIBAL-H gave directly aldehyde **13**, which was smoothly transformed into intermediate β -keto ester **14** by using ethyl diazoacetate and 5 mol-% of NbCl₅ as catalyst.^[23] This opened the door for the anticipated asymmetric hydrogenation.^[24] By using 1 mol-% of (*R*)-[RuCl(tol-BINAP)]₂(μ -Cl)₃[(NH₂Me)₂] and a hydrogen pressure of 20 bar, we were rewarded with β -hydroxy ester **15** in good yield and with an excellent stereoselectivity

Scheme 1. Retrosynthetic analysis of mycoside B.

Scheme 2. Reagents and conditions: a) $\text{Cu}(\text{OTf})_2$ (0.5 mol-%), (*S,R,R*)-phosphoramidite (1 mol-%), Me_2Zn , toluene, -25°C ; then EtI, HMPA, 0°C , 83%, >20:1 *dr trans/cis*, 97.5:2.5 *er* (for *trans*); b) *m*CPBA, CH_2Cl_2 , reflux, 60%; c) K_2CO_3 , MeOH, room temp., 90%; d) NaH, MeI, DMF, room temp., 92%; e) DIBAL-H, Et_2O , -84°C , 86%; f) ethyl diazoacetate, NbCl_5 (5 mol-%), CH_2Cl_2 , 86%; g) (*R*)- $[(\text{RuCl}(\text{tol-BINAP}))_2(\mu\text{-Cl})_3][\text{NH}_2\text{Me}_2]$ (1 mol-%), 20 bar H_2 , EtOH, room temp., 76%, *dr* >99:1; h) AlMe_3 , $\text{MeNH}(\text{OMe})\cdot\text{HCl}$, THF, 73%. HMPA = hexamethylphosphoramide, *m*CPBA = *m*-chloroperbenzoic acid, DIBAL-H = diisobutylaluminium hydride.

(>99:1 *dr*). Treatment of ester **15** with AlMe_3 and *N,O*-dimethylhydroxylamine afforded Weinreb amide **16** in 76% yield, a better result than that obtained by using the corresponding lithium amide.

The installation of the long spacer of mycoside B was preceded by a four-step synthesis of building block **20**, as depicted in Scheme 3. Despite the potential of the alkyne zipper reaction to afford α,ω -bifunctionalized aliphatic chains of different lengths, its application to natural product synthesis has been very infrequent since its introduction by Brown and Yamashita in 1975.^[25,26] Here we used the reaction to shift the triple bond in commercially available alkyne **7** to the terminal position (compound **17**). Further elaboration involved TMS-protection of the acetylide unit, tosylation of the hydroxy group, and nucleophilic displacement with NaI, providing alkyne iodide **20** in a good overall yield.

The addition of **20**, after the formation of the corresponding alkyl Li reagent, to Weinreb amide **16** turned out not to be trivial (Scheme 4). First, a stepwise procedure with initial deprotonation of the hydroxy group in **16** was investigated. The deprotonation is important as it avoids elimination to the corresponding unsaturated amide. The use of NaH and *t*BuMgCl proved to be inconvenient. However, *t*BuLi could be used for this purpose as long as the amount of base did not exceed 1 equiv., otherwise the excess reagent formed a *tert*-butyl ketone by nucleophilic attack on the amide. At the same time, *t*BuLi was used to lithiate **20** by Li/halogen exchange. For this reason, the added amount of *t*BuLi for the exchange had to be carefully controlled to prevent any excess leading to the undesired formation of the inseparable *tert*-butyl ketone. Optimization showed that a ratio of **20**/*t*BuLi of 1:1.6 for the lithiation avoided that problem. For reasons of simplification and ro-

Scheme 3. Reagents and conditions: a) NaH, 1,3-diaminopropane, 70°C , 61%; b) *n*BuLi, TMSCl, THF, -40°C to room temp., 92%; c) *p*TsCl, pyridine, CHCl_3 , room temp., 87%; d) NaI, acetone, room temp., 86%.

Scheme 4. Reagents and conditions: a) **20**, *t*BuLi, Et₂O, −84 °C, 2 h, then amide **16**, 81%; b) NH₄BH(OAc)₃, MeCN, AcOH, THF, −25 °C, 75%; c) MeOH, K₂CO₃, room temp., quant. TMS = trimethylsilyl, *p*TsCl = *p*-toluenesulfonyl chloride.

business, we finally decided to discard the stepwise process and use an excess of lithiated **20** for both deprotonation and alkylation. After extensive optimization, we were very pleased to see the exclusive formation of the desired β -hydroxy ketone **21** in 81% yield.

Having both defined the third stereocenter and installed the spacer, the 1,3-diol in the required *anti* configuration had to be prepared from the β -hydroxycarbonyl moiety.^[27] Initially we applied the method reported recently by Phansavath and co-workers by diastereoselective hydrogenation with catalytic RuCl₃ and PPh₃.^[28] Although this provided the desired *anti*-diol, it also unfortunately resulted in concomitant reduction of the triple bond. Fortunately, the methodology of Evans and Chapman using NH₄BH(OAc)₃ gave **22** in good yield.^[29] The solvent for the reaction had to be adapted to secure sufficient solubility. With a view to the subsequent Sonogashira reaction, the TMS

group had to be removed. Stirring **22** in MeOH/K₂CO₃ completed this step to give the central building block **5** in quantitative yield.

At this point we turned our attention to the synthesis of rhamnoside **3**. The major challenge was to selectively methylate the hydroxy group at C-2. This was achieved by a strategy reported by Fürstner and Müller (Scheme 5).^[30] Peracetylation of L-rhamnose was followed by the formation of rhamnosyl bromide and subsequent reflux in ethanol with *sym*-collidine as an acid scavenger to provide orthoester **25**. One-pot acetate hydrolysis and benzylation of the hydroxy groups at C-3 and C-4 provided **26**, which, upon acidic hydrolysis, afforded a mixture of acetates **27** at C-1 and C-2. Separation was not necessary because under the conditions used for the formation of trichloroacetimidate **28**, both acetates rapidly interconvert, but only the rhamnoside with the acetate at C-2 is transformed into **28**.

Scheme 5. Reagents and conditions: a) Ac₂O, pyridine, room temp., 98%; b) HBr in AcOH, Ac₂O; c) *sym*-collidine, EtOH, Bu₄Ni, 80 °C, 8 h, 66% over both steps; d) BnBr, KOH, THF, reflux, 8 h, 78%; e) HOAc/H₂O (4:1), room temp., 16 h, 90%; f) Cl₃CCN, cat. NaH, CH₂Cl₂, 75% α + 11% β ; g) 4-iodophenol, TMSOTf, CH₂Cl₂, −45 °C to room temp., 90%; h) MeONa, MeOH, room temp., 87%; i) MeI, NaH, DMF, 0 °C, 95%. TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Although the formation of **28** has previously been achieved with Cs_2CO_3 as a catalyst, we were not satisfied with the reported yield. The use of NaH as base greatly improved the yield and gave **28** as an 87:13 mixture of α and β anomers in 86% yield.^[31]

The next step was the glycosylation of **28** with 4-iodophenol. A high α selectivity was ensured by participation of the acetyl group at C-2, which afforded **29** in 90% yield. Although we chose to use pure **28a** for the glycosylation, **28b** can also be used in this step with a similar result. Finally, the 2-acetyl group was methanolized and the resulting hydroxy function methylated to give **3** in high yield.

With both **5** and **3** in hand we proceeded with the Sonogashira reaction, a key step in our synthesis (Scheme 6). Pleasingly, the use of catalytic $[\text{PdCl}_2(\text{PPh}_3)_2]$ and CuI gave **31** in 91% yield.

The synthesis of mycocerosic acid (**4**) in 12% yield over 15 steps has previously been reported by our group.^[17c] Our methodology for the stereoselective synthesis of 1,3-methyl arrays was based on an iterative protocol. The first step involves a highly enantioselective Cu-catalyzed conjugate addition of MeMgBr to an α,β -unsaturated thioester (starting with achiral compound **8**). The reduction of the thioester to its aldehyde followed by olefination elongates the chain and leads to a new α,β -unsaturated thioester. For this synthesis of mycocerosic acid we applied the refinements developed in the synthesis of mycolipenic acid, using DIBAL-H for the reduction (replacing the Pd/C/Et₃SiH system) and Horner–Wadsworth–Emmons instead of Wittig olefinations.^[17d,17e]

Esterification of **31** with mycocerosic acid (**4**) was accomplished by employing EDC and DMAP in a moderate but acceptable 60% yield. As planned, the triple bond in ester **32** was completely reduced with Pd/C and 1 bar of H₂

with simultaneous removal of both benzyl protecting groups in the final step. In this way, mycoside B was prepared in 14 steps in an overall yield of 4.3% (linear sequence starting from cycloheptenone **6**). Full analysis of the resulting compound by NMR spectroscopy, MS, and optical rotation showed **1** to be identical to natural mycoside B.^[6]

With the experience gained in the synthesis of building block **3**, a synthetic route to *p*-HBAD-I (**2**) was planned. Most likely, methoxycarbonylation of **3** followed by debenzoylation would provide **2**. However, orthogonal protection with benzyl groups, as in the synthesis of mycoside B, was not required in the synthesis of *p*-HBAD-I. Therefore we opted for an alternative and more efficient synthesis.

Again, methylation at O-2 was the key and for this, selective protection of 3-OH and 4-OH was required. Unfortunately, methods that simultaneously protect two hydroxy groups in L-rhamnose-like acetals and orthoesters lead to *cis*-fused five-membered rings involving O-2 and O-3. Protection of diequatorial *trans*-1,2-diols with 1,2-diacetals according to Ley and co-workers, however, seemed to be a perfect alternative to protect 3-OH and 4-OH.^[32] To achieve this, Frost modification of Ley's methodology using 2,2,3,3-tetramethoxybutane was most convenient in terms of cost, ease of preparation, and selectivity.^[33]

Therefore peracetylated L-rhamnose **23** was subjected to BF₃·OEt₂-mediated glycosylation with methyl *p*-hydroxybenzoate (Scheme 7). Upon removal of the acetyl groups, triol **34** was successfully protected at O-3 and O-4 with 2,2,3,3-tetramethoxybutane, and O-2 was subsequently methylated. Both the protection and methylation steps were carried out in a convenient one-pot procedure in a moderate 43% yield.^[34] Treatment with TFA/water afforded the desired *p*-HBAD-I (**2**) in 50% yield. In retrospect, this

Scheme 6. Reagents and conditions: a) $[\text{PdCl}_2(\text{PPh}_3)_2]$ (5 mol-%), PPh_3 (5 mol-%), CuI (10 mol-%), Et₃N, 40 °C, 91%; b) EDC·HCl, DMAP, CDCl_3 , 62%; c) Pd/C, 1 bar H₂, EtOAc, EtOH, room temp., 76%. EDC·HCl = *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, DMAP = 4-(dimethylamino)pyridine, TMS = trimethylsilyl.

Scheme 7. Reagents and conditions: a) Ac_2O , pyridine, room temp., 98%; b) methyl 4-hydroxybenzoate, $\text{BF}_3\cdot\text{OEt}_2$, room temp., 18 h, 72%; c) MeONa , MeOH , room temp., 94%; d) i. CH_3CN , 2,2,3,3-tetramethoxybutane, $\text{BF}_3\cdot\text{OEt}_2$, 0 °C; ii. NaH , MeI , 0 °C, 43%; e) TFA /water 9:1, 50%.

route, comprising only five steps, could function as an alternative to the synthesis of building block **3**, requiring only benzylation at O-3 and O-4. Increasing the yield of the sequence **34**→**35**→**3** requires attention, however.

Conclusions

A first synthesis of mycoside B (**1**) has been achieved. The approach provides full stereocontrol; Cu-catalyzed asymmetric conjugate addition of MeMgBr and Me_2Zn introduces the methyl groups into the mycocerosic acid and the phthiocerol chain and Ru^{II} -catalyzed stereoselective hydrogenation followed by *anti* reduction defines the stereochemistry of the 1,3-diol. In the final stages of the synthesis, Sonogashira cross-coupling proved to be a versatile tool for connecting the glycosyl moiety. Taken together, this demonstrates the applicability of our approach to the synthesis of PGL-tb1 and mycoside B and therefore could be applied to the synthesis of other PGLs found in mycobacteria. In addition, *p*-HBAD-I (**2**) has been synthesized for the first time. Ley-type protection provides the desired compound in only five steps from rhamnose, and this should elicit further studies on the role of this compound in the attenuation of the host immune response.

Experimental Section

All reactions were performed by using oven- or flame-dried glassware and dry solvents. Solvents were distilled prior to use: MTBE, Et_2O , and THF over Na/benzophenone , and CH_2Cl_2 over CaH_2 . All other reagents were purchased from Sigma–Aldrich, Acros, TCI Europe, Alfa Aesar, Merck, and Apollo Scientific, and used without further purification unless noted otherwise. Grignard and organolithium reagents were titrated by using *s*BuOH and catalytic amounts of 1,10-phenanthroline. All moisture-sensitive reactions were performed under nitrogen.

^1H and ^{13}C NMR spectra were recorded with a Varian AMX400 or 400-MR spectrometer (400 and 100.59 MHz, respectively) using CDCl_3 or CD_3OD as solvent, unless stated otherwise. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl_3 : $\delta = 7.26$ ppm for ^1H , $\delta = 77.0$ ppm for ^{13}C ; CD_3OD : $\delta = 3.31$ ppm for ^1H). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants *J*, and integration. Due to the (multiple) long alkyl chains in some of the compounds, we were not able to resolve all the individual ^{13}C signals in the spectra. High-resolution mass spectra were recorded with a Thermo Scientific LTQ Orbitrap. Optical rotations were measured with a Propol automatic polarimeter (sodium D line, $\lambda = 589$ nm). HPLC analysis was performed with a Chiralcel AD 250 $\times$ 4.6 mm column with an ELS detector (ELSD).

Flash chromatography was performed by using SiliCycle SiliaFlash P60 (230–400 mesh), as obtained from Screening Devices, or by automated column chromatography using a Reveleris flash system purchased from Grace Davison Discovery Sciences. TLC analysis was performed on Merck silica gel 60/Kieselguhr F254 (0.25 mm). Compounds were visualized by using either Seebach's reagent [a mixture of phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H_2O (500 mL), and H_2SO_4 (25 mL)] or a KMnO_4 stain [K_2CO_3 (40 g), KMnO_4 (6 g), H_2O (600 mL), and 10% NaOH (5 mL)].

(6*S*,7*R*)-7-Methoxy-6-methylnonanal (13): For the complete synthesis of building block **12** from 2-cyclohepten-1-one (**6**), see ref.^[18] Diisobutylaluminum hydride (1 M in CH_2Cl_2 , 4.33 mL, 4.33 mmol) was added dropwise to a stirred solution of methyl (6*S*,7*R*)-7-methoxy-6-methylnonanoate (**12**;^[18] (780 mg, 3.61 mmol) in Et_2O (10 mL) at -84 °C under nitrogen. After completion of the reaction (20 min), as indicated by TLC (pentane/ Et_2O , 85:15), a few drops of MeOH were added to quench the reaction and the solution was warmed to room temp. A saturated solution of Rochelle's salt (3 mL) was added and the mixture was stirred for 30 min. Then the reaction mixture was diluted with Et_2O (40 mL), the layers were separated and the organic layer was washed with brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure

and the product was purified by flash chromatography to give aldehyde **13** (560 mg, 3.01 mmol, 89% yield) as a colorless oil together with a small amount of the related alcohol (18 mg, 3% yield). The spectroscopic data were in agreement with a previous report.^[18]

Ethyl (8*S*,9*R*)-9-Methoxy-8-methyl-3-oxoundecanoate (14): NbCl₅ (38.9 mg, 0.144 mmol) was added to a stirred solution of aldehyde **13** (536 mg, 2.88 mmol) in CH₂Cl₂ (30 mL) under nitrogen. After 5 min, ethyl diazoacetate (0.527 mL, 4.32 mmol) was added dropwise to the solution, taking care with the gas evolution. After completion of the reaction (2 h), as indicated by TLC (pentane/Et₂O, 85:15), the reaction mixture was mixed with water (30 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na₂SO₄). The CH₂Cl₂ was removed under reduced pressure and the product was purified by flash chromatography to give **14** (677 mg, 2.49 mmol, 86% yield) as a colorless oil. $[α]_D^{25} = -4.0$ (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 4.16 (q, *J* = 7.1 Hz, 2 H), 3.40 (s, 3 H), 3.30 (s, 1 H), 2.82 (ddd, *J* = 7.4, 5.3, 4.1 Hz, 2 H), 2.51 (t, *J* = 7.3 Hz, 1 H), 1.70–1.51 (m, 5 H), 1.48–1.29 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.28–1.14 (m, 2 H), 1.06 (m, 1 H), 0.87 (t, *J* = 7.4 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 202.8 (s), 167.2 (s), 86.5 (d), 61.3 (t), 57.3 (q), 49.2 (t), 42.9 (t), 34.6 (d), 32.3 (t), 26.9 (t), 23.7 (t), 22.3 (t), 14.7 (q), 14.0 (q), 9.9 (q) ppm. HRMS (ESI⁺): calcd. for C₁₅H₂₈O₄Na [M + Na]⁺ 295.1885; found 295.1866.

Ethyl (3*R*,8*S*,9*R*)-3-Hydroxy-9-methoxy-8-methylundecanoate (15): (R)-[{RuCl(tol-BINAP)}₂(μ-Cl)₃][NH₂Me₂] (34.4 mg, 0.019 mmol) was added to a solution of keto ester **14** (525 mg, 1.93 mmol) in degassed EtOH (10 mL) under nitrogen. This solution was placed in an autoclave and purged with N₂ and H₂. Hydrogen was introduced (20 bar) and the reaction mixture was stirred at room temp. overnight. After the hydrogen pressure was released, toluene (20 mL) was added and the solution was concentrated under reduced pressure to remove most of the ethanol. The resulting mixture was directly purified by flash chromatography to give **15** (400 mg, 1.46 mmol, 76% yield) as a colorless oil. $[α]_D^{25} = -15.8$ (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 4.13 (q, *J* = 7.1 Hz, 2 H), 3.96 (m, 1 H), 3.29 (s, 3 H), 3.01 (d, *J* = 3.8 Hz, 1 H), 2.82 (ddd, *J* = 7.7, 5.1, 4.0 Hz, 1 H), 2.46 (dd, *J* = 16.3, 3.3 Hz, 1 H), 2.35 (dd, *J* = 16.4, 8.9 Hz, 1 H), 1.75–1.57 (m, 1 H), 1.55–1.27 (m, 7 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.30–1.10 (m, 2 H), 1.11–0.97 (m, 1 H), 0.87 (t, *J* = 7.4 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 173.0 (s), 88.1 (d), 67.9 (d), 60.5 (t), 57.3 (q), 41.3 (t), 36.5 (t), 34.7 (d), 32.5 (t), 27.4 (t), 25.7 (t), 22.3 (t), 14.7 (q), 14.1 (q), 10.0 (q) ppm. HRMS (ESI⁺): calcd. for C₁₅H₃₁O₄ [M + H]⁺ 275.2217; found 275.2205.

A mixture of epimers was obtained for reference by the reduction of **14** with NaBH₄ to determine the diastereoselectivity of the reaction by chiral HPLC using the following conditions: Chiralcel AD column, 250 × 4.6 mm; eluent: heptane/IPA, 95:5; 6.56 min (major), 6.92 min (minor); *de* >99.5%.

(3*R*,8*S*,9*R*)-3-Hydroxy-*N*,9-dimethoxy-*N*,8-dimethylundecanamide (16): A solution of AlMe₃ in toluene (2 M, 2.71 mL, 5.41 mmol) was added to a stirred mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (528 mg, 5.41 mmol) in THF (15 mL) at 0 °C. The reaction was stirred for 2 h while warming up slowly to room temp. Subsequently the reaction was cooled to 0 °C and a solution of the hydroxy ester **15** (495 mg, 1.80 mmol) was slowly added. After completion of the reaction, as indicated by TLC (pentane/Et₂O, 3:7, 4 h), the reaction was quenched by adding 20% Rochelle's salt solution (5 mL) and the mixture was stirred for 30 min. Then

EtOAc (100 mL) and 2 M aq. NaOH (5 mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried (Na₂SO₄). The solvent was removed under reduced pressure and the product was purified by flash chromatography to give **16** (382 mg, 1.32 mmol, 73% yield) as a colorless oil.

$[α]_D^{25} = -48.6$ (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 4.01 (m, 1 H), 3.77 (s, 1 H), 3.68 (s, 3 H), 3.33 (s, 3 H), 3.19 (s, 3 H), 2.86 (ddd, *J* = 7.6, 5.0, 4.0 Hz, 1 H), 2.66 (d, *J* = 16.6 Hz, 1 H), 2.43 (dd, *J* = 17.0, 9.7 Hz, 1 H), 1.69 (d, *J* = 6.6 Hz, 1 H), 1.61–1.17 (m, 12 H), 1.17–1.04 (m, 1 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 173.6 (s), 86.4 (d), 67.6 (d), 61.0 (q), 57.1 (q), 38.0 (t), 36.4 (t), 34.5 (d), 32.4 (t), 31.5 (q), 27.3 (t), 25.6 (t), 22.1 (t), 14.5 (q), 9.8 (q) ppm. HRMS (ESI⁺): calcd. for C₁₅H₃₂NO₄ [M + H]⁺ 290.2331; found 290.2314.

Hexadec-15-yn-1-ol (17): NaH (60% in mineral oil, 6.41 g, 147 mmol) was washed with pentane and carefully added to a flask containing 1,3-diaminopropane (70 mL, highly hygroscopic!). The mixture was heated at 50 °C until it became clear (approx. 1 h). Then the mixture was cooled to room temp. and alkyne **7** (5.0 g, 21 mmol) was added. The mixture was then heated to 69 °C and stirred for 24 h. It was then poured into a beaker containing ice/water and extracted with Et₂O (3 × 75 mL). The combined organic extracts were washed with 0.1 M aq. HCl (30 mL), brine, and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified by flash chromatography to give **17** (3.05 g, 12.8 mmol, 61% yield) as a white solid. The spectroscopic data were in agreement with the literature.^[35] ¹H NMR (400 MHz, CDCl₃): δ = 3.60 (t, *J* = 6.7 Hz, 2 H), 2.15 (dt, *J* = 2.6, *J* = 7.1 Hz, 2 H), 1.91 (t, *J* = 2.6 Hz, 1 H), 1.67 (s, 1 H), 1.52 (m, 4 H), 1.38–1.24 (m, 20 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 84.6 (s), 67.9 (d), 62.8 (t), 32.6 (t), 29.56 (t), 29.54 (t), 29.52 (t), 29.43 (t), 29.37 (t), 29.03 (t), 28.6 (t), 28.4 (t), 25.6 (t), 18.3 (t) ppm.

16-(Trimethylsilyl)hexadec-15-yn-1-ol (18): *n*BuLi (1.6 M, 15.7 mL, 25.1 mmol) was added to a solution of alkynol **17** (2.72 g, 11.4 mmol) in THF (150 mL) at –45 °C. The mixture was stirred for 3 h, allowing the reaction to slowly warm to room temp. during this time. TMSCl (3.2 mL, 25.1 mmol) was then added and the cloudy mixture became clear in a few minutes. The reaction was monitored by quenching small samples of the reaction mixture with Et₂O/aq. NH₄Cl and analyzing the organic layer by TLC (pentane/EtOAc, 9:1). When full conversion was observed (TLC, ca. 1.5 h), aq. HCl (2 M, 5 mL) was added and the mixture was stirred for 30 min. Then most of the THF was removed under reduced pressure, water was added (60 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The solvent was removed under reduced pressure and the product was purified by flash chromatography to give **18** (3.25 g, 10.5 mmol, 92% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 3.62 (t, *J* = 6.7 Hz, 2 H), 2.19 (t, *J* = 7.2 Hz, 2 H), 1.58–1.44 (m, 5 H), 1.29 (m, 20 H), 0.13 (s, 9 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 107.8 (s), 84.2 (s), 63.0 (t), 32.8 (t), 29.6 (t), 29.58 (t), 29.56 (t), 29.45 (t), 29.41 (t), 29.04 (t), 28.76 (t), 28.60 (t), 25.7 (t), 19.8 (t), 0.2 (q) ppm. HRMS (ESI⁺): calcd. for C₁₉H₃₈OSiNa [M + Na]⁺ 333.2584; found 333.2581.

16-(Trimethylsilyl)hexadec-15-ynyl 4-Toluenesulfonate (19): Alkyne **18** (2.3 g, 7.4 mmol) and pyridine (1.8 mL, 22 mmol) were dissolved in CHCl₃ (10 mL) and the mixture stirred at 0 °C. Then, *p*-toluenesulfonyl chloride (2.82 g, 14.8 mmol) was added and the mixture was stirred until full conversion was observed by TLC (5 h). Subsequently, the mixture was diluted with Et₂O (75 mL) and washed

with water (10 mL), aq. HCl (2 M, 10 mL), aq. satd. NaHCO₃ (10 mL), and brine (10 mL). The organic extract was dried (MgSO₄), the solvent removed under reduced pressure, and the product purified by flash chromatography to give **19** (3.0 g, 6.5 mmol, 87% yield) as a colorless solid. ¹H NMR (400 MHz, CDCl₃): δ = 7.78 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 4.01 (t, *J* = 6.5 Hz, 2 H), 2.44 (s, 3 H), 2.20 (t, *J* = 7.2 Hz, 2 H), 1.62 (dt, *J* = 6.6, *J* = 13.5 Hz, 2 H), 1.50 (dt, *J* = 6.6, *J* = 13.5 Hz, 2 H), 1.40–1.21 (m, 20 H), 0.14 (s, 9 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 144.5 (s), 133.2 (s), 129.7 (d), 127.8 (d), 107.7 (s), 84.2 (s), 70.7 (d), 29.58 (d), 29.56 (d), 29.54 (d), 29.45 (d), 29.35 (d), 29.04 (d), 28.89 (d), 28.78 (d), 28.75 (d), 28.59 (d), 25.29 (d), 21.59 (d), 19.8 (d), 0.2 (q) ppm. HRMS (ESI⁺): calcd. for C₂₆H₄₄O₃SiNa [M + Na]⁺ 487.2678; found 487.2686.

(16-Iodoheptadec-1-ynyl)trimethylsilane (20): Tosylate **19** (1.71 g, 3.68 mmol) and sodium iodide (1.82 g, 12.1 mmol) were dissolved in acetone (40 mL) under nitrogen. The mixture was stirred until full conversion was observed by TLC (48 h). Then the mixture was diluted in EtOAc (50 mL), most of the acetone was removed under reduced pressure, and more EtOAc (50 mL) was added. The mixture was washed with aq. Na₂S₂O₃ (10%, 10 mL), water (10 mL), and brine (10 mL), and then dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified to give **20** (1.33 g, 3.16 mmol, 86% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 3.18 (t, *J* = 7.1 Hz, 2 H), 2.21 (t, *J* = 7.1 Hz, 2 H), 1.82 (q, *J* = 7.1 Hz, 2 H), 1.51 (q, *J* = 7.1 Hz, 2 H), 1.41–1.33 (m, 2 H), 1.31–1.24 (m, 18 H), 0.14 (s, 9 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 107.7 (q), 84.2 (q), 33.6 (t), 30.5 (t), 29.59 (t), 29.55 (t), 29.52 (t), 29.46 (t), 29.40 (t), 29.05 (t), 28.76 (t), 28.61 (t), 28.52 (t), 19.8 (t), 7.2 (t), 0.18 (q) ppm. HRMS (ESI⁺): calcd. for C₁₉H₃₇ISiNa [M + Na]⁺ 443.1607; found 443.1609.

(3R,4S,9R)-9-Hydroxy-3-methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yn-11-one (21): *t*BuLi (1.7 M, 3.58 mL, 6.08 mmol) was added to a stirred solution of iodoalkyne **20** (1.59 g, 3.79 mmol) in Et₂O (40 mL) at –84 °C (EtOAc/liq. N₂ bath). After 1 h at this temperature, a solution of Weinreb amide **16** (332 mg, 1.15 mmol) in Et₂O (20 mL) was added. The mixture was stirred until full conversion was observed by TLC (1 h). Then a saturated aqueous solution of NH₄Cl (10 mL) was added to quench the reaction. The mixture was diluted with additional Et₂O (20 mL), the aqueous layer was removed, and the organic layer washed with water (10 mL) and brine (10 mL). Et₂O was removed under reduced pressure and the product purified by flash chromatography to give compound **21** (484 mg, 0.926 mmol, 81% yield) as a colorless oil. [α]_D²⁵ = –13.6 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 4.00 (m, 1 H), 3.31 (s, *J* = 0.6 Hz, 3 H), 3.07 (s, 1 H), 2.85 (ddd, *J* = 7.7, 5.2, 4.2 Hz, 1 H), 2.57 (dd, *J* = 17.4, 2.6 Hz, 1 H), 2.47 (dd, *J* = 17.4, 8.9 Hz, 1 H), 2.40 (t, *J* = 7.4 Hz, 2 H), 2.19 (t, *J* = 7.1 Hz, 2 H), 1.72–1.62 (m, 1 H), 1.60–1.32 (m, 13 H), 1.31–1.15 (m, 20 H), 1.13–1.01 (m, 1 H), 0.89 (t, *J* = 7.4 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.12 (s, 9 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 212.6 (s), 107.7 (s), 86.6 (d), 84.2 (s), 67.6 (d), 57.3 (q), 48.9 (t), 43.7 (t), 36.4 (t), 34.8 (d), 32.6 (t), 29.59 (t), 29.55 (t), 29.54 (t), 29.44 (t), 29.41 (t), 29.34 (t), 29.13 (t), 29.0 (t), 28.8 (t), 28.6 (t), 27.4 (t), 25.8 (t), 23.6 (t), 22.3 (t), 19.8 (t), 14.8 (q), 10.0 (q), 0.1 (q) ppm. HRMS (ESI⁺): calcd. for C₃₂H₆₂O₃SiNa [M + Na]⁺ 545.4366; found 545.4355.

(3R,4S,9R,11R)-3-Methoxy-4-methyl-27-(trimethylsilyl)heptacos-26-yne-9,11-diol (22): Tetramethylammonium triacetoxymethylborohydride (1.69 g, 6.43 mmol) was added in portions over 30 min to a solution of **21** (480 mg, 0.918 mmol) in a mixture of AcOH (40 mL), MeCN (40 mL), and THF (3 mL) at –25 °C. The mixture

was stirred at this temperature for 5.5 h when TLC analysis showed full conversion (solvents were removed from the TLC spot with a heat gun before eluting with a pentane/Et₂O, 75:25 mixture). Subsequently, the reaction was quenched with an aqueous solution of Rochelle's salt (20%, 20 mL) and the mixture stirred at room temp. for 30 min. Water (300 mL) was then added to the mixture, which was then extracted with CH₂Cl₂ (4 × 75 mL) and Et₂O (75 mL). The organic extracts were combined and neutralized by adding water (30 mL) and solid NaHCO₃ until pH > 7. Then the aqueous layer was separated and the organic layer washed with water (20 mL) and brine (20 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified by flash chromatography to give compound **22** (360 mg, 0.686 mmol, 75% yield) as a white waxy solid. [α]_D²⁵ = –4.0 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 3.89 (m, 2 H), 3.31 (s, 3 H), 2.85 (ddd, *J* = 7.6, 5.3, 3.9 Hz, 1 H), 2.79 (br. s, 2 H), 2.18 (t, *J* = 7.2 Hz, 2 H), 1.73–1.60 (m, 1 H), 1.56 (t, *J* = 5.6 Hz, 2 H), 1.53–1.30 (m, 15 H), 1.33–1.16 (m, 20 H), 1.13–1.01 (m, 1 H), 0.89 (t, *J* = 7.3 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 0.12 (s, 9 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 107.7 (s), 86.7 (d), 84.2 (s), 69.30 (d), 69.25 (d), 57.3 (q), 42.2 (t), 37.45 (t), 37.43 (t), 34.8 (d), 32.6 (t), 29.63 (t), 29.62 (t), 29.60 (t), 29.55 (t), 29.45 (t), 29.03 (t), 28.74 (t), 28.58 (t), 27.5 (t), 26.1 (t), 25.8 (t), 22.3 (t), 19.8 (t), 14.8 (q), 10.0 (q), 0.1 (q) ppm. HRMS (ESI⁺): calcd. for C₃₂H₆₄O₃SiNa [M + Na]⁺ 547.4517; found 547.4514.

Note: The hydroxy ketone **21** has low solubility in AcOH/MeCN at –25 °C and therefore a high dilution was required. The mixture was not heterogeneous but cloudy, although it was not determined whether that was because of the low solubility or because AcOH was freezing.

(3R,4S,9R,11R)-3-Methoxy-4-methylheptacos-26-yne-9,11-diol (5): K₂CO₃ (142 mg, 10.3 mmol) was added to a solution of diol **22** in MeOH (15 mL) and the mixture was stirred overnight at room temp. Then the mixture was diluted with EtOAc (50 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified by short-column flash chromatography to give compound **5** (312 mg, 0.689 mmol, quantitative) as a white waxy solid. [α]_D²⁵ = –5.8 (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 3.92 (m, 2 H), 3.32 (s, 3 H), 2.86 (ddd, *J* = 7.7, 5.2, 4.3 Hz, 1 H), 2.40 (s, 2 H), 2.17 (td, *J* = 7.1, 2.7 Hz, 2 H), 1.92 (t, *J* = 2.6 Hz, 1 H), 1.73–1.63 (m, 1 H), 1.59 (t, *J* = 5.6 Hz, 2 H), 1.45 (dddd, *J* = 23.6, 21.3, 10.8, 5.0 Hz, 14 H), 1.34–1.16 (m, 21 H), 1.16–1.01 (m, 1 H), 0.90 (t, *J* = 7.4 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 86.7 (d), 84.8 (s), 69.42 (d), 69.37 (d), 68.0 (d), 57.5 (q), 42.3 (t), 37.48 (t), 37.47 (t), 34.8 (d), 32.6 (t), 29.63 (t), 29.58 (t), 29.48 (t), 29.08 (t), 28.7 (t), 28.5 (t), 27.5 (t), 26.1 (t), 25.8 (t), 22.3 (t), 18.4 (t), 14.8 (q), 10.0 (q) ppm. HRMS (ESI⁺): calcd. for C₂₉H₅₆O₃Na [M + Na]⁺ 475.4122; found 475.4123.

1,2,3,4-Tetra-O-acetyl-L-rhamnose (23): L-Rhamnose monohydrate (10.2 g, 62.2 mmol) was dissolved in acetic anhydride (65 mL) and pyridine (65 mL) and stirred for 16 h. Then, the solvents were removed under reduced pressure and the crude was purified by flash chromatography to give **23** (20.2 g, 61.0 mmol, 98% yield) as a colorless oil.

2-O-Acetyl-3,4-di-O-benzyl-α-L-rhamnosyl Trichloroacetimidate (28α) and 2-O-Acetyl-3,4-di-O-benzyl-β-L-rhamnosyl Trichloroacetimidate (28β): For the complete synthesis of compound **27** from L-rhamnose, see ref.^[30a] Compound **27** (a mixture of 1-O- and 2-O-acetyl rhamnosides, both α and β anomeric configurations; 11.3 g, 29.2 mmol) was dissolved in CH₂Cl₂ (45 mL). A catalytic amount of NaH (60% in mineral oil, 100 mg, 2.4 mmol) was added and the

mixture was stirred at 0 °C. Then Cl_3CCN (20.5 mL, 205 mmol, 7 equiv.) was added and the mixture stirred until consumption of the starting material (1.5 h). Silica gel (ca. 500 mg) was added to quench the reaction, and the mixture was filtered and concentrated under reduced pressure. The product was purified by flash chromatography to give compound **28a** (11.7 g, 22.1 mmol, 75% yield) and its anomer **28b** (1.7 g, 3.2 mmol, 10.9% yield). The spectroscopic data are in agreement with those of previous reports for these compounds.^[30]

28a: ^1H NMR (400 MHz, CDCl_3): δ = 8.67 (s, 1 H), 7.40–7.29 (m, 10 H), 6.20 (d, J = 1.9 Hz, 1 H), 5.51 (dd, J = 3.3, 2.0 Hz, 1 H), 4.95 (d, J = 10.8 Hz, 1 H), 4.75 (d, J = 11.2 Hz, 1 H), 4.66 (d, J = 10.8 Hz, 1 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.02 (dd, J = 9.5, 3.4 Hz, 1 H), 3.97 (dq, J = 9.8, 6.3 Hz, 1 H), 3.55 (t, J = 9.6 Hz, 1 H), 2.21 (s, 3 H), 1.38 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.0 (s), 160.1 (s), 138.1 (s), 137.5 (s), 128.4 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.89 (d), 127.85 (d), 95.2 (d), 79.3 (d), 77.2 (d), 75.6 (t), 72.0 (t), 70.7 (d), 67.6 (d), 21.0 (q), 18.0 (q) ppm.

28b: ^1H NMR (400 MHz, CDCl_3): δ = 8.66 (s, 1 H), 7.51–7.18 (m, 10 H), 5.90 (d, J = 2.9 Hz, 2 H), 4.96 (d, J = 10.9 Hz, 1 H), 4.79 (d, J = 11.2 Hz, 1 H), 4.66 (d, J = 10.9 Hz, 1 H), 4.55 (d, J = 11.2 Hz, 1 H), 3.77 (dd, J = 8.7, 3.1 Hz, 1 H), 3.68–3.46 (m, 2 H), 2.22 (s, 3 H), 1.44 (d, J = 5.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.23 (s), 160.17 (s), 138.07 (s), 137.35 (s), 128.39 (d), 128.32 (d), 128.07 (d), 127.95 (d), 127.82 (d), 127.75 (d), 95.04 (d), 79.49 (d), 79.01 (d), 75.35 (t), 72.79 (d), 71.49 (t), 66.47 (d), 20.85 (q), 17.79 (q) ppm.

The four compounds interconvert under these conditions and converge into a single product. Similarly, both **28a** and **28b** can be used in the next step to give a very similar result.

p-Iodophenyl 2-O-Acetyl-3,4-di-O-benzyl- α -L-rhamnopyranoside (29): A solution of **28a** (4.80 g, 9.04 mmol) in CH_2Cl_2 (15 mL) was added to a suspension of 4-iodophenol (3.78 g, 17.2 mmol) in CH_2Cl_2 (40 mL) at –45 °C. Then TMSOTf (163 μL , 0.9 mmol) was added and the mixture stirred while slowly warming to 20 °C. When **28a** had been completely consumed (1.5 h), pyridine (1 mL) was added to quench the reaction. The mixture was filtered and the solvents removed under reduced pressure. The residue was diluted in EtOAc (300 mL) and washed with a 3 M NaOH solution (2×30 mL), water (20 mL), NH_4Cl (20 mL), and brine (20 mL). The organic layer was dried with Na_2SO_4 , the solvent removed under reduced pressure, and the residue purified by flash chromatography to give compound **29** (4.79 g, 90% yield) as a colorless oil. $[\alpha]_D^{25}$ = –49.6 (c = 1.0, CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ = 7.58 (d, J = 8.7 Hz, 2 H), 7.42–7.29 (m, 10 H), 6.81 (d, J = 8.7 Hz, 2 H), 5.53 (m, 1 H), 5.44 (s, 1 H), 4.96 (d, J = 10.8 Hz, 1 H), 4.78 (d, J = 11.2 Hz, 1 H), 4.65 (d, J = 10.6 Hz, 1 H), 4.63 (d, J = 11.1 Hz, 1 H), 4.13 (dd, J = 9.3, 3.3 Hz, 1 H), 3.82 (dq, J = 9.8, 6.3 Hz, 1 H), 3.53 (t, J = 9.4 Hz, 1 H), 2.20 (s, 3 H), 1.31 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 170.3 (s), 155.7 (s), 138.4 (d), 138.2 (s), 137.8 (s), 128.4 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 118.6 (d), 95.8 (d), 85.1 (s), 79.8 (d), 77.6 (d), 75.5 (t), 72.0 (t), 68.66 (d), 68.67 (d) 21.0 (q), 17.94 (q) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{28}\text{H}_{28}\text{IO}_5\text{Na}$ [$\text{M} + \text{Na}$]⁺ 611.0910; found 611.0914.

p-Iodophenyl 3,4-Di-O-benzyl- α -L-rhamnopyranoside (30): Sodium methoxide (188 mg, 3.48 mmol) was added to a solution of compound **29** (4.1 g, 6.97 mmol) in MeOH (40 mL) and the mixture was stirred at room temp. until completion (24 h). The resulting solution was diluted with EtOAc (200 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue puri-

fied by flash chromatography to give compound **30** (3.32 g, 6.08 mmol, 87% yield) as a colorless oil. $[\alpha]_D^{25}$ = –113.6 (c = 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 7.58 (d, J = 9.0 Hz, 2 H), 7.44–7.30 (m, 10 H), 6.83 (d, J = 9.0 Hz, 2 H), 5.52 (d, J = 1.7 Hz, 1 H), 4.92 (d, J = 10.9 Hz, 1 H), 4.81 (d, J = 11.9 Hz, 1 H), 4.75 (d, J = 11.5 Hz, 1 H), 4.68 (d, J = 10.9 Hz, 1 H), 4.20 (dt, J = 3.1, 1.5 Hz, 1 H), 4.04 (dd, J = 9.1, 3.4 Hz, 1 H), 3.80 (dq, J = 9.8, 6.3 Hz, 1 H), 3.55 (t, J = 9.4 Hz, 1 H), 2.73 (d, J = 1.5 Hz, 1 H), 1.29 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 155.9 (s), 138.3 (d), 138.1 (s), 137.7 (s), 128.6 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.82 (d), 127.76 (d), 118.5 (d), 97.0 (d), 84.7 (s), 79.67 (d), 79.64 (d), 75.4 (t), 72.3 (t), 68.29 (d), 68.22 (d), 17.9 (q) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{26}\text{H}_{27}\text{IO}_5\text{Na}$ [$\text{M} + \text{Na}$]⁺ 569.0795; found 569.0807.

p-Iodophenyl 3,4-Di-O-benzyl-2-O-methyl- α -L-rhamnopyranoside (3): NaH (55% dispersion in mineral oil, 527 mg, 12.1 mmol) was added at 0 °C to a solution of **30** (3.30 g, 6.04 mmol) and methyl iodide (1.50 mL, 24.2 mmol) in DMF (30 mL). The mixture was stirred at 0 °C until completion (1 h), quenched with a saturated solution of NH_4Cl (20 mL), and diluted with Et_2O (300 mL). The organic layer was washed with NH_4Cl (20 mL) and brine (20 mL), dried (Na_2SO_4), the solvent removed under reduced pressure, and the residue purified by flash chromatography to give compound **3** (3.20 g, 5.71 mmol, 95% yield) as a colorless oil. $[\alpha]_D^{25}$ = –101.2 (c = 1.0, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 7.57 (d, J = 9.0 Hz, 1 H), 7.47–7.29 (m, 10 H), 6.82 (d, J = 9.0 Hz, 2 H), 5.49 (d, J = 1.9 Hz, 1 H), 4.96 (d, J = 10.8 Hz, 1 H), 4.81 (d, J = 12.5 Hz, 1 H), 4.77 (d, J = 12.5 Hz, 1 H), 4.66 (d, J = 10.8 Hz, 1 H), 4.04 (dd, J = 9.3, 3.2 Hz, 1 H), 3.73 (dq, J = 9.8, 6.3 Hz, 1 H), 3.70 (dd, J = 3.2, 2.0 Hz, 1 H), 3.60 (t, J = 9.5 Hz, 1 H), 3.58 (s, 3 H), 1.29 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 156.1 (s), 138.35 (s), 138.30 (d), 138.26 (s), 128.4 (d), 128.3, 127.9 (d), 127.8 (d), 127.73 (d), 127.66 (d), 118.5 (d), 95.5 (d), 84.7 (s), 80.2 (d), 79.5 (d), 77.8 (d), 75.5 (t), 72.5 (t), 68.8 (d), 59.6 (q), 17.9 (q) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{27}\text{H}_{29}\text{IO}_5\text{Na}$ [$\text{M} + \text{Na}$]⁺ 583.0952; found 583.0964.

4-[(17R,19R,24S,25R)-17,19-Dihydroxy-25-methoxy-24-methylheptacos-1-ynyl]phenyl 3,4-Di-O-benzyl-2-O-methyl- α -L-rhamnopyranoside (31): A stock solution of the catalyst was prepared by mixing PPh_3 (7.0 mg, 26.8 μmol), CuI (10.2 mg, 53.6 μmol), and $[\text{PdCl}_2(\text{PPh}_3)_2]$ (18.8 mg, 26.8 μmol) in freshly distilled Et_3N (8.9 mL) and stirring this solution at 40 °C for 15 min. Then this stock solution (1.8 mL, equivalent loading of 5 mol-% Pd, 5 mol-% PPh_3 , and 10 mol-% Cu) was added to a solution of compound **5** (58.2 mg, 128 μmol) and monosaccharide **3** (60.0 mg, 107 μmol) in freshly distilled Et_3N (0.3 mL). The mixture was then stirred at 40 °C until completion (5 h). Triethylamine was removed under a stream of nitrogen and the residue dissolved in toluene and purified by column chromatography to give compound **31** (86.0 mg, 97 μmol , 91% yield) as a waxy solid. $[\alpha]_D^{25}$ = –67.5 (c = 0.5, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ = 7.42 (d, J = 6.6 Hz, 2 H), 7.38–7.27 (m, 10 H), 6.93 (d, J = 8.9 Hz, 2 H), 5.51 (d, J = 1.8 Hz, 1 H), 4.95 (d, J = 10.8 Hz, 1 H), 4.81 (d, J = 12.2 Hz, 1 H), 4.75 (d, J = 12.5 Hz, 1 H), 4.64 (d, J = 10.8 Hz, 1 H), 4.04 (dd, J = 9.3, 3.2 Hz, 1 H), 3.93 (br. s, 2 H), 3.73 (dq, J = 9.8, 6.5 Hz, 1 H), 3.68 (dd, J = 3.2, 2.0 Hz, 1 H), 3.58 (d, J = 9.4 Hz, 1 H), 3.56 (s, 3 H), 3.34 (s, 3 H), 2.87 (ddd, J = 7.5, 5.2, 4.0 Hz, 1 H), 2.37 (t, J = 7.1 Hz, 2 H), 2.34 (s, 2 H), 1.72–1.02 (m, 39 H), 0.92 (t, J = 7.4 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 155.5 (s), 138.43 (s), 138.33 (s), 132.8 (d), 128.4 (d), 128.4 (d), 128.0 (d), 127.9 (d), 127.8 (d), 127.7 (d), 117.8 (s), 116.1 (d), 95.3 (d), 89.4 (s), 86.7 (d), 80.3 (d), 80.0 (s), 79.5 (d), 77.9 (d), 75.5 (t), 72.5 (t), 69.50 (d), 69.45 (d), 68.8 (d), 59.6 (q), 57.4 (q), 42.3 (t),

37.5 (t), 34.8 (d), 32.6 (t), 29.69 (t), 29.65 (t), 29.63 (t), 29.61 (t), 29.60 (t), 29.54 (t), 29.17 (t), 28.93 (t), 28.83 (t), 27.6 (t), 26.1 (t), 25.8 (t), 22.4 (t), 19.4 (t), 17.9 (q), 14.8 (q), 10.1 (q) ppm. HRMS (ESI⁺): calcd. for C₅₆H₈₄O₈Na [M + Na]⁺ 907.6064; found 907.6068.

4-[(17R,19R,24S,25R)-17,19-dimycocerosyloxy-25-methoxy-24-methylheptacos-1-ynyl]phenyl 3,4-Di-O-benzyl-2-O-methyl- α -L-rhamnopyranoside (32): A mixture of diol **31** (6.4 mg, 7.1 μ mol), mycroceroic acid (**4**; 13.8 mg, 29 μ mol), EDC hydrochloride (5.5 mg, 29 μ mol), and DMAP (7.0 mg, 57 μ mol) were dissolved in CDCl₃ (0.6 mL) and the mixture was stirred overnight. After completion of the reaction, as determined by ¹H NMR of the crude, the reaction was quenched by adding HCl (1 M in Et₂O solution, 0.2 mL), diluted with toluene, and the solvents partially removed under a nitrogen stream. The crude was purified by flash chromatography (pentane/Et₂O from 2:1 to 1:1) to give compound **32** (8.0 mg, 4.4 μ mol, 62% yield). $[\alpha]_D^{25} = -35.0$ (*c* = 0.4, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.42 (d, *J* = 6.6 Hz, 2 H), 7.38–7.27 (m, 10 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 5.51 (d, *J* = 1.8 Hz, 1 H), 4.95 (d, *J* = 10.8 Hz, 1 H), 4.84 (s, 2 H), 4.78 (s, 2 H), 4.64 (d, *J* = 10.8 Hz, 1 H), 4.04 (dd, *J* = 9.3, 3.1 Hz, 1 H), 3.78–3.65 (m, 2 H), 3.59 (t, *J* = 9.5, 8.2 Hz, 1 H), 3.56 (s, 3 H), 3.33 (s, 3 H), 2.86 (dt, *J* = 9.0, 4.6 Hz, 1 H), 2.65–2.43 (m, 2 H), 2.37 (t, *J* = 7.1 Hz, 2 H), 1.79–0.97 (m, 133 H), 0.96–0.77 (m, 39 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 176.04 (s), 175.97 (s), 155.5 (s), 138.4 (s), 138.3 (s), 132.8 (d), 128.42 (d), 128.36 (d), 128.0 (d), 127.9 (d), 127.74 (d), 127.66 (d), 117.9 (s), 116.1 (d), 95.4 (d), 89.3 (s), 86.7 (d), 80.3 (d), 80.0 (s), 79.6 (d), 78.0 (d), 75.5 (t), 72.5 (t), 70.3 (d), 68.8 (d), 59.6 (q), 57.4 (q), 45.3 (t), 41.0 (t), 37.7 (d), 36.6 (t), 34.8 (t), 31.9 (t), 30.3 (d), 30.1 (t), 29.9 (d), 29.7 (t), 29.36 (t), 29.36 (t), 28.99 (t), 28.88 (t), 28.1 (d), 27.5 (t), 27.2 (d), 27.0 (t), 25.6 (t), 25.2 (t), 22.7 (t), 22.3 (t), 20.8 (q), 20.5 (q), 20.41 (q), 20.38 (q), 19.4 (t), 18.4 (q), 17.9 (q), 14.1 (q), 10.1 (q) ppm. HRMS (ESI⁺): calcd. for C₁₂₀H₂₀₈O₁₀Na [M + Na]⁺ 1833.5693; found 1833.5673.

Mycoside B (1): Palladium on carbon (10% dry basis Degussa type E101 NE/W, 9.4 mg of wet compound, 1 equiv.) was added to a solution of diester **32** (8.0 mg, 4.4 μ mol) in a mixture of EtOAc (0.8 mL) and EtOH (0.2 mL) under nitrogen. A balloon filled with H₂ was attached to the apparatus and the reaction was stirred for 4 h. Then the catalyst was removed by filtration through a plug of cotton and Celite, eluting with additional EtOAc (20 mL). The solvent was removed under reduced pressure and the crude was purified by flash chromatography to give mycoside **B (1)**; 5.5 mg, 3.4 μ mol, 76% yield) as a waxy solid. The spectroscopic data coincide with that reported for the natural product.^[6] $[\alpha]_D^{25} = -19.5$ (*c* = 0.275, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.10 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.5 Hz, 2 H), 5.54 (s, 1 H), 4.84 (t, *J* = 6.1 Hz, 2 H), 3.92 (dd, *J* = 9.5, 2.8 Hz, 1 H), 3.75 (dq, *J* = 10.5, 6.2 Hz, 1 H), 3.66 (d, *J* = 2.4 Hz, 1 H), 3.52 (s, 3 H), 3.44 (t, *J* = 9.5 Hz, 3 H), 3.33 (s, 3 H), 2.85 (d, *J* = 4.9 Hz, 1 H), 2.55 (d, *J* = 7.6 Hz, 2 H), 1.98–0.79 (m, 176 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 175.99 (s), 175.96 (s), 154.48 (s), 136.88 (s), 129.32 (d), 116.12 (d), 94.73 (d), 86.65 (d), 80.16 (d), 74.00 (d), 71.41 (d), 70.29 (d), 68.36 (d), 58.97 (q), 57.37 (q), 45.51 (t), 45.30 (t), 40.98 (t), 38.45 (t), 37.78 (d), 37.74 (d), 36.63 (t), 35.13 (t), 34.81 (t), 34.70 (d), 32.62 (t), 31.93 (t), 31.69 (t), 30.09 (t), 29.94 (d), 29.79 (t), 29.72 (t), 29.66 (t), 29.58 (t), 29.55 (t), 29.36 (t), 29.34 (t), 28.05 (d), 27.49 (t), 27.21 (d), 26.97 (t), 25.56 (t), 25.16 (t), 22.69 (t), 22.35 (t), 20.76 (q), 20.46 (q), 20.42 (q), 20.39 (q), 18.43 (q), 17.56 (q), 14.72 (q), 14.12 (q), 10.10 (q) ppm. HRMS (ESI⁺): calcd. for C₁₀₆H₂₀₀O₁₀Na [M + Na]⁺ 1657.5067; found 1657.5058.

4-(Methoxycarbonyl)phenyl 2,3,4-Tri-O-acetyl- α -L-rhamnose (33): Peracetylated rhamnose **23** (2.00 g, 6.02 mmol) and methyl *p*-hy-

droxybenzoate (1.83 g, 12.04 mmol) were dissolved in CH₂Cl₂ (30 mL). The solution was cooled to 0 °C and BF₃·OEt₂ (2.3 mL, 18.1 mmol) was added. The reaction was allowed to warm to room temp. and stirred for 18 h. The reaction was subsequently quenched with a saturated solution of NaHCO₃ (30 mL) and diluted with EtOAc (200 mL). The organic layer was washed with a saturated solution of NaHCO₃ (30 mL) and brine (30 mL), dried (Na₂SO₄), and the solvent removed under reduced pressure. The crude was purified by flash chromatography to give compound **33** (1.83 g, 4.31 mmol, 72% yield) as a white solid containing less than 4% of the β anomer, m.p. 115.1–115.7 °C. $[\alpha]_D^{25} = -91.8$ (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, *J* = 8.9 Hz, 2 H), 7.09 (d, *J* = 8.9 Hz, 2 H), 5.52 (d, *J* = 1.4 Hz, 1 H), 5.48 (dd, *J* = 10.1, 3.5 Hz, 1 H), 5.42 (dd, *J* = 3.4, 1.8 Hz, 1 H), 5.14 (t, *J* = 10.0 Hz, 1 H), 3.92 (dq, *J* = 8.7, 5.6 Hz, 1 H), 3.87 (s, 3 H), 2.18 (s, 3 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.18 (d, *J* = 6.3 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 169.94 (s), 169.93 (s), 169.85 (s), 166.5 (s), 159.2 (s), 131.6 (d), 124.5 (s), 115.8 (d), 95.3 (d), 70.7 (d), 69.4 (d), 68.7 (d), 67.4 (d), 51.9 (q), 20.8 (q), 20.71 (q), 20.67 (q), 17.4 (q) ppm. HRMS (ESI⁺): calcd. for C₂₀H₂₄O₁₀Na [M + Na]⁺ 447.1262; found 447.1260.

4-(Methoxycarbonyl)phenyl α -L-Rhamnose (34): Sodium methoxide (17 mg, 0.32 mmol) was added to a solution of compound **33** (1.37 g, 3.23 mmol) in MeOH (10 mL) and the mixture was stirred at room temp. until complete conversion was observed by TLC (2 h). The reaction was quenched by the addition of Amberlite H⁺ (10 g) and the mixture stirred for 5 min. The mixture was filtered, the solvent removed under reduced pressure, and the crude was purified by flash chromatography to give compound **34** (903 mg, 3.03 mmol, 94% yield) as a white solid, m.p. 44–46 °C. $[\alpha]_D^{25} = -119.4$ (*c* = 1.0, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 7.97 (d, *J* = 9.0 Hz, 2 H), 7.06 (d, *J* = 9.0 Hz, 2 H), 5.59 (d, *J* = 1.5 Hz, 1 H), 4.18 (br. s, 1 H), 4.01 (dt, *J* = 8.3, 4.0 Hz, 1 H), 3.89 (s, 3 H), 3.71 (dq, *J* = 10.2, 6.1 Hz, 1 H), 3.60 (td, *J* = 9.5, 2.2 Hz, 1 H), 3.46 (d, *J* = 5.0 Hz, 1 H), 3.28 (d, *J* = 3.6 Hz, 1 H), 3.05 (br. s, 1 H), 1.27 (d, *J* = 6.1 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 166.7 (s), 159.5 (s), 131.5 (d), 124.0 (s), 115.6 (d), 97.4 (d), 72.7 (d), 71.4 (d), 70.7 (d), 69.2 (d), 52.0 (q), 17.5 (q) ppm. HRMS (ESI⁺): calcd. for C₁₄H₁₈O₇Na [M + Na]⁺ 321.0945; found 321.0944.

4-(Methoxycarbonyl)phenyl 3,4-O-Ley-protected-2-O-Methyl- α -L-rhamnose (also Methyl 4-[(2R,3R,4aS,5S,7S,8R,8aR)-2,3,8-trimethoxy-2,3,5-trimethylhexahydro-2H-pyrano[3,4-*b*][1,4]dioxin-7-yl]oxy}benzoate, 35): Amberlite-H⁺ 1200 (6.5 g) was added to a solution of 2,3-butadione (11.7 g, 136 mmol) and trimethyl orthoformate (60 mL, 544 mmol) in methanol (225 mL). The mixture was heated at reflux for 2 d (GC analysis shows, though, little difference between 24 and 48 h) and then filtered. The volatiles were removed under reduced pressure in a rotavap to give a dark crude oil. ¹H and ¹³C NMR analysis of this oil showed 2,2,3,3-tetramethoxybutane as the product. (GC–MS analysis also showed a peak corresponding to 2,3,3-trimethoxy-1-butene, but this is probably due to partial elimination of methanol in the injector). The crude oil was used in the next step without further purification.

BF₃·OEt₂ (5.1 μ L, 40 μ mol) was added at 0 °C to a solution of monosaccharide **34** (400 mg, 1.34 mmol) and crude 2,2,3,3-tetramethoxybutane (311 mg, 1.74 mmol) in acetonitrile (4 mL). The reaction was stirred until TLC analysis showed complete consumption of **34** (2.5 h). Then iodomethane (335 μ L, 5.36 mmol) and NaH (60% in mineral oil, 215 mg, 5.36 mmol) were added to the reaction, which was stirred until complete conversion of the intermediate alcohol (1 h). The reaction was diluted with EtOAc

(70 mL) and washed with water (15 mL) and brine (15 mL). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude was purified by flash chromatography to give compound **35** (246 mg, 0.58 mmol, 43% yield) as a white solid containing 10% of a minor diastereomer (in the dioxolanone ring), m.p. 176–178 °C. $[\alpha]_D^{25} = -254.2$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.98$ (d, $J = 9.0$ Hz, 2 H), 7.06 (d, $J = 8.9$ Hz, 2 H), 5.60 (d, $J = 1.6$ Hz, 1 H), 4.20–4.15 (m, 1 H), 3.87 (s, 3 H), 3.83–3.72 (m, 2 H), 3.65 (dd, $J = 3.1$, 1.7 Hz, 1 H), 3.56 (s, 3 H), 3.34 (s, 3 H), 3.25 (s, 3 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.21 (d, $J = 5.7$ Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): $\delta = 166.67$ (s), 159.8 (s), 131.5 (d), 123.9 (s), 115.7 (d), 100.0 (s), 99.6 (s), 95.7 (d), 78.3 (d), 68.35 (d), 68.05 (d), 68.00 (d), 59.4 (q), 51.9 (q), 48.00 (q), 47.6 (q), 17.77 (q), 17.76 (q), 16.6 (q) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{21}\text{H}_{30}\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$ 449.1782; found 449.1783.

4-(Methoxycarbonyl)phenyl 2-O-Methyl- α -L-rhamnose (*p*-HBAD-I, **2):** Compound **35** (240 mg, 0.56 mmol) was dissolved in TFA/water (9:1) at room temp. and after 2 min the volatiles were evaporated under reduced pressure. The crude was purified by flash chromatography to give compound **2** (87 mg, 0.28 mmol, 50% yield) as a white solid. The spectroscopic data coincide with that reported for the natural product, m.p. 113–114 °C. $[\alpha]_D^{25} = -94.6$ ($c = 1.0$, CHCl_3). ^1H NMR (400 MHz, CDCl_3): $\delta = 8.00$ (d, $J = 7.4$ Hz, 3 H), 7.10 (d, $J = 7.4$ Hz, 2 H), 5.65 (s, 1 H), 3.98–3.89 (m, 1 H), 3.89 (s, 3 H), 3.67 (dd, $J = 14.4$, 5.0 Hz, 2 H), 3.54 (s, 3 H), 3.46 (t, $J = 9.1$ Hz, 1 H), 2.58 (s, 2 H), 1.26 (d, $J = 5.3$ Hz, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): $\delta = 166.6$ (s), 159.8 (s), 131.5 (d), 123.9 (s), 115.7 (d), 94.4 (d), 80.0 (d), 73.1 (d), 71.1 (d), 69.0 (d), 59.1 (q), 51.87 (q), 17.5 (q) ppm. HRMS (ESI⁺): calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_7\text{Na}$ $[\text{M} + \text{Na}]^+$ 335.1101; found 335.1107.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all compounds, except for those, which are previously reported in the literature and are properly referred to in the text (6; 9–13; 23–27).

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