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Dimethyldioxirane Oxidation of Aminobacteriohopanetriol : Obtention of a Putative Intermediate in Bacterial Hopanoid Biosynthesis

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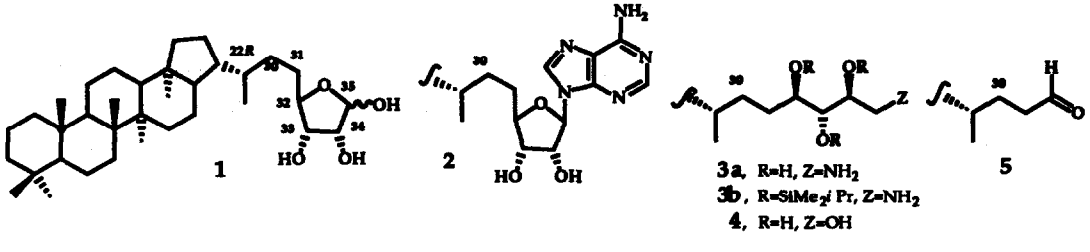
Abstract : Once protected as *O*-dimethylisopropylsilylethers, aminobacteriohopanetriol **3b** could be satisfactorily converted in a one pot procedure, featuring dimethyldioxirane as an oxidant, into the new *C*-ribosylhopane **1**, a postulated precursor of the bacteriohopanepolyol series.

Although yet unknown as a natural compound, *C*-ribosylhopane **1** represents a likely precursor for the biosynthesis of the many C_{35} triterpenoids from the bacteriohopane series encountered in Eubacteria. Indeed, not only is this lactol susceptible to generate after adenylation the remarkable *C*-adenosylhopane **2** or after reductive amination or reduction hopanoids derived from aminotriol **3a** or tetrol **4**, but its structure does satisfy also the intervention of D-ribose established so far in the formation of bacteriohopanoid side-chains.[1]

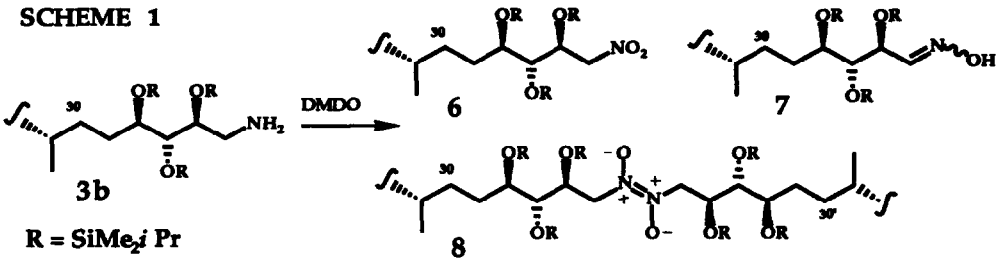
A multistep synthesis, with 15 % overall yield, of the fully protected 33,34-bis-*O*-isopropylidene-35β-methoxy derivative of **1** starting from the C_{30} hop-22(29)-ene, has already been published.[2] Apart from its modest yield, this preparation was not conducted to completion, not delivering free lactol **1** itself and was in addition not stereoselective, giving in fact a mixture of 22*R* and 22*S* epimers. Taking advantage of the availability of aminotriol **3a** in our laboratory, we present here an access to lactol **1** as such or as a triacetylated derivative, featuring the use of dimethyldioxirane (DMDO) as a powerful oxidant of aliphatic amines.[3]

All our initial experiments performed directly on the free aminotriol **3a** failed, whatever the method recommended for the oxidation of amines we chose (DMDO,[3] H_2O_2-Na_2WO_4, [4] Cu_2Cl_2-O_2-Py, [5] argentic picolinate [6]), being hampered by the lack of solubility of the amphiphilic starting material in nearly any solvent and yielding eventually on completion and after acetylation complex mixtures in which low yields (at best 15 %) of the required triacetylated lactols as well as the C_{32} aldehyde **5** could be found.



To circumvent both the lack of solubility of aminotriol **3a** and its tendency to degradation, we switched to oxidation experiments on a derivative possessing suitably protected hydroxyl groups. Protection of **3a** as a tris-*O*-dimethylisopropylsilylether **3b**, leaving the terminal amino group free, proved particularly convenient. Indeed, not only could this derivative be obtained with very good yield (*ca.* 90 %) in a one step procedure from **3a**, provided the quality of the commercial silylating agent used was correct,[7] but this protection appeared in addition, as expected,[8] to resist quite well to the action of DMDO (Scheme 1), enabling a good conversion (*ca.* 70 %) of **3b** into valuable oxidation products.[9]

SCHEME 1



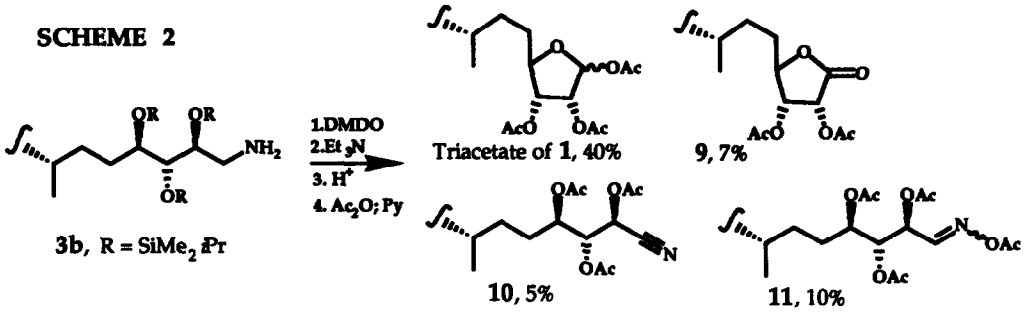
Contrary to the original work on DMDO oxidations of amines, which only mentioned access to the corresponding nitro-derivatives,[3a] we observed in our case, next to the expected nitro compound **6**, both the oxime **7** and the dimer of the nitroso derivative **8**, thus matching closely the results reported later by J.K. Crandall and T. Reix.[3b] If the structure assignment of oxime **7** could be easily deduced from its spectroscopic data,[10] differentiation between the two other compounds **6** and **8**, of similar SiO_2-tlc polarity, appeared more delicate. Indeed the latter did offer not only similar ^{1}H-nmr spectra,[10] but also similar ms spectra under electronic impact, the nitro compound loosing easily 16 D and the dimer **8** being dissociated during the analyses. Isobutane ci-ms analyses appeared more conclusive and enabled in the case of **6** to identify the molecular ion thanks to the two diagnostic peaks at m/z = 876 $[M+H]^+$ and m/z = 932 $[M+C_4H_9]^+$, whereas **8** appeared as the monomeric nitroso derivative only, exhibiting peaks at m/z = 860 $[M/2 + H]^+$ and m/z = 917 $[M/2 + C_4H_9]^+$, every attempt to visualise its dimeric structure having failed. At this stage, the dimeric structure of **8** relied on the fact that aliphatic nitroso-compounds are known to be stable as the colorless dimers only, let alone particularly hindered ones such as the blue *t*-nitrosobutane.[11]

Our special interest in **8**, the first known dimer in a hopanoid series, incited us to reduce it in order to accede to more stable derivatives, resisting in particular to ms analyses. Indeed, its LAH reduction resulted in the formation of the corresponding asymmetric azoxy-derivative (RN(O)=NR), the molecular ion of which could be in this case deduced by isobutane ci-ms from the ion at m/z = 1705 $[M+H]^+$.

Although the DMDO oxidation of **3b** afforded a good conversion in oxidized products, relative proportions between **6**, **7** and **8** appeared to vary notably in four independent experiments performed apparently under the same conditions, illustrating probably the tendency of **8** to dissociate to oxime **7** with small variations of pH and/or temperature. We thus gave up trying to convert each of these products separately into the required lactols and opted for a one pot conversion as presented in Scheme 2.

Next to the minor new hopanoids **10** and **11**, correct yields of the acetylated lactol fraction containing small amounts of the corresponding lactone **9** were obtained in two independent experiments involving after the oxidation step both basic (CH_2Cl_2:hexane:Et_3N, 2:3:0.1,v:v:v, reflux, 1h30) and acidic (1N HCl in dioxane, 1h30, 20°C) treatments.

SCHEME 2



Under these conditions, neither nitro nor nitroso derivatives were obtained. After a final tlc separation, structure determination of the two anomers corresponding to the acetylated lactols was straightforward, the α anomer offering in particular in ^{1}H-nmr a characteristic larger $J_{34\text{-}H,35\text{-}H}$ coupling constant compared to its β-epimer.[10]

Although at this stage our goal was already satisfied with the obtention of acetylated lactol **1**, which could serve as a reference for its search in acetylated bacterial extracts, we tried further to accede to the free derivative, by action of freshly prepared polymeric Amberlyst A-26 (OH^- form) during 12 h at 20 °C, a procedure well-tried in our laboratory for the quantitative deacetylation of hopanoids.[12]

This treatment proved unsatisfactory for the first time in the bacteriohopane series, yielding on tlc a complex mixture in which the aldehyde **5** was recognised (^{1}H-nmr, gc). As deacetylation under acidic conditions using a polymer-supported reagent (Amberlite IR 120, H^+ form) failed also, leaving in that case the acetylated lactol unchanged after 12 h at 20°C, we decided to repeat the procedure outlined in Scheme 2 without the final acetylation. Under these conditions, the required lactol **1** could be isolated after tlc using Cy : EtOAc (1:4, v/v) as eluent (R_f = 0.25), but with a modest yield only (25 %), reflecting most probably the difficulties to recover such a polar and amphiphilic compound from silicagel. Apart from the characteristic hopane methyl pattern, nmr analysis of a saturated CDCl3 solution of the free lactol did not appear very informative so that evidence for the obtention of **1** came from the analysis of its triacetate.

Although access to the free lactol remains to be optimized, using for instance for its final tlc purification other supports more adapted to polar compounds, we could satisfactorily convert in two steps the polyfunctionnalized bacteriohopanoid **3a** into the triacetate of **1**. This hopanoid will on the one hand serve as reference material or as carrier in biosynthetic studies on the formation of the C35 bacteriohopanoid skeleton and on the other hand as starting material for the introduction of purine or pyrimidine bases to yield for instance *C*-adenosylhopane **2** or its analogues.

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7. *Silylation procedure* : To the suspension in CH_3CN : MeOH (1:1, v/v) (4 ml) of a cellular residue (130 mg) containing 45 % of aminotriol **3a** was added DBU (1 ml) and dimethylisopropylchlorosilane (1.3 ml). After 3 h of stirring at 20°C, the suspension was filtered. The filtrate was concentrated *in vacuo*, redissolved into $CHCl_3$ (3 ml) and submitted to SiO_2 tlc purification in $CHCl_3$: MeOH (97:3, v/v) to yield **3b** (R_f = 0.4, 90 mg).

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9. *Typical procedure*. To a solution of protected **3b** (25 mg) in dry CH_2Cl_2 (2 ml) was added a 0.07 M acetonic solution of DMDO (3 ml) freshly prepared according to W. Adam, J. Bialas and L. Hadjiarapoglou, *Chem. Ber.*, 1991, **124**, 2377. After 30 min of stirring at 20°C, the medium was brought to dryness and submitted three times more to DMDO oxidation. Tlc purification using Cy : $CHCl_3$ (3:2, v/v) as eluent gave : **6** (R_f = 0.6, 5 mg), **7** (R_f = 0.2, 8.5 mg) and **8** (R_f = 0.7, 4 mg).

10. All new compounds gave spectral and analytical data in full accordance with the structures proposed. Selected data : **1** *Triacetate of α-anomer* ^{1}H-nmr : δ, 0.690 (3H, s), 0.791 (3H, s), 0.814 (3H, s), 0.845 (3H, s), 0.918 (3H, d, J = 6.5 Hz), 0.946 (6H, s), 2.057 (3H,s), 2.102 (3H, s), 2.112 (3H, s), 4.18 (1H, m), 5.04 (1H, dd, J = 3.5 & 7 Hz), 5.21 (1H, dd, J = 4.5 & 7 Hz), 6.36 (1H, d, J = 4.5 Hz) ; **1** *Triacetate of β-anomer* ^{1}H-nmr : δ, 0.693 (3H, s), 0.790 (3H, s), 0.813 (3H, s), 0.844 (3H, s), 0.919 (3H, d, J = 6.5 Hz), 0.947 (6H, s), 2.064 (3H, s), 2.077 (3H, s), 2.110 (3H, s), 4.12 (1H, m), 5.18 (1H, dd, J = 5 & 6.5 Hz), 5.32 (1H, dd, J = 1.5 & 5 Hz), 6.12 (1H, d, J = 1.5 Hz) ; **3b** ^{1}H-nmr : δ, 0.051 (3H, s), 0.066 (3H, s), 0.083 (6H, s), 0.091 (3H, s), 0.010 (3H, s), 0.699 (3H, s), 0.793 (3H, s), 0.816 (3H, s), 0.846 (3H, s), 2.83 (1H, broad dd, J = 3 & 13.5 Hz), 2.97 (1H, broad dd, J = 3 & 13.5 Hz), 3.7 (3H, m) ; **6** ^{1}H-nmr : δ, 0.033 (3H, s), 0.063 (6H, s), 0.076 (3H, s), 0.090 (3H, s), 0.116 (3H, s), 0.705 (3H, s), 0.794 (3H, s), 0.818 (3H, s), 0.848 (3H, s), 3.62 (2H, m), 4.26 (1H, m), 4.55 (2H, m) ; *i*-butane ci-ms : 932 (8 %), 876 (13 %), 832 (8 %), 758 (16 %), 640 (15 %), 555 (21 %), 437 (16 %), 421 (16 %), 260 (100 %), 246 (73 %) ; **7** ^{1}H-nmr : δ, 0.041 (3H, s), 0.052 (3H, s), 0.062 (6H, s), 0.071 (3H, s), 0.078 (3H, s), 0.700 (3H, s), 0.793 (3H, s), 0.817 (3H, s), 0.847 (3H, s), 3.64 (2H, m), 4.27 (1H, dd, J = 4.5 & 8 Hz), 6.72 (*ca.* 1/3 H, d, J = 6 Hz : H-35 of oxime *syn*), 6.89 (1H, broad s), 7.29 (*ca.* 2/3 H, d, J = 8 Hz : H-35 of oxime *anti*) ; **8** ^{1}H-nmr : δ, 0.030 (6H,s), 0.036 (6H, s) 0.051 (6H, s), 0.069 (6H, s), 0.087 (6H, s), 0.116 (6H, s), 0.703 (6H, s), 0.793 (6H, s), 0.818 (6H, s), 0.848 (6H, s), 3.62 (4H, m), 4.25 (2H, m), 4.55 (4H, m) ; *i*-butane ci-ms : 917 (2 %), 860 (16 %), 624 (21 %), 555 (100 %), 437 (58 %).

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