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Enzymatic Desymmetrization of a Prochiral 1,3,5-Pentanetriol Derivative. Application to the Synthesis of a Cyanobacterial Heterocyst Glycolipid

Annunziata Soriente, Giovanna Laudisio, Maurizio Giordano and Guido Sodano*

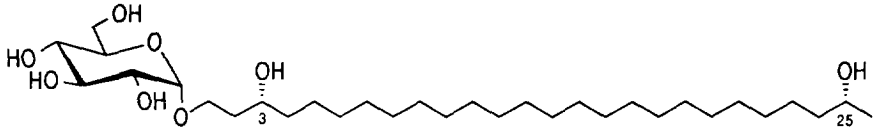
Dipartimento di Chimica, Università di Salerno, 84081 Baronissi (SA) - Italy

Abstract: (*R*)-3-*t*-butyldimethylsilyloxy-5-acetoxy-1-pentanol has been obtained by PFL catalyzed hydrolysis of the corresponding diacetate and has been utilized for the formal synthesis of the most widespread heterocyst glycolipid of N_2-fixing cyanobacteria.

Our recent interest in the chemistry of heterocyst glycolipids of nitrogen fixing cyanobacteria[1] has stimulated us in the synthesis of the most widespread of these compounds, **1**. We envisaged a suitably protected 1,3,5-pentanetriol (e.g. **4**, Scheme 1) as an useful chiral building block for the projected synthesis and looked for a simple preparation of such a compound.

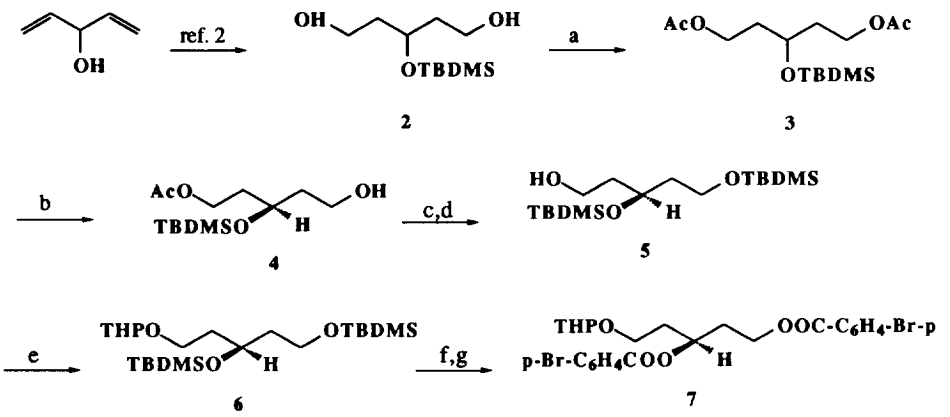
Recently[2], a method for the resolution of racemic 1,3-alkanediols, involving their conversion into diastereomeric spiroacetals derived from *l*-menthone, has been described. The method, which has been successfully applied to the resolution of a series of 1,3,5-alkanetriol derivatives and is also useful for the determination of the absolute configuration of these compounds, is of general use but requires several steps. On the other hand, it has been recently reported[3] that *Pseudomonas fluorescens* lipase (PFL) shows a high degree of enantiotopic discrimination in the hydrolysis of a complex molecule possessing a 1,3-*syn* diol structure and therefore we decided to explore the desymmetrization of the prochiral compound **3** by PFL.

3 was obtained by acetylation of the corresponding diol **2**, prepared as previously described[2], and subjected to PFL hydrolysis in phosphate buffer solution[3] (Scheme 1). After 7 days, the usual work up afforded **4**[4] in 55% yield with a > 98% ee, as determined by HPLC[5] of the (*S*)-Mosher ester. The absolute configuration of **4** was established by the application of the CD-exciton chirality method[6] to the bis-*p*-Br-benzoate derivative **7**, obtained as shown in Scheme 1. The CD spectrum of **7**[7] exhibits first a positive and then a negative Cotton effect and, accordingly[6], the absolute configuration is that shown. Compound **4** is an useful chiral building block which could be used in the synthesis of many natural products. Moreover, compounds having an opposite configuration at the centre deriving from the secondary carbon atom of **4** could be also easily prepared reversing



1

Scheme 1



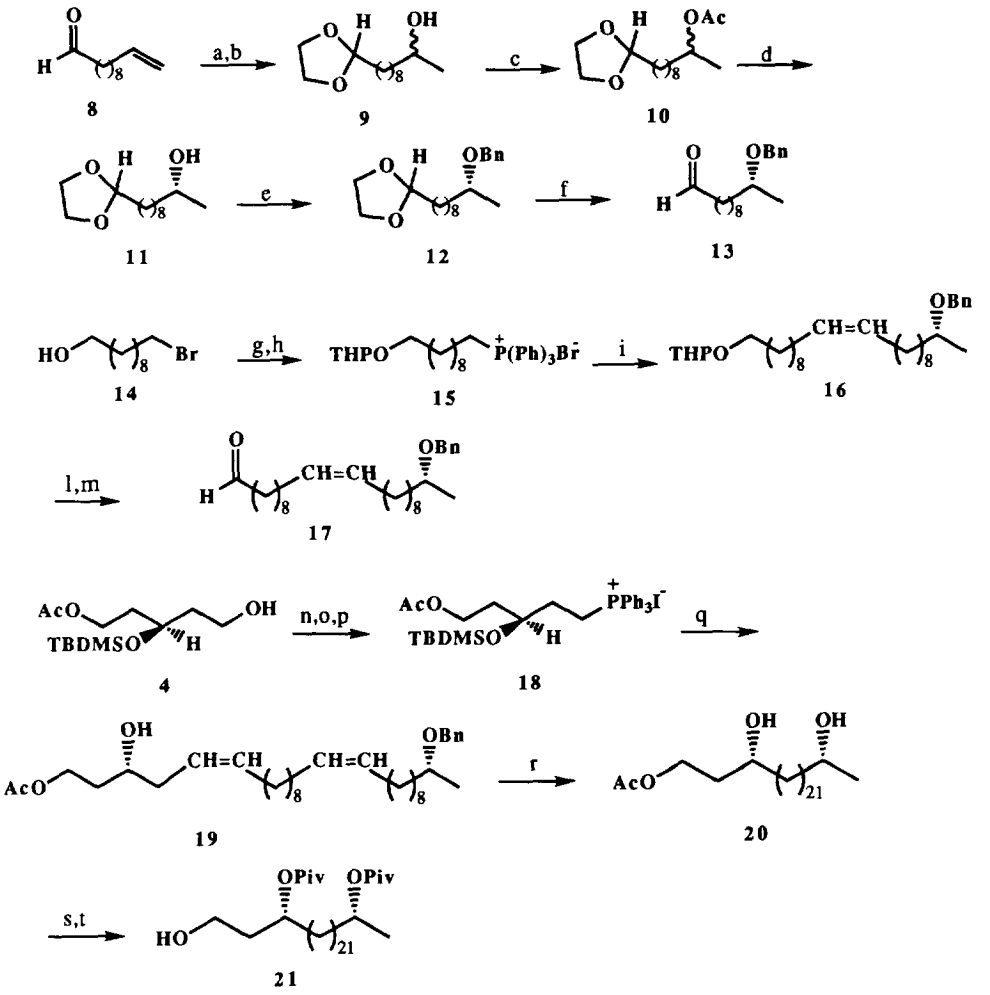
a) Ac_2O, Py (75%); b) PFL, phosphate buffer (55%); c) *t*-Bu(Me)$_2$SiCl, DMF, imidazole; d) Na_2CO_3, MeOH (c + d, 81%); e) DHP, CH_2Cl_2, PPTS (88%); f) (*t*-Bu)$_4N^+F^-$, THF (86%); g) *p*-Br-C_6H_4COCl, DMAP, Py, (44%).

the free end of the 1,3,5-pentanetriol derivative by the usual protection-deprotection procedure, as exemplified by the transformation of **4** into **5**.

For the synthesis of **1**, the C_{21} unit **17** was assembled as reported in Scheme 2. The chiral centre at C-25 was obtained in the desired[8] configuration by PFL hydrolysis of the acetate **10**, which yielded **11**[9] in 34% yield and in an unexpectedly[8] high ee (90%), as estimated by ^{1}H-NMR analysis of the Mosher ester derivatives. The absolute configuration was also derived by the $\Delta\delta$ value[10] (-0.08) of the C-25 methyl groups in the Mosher esters of **11**. The best method for connecting the aldehyde **13** with the C_{10} unit **15** was found to be the mild Wittig reaction carried out in heterogeneous medium[11], since in these conditions the formation of aldol products from the unstable aldehyde **13** is minimized.

Since we decided to use the mild Wittig reaction in heterogeneous medium also for assembling the C_5 and C_{21} units leading to the synthesis of the aglycone of **1**, **4** was transformed into the phosphonium salt **18** (Scheme 2). The Wittig reaction of the aldehyde **17** with the phosphonium salt **18** however in this case resulted in low yields (30%) and in the loss of the TBDMS protecting group. The resulting C_{26} derivative **19** was transformed into the monoacetate of the aglycone of **1** (**20**[12]) by hydrogenolysis and concomitant reduction of the double bonds. Protection of the two secondary alcholic functions in **20** as pivaloyl derivatives and subsequent hydrolysis of the acetate yielded **21**[13]. The obtainement of **21** constitutes a formal synthesis of **1**, since **21** was an advanced intermediate in a previous total synthesis of **1** which appeared[14] while this work was in progress.

Scheme 2



a) 2-methoxy-1,3-dioxolane, *p*-TsOH (83%); b) $Hg(OAc)_2$, $NaBH_4$, NaOH (45%); c) Ac_2O, Py (quant.); d) PFL, phosphate buffer/acetone (35%); e) $PhCH_2Br$, THF, NaH, $Bu_4N^+I^-$ (78%); f) 33% aq. AcOH (87%); g) DHP, PPTS, CH_2Cl_2 (90%); h) Ph_3P, 150°; i) **13**, Na_2CO_3,H_2O, dioxane (41%); l) PPTS, MeOH (95%); m) PDC, CH_2Cl_2; n) TsCl, $CHCl_3$, Py,0°C (85%); o) NaI, acetone; p) Ph_3P, 150°; q) **17**, Na_2CO_3,H_2O,dioxane (30%); r) H_2/Pd-C(quant.); s) PvCl, Py, 50°, 7 d, (70%); t) Na_2CO_3,MeOH, rt, 2h (90%)

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REFERENCES AND NOTES

1. Soriente, A., Bisogno, T., Gambacorta, A., Romano, I., Sili, C., Trincone, A., Sodano, G. *Phytochemistry* , in press.
2. Harada, T., Kurokawa, H., Kagamihara, Y., Tanaka, S., Inoue, A., Oku, A. *J. Org. Chem.* **1992**, *57*, 1412.
3. Bonini, C., Racioppi, R., Righi, G., Viggiani, L. *J. Org. Chem.* **1993**, *58*, 802.
4. $[\alpha]_D$ -2.6 (c = 3.5; $CHCl_3$). ^{1}H-NMR, δ ($CDCl_3$) 0.08 (s; Me_2Si), 0.90 (s; Me_3CSi), 1.72 (m; CH_2CH_2OAc), 1.83 (m; CH_2CH_2OH), 2.07 (s; CH_3CO), 3.75 (m; CH_2OH), 4.04 (p; J = 6.0 Hz; CHOSi), 4.14 (m; CH_2OAc). ^{13}C-NMR, δ ($CDCl_3$) -4.7 and -4.8 (2 x CH_3Si), 17.9 (CSi), 20.9 (CH_3CO), 25.7 (Me_3CSi), 35.5 (CH_2CH_2OAc), 38.4 (CH_2CH_2OH), 59.7 (CH_2OH), 61.2 (CH_2OAc), 68.1 (CHOSi), 171.0 (C=O). No molecular ion in the EI MS spectrum.
5. μ-Porasil column; *n*-hexane/EtOAc 94:6.
6. Harada, N., Saito, A., Ono, H, Gawronski, J., Gawronska, K., Sagioka, J, Uda, H., Kurki, T. *J. Am. Chem. Soc.* **1991**, *113*, 3842.
7. *n*-Hexane; λ_{ext} 252.0 nm, Δε +9.8; λ_{ext} 235.7 nm, Δε -3.5; A = +13.3.
8. Kazlauskas, R.J., Weissfloch, A.N.E., Rappaport, A.T., Cuccia, L.A. *J. Org. Chem.* **1991**, *56*, 2656.
9. $[\alpha]_D$ -4.8 (c = 3.3; $CHCl_3$). ^{1}H-NMR, δ (C_6D_6) 1.12 (d, 3H, J = 6.2 Hz), 1.21 (bs; alkyl chain), 1.66 (q, 2H, J = 4.7 Hz), 3.59 (ddd, 4H, J = 10.3 and 6.8 Hz), 3.68 (m, 1H), 4.75 (t, 1H, J = 4.7 Hz). ^{13}C-NMR, δ (C_6D_6) 23.8, 24.5, 25.8, 29.4, 30.0, 34.5, 39.8, 64.8, 67.7, 104.9. EIMS m/z 229 (M^+-H), 211.
10. Dale, J.A., Mosher, H.S. *J . Am. Chem. Soc.* **1973**, *95*, 512.
11. Le Bigot, Y., Delmas, M., Gaset, A. *J. Agric. Food Chem.* **1983**, *31*, 1096.
12. ^{1}H-NMR, δ (C_6D_5N) 4.61 (t, 2H, J = 6.8 Hz), 4.1 (m, 3H), 2.08 (s, 3H), 1.44 (d, 3H, J = 6.1.Hz), 1.37 (m, methylene chain). ^{13}C-NMR, δ (C_6D_5N) 67.9, 67.2, 62.6, 40.4, 36.8, 37.3, 30.3, 30.1 (methylene chain), 26.6, 26.4, 24.5, 21.0.
13. Compound **21** was identified on the basis of the reported data[14]. However, it should be noted that few chemical shift values in the reported ^{1}H NMR spectrum are to be subjected to minor changes, as follows: δ 1.26 (methylene chain and 26-H_3), 1.22 and 1.18 (each s, 18H, 2 x CMe_3).
14. Mori, K., Qian, Z.-H. *Liebigs Ann. Chem.* **1994**, 35.

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