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UTILIZATION OF THE CHIRAL SYNTHON, METHYL 3-O-BENZYL-2,4,6-TRIDEOXY-6-IODO-α-D-ERYTHRO-HEXOPYRANOSIDE IN THE SYNTHESIS OF A POTENT HMG-CoA REDUCTASE INHIBITOR

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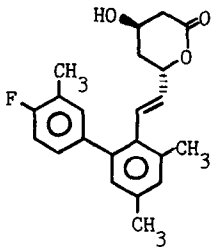
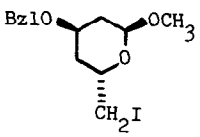
ABSTRACT: Compound **1**, a potent synthetic HMG-CoA reductase inhibitor, has been synthesized from the chiral synthon, methyl 3-O-benzyl-2,4,6-trideoxy-6-iodo-α-D-erythro-hexopyranoside (**2**), utilizing a novel palladium-mediated procedure for benzyl ether cleavage.

Compound **1**[1] is a potent synthetic inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA reductase), the enzyme which is rate-limiting and the natural point of regulation of cholesterogenesis in mammals.[2] The synthesis of **1** utilizing chiral synthon **2**[3] seemed to offer advantages over the initial procedure[1] which was based on the resolution of racemic material. To achieve this objective two formidable synthetic problems had to be solved. The first was to link a severly hindered bottom piece to the synthon and to generate efficiently the desired trans olefin linkage. The second problem was to remove the benzyl protecting group in the presence of the olefin. We report here the successful solutions to these problems which resulted in a convenient synthesis of **1**. This work also constitutes a chemical proof of the absolute configuration of **1** by relating it via synthon **2** to D-glucose.

The synthesis of the bottom piece and its linkage to the synthon are illustrated in Scheme I. Thus, aldehyde **3**[1] was treated successively with (a) $NaBH_4$, (b) $SOCl_2$, (c) $C_6H_5S^-$ and (d) m-CPBA (-78°C, CH_2Cl_2) to give sulfoxide **4** (90% overall). The anion of **4** was formed (2 equiv., NaH, DMSO) and treated with synthon **2** (1 equiv.) to give, after chromatography, a mixture of diasteoisomers **5** (38%) and elimination product **6**. A similar synthon is reported to give severe elimination and no alkylation.[3f] In contrast to several other approaches in our laboratories which gave mixtures of cis and trans olefins, the mixture of diastereoisomers **5** when refluxed in toluene[4] in the presence of anhydrous potassium carbonate, gave cleanly the desired trans olefin, chiral **7a**[5] (85%). Molecular models suggest that clean trans geometry is generated here because of steric reasons.

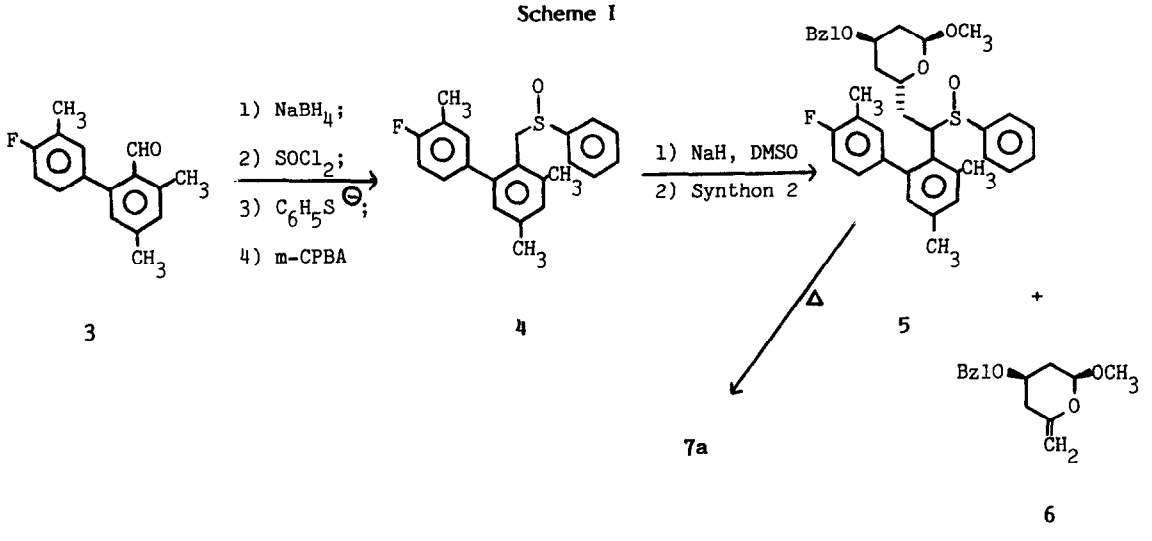


1



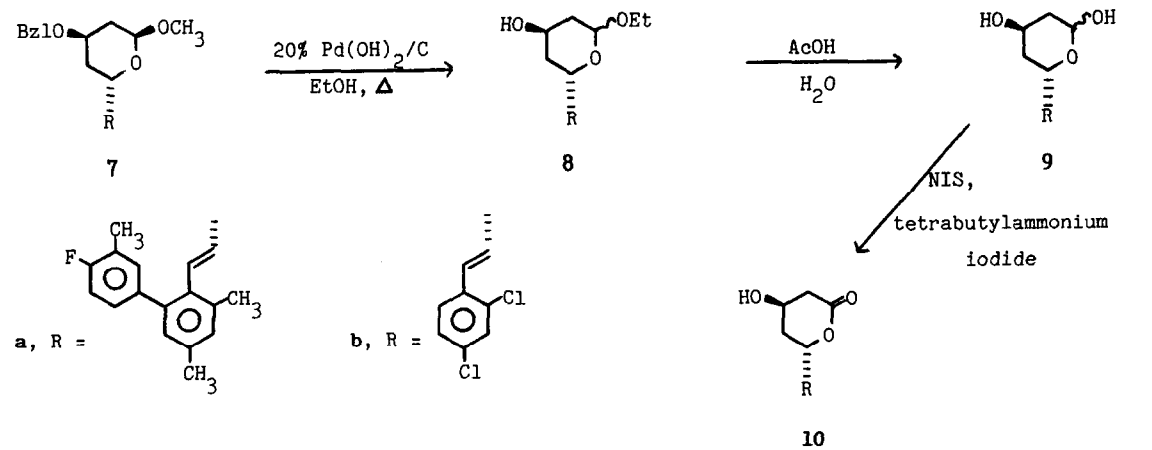
2

Scheme I



We elected to study the deblocking of **7** by selecting a racemic model **7b** which was prepared by successively treating racemic **10b**[1] with DIBAL-H;[6] MeOH, TFA; chromatographic separation of the β anomer; butyl Li, THF; and then benzyl bromide, DMF. After considerable effort it was discovered that the benzyl group of **7b** (Scheme II) could be removed efficiently to give **8b** (20% $Pd(OH)_2$ = Pearlman's catalyst, 120 mg/mmole, ethanol, reflux 8-50 hr). This was accompanied by anomeric exchange and scrambling with solvent, but with no effect on the olefin. These conditions constitute a novel, benzyl ether cleavage and we have explored the reaction further. A preliminary report on its scope and mechanism of action follows (vida infra). Hydrolysis of **8b** (80% aq. AcOH, 90°C, 30 min) gave a mixture of lactols **9b**. Oxidation of the lactols was accomplished with N-iodosuccinimide and tetrabutylammonium

Scheme II



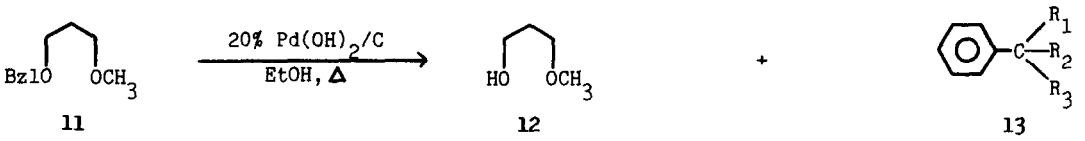
iodide[7] (all yields >69%). Using these model conditions (Scheme II) **7a** was converted to **8a** (20% $Pd(OH)_2/C$, 120 mg/mmole, refluxing EtOH, 84%). Hydrolysis of **8a** gave lactols **9a** (76% aq. AcOH; RT, 30 hr, 83%).[8a] Oxidation of the lactols with N-iodosuccinimide and tetrabutylammonium iodide[7] gave the target lactone I[8b] (57%) which proved identical to the known[1] dextrorotatory active isomer prepared by resolution of racemic material, $[\alpha]_D^{23} = +39.9^o$ mp 88-90°C.

On the Mechanism and the Scope of the Benzyl Ether Cleavage. After attempts to cleave the ethers of **7b** with chemical reagents failed, transfer hydrogenolysis of the benzyl group in the presence of the hindered olefin was tried ($Pd(OH)_2/C$, cyclohexene, refluxing EtOH). This gave benzyl ether cleavage, saturation of the olefin and exchange of the β methoxy group for an anomeric ethoxyl mixture. In exploring the possible role of the catalyst in anomeric scrambling, the experiment was repeated omitting the cyclohexene. To our amazement, along with anomeric exchange with solvent and scrambling, the benzyl group was cleaved without affecting the olefin. This novel reaction was found to proceed poorly for simple benzyl ethers such as 1-benzyloxy-9-decene. We reasoned that since the benzyloxy group and methoxyl group of **7b** were in a 1,3-diaxial relationship, the methoxyl group might be acting as a second ligand to stabilize binding to palladium.[9] If this is true, then the benzyl group of compound **11** (whose ether groups can adopt a similar conformation) should be cleaved, and it was, supporting the idea of an essential role for the second ligand. We then used **11** as a model to determine the fate of the benzyl group. Under the reaction conditions used, the benzyl ether was transformed into **13a** (major product) accompanied by **13b–e** (minor products) and <2% toluene indicating an oxidative cleavage.[10]

With the mild conditions for the efficient removal of the benzyl group in the presence of an olefin now available, synthon **2** should find general applicability in the synthesis of HMG-CoA reductase inhibitors.

Acknowledgement. We wish to thank R. L. Smith for helpful suggestions.

Scheme III

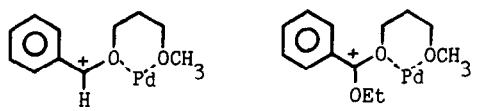


11 **12** **13**

a, $R_1=R_2=OEt$, $R_3=H$; **b**, $R_1R_2=O$, $R_3=H$

c, $R_1=O(CH_2)_3OCH_3$, $R_2=OEt$, $R_3=H$

d, $R_1R_2=O$, $R_3=OEt$; **e**, $R_1R_2=O$, $R_3=O(CH_2)_3OCH_3$



14 **15**

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(2) V. W. Rodwell, D. J. McNamara and D. J. Shapiro, Adv. Enzymol., 373 (1973).

(3) a) For a preliminary account of the synthesis of **2** from D glucose see: J. D. Prugh and A. A. Deana, Tetrahedron Lett., 281 (1982). Subsequently, other synthon approaches have appeared: b) Y. L. Yang and J. R. Falk, Tetrahedron Lett., 4305 (1982); c) P. T. Ho and S. Chung, Carbohydr. Res., 125, 318 (1984); d) Y. L. Yang, S. Manna and J. R. Falk J. Am. Chem. Soc., 106, 3811 (1984); e) K. Prasad and O. Repie, Tetrahedron Lett., 2435 (1984); f) T. Rosen, M. J. Taschner and C. H. Heathcock, J. Org. Chem., 49, 3994 (1984); g) J. R. Wareing, U.S. Patent 4,474,971.

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(5) Physical data on critical intermediate **7a**: ^{1}H NMR ($CDCl_3$) (360 MHz) δ 1.54 (1 H, d, d, d, H_{4a}, J_{gem} = 13.5 Hz, J_{4a-5} = 12 Hz, J_{4a-3} = 3 Hz), 1.74 (1 H, br d, 4e, J_{gem} = 13.5 Hz), 1.82 (1 H, d, t, H_{2a}, J_{gem} = 15 Hz, J_{2a-1} = 4.5 Hz, J_{2a-3} = 4.5 Hz), 1.96 (1 H, br d, H_{2e}, J_{gem} = 15 Hz), 2.28 (3 H, d, CH_3, J = 2 Hz), 2.34 (3 H, s, CH_3), 2.37 (3 H, s, CH_3), 3.38 (3 H, s, OCH_3), 3.69 (1 H, p, H_3, J$\sim$4 Hz), 4.52 (1 H, d, benzyl, J_{gem} = 12 Hz), 4.61 (1 H, m, H_5), 4.63 (1 H, d, benzyl, J_{gem} = 12 Hz), 4.67 (1 H, t, H_1, J_{1-2a} = J_{1-2e} = 4.5 Hz), 5.44 (1 H, dd, H_6, J_{5-6} = 6 Hz, J_{6-7} = 16.5 Hz), 6.43 (1 H, d, H_7, J_{6-7} = 16.5 Hz), 6.90-7.42 (10 H, m, Ar). ^{19}F NMR ($CDCl_3$) (360 MHz): 121.497 (1 F, m); $[\alpha]_D^{24}$ = +62.72 (c = 0.59, $CHCl_3$). All new compounds gave satisfactory NMR spectral data, microanalysis and/or exact mass spectra, except **6** which has a ^{1}H NMR (360 MHz) only.

(6) J. Schmidlin and A. Wettstein, Helv., 46, 2799 (1963).

(7) S. Hanessian, D. H. Wong and M. Therien, Synthesis, 394 (1981).

(8) a) Prolonged room temperature conditions are necessary to avoid acid-catalyzed epimerization at the allylic 6-position of the ring via a carbonium ion; b) a small amount of epimerization in the oxidation step necessitated chromatography to remove low levels of the unwanted cis isomer and to avoid attendant loss of the final product.

(9) Late in the synthesis of **1**, it was found that the debenzylation of **7a** could be achieved using 10% Pd/C (pH of an aqueous slurry of catalyst $\sim$10) without anomeric scrambling and exchange with ethanol solvent. We have not observed debenzylation of the equatorial methoxy anomer of **7b** with any palladium catalyst without concomitant anomeric scrambling and exchange with ethanol solvent. It is our hypothesis that the axial alkoxy anomeric group is much more effective than the equatorial alkoxy anomeric group in anchimeric binding with palladium. The magnitude of this difference is under current investigation.

(10) Two successive hydride ion transfers to catalyst are formally represented in **14** and **15** and their reaction with ethanol or water (from moist Pearlman's catalyst) account for the observed products. The detailed mechanism as well as other potential applications of this novel debenzylation reaction are under investigation.

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