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Synthesis of 3β-(5′-D-ribityl)cholestane, a putative biological precursor for fossil 3-alkylsteranes

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Abstract

A putative biological precursor for the widespread class of sedimentary 3-alkylsteranes was synthesised from cholestanone in a stepwise stereoselective manner. This unusual cholestane derivative bearing a C_5 tetrol side chain at carbon C-3 represents the equivalent of bacteriohopanetetrol and may prove a useful tool in the search for such compounds in microorganisms. In addition, the synthetic protocol represents a general entry into the preparation of sterols with side chains at C-3. © 2000 Elsevier Science Ltd. All rights reserved.

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Molecular fossil steroids bearing an additional alkyl or carboxyalkyl side chain linked to carbon C-3 by a carbon–carbon bond are often found in the organic matter of sediments and crude oils.[1] Their widespread presence raised questions about their origin.[1b] Such alkylated steranes are most likely degradation products of 3-polyhydroxyalkylsteranes from microorganisms, which would represent in the sterane series the analogues of the bacteriohopanepolyols, and might result from a process similar to that implied in the formation of geohopanoids from biohopanoids (Fig. 1).[2] Bacteria generally do not produce sterols, but often synthesise bacteriohopanepolyols, which serve as sterol surrogates and stabilise the cell membrane.[2b] Owing to their amphiphilic nature and quasi-planar rigid structure, polyhydroxyalkylsteranes would closely resemble bacteriohopanepolyols. They could therefore play a similar biological function. Most bacteriohopanepolyols have an extended C_5 side chain corresponding to a D-ribose derivative linked via its C-5 carbon atom to the isopropyl group of the triterpenic moiety.[3] Bacteriohopanetetrol derivatives are the most widespread bacterial hopanoids. A sterane analogue of bacteriohopanetetrol was therefore synthesised: it contains the same side chain and was proposed as a putative precursor for the 3-alkylsteranes found in sediments.[1b]

We have recently reported a new synthesis for 29-(5′-D-ribosyl)hopane and bacteriohopanetetrol.[4] A related synthetic protocol, starting from cholestanone **1**, was adapted to the synthesis of the acetylated tetrol **9** (Figs. 1 and 2). The side chain was initially introduced by means of a Wittig reaction between

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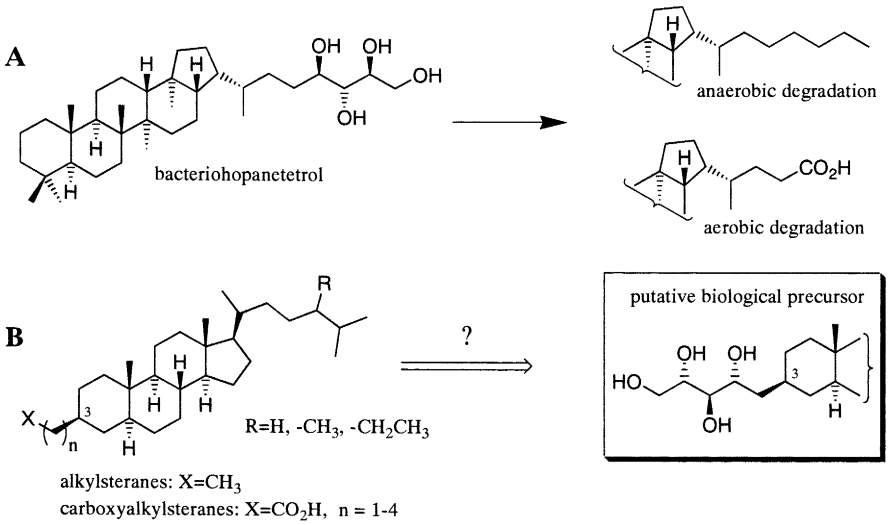

Fig. 1. **A**: Anaerobic and aerobic degradation of bacteriohopanetetrol. **B**: putative biological precursors for 3-alkylsteranes and 3-carboxyalkylsteranes

cholestanone **1** and hydroxyethyltriphenylphosphine chloride (Fig. 2). This reaction produced an inseparable mixture of the *E* and *Z* alkenes **2a** and **2b**. The isomeric mixture was reduced by catalytic hydrogenation to the saturated alcohols **3a** and **3b** with the 3β and 3α configurations in a 2:1 ratio, which were separated by chromatography on silica gel. Alcohols **3a** and **3b** were separately oxidised under Swern conditions to the aldehydes **4a** and **4b**. The C-3 configuration was determined by NOESY experiments on these aldehydes **4a** and **4b**. The signal of the 3-H proton was identified by homonuclear $^{1}H/^{1}H$ and heteronuclear $^{1}H/^{13}C$ correlations, including long range (HMQC) correlations. Strong nuclear Overhauser effects between H-3 and the methyl protons H-19 were only observed for the 3-α epimer **4b**, whereas they were absent for the 3β epimer **4a**.

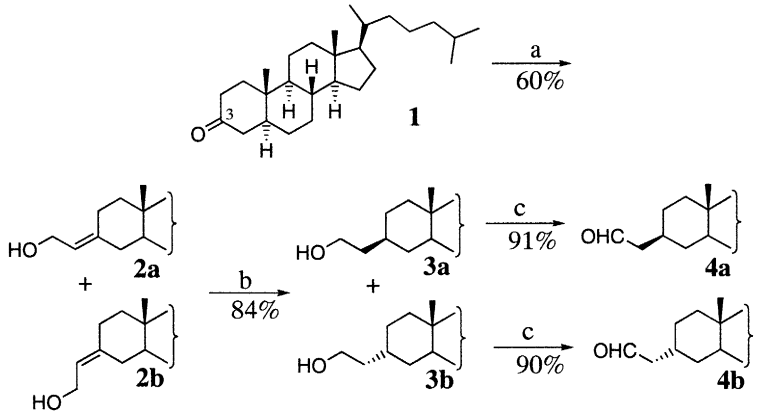

Fig. 2. Introduction of the side chain at C-3. (a) HO-$CH_2CH_2PPh_3^+Cl^-$ (1.7 equiv.) *n*-BuLi (3.4 equiv.), THF, rt; (b) H_2 (1 atm), PtO_2 (cat.), THF; (c) $(COCl)_2$/DMSO (Swern), CH_2Cl_2, −78°C

Addition of lithium ethylpropiolate to aldehyde **4a** at −78°C provided an inseparable 1:1 mixture of the propargylic alcohols **5a** and **5b** (Fig. 3). This alcohol mixture was oxidised in good yield using Jones reagent to the corresponding ketone **6**, which could be reduced stereoselectively back to epimer **5a**[5] in moderate 60% diastereomeric excess by borane-mediated reduction in the presence of the

chiral oxazaborolidine **10** as described earlier.[4–6] The triple bond was reduced to a *cis* double bond by hydrogenation over Lindlar catalyst, and the resulting alkene was directly converted into a lactone by treating the crude ester with NaH in THF, yielding the unsaturated butenolide **7**.[7] Dihydroxylation of the butenolide in pyridine with stoichiometric quantities of OsO_4 solely proceeded with addition from the least hindered α side.[8] The diol was first acetylated to diacetate **8** for chromatographic purposes. The reduction of the diacetate **8** with $LiAlH_4$ afforded the free tetrol. Due to its very amphiphilic character, the ribitylsterane was most conveniently purified and characterised as the corresponding tetra-acetate **9**.[9]

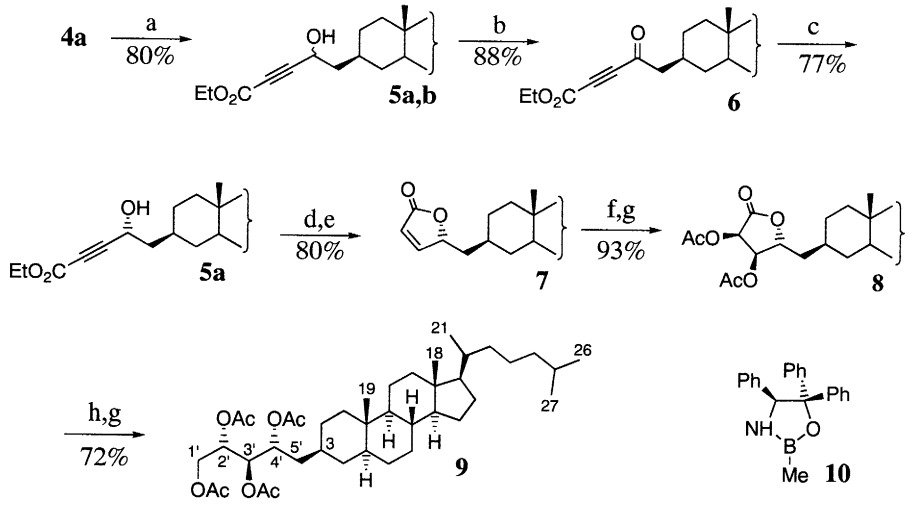

Fig. 3. Chain elongation and synthesis of the ribityl chain. (a) $HCCCO_2Et$/*n*-BuLi, THF, −78°C; (b) CrO_3/H_2SO_4 (Jones reagent), THF/acetone, rt; (c) B_2H_6:THF (0.5 equiv.), oxazaborolidine **10** (0.8 equiv.), THF, 0°C, (60% d.e.); (d) H_2 (1 atm.), $Pd/CaCO_3$ (Lindlar)/quinoline, benzene; (e) NaH, THF, rt; (f) OsO_4 (1.2 equiv.), pyridine, rt; (g) Ac_2O/pyridine, rt; (h) $LiAlH_4$, Et_2O, reflux; (g) Ac_2O/pyridine, rt

This synthesis of a tetrol side chain at C-3 of cholestane can be applied to diverse sterols structurally related to those found in sediments and oils and should also be useful for the introduction of diverse side chains similar to those found in bacterial hopanoids. Finally, the acetylated ribitylsterane **9** will serve as a useful reference material for the search of the biological precursors of fossil 3-alkylsteranes and 3-carboxyalkylsteranes.

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5. The stereochemical outcome of the reduction is based on our previous experiences using the same reaction conditions on a propargylic ketone in the hopane series[4] and the proposed mechanism of the reduction.[6] The ratio of the epimers **5a** and **5b** was determined by ^{1}H NMR after converting the mixture to the corresponding Mosher esters with (*R*)- or (*S*)-α-methoxy-α-trifluoromethyl acetyl chloride.
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7. Attempts to purify on silica gel the alkene **7** resulted in partial lactonisation.
8. Catalytic osmylation procedures were unsuccessful, and dihydroxylation using $KMnO_4$/18-crown-6 gave with moderate yields a mixture of diols resulting from the preferred addition on the α face with a significant contribution (ca. 20%) of the addition from the most hindered β face.
9. Spectroscopic data for **9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm=5.22 (2H, m, 3′- and 2′-H), 5.18 (1H, m, 4′-H), 4.38 (1H, dd, J=2.2 and 12.3 Hz, 1′-H_a), 4.14 (1H, dd, J=6.2 and 12.3 Hz, 1′-H_b), 2.08 (3H, s, -$COCH_3$), 2.07 (3H, s, -$COCH_3$), 2.05 (3H, s, -$COCH_3$), 2.05 (3H, s, -$COCH_3$), 0.89 (3H, d, J=6.7 Hz, 21-H), 0.86 (3H, d, J=6.7 Hz, 26- or 27-H), 0.85 (3H, d, J=6.7 Hz, 26- or 27-H), 0.73 (3H, s, 19-H), 0.63 (3H, s, 18-H). ^{13}C NMR (100 MHz) δ/ppm (tentative assignments; assignments bearing the same superscript may be interchanged)=170.8, 170.4, 170.2 and 169.8 (4×-**C**OCH_3), 71.9 (C-2′), 69.9 (C-3′), 69.4 (C-4′), 62.2 (C-1′), 56.6 and 56.3 (C-14 and C-17), 54.6 (C-9), 46.6 (C-5), 42.6 (C-13), 40.1 (C-12), 39.6 (C-1), 38.3 (C-24), 37.0$^{\#}$ (C-22), 36.0 (C-20), 35.8 (C-8 and C-10), 35.6$^{\#}$ (C-5′), 34. 8 (C-3), 34.2 (C-4), 32.2 (C-2), 32.1 (C-7), 28.9 (C-6), 28.3 (C-25), 28.0 (C-16), 24.2 and 23.9 (C-15 and C-23), 22.9 and 22.6 (C-26 and C-27), 21.05 (C-11), 21.01, 20.95, 20.81 and 20.78 (4×-CO**C**H_3), 18.7 (C-21), 12.3 (C-16), 12.1 (C-19). EI MS (direct inlet): *m/z* (%)=674 (M^+, 78), 659 (M^+-Me, 83), 614 (M^+-AcOH, 36), 599 (M^+-AcOH−Me, 16), 519 (ring D cleavage, 43), 494 (68), 452 (100), 262 (ring B cleavage, 27).