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TETRAHEDRON

Synthesis of Ribosylhopane, the Putative Biosynthetic Precursor of Bacterial Triterpenoids of the Hopane Series

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Abstract. A versatile, efficient route to ribosylhopane with control over all asymmetric carbon atoms of the side-chain is presented. The synthesis is based on two chain elongations starting from diploptene by subsequent additions of two acetylenic moieties. In a key step a keto-propiolate is stereoselectively reduced to the corresponding hydroxy-propiolate by means of a chiral oxazaborolidine assisted hydroboration. This synthetic protocol represents a useful tool for the access to natural and unnatural bacteriohopanepolyol derivatives of biological interest as well as to labeled ribosylhopane and bacteriohopanetetrol for biosynthetic studies.

Keywords: bacterial triterpenoids, bacteriohopanetetrol, hopanoids, ribosylhopane.

INTRODUCTION

Bacteriohopanepolyols represent a particularly interesting class of triterpenoids.[1] They are widespread in bacteria, and their role as membrane stabilizers in prokaryotes is well accepted.[2] These remarkable triterpenoids can be easily distinguished by the presence of an extended non-terpenoid side-chain of carbohydrate origin attached to a pentacyclic triterpenic moiety via a carbon-carbon bond.[3] A large number of such bacterial hopanoids have been characterized, showing a huge diversity in both structures and functionalities, especially in the side-chain.[2a] Some rather peculiar features include groups such as adenine, carbohydrates and amino-acids which have sparked speculations of other possible important biological roles for at least some of these compounds.[4]

Biosynthetic studies primary focused on the formation of the side-chain more than ten years ago led to the surprising discovery of an alternative non-mevalonate pathway for isoprenoid biosynthesis, which is now well documented in bacteria, algae and higher plants.[3,5] Several aspects concerning the biosynthesis of the hopanoid side-chain, however, still remain largely obscure. The majority of these side-chains consists of a polyhydroxyla-

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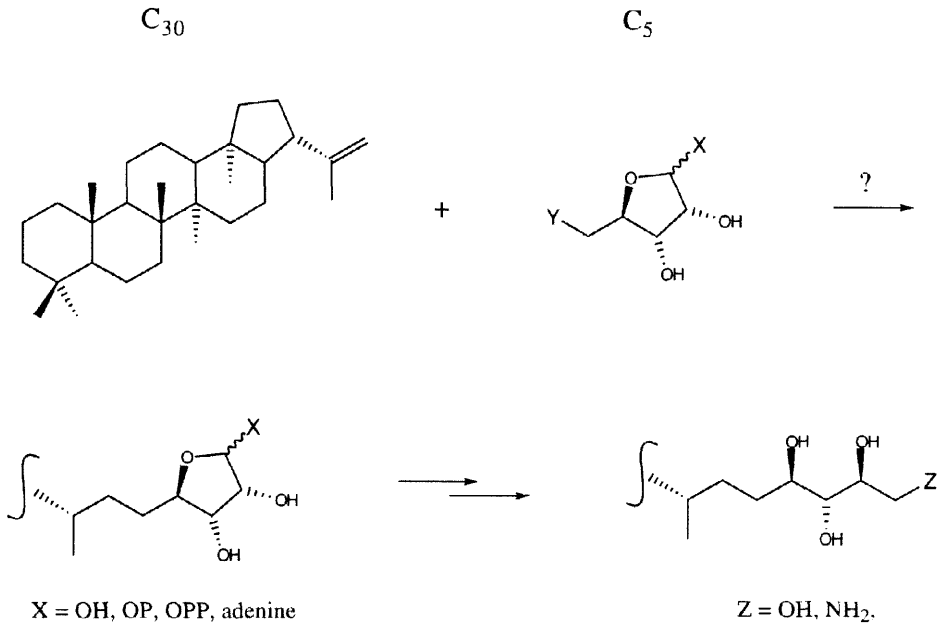
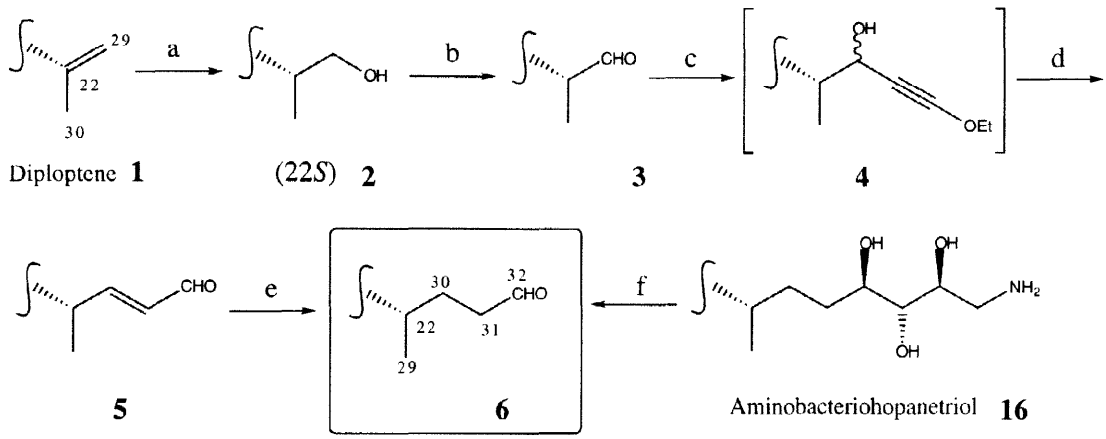


Scheme 1. Hypothetic biogenetic scheme for bacteriohopanepolyol biosynthesis. Ribosylhopane derivative as putative precursor of bacteriohopanepolyols.

ted C_5 unit often terminally substituted with other functional groups as mentioned above. Incorporation experiments using isotope labeled metabolites have demonstrated the origin of the side-chain from a D-pentose precursor (Scheme 1).[3,6] Neither the exact nature of the precursors for the pentose and of the triterpene moieties, nor the mechanism allowing the insertion of the side-chain are so far known. The C_5 side-chain is normally present with a D-ribo configuration,[7] which suggests the existence of a single biogenetic precursor such as ribosylhopane (Scheme 1),[1b] although this compound itself has never been detected in bacteria. This hypothesis is further supported by the recent finding of the corresponding lactone in the chemo-autotrophic bacterium *Nitrosomonas europaea*.[8] This lactone represents the oxidized putative ribosylhopane precursor. Several attempts aimed at synthesizing ribosylhopane in order to elucidate the biosynthesis of bacteriohopanepolyols have been carried out. In a first approach, one made use of appropriate D-ribose precursors coupled to the triterpenic skeleton by Wittig type reactions.[9-11] This biomimetic strategy, inspired by the proposed biogenetic route to the bacteriohopane skeleton, afforded the desired ribosylhopane, although always in unsatisfactory yields. In a second approach, ribosylhopane was formed by oxidation of an aminobacteriohopanetriol **16** derivative by dimethyldioxirane.[12] The latter method was of limited synthetic value due to the lack of available starting material and to the few possible synthetic variations for the preparation of alternative related analogs. In this paper, we wish to present a new convenient strategy of general utility leading

to this putative biosynthetic ribosylhopane precursor in a stepwise stereoselective manner in good overall yields using available starting materials. This synthetic strategy also offers a more general approach for side-chain construction of bacteriohopanepolyols and should therefore be of value in the preparation of numerous natural as well as unnatural analogs for the evaluation of their possible biological roles.



Scheme 2. Synthesis of bis-homohopan-32-al **6** from diploptene **1** or from aminobacteriohopanetriol **16**. a) 9-BBN, THF, rt; $NaOH/H_2O_2$. (b) $(COCl)_2$/DMSO, CH_2Cl_2, -78°C. (c) LiC≡COEt, THF, -78°C. (d) $LiAlH_4$, Et_2O, reflux; H_2SO_4. (e) H_2, $Pd/CaCO_3$, THF. (f) H_5IO_6, THF/H_2O.

RESULTS AND DISCUSSION

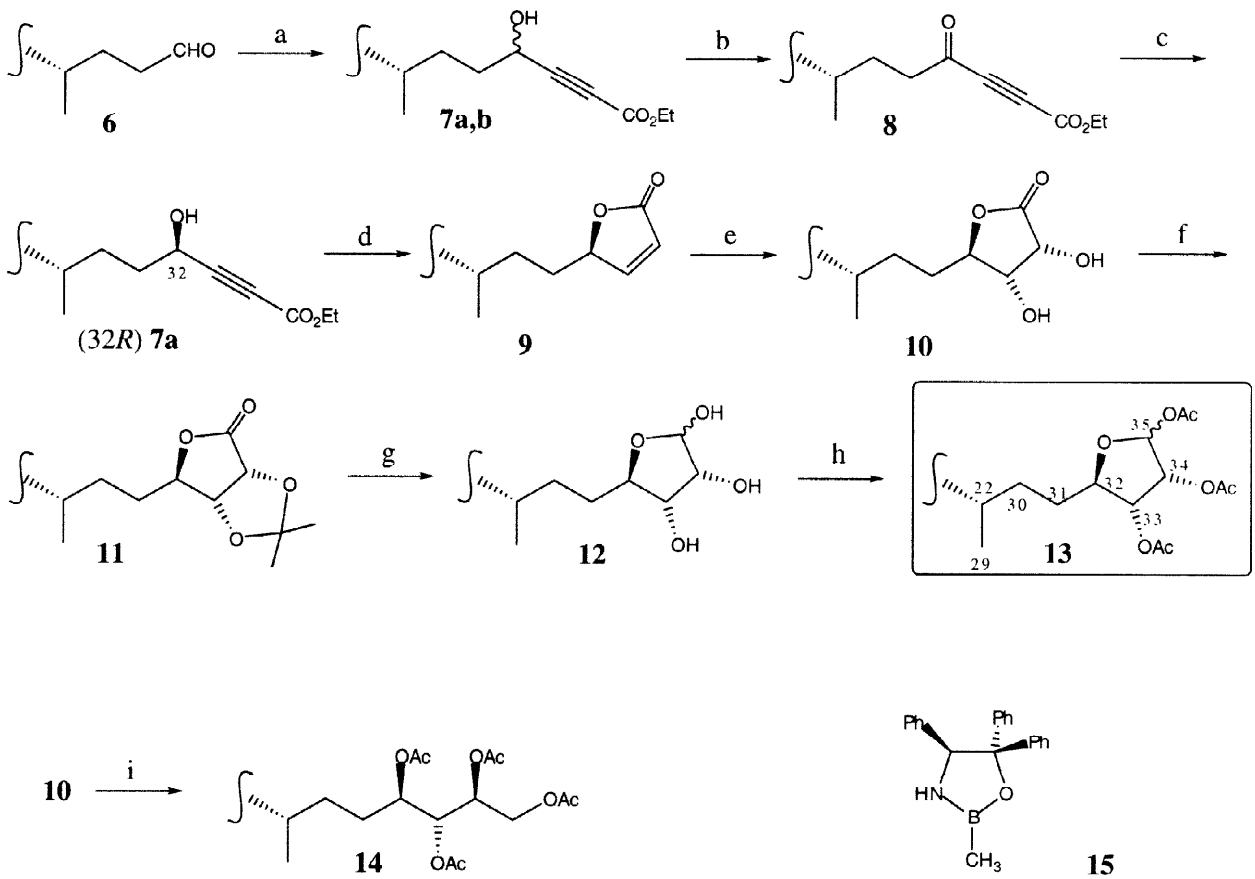
The synthetic strategy was to take advantage of the coupling of a C_3 unit in the form of lithium ethyl propiolate to an appropriate C_{32} aldehyde **6**, synthesized in good yields from diploptene **1** in a stereoselective manner (Scheme 2). After the coupling of lithium ethyl propiolate to the aldehyde, the propargylic moiety could efficiently be transformed further to the unsaturated lactone **9**, which could finally be derivatized to the desired ribosylhopane **12** (Scheme 3). The addition of lithium propiolate to the C_{32} aldehyde produced two epimers of propargylic alcohol **7a,b** in equal amounts. After considerable experimentation, the configuration of C-32 could be controlled by an oxidation-reduction procedure in which the propargylic alcohols **7a,b** were first oxidized to the corresponding ketone **8**, and then stereoselectively reduced back to the alcohol **7a** with diborane in presence of the chiral oxazaborolidine **15**.[13] Asymmetric reductions of propargylic ketones by this method have previously been of little success,[14] and, only recently, a few reports appeared for oxazaborolidine assisted

reductions of propargylic ketones with a trimethylsilyl substituted acetylenic bond.[15] Other known methods for asymmetric reductions of propargylic ketones, including Alpine® borane[16] and $LiAlH_4$ modified with various chiral auxiliaries such as *N*-methylephedrine[17] and binaphtol,[18] failed to afford acceptable stereochemical control. To the best of our knowledge, this is the first report of oxazaborolidine assisted hydroboration of a ketopropiolate.

The starting C_{32} aldehyde **6** was obtained in excellent yields by a sequence as outlined in Scheme 2. Diploptene **1** was initially hydroborated with 9-BBN to yield alcohol **2** in 90% d.e., in favor of the 22*S* epimer with the configuration of the natural biohopanoids, which could be easily separated from the 22*R* epimer by ordinary silica gel chromatography. The alcohol **2** was quantitatively oxidized to the corresponding aldehyde **3** by the Swern oxidation. Reaction of this aldehyde with lithium **ethoxyacetylene** [19] followed by $LiAlH_4$ reduction of the resulting acetylenic compound **4** afforded the α,β-unsaturated aldehyde **5**. Finally, hydrogenation of **5** over Lindlar catalyst yielded the desired C_{32} aldehyde **6**. The same aldehyde could alternatively be obtained by treating aminobacteriohopanetriol **16** (Scheme 2) with periodic acid.[20] The two aldehydes were identical in all respects as shown by comparison of the NMR spectra and the melting points.

The C_{32} aldehyde **6** was reacted with lithium ethyl propiolate at low temperature to form a 1:1 mixture of the 32*S* and 32*R* epimers of propargyl alcohols **7a,b**. The oxidation/reduction procedure discussed above afforded propargylic alcohol **7a** with the desired 32*R* configuration in 84% d.e. as predicted from a mechanistic viewpoint[15a] and later shown by comparison of the acetylated bacteriohopanetetrol resulting from this synthesis with the acetylated natural compound of known configuration.[7] The diastereomeric excess was evaluated by ^{1}H-NMR of the Mosher esters of the propargylic alcohols **7a,b** obtained after treatment with (*R*)- or (*S*)-α-methoxy-α-trifluromethylphenylacetyl chloride. Attempts to purify the largely predominant 32*R* epimer, including different HPLC systems, did not succeed. Strong oxidation conditions using Jones reagent were required for the oxidation of propargylic alcohols **7a,b** to the corresponding ketone **8**. The best result of the asymmetric reduction of propargylic ketone **8** was obtained when the propargylic ketone was slowly added at 0°C to a mixture of excess diborane and freshly synthesized oxazaborolidine **15** (0.2 to 0.8 equivalents).[15a] The triple bond was reduced to a *cis* double bond by hydrogenation over Lindlar catalyst and directly lactonized by treating the crude ester with NaH in THF yielding the α,β-unsaturated lactone **9**. Attempts to directly purify the resulting acyclic α,β-unsaturated ester on silica gel caused partial lactonisation. Dihydroxylation of unsaturated furanone **9** in pyridine with stoechiometric amounts of OsO_4 solely proceeded with attack from the less hindered

side (α face). Procedures using catalytic amounts of OsO_4[21] gave only poor yields of the desired diol, and 18-crown-6 catalyzed dihydroxylation using $KMnO_4$[22] was much less stereoselective than OsO_4, producing ca. 25% of the undesired diol. The resulting diol **10** was protected with an acetonide group, and lactone **11** was then reduced to a lactol by DIBAL in toluene at low temperature, and the acetonide group was split off upon heating in aqueous acetic acid, affording the desired ribosylhopane **12** which was most conveniently purified and characterized as triacetate **13**. Direct reduction of crude lactone **10** with $LiAlH_4$ followed by acetylation yielded the tetraacetate of bacteriohopanetetrol **14** which was identical in all respects to the natural (32*R*,33*R*,34*S*)-bacteriohopanetetrol,[7] demonstrating the absolute configuration of all asymmetric carbon atoms of our synthetic samples.



Scheme 3. Synthesis of acetylated ribosylhopane **13** and bacteriohopanetetrol **14**.

(a) $LiC{\equiv}CCO_2Et$, THF, -78°C. (b) CrO_3/H_2SO_4, acetone/THF/water. (c) B_2H_6/chiral oxazaborolidine **15**, THF, 0°C. (d) $H_2/PdCO_3$, quinoline, benzene; NaH, THF, rt. (e) OsO_4, pyridine, rt,. (f) 2,2-dimethoxypropane/TsOH. (g) DIBAL, toluene, -78°C; AcOH, H_2O, Δ. (h) Ac_2O/pyridine. (i) $LiAlH_4$, THF, reflux; Ac_2O/pyridine.

This new synthesis of ribosylhopane not only represents an efficient method for the preparation of the putative biogenetic precursor of bacterial hopanoids that can be used for their detection in living bacteria or, as molecular fossil, in the organic matter of sediments, but also a versatile method for the preparation of various natural and unnatural analogs of bacteriohopanepolyols with potential biological importance. Ribosylhopane derivatives **11**, **12** and **13** can, for instance, be employed for the preparation of naturally occurring adenosylhopane by known methods. Aminolysis of the corresponding lactone **11** followed by reduction as described previously[11] can be used for the preparation of aminobacteriohopanetriol **16** as well as its amino acid containing derivatives.[4b] The synthetic methodology here presented could also be of use in the preparation unsubstituted analogs often encountered in sediments and oils as molecular fossils.[23] Application of a similar synthetic protocol has also been employed for the construction of other terpenoids with polyhydroxylated C_5 side-chains and will be published in due course.

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EXPERIMENTAL SECTION

General

Reagents were of analytical grade or of similar purity and used as purchased. All solvents were redistilled before use. Anhydrous solvents were dried as follows. THF and Et_2O were distilled from sodium benzophenone ketyl immediately before use. CH_2Cl_2 was distilled from CaH_2. Acetone, hexanes, pentane, toluene and DMSO were stored for several days over a bed of molecular sieves (4Å) and then carefully distilled. Progress of reactions was monitored by TLC using 0.25 mm aluminum-coated silica sheets (Merck 60 F254). Products were visualized by spraying with diluted H_2SO_4 followed by heating or, whenever possible, under UV light (254 nm). Products were purified by flash column chromatography (FCC) using wet packed silica gel (Merck 60, 230-400 mesh) and moderate overpressure or by preparative TLC on glass-coated silica gel plates (Merck 60. F_{254}, 0.25 mm layer). Eluted preparative TLC were sprayed with a 0.1% ethanolic solution of berberine hydrochloride and visualized under UV light (366 nm). Analytical samples of crystalline compounds were obtained from CH_2Cl_2/MeOH after careful evaporation of CH_2Cl_2. Melting points were measured on a Reichert Thermovar microscope and are uncorrected. NMR spectra were recorded on a Bruker AC 200 or a Bruker AC 500. All NMR experiments were carried out in $CDCl_3$ using the signal of $CHCl_3$ as internal standard (δ=7.26 ppm) for ^{1}H-NMR and of $CDCl_3$ (δ=77.56 ppm) for ^{13}C-NMR. Assignments of NMR spectra are based on extensive structure elucidations previously carried out by our group on similar or related hopanoids.[7,10] ^{13}C chemical shifts of the carbon atoms of the pentacyclic skeleton were identical in the spectra of all hopanoids. For the sake of clarity, only those of the carbon atoms of the side-chain were indicated. Mass spectra were recorded

in the electron impact mode on a Finnigan TSQ 700 spectrometer at 70 eV by direct inlet. GLC analysis were carried out with a Carlo Erba 4160/00 equipped with an "on column" injector and a flame ionization detector. Semipolar capillary columns (DB-1 or DB-5) were used with temperature program: 50°C - 220°C (20°C/min.), 220°C-310°C (6°C/min.), 310°C (30 min.).

(22*S*)-Hopan-29-ol (2)

Diplopterol was isolated from commercially available Dammar resin.[24] A 3:2 mixture of diploptene and hop-21-ene was obtained by treating diplopterol with an an excess of $SOCl_2$ in pyridine/CH_2Cl_2.[24] To this olefin mixture (320 mg, ca. 0.46 mmol diploptene) in solution in dry THF (20 ml) under an atmosphere of argon was added a solution of 9-BBN in THF (0.5 M, 13 ml, 6.5 mmol). The reaction mixture was stirred for 24 h at room ttemperature, after which time no diploptene could be detected by GLC. To the stirred reaction mixture was added dropwise an aqueous solution of NaOH (3M, 10 ml) followed by 30% H_2O_2 (10 ml). The two phases were vigorously stirred for 1 h at 40 °C and then separated. The aqueous phase was extracted twice with ether. The combined organic phases were washed with brine, dried (Na_2SO_4) and solvents were evaporated under reduced pressure. An aliquot of the crude mixture was acetylated (Ac_2O/pyridine 1:1, 0.2 ml) and GLC analysis of the acetylated crude mixture revealed a ratio 94:6 between the diastereomers 22*S*/22*R*. The crude colorless powder was purified by FCC (toluene/EtOAc, 95:5) to yield the (22*S*) alcohol (158 mg, 81%, R_f 0.24, toluene/EtOAc, 95:5) and 22*R* (9 mg, 4%, R_f 0.28) and unreacted hop-21-ene (115 mg, R_f 0.85).

M.p. 209-210°C. IR (KBr) ν/cm^{-1} = 3357 (OH). ^{1}H NMR (200 MHz) δ/ppm = 3.62 (1H, dd, J=2.6 and 9.5 Hz, 29-H_a), 3.40 (1H, dd, J=5.6 and 9.5 Hz, 29-H_b), 1.05 (3H, d, J=6.2 Hz, 22-Me), 0.95 (6H, s, 8β- and 14α-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.72 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 67.8 (C-29), 56.8 (C-5), 54.3 (C-17), 50.5 (C-9), 49.4 (C-13), 44.5 (C-18), 42.67 (C-21), 42.2 (C-3), 41.7 (C-14), 40.4 (C-1), 39.7 (C-22), 37.5 (C-10), 33.7 (C-15), 33.4 (C-4 and C-7), 27.2 (C-20), 24.1 (C-12), 22.7 (C-16), 21.6 (C-24), 21.0 (C-11), 18.8 (C-2 and C-6), 18.2 (C-30), 16.7 (C-26), 16.0 (C-25), 15.8 (C-28).

(22*S*)-Hopan-29-al (3)

A solution of $(COCl)_2$ (0.2 ml, 2.2 mmol) in dry CH_2Cl_2 (0.7 ml) was cooled to -78°C under an atmosphere of argon, and dry DMSO (0.2 ml, 2.81 mmol) was added slowly by syringe. The alcohol **2** (120 mg, 0.28 mmol) in dry CH_2Cl_2 (1.5 ml) was added within 2 min, and the reaction mixture was stirred at -78°C for 3h. After this time the reaction was quenched with Et_3N (1 ml) at -78°C, and the mixture was allowed to reach room temperature. Water and ether were added and the two phases were separated. The aqueous layer was extracted once with ether. The combined organic phases were dried (Na_2SO_4) and solvents were evaporated under reduced pressure yielding an almost pure crystalline product (120 mg, 100%) which was purified by FCC (toluene/EtOAc, 95:5) (113 mg, 94%, R_f 0.62, toluene/EtOAc, 95:5).

M.p. 180-181°C. IR (KBr) ν/cm^{-1} = 1727 (-CHO). ^{1}H NMR (200 MHz) δ/ppm= 9.42 (1H, d, J=4.4 Hz, 29-H), 2.49 (1H, m, 22-H), 1.10 (3H, d, J=6.6 Hz, 22-Me), 0.96 (6H, s, 8β- and 14α-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.74 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 205.2 (C-29), 50.6 (C-22), 41.0 (C-21), 27.8 (C-20), 16.7 (C-29).

(22*S*)-Bis-homohop-30(30*E*)-en-32-al (5)

A solution of ethoxyacetylene (50% in hexane, 0.28 ml, 1 mmol) in dry THF (0.3 ml) was cooled at -78°C under an atmosphere of argon and *n*-BuLi (1.6 M in hexanes, 0.3 ml, 0.48 mmol) was added dropwise. After 1 h stirring, aldehyde **3** (40 mg, 0.094 mmol) dissolved in dry THF (0.4 ml) was added dropwise, and the reaction mixture was stirred at -78°C for 3 h, after which time no starting material could be detected by TLC. The reaction mixture was diluted with ether and quenched with a saturated aqueous solution of NH_4Cl (2 ml). The two phases were separated, and the aqueous phase was extracted once with ether. The combined organic phases were washed with brine and dried (Na_2SO_4). Evaporation of solvents under reduced pressure yielded a colorless solid which was dissolved in dry ether (6 ml), and $LiAlH_4$ (35 mg, 0.9 mmol) was added portion

wise. The suspension was refluxed for 1 h under an atmosphere of argon. After this time, excess $LiAlH_4$ was destroyed by careful addition of MeOH, and the aluminates were hydrolyzed by stirring with 10% H_2SO_4 (4 ml) at room temperature for 10 min. The two phases were separated, and the aqueous phase was extracted once with ether. The combined organic extracts were washed five times with brine (until the washings became neutral) and dried (Na_2SO_4). Solvents were removed under reduced pressure to yield an almost pure crystalline product which was purified by FCC (toluene) (35 mg, 82%, R_f 0.57, toluene/EtOAc, 95:5).
M.p. 191-192°C. IR (KBr) ν/cm^{-1} = 1699 (C=O), 1687 (-C=C-), 1459 (C=C-H). ^1H NMR (200 MHz) δ/ppm = 9.49 (1H, d, J=9.5 Hz, 32-H), 6.60 (1H, dd, J=9.6 and 15.5 Hz, 30-H), 6.02 (1H, dd, J=7.9 and 15.5 Hz, 31-H), 2.58 (1H, m, 22-H), 1.11 (3H, d, J=6.3 Hz, 22-Me), 0.96 (6H, s, 8β- and 14α-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 194.5 (C-32), 164.3 (C-30), 131.3 (C-31), 44.8 (C-21), 41.3 (C-22), 27.8 (C-20), 22.0 (C-29).

(22*S*)-Bis-homohopan-32-al (6)
A solution of unsaturated aldehyde **5** (20 mg, 0.044 mmol) in THF (3 ml) was stirred vigorously under an atmosphere of hydrogen in the presence of Lindlar catalyst (7 mg). After 3 h, no UV absorption (254 nm) of the TLC spot could be seen, indicating complete saturation of the C=C bond. The catalyst was filtered off by passing the reaction mixture through a short plug of silica, and solvents were evaporated under reduced pressure yielding quantitatively the saturated aldehyde **6** as colorless crystals (20 mg, 100%, R_f 0.60, toluene/EtOAc, 95:5).
M.p. 183-184°C. IR (KBr) ν/cm^{-1} = 1728 (C=O). ^1H NMR (200 MHz) δ/ppm = 9.77 (1H, t, J=1.9 Hz, 32-H), 2.38 (1H, m, 31-H), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.4 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 203.2 (C-32), 46.0 (C-21), 41.1 (C-31), 36.4 (C-22), 27.9 (C-30), 19.9 (C-29). EI MS (direct inlet) *m/z* = 454.4 (M^+, 10%), 439.4 (M^+ - Me), 369.4 (M^+ - side-chain, 23%), 233.2 (ring C cleavage, 78%), 215.2 (41%), 191.2 (ring C cleavage, 100%).

(22*S*)-Bis-homohopan-32-al (6) (from aminobacteriohopanetriol **16**)
To a crude *Streptomyces* extract fraction (500 mg) containing ca. 40% of aminobacteriohopanetriol (i.e. ca. 220 mg, 0.40 mmol) suspended in THF/water 4:1 (10 ml), was added solid H_5IO_6 (1.4 g, 6.14 mmol). The reaction mixture was vigorously stirred at room temperature for 1.5 h. Water was added, and the aqueous suspension was extracted twice with ether. The combined organic extracts were dried (Na_2SO_4), and solvents were removed under reduced pressure yielding a pale yellow solid. The crude product was purified by FCC (toluene/EtOAc, 95:5) yielding pure aldehyde **6** as colorless crystals (180 mg, R_f 0.60, toluene/EtOAc, 95:5).
M.p. 182-184°C. IR (KBr) ν/cm^{-1} = 1728 (C=O). ^1H NMR (200 MHz) δ/ppm = 9.77 (1H, t, J=1.9 Hz, 32-H), 2.38 (1H, m, 31-H), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.3 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 203.2 (C-32), 46.0 (C-21), 41.1 (C-31), 36.4 (C-22), 27.9 (C-30), 19.9 (C-29). EI MS (direct inlet) *m/z* = 454.4 (M^+, 10%), 439.4 (M^+ - Me), 369.4 (M^+ - side-chain, 23%), 233.2 (ring C cleavage, 78%), 215.2 (41%), 191.2 (ring C cleavage, 100%).

(22*S*,32*RS*)-Propargylic alcohols (7a,b)
A solution of ethyl propiolate (194 mg, 1.90 mmol) in dry THF (3 ml) was cooled at -78°C under an atmosphere of argon, and *n*-BuLi (ca. 1.6 M in hexanes, 1.1 ml, 1.76 mmol) was added dropwise producing a pale red solution. After 10 min, a solution of aldehyde **6** (440 mg, 0.97 mmol) in dry THF (3 ml) was slowly added, and stirring was continued for 1 h, after which time no starting material could be observed by TLC. The reaction was quenched at -78°C with AcOH (0.5 ml), and the reaction mixture was allowed to attain room temperature. Water was added, and the two phases were separated. The aqueous phase was extracted once with ether, and the combined organic extracts were dried (Na_2SO_4). Solvents were removed under reduced pressure yielding a pale yellow solid which was purified by FCC (hexanes/ether, 4:1) to yield propargyl alcohol **7** as a pale yellow solid

(440 mg, 82 %, R_f 0.33, toluene/EtOAc, 95:5).
IR (KBr) ν/cm^{-1} = 3499 (O-H), 1717 (C=O, ester). ^{1}H NMR (200 MHz) δ/ppm = 4.44 (1H, dd, J=5.8 and 6.0 Hz, 32-H), 4.24 (2H, q, J=7.1 Hz, -CO_2**CH_2**CH_3), 1.31 (3H, t, J=7.1 Hz, -CO_2CH_2**CH_3**), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.2 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 153.5 (C-35), 88.0 (C-33 and C-34), 62.7 and 62.5 (C-32*RS*), 62.2 (-CO_2**CH_2**CH_3), 46.0 (C-21), 30.9 (C-31), 29.8 (C-30), 27.6 (C-20), 20.1 (C-29), 14.1 (-CO_2CH_2**CH_3**). EI MS (direct inlet) *m/z* = 552.4 (M^+, 4%), 537.4 (M^+ - Me, 6 %), 369.4 (M^+ - side-chain. 18%), 331.2 (ring C cleavage, 100%), 191.2 (92 %, ring C cleavage).

(22*S*)-Propargylic ketone (8)
To a solution of propargylic alcohol **7a,b** (63 mg, 0.11 mmol) in acetone (0.7 ml) and THF (50 µl) was added dropwise a solution of Jones reagent prepared from CrO_3 (55 mg, 0.55 mmol), water (0.3 ml) and concentrated H_2SO_4 (80 µl). The resulting green reaction mixture was vigorously stirred overnight. After this time, no starting propargyl alcohol could be detected by TLC. Ether and water were added, and the two phases were separated. The aqueous layer was extracted once with ether and the combined ethereal layers were washed three times with brine (until the washings were neutral) and dried (Na_2SO_4). Evaporation of solvents under reduced pressure yielded almost pure ketone as a thick colorless oil. The crude product was passed through a short plug of silica gel with toluene/EtOAc, 95:5 yielding pure propargylic ketone **8** (58 mg, 92%, R_f 0.70, toluene/EtOAc, 95:5).
Mp. 163-165°C. IR (KBr) ν/cm^{-1} = 1717 (C=O, ester), 1692 (C=O, ketone). ^{1}H NMR (200 MHz) δ/ppm = 4.30 (2H, q, J=7.1 Hz, -CO_2**CH_2**CH_3), 2.60 (2H, m, 31-H), 1.33 (3H, t, J=7.1 Hz, -CO_2CH_2**CH_3**), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.4 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 186.6 (C-32), 152.7 (C-35), 129.1 (C-33 or C-34), 128.2 (C-33 or C-34), 63.8 (-CO_2**CH_2**CH_3), 45.9 (C-21), 42.2 (C-31), 29.3 (C-30), 27.5 (C-20), 19.8 (C-29), 14.0 (-CO_2CH_2**CH_3**).

(22*S*,32*R*)-Propargylic alcohol (7a)
A solution of B_2H_6.THF complex (0.1 M, 0.9 ml, 0.09 mmol) and (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine[15a] (ca. 0.20 M in toluene, 0.56 ml, 0.11 mmol) was cooled to 0°C under an atmosphere of argon, and a solution of propargylic ketone **8** (75 mg, 0.136 mmol) in dry THF (0.4 ml) was slowly added with a syringe (10 min.). The reaction mixture was stirred at 0°C for 1 h, after which time no starting material could be observed by TLC. The reaction was quenched by careful addition of MeOH (0.5 ml). The mixture was allowed to attain room temperature, and stirring was continued for 15 min. Solvents were evaporated under reduced pressure yielding a semi-crystalline solid which was purified by FCC (toluene/EtOAc, 95:5) to yield propargylic alcohol **7a** as colorless crystals (68 mg, 90%, R_f 0.31, toluene/EtOAc, 95:5).
M.p. 164-166°C. IR (KBr) ν/cm^{-1} = 3499 (-OH), 1717 (-C=O, ester). ^{1}H NMR (200 MHz) δ/ppm = 4.44 (1H, dd, J=6.1 Hz, 32-H), 4.30 (2H, q, J=7.1 Hz, -CO_2**CH_2**CH_3), 2.60 (2H, m, 31-H), 1.33 (3H, t, J=7.1 Hz, -CO_2CH_2**CH_3**), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.2 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 153.5 (C-35), 88.0 (C-33 and C-34), 62.5 (C-32*R*), 62.2 (-CO_2**CH_2**CH_3), 46.0 (C-21), 30.9 (C-31), 29.8 (C-30), 27.6 (C-20), 20.1 (C-29), 14.1 (-CO_2CH_2**CH_3**).
The diastereomeric excess (84 %) was calculated from the relative intensities of the methoxy group signals in the ^{1}H NMR spectrum of the major (32*S*) ester of **7a** containing minor amounts of the (32*R*) ester of **7b** obtained with each enantiomer of the MTPA chloride Only the spectrum of the ester obtained with S enantiomer of Mosher's acid is described.
(*S*) MTPA ester of **7a**: ^{1}H NMR (300 MHz) δ/ppm = 7.52-7.39 (5H, m, Ph), 5.61 (1H, dd, J=5.3 Hz, 32-H), 4.25 (2H, q, J=7.1 Hz, -CO_2**CH_2**CH_3), 3.59 (92% 3H, d, J=0.8 Hz, -OMe, ester of **7a**) and 3.56 (8% 3H, d, J=0.8 Hz, -OMe, ester of **7b**), 0.95 (3H, s, 8β- or 14α-Me), 0.94 (3H, s, 8β- or 14α-Me), 0.87 (3H, d, 6.5 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.80 (3H, s, 4β-Me), 0.69 (8% 3H, s, 18α-Me,

ester of **7b**) and 0.66 (92% 3H, s, 18α-Me, ester of **7a**).

α,β-Unsaturated lactone (9)

A. Propargylic alcohol **7a** (30mg, 0.054 mmol) was dissolved in benzene (1 ml) and vigorously stirred at room temperature under an atmosphere of hydrogen (1 atm) in the presence of Lindlar's catalyst (8 mg) for 15 min only. The triple bond was completely reduced to yield the saturated compound upon prolonged reaction time. The catalyst was filtered off, yielding the corresponding acyclic α,β-unsaturated ester of sufficient purity for the next step (30 mg, 100%, R_f 0.20, toluene/EtOAc, 95:5). Attempted purification of the unsaturated ester using silica gel already caused partial lactonisation.

B. NaH (13 mg, 60% in mineral oil) was placed in a dry round bottom flask under argon and washed three times with pentane and then suspended in dry THF (0.5 ml). To the stirred suspension of NaH was injected a solution of the crude α,β-unsaturated ester from the former step (70 mg, ca. 0.13 mmol) in dry THF (3 ml). The reaction mixture was stirred at room temperature until no starting material could be detected by TLC (ca. 30 min), and then poured into a saturated aqueous solution of NH_4Cl. The aqueous solution was extracted twice with ether, and the combined organic layers were washed once with brine and dried (Na_2SO_4). Solvents were removed under reduced pressure yielding α,β-unsaturated lactone **9** as a colourless solid which was purified by FCC (toluene/EtOAc, 95:5), (52 mg, 80% yield from propargylic alcohol **7a**, R_f 0.29, toluene/EtOAc, 95:5).
M.p. 241-243°C. IR (KBr) ν/cm^{-1} = 1756 (C=O, lactone). ^{1}H NMR (200 MHz) δ/ppm = 7.42 (1H, dd, J=1.5 and 5.7 Hz, 33-H), 6.09 (1H, dd, J=1.9 and 5.7 Hz, 34-H), 5.00 (1H, m, 32-H), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.2 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.69 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 173.2 (C-35), 156.3 (C-33), 121.6 (C-34), 83.8 (C-32), 45.9 (C-21), 36.4 (C-22), 30.8 (C-30), 30.0 (C-31), 20.0 (C-29). EI MS (direct inlet) m/z = 508.4 (M^+, 6%), 493.4 (M^+ - Me, 6%), 369.4 (M^+ - side-chain), 287.2 (ring C cleavage, 100%), 191.2 (ring C cleavage, 65%).

Lactone (10)

To a solution of furanone **9** (30 mg, 0.058 mmol) in pyridine (1.5 ml), crystalline OsO_4 (25 mg, 0.098 mmol) was added. The resulting brown reaction mixture was stirred at room temperature, for 20 h. After this time pyridine (1.5 ml) and a saturated aqueous solution of sodium sulfite (2 ml) were added and the dark brown suspension was vigorously stirred for 3h. Brine (10 ml) was added, and the aqueous suspension was extracted five times with $CHCl_3$. The combined organic extracts were dried, and solvents were evaporated under reduced pressure yielding essentially pure lactone **10** as a colorless solid material, (31 mg, 97%, R_f 0.25, toluene/EtOAc, 1:1) which was directly used in the next reaction. For NMR analysis, a sample of crude diol (3 mg) was acetylated overnight (pyridine/Ac_2O, 1:1, v/v, 0.2 ml), and the resulting diacetate of **10** was purified by TLC (3.2 mg, 92%, R_f 0.33, toluene/EtOAc, 95:5).
Diacetate of lactone **10**. ^{1}H NMR (200 MHz) δ/ppm = 5.62 (1H, d, J=5.6 Hz, 34-H), 5.29 (1H, d, J=5.6 Hz, 33-H), 4.45 (1H, dd, J=5.4 and 8.0 Hz, 32-H), 2.16 (3H, s, -$COCH_3$), 2.11 (3H, s, -$COCH_3$), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.2 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 170.2 (C-35*), 169.8 (-**CO**CH_3*), 169.3 (-**CO**CH_3*), 83.6 (C-32), 70.9 (C-34), 65.6 (C-33), 45.9 (C-21), 36.1 (C-22), 31.2 (C-30), 29.5 (C-31), 20.6 (-CO**CH$_3$**), 20.2 (-CO**CH$_3$**), 20.0 (C-29). Assignments of the signals from carbonyl carbon atoms are labeled with * and may be interchanged. ^{1}H and ^{13}C NMR spectra were identical with those of the corresponding natural compound obtained from *N. europaea* .[8]

Lactone acetonide (11)

To a suspension of crude lactone **10** (24 mg, 0.044 mmol) in $CHCl_3$ (2 ml), were added 2,2-dimethoxypropane (0.1 ml) and a trace of TsOH (<1 mg). The reaction mixture was stirred at room temperature until no starting material could be detected by TLC (ca. 30 min, after which time the reaction mixture became clear). Brine was added and the aqueous layer was extracted three times with ether. The combined ethereal layers were washed with brine, dried (Na_2SO_4) and solvents were evaporated under reduced pressure. The acetonide protected

lactone **11** was purified by TLC yielding colorless crystals (20 mg, 80%, R_f 0.40, toluene/ EtOAc, 95:5). Mp. 238-240°C. IR (KBr) ν/cm^{-1} = 1783 (C=O, lactone), 1260 and 1226 (C-O, ether bond). ^1H NMR (200 MHz) δ/ppm = 4.74 (1H, d, J=5.7 Hz, 34-H), 4.51 (1H, d, J=5.7 Hz, 33-H), 4.50 (1H, m, 32-H), 1.48 (3H, s, -CMe_2), 139 (3H, s, -CMe_2), 0.95 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.2 Hz, 22-Me), 0.85 (3H, s, 4α-Me), 0.82 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.70 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 173.6 (C-35), 113.9 (-**C**Me_2), 83.3 (C-32), 79.6 (C-34), 74.9 (C-33), 36.2 (C-22), 30.5 (C-30), 29.7 (C-31), 26.8 (-**C**$\mathbf{Me_2}$), 25.7 (-$\mathbf{CMe_2}$).

Ribosylhopane (12) and ribosylhopane triacetate (13)

The acetonide protected lactone **11** (16 mg, 0.027 mmol), was dissolved in dry toluene (0.5 ml) and cooled to -78°C. To the cooled solution was added a solution of DIBAL (1M in toluene, 0.2 ml). Stirring was continued until no starting material could be detected by TLC (ca. 10 min). The reaction was then quenched with MeOH (0.4 ml) and allowed to attain room temperature A saturated aqueous solution of NH_4Cl (0.5 ml) and a phosphate buffer (pH 7) were added, and the two phases were vigorously stirred for 10 min. $CHCl_3$ was added, and the two phases were separated. The organic phase was washed once with brine, dried (Na_2SO_4) and solvents were removed under reduced pressure yielding the acetonide protected lactol **12** (16 mg, 100%, R_f 0.21, toluene/EtOAc, 95:5). This crude lactol was dissolved in AcOH/H_2O (7:3, v/v, 1 ml) and heated at 90°C for 2 h yielding the corresponding free triol **12**. Solvents were co-evaporated under reduced pressure with toluene, and the crude product was acetylated overnight (pyridine/Ac_2O, 1:1, v/v, 1 ml). The α **13a** and β **13b** anomers of the triacetate **13** were separated by TLC yielding two colorless compounds (35α-anomer **13a**: 5 mg, 31%, R_f 0.19, toluene/EtOAc, 95:5; 35β-anomer **13b**: 9 mg, 56%, R_f 0.26).

IR (KBr) (mixture of α and β anomers) ν/cm^{-1} = 1751 (C=O, acetate), 1254 and 1222 (C-O, acetate).

35α-Anomer **13a**. ^1H NMR (200 MHz) δ/ppm = 6.36 (1H, d, J=4.5 Hz, 35β-H), 5.21 (1H, dd, 4.5 and 6.8 Hz, 34-H), 5.04 (1H, dd, J=3.3 and 6.8 Hz, 33-H), 4.19 (1H, m, 32-H), 2.12 (3H, s, -$COCH_3$), 2.11 (3H, s, -$COCH_3$), 2.06 (3H, s, -$COCH_3$), 0.94 (6H, s, 8β- and 14α-Me), 0.93 (3H, d, J=6.8 Hz, 22-Me), 0.84 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.69 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ/ppm = 170.1 (-**CO**CH_3, x2), 169.9 (-**CO**CH_3), 94.0 (C-35), 83.9 (C-32), 74.9 (C-34), 73.9 (C-33), 46.0 (C-21), 36.5 (C-22), 31.0 (C-30), 30.9 (C-31), 21.1 (-CO$\mathbf{CH_3}$), 20.5 (-CO$\mathbf{CH_3}$), 20.5 (-CO$\mathbf{CH_3}$), 20.1 (C-29).

35β-Anomer **13b**. ^1H NMR (200 MHz) δ/ppm = 6.12 (1H, d, J=1.2 Hz, 35α-H), 5.32 (1H, dd, J=1.2 and 4.9 Hz, 34-H), 5.18 (1H, dd, J=4.9 and 6.4 Hz, 33-H), 4.12 (1H, m, 32-H), 2.11 (3H, s, -$COCH_3$), 2.08 (3H, s, -$COCH_3$), 2.06 (3H, s, -$COCH_3$), 0.94 (6H, s, 8β- and 14α-Me), 0.92 (3H, d, J=6.8 Hz, 22-Me), 0.84 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.69 (3H, s, 18α-Me). ^{13}C NMR (50 MHz) δ = 169.9 (-**CO**CH_3, x2), 169.6 (-**CO**CH_3), 98.4 (C-35), 82.5 (C-32), 74.9 (C-34), 73.9 (C-33), 46.0 (C-21), 36. 5 (C-22), 31.0, (C-30), 30.9 (C-31), 21.0 (-CO$\mathbf{CH_3}$), 20.5 (-CO$\mathbf{CH_3}$), 20.6 (-CO$\mathbf{CH_3}$), 20.1 (C-29). EI MS (mixture of α and β anomers, direct inlet) m/z = 670.4 (M^+, 2%), 610.4 (M^+ - AcOH, 35%), 595.4 (M^+ - AcOH - Me, 11%), 449.2 (ring C cleavage, 16%), 389.2 (ring C cleavage - AcOH, 88%), 369.4 (ring C-cleavage, 24%), 191.2 (ring C cleavage, 100%).

(32*R*,33*R*,34*S*)-Bacteriohopanetetrol tetraacetate 4

A solution of lactone **10** (6 mg, 0.009 mmol) in dry THF (0.5 ml) was added to a suspension of $LiAlH_4$ (4 mg, 0.1 mmol) in dry THF (0.3 ml). The reaction was refluxed for 2 h, then quenched with a saturated aqueous solution of Na_2SO_4 (a few drops) giving a white precipitate. Stirring was continued for 30 min. Solvents were removed under reduced pressure (co-evaporated with toluene), and the solid crude mixture was acetylated overnight (pyridine/Ac_2O, 1:1, v/v, 1 ml). Inorganic salts were filtered off and the tetraacetate was purified by TLC (4.5 mg, 65%, R_f 0.27, toluene/EtOAc, 9:1).

M.p. 179-181°C (Lit. 180-182°C).[7] ^1H NMR (400 MHz) δ/ppm = 5.26 (1H, m, 34-H), 5.22 (1H, m, 33-H), 5.03 (1H, dt, J= 3.9 and 9.6 Hz, 32-H), 4.38 (1H, dd, J=2.6 and 12.0 Hz, 35-H_a), 4.14 (1H, dd, J=6.7 and 12.0 Hz, 35-H_b), 2.08 (3H, s, -$COCH_3$), 2.07 (3H, s, -$COCH_3$), 2.06 (3H, s, -$COCH_3$), 2.05 (3H, s,

-$COCH_3$), 0.94 (6H, s, 8β- and 14α-Me), 0.90 (3H, d, J=6.4 Hz, 22-Me), 0.84 (3H, s, 4α-Me), 0.81 (3H, s, 10β-Me), 0.79 (3H, s, 4β-Me), 0.68 (3H, s, 18α-Me). ^{13}C NMR (100 MHz) δ/ppm = 170.7 (-**C**OCH_3), 170.4 (-**C**OCH_3), 170.3 (-**C**OCH_3), 169.8 (-**C**OCH_3), 72.0 (C-34), 71.7 (C-33), 69.6 (C-32), 62.2 (C-35), 45.9 (C-21), 36.1 (C-22), 30.9 (C-30), 26.2 (C-31), 21.0 (-CO**C**H_3), 20.9 (-CO**C**H_3), 20.8 (-CO**C**H_3), 20.8 (-CO**C**H_3), 19.9 (C-29). EI MS (direct inlet) *m/z* =714.5 (M^+, 6%), 699.4 (M^+ - Me, 4%), 654.4 (M+ - AcOH, 5%), 493.2 (ring C cleavage, 100%), 369.3 (M^+ - side-chain, 21%), 191.2 (ring C cleavage, 9%).

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