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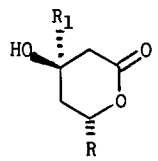
METHYL 3-O-BENZYL-2,4,6-TRIDEOXY-6-IODO-α-D-ERYTHRO-HEXOPYRANOSIDE, A CHIRAL SYNTHON FOR THE SYNTHESIS OF INHIBITORS OF HMG-CoA REDUCTASE

John D. Prugh* and Albert A. Deana
Department of Medicinal Chemistry
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

SUMMARY: Methyl 3-O-benzyl-2,4,6-trideoxy-6-iodo-α-D-erythro-hexopyranoside (2) was prepared from D-glucose and demonstrated to have potential utility as a chiral synthon for the elaboration of HMG-CoA reductase inhibitors.

Recent reports[1-5] have described natural products 1a,b[1,2] and synthetic analogs 1c,d[3,5] which specifically inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme and natural point of cholesterogenesis regulation in mammals.[6] A common structural feature of compounds 1a-d is the 4β-hydroxy-6α-substituted-3,4,5,6-tetrahydro-2H-pyran-2-one fragment or the corresponding 4-methyl derivative. The absolute stereochemistry of compound 1b (mevinolin)[2a] is as indicated in the structural formula shown below and, presumably, is identical to that of compound 1a (compactin).[1] Furthermore, it is likely that the biologically active optical isomers of synthetic analogs 1c,d[3-5] also possess this absolute stereochemistry.



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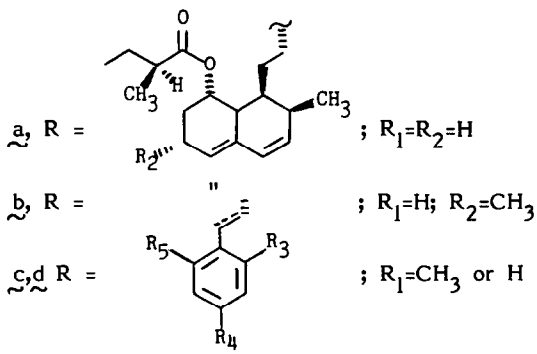


a, R = ; R_1=R_2=H

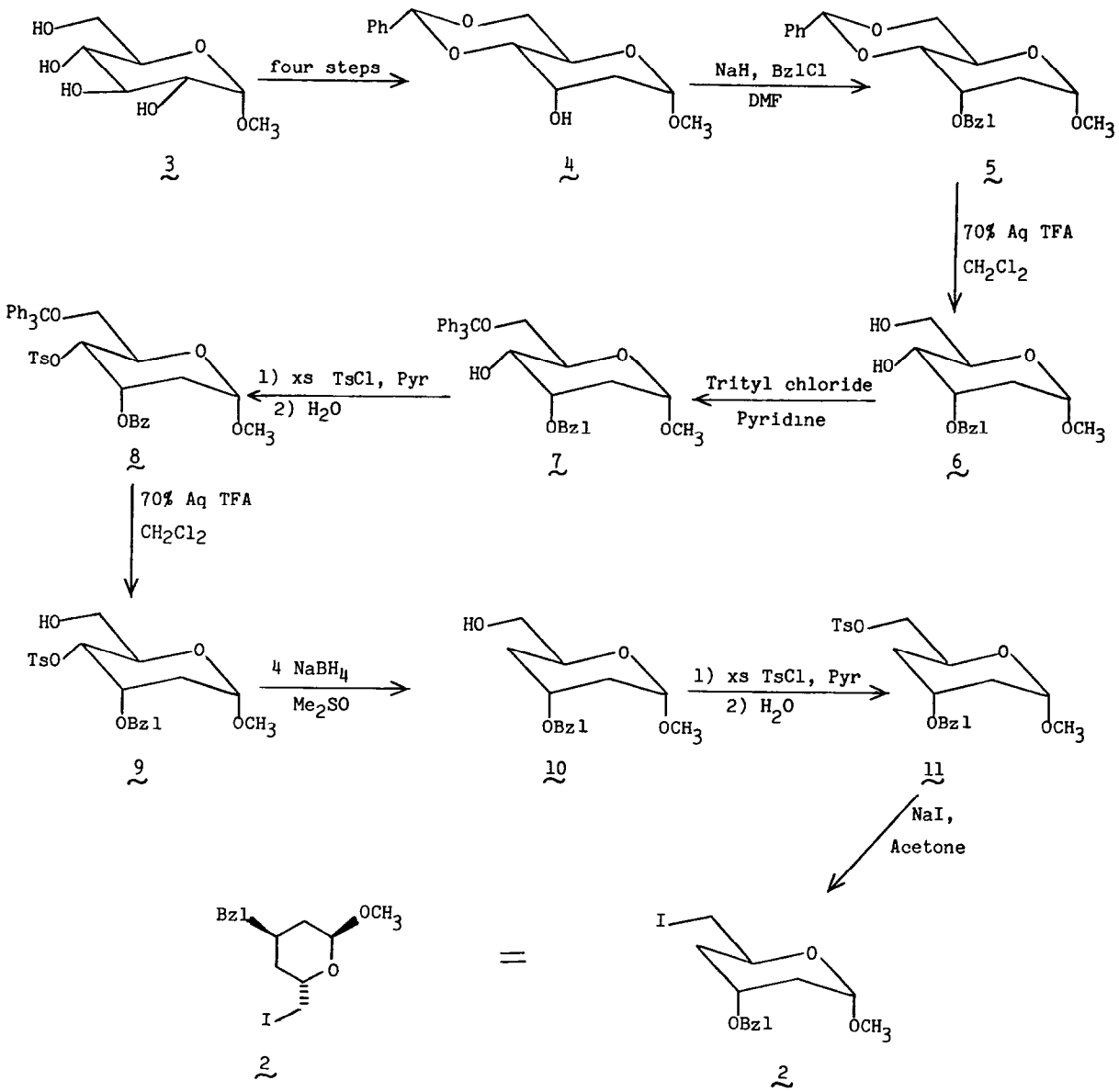
b, R = " ; R_1=H; R_2=CH_3

c,d R = ; R_1=CH_3 or H

It occurred to us that the lactone fragment of these potent inhibitors could be synthesized from D-glucose, a readily available starting material embued with the requisite absolute stereochemistry. Herein, we wish to report the synthesis of the O-protected chiral synthon 2 from D-glucose (Scheme I), and to demonstrate its potential synthetic utility by the preparation of model structures 12a-c.

The synthetic sequence developed for the elaboration of chiral synthon 2 from D-glucose is outlined in Scheme I. The benzylidene derivative 4,[7] readily prepared in four steps[7,8] from commercially available methyl α-D-glucopyranoside (3), was converted to benzyl ether 5[9] via alkylation with benzyl chloride in

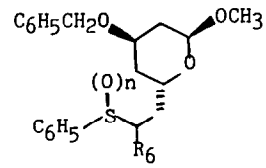
Scheme I[a]



[a]Bzl = benzyl

DMF. Treatment of 5 (7.2 g) with 70% aqueous TFA (4.8 mL) in CH_2Cl_2 (100 mL) at ambient temperature for 10 min followed by aqueous sodium carbonate work-up afforded diol 6.[10] Conversion of 6 to tosylate 8[11] was accomplished by the selective O-alkylation of the primary carbinol group with trityl chloride[12] and subsequent treatment of the product with p-TsCl in pyridine. Detritylation of 8 using 70% aqueous TFA in CH_2Cl_2 provided intermediate 9, mp 101-102 °C. Reductive detosyloxylation of 9 using sodium borohydride (4 molar equiv)[13] in Me_2SO[14] at 80 °C for 4 days under N_2 afforded the 2,4-dideoxy derivative 10 in 81% yield.[15,16] Formation of tosylate 11 followed by treatment with 10% sodium iodide in acetone (reflux) in the dark for 24 hr under N_2 gave the desired chiral synthon 2.[16] Each new step in this synthetic sequence was accomplished in good yield (≥80%).

Model compounds 12a-c were prepared by alkylating the appropriate methylene sulfone or sulfoxide anion[17] with iodide 2.[18] No attempt was made to separate the resulting diastereomers. Procedures have been devised for the reductive removal of the benzenesulfonyl groups from 12a and c,[19] as well as for



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a, R_6 = 2,4-dichlorophenyl, n = 2
b, R_6 = 2,4-dichlorophenl, n = 1
c, R_6 = cyclohexyl, n = 2

the thermal elimination of benzenesulfinic acid from 12b to generate the corresponding double bond. Conditions for removing the blocking groups from the synthon derived moiety, and its oxidation to the lactone stage also have been developed. These aspects will be the subject of a future publication.

Acknowledgments

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References and Notes

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(10) The refluxing aqueous methanolic HCl conditions (Ref. 9a) gave poor results. Our conditions resulted in smooth hydrolysis of the benzylidene group without side reactions. See also Ref. 9b.

(11) This sequence (i.e., 6 ——→ 8) can be carried out in one pot without isolation of intermediate 7.

(12) A. M. Michelson and A. Todd, J. Chem. Soc., 3459 (1956).

(13) One equivalent is consumed by the OH group. A 20% increase in yield was observed when 4 moles of $NaBH_4$ rather than 3 were used; also see S. Krishnamurthy and H. C. Brown, J. Org. Chem., 45, 849 (1980) and ref. 12 therein.

(14) R. O. Hutchins et al., J. Org. Chem., 43, 2259 (1978).

(15) The use of this procedure to prepare a 4-deoxy sugar appears to be unprecedented.

(16) Physical data on critical compounds: 10; ^{1}H NMR (90 MHz) ($DCCl_3$) δ 1.40-2.25 (4H, m); 3.40 (3H, s); 3.60 (2H, m); 3.80 (1H, m); 4.25 (1H, m); 4.60 (2H, q); 4.80 (1H, d); 7.20-7.48 (5H, m); $[\alpha]_D^{24}$ = +94.00 (C 0.55, $CHCl_3$). 2; ^{1}H NMR (300 MHz) ($DCCl_3$) δ 1.52 (1H, m); 1.75 (1H, m); 1.95 (1H, m); 2.02 (1H, m); 3.21 (2H, m); 3.47 (3H, s); 3.78 (1H, m); 4.10 (1H, m); 4.56 (2H, q); 4.81 (1H, d); 7.24-7.42 (5H, m); $[\alpha]_D^{24}$ = +53.45 (C 0.66, $CHCl_3$). Remaining new compounds $[\alpha]_D^{25}$ 7, + 87.23 (C 0.35, $CHCl_3$); 8, + 66.24 (C 1.0, $CHCl_3$); 9, + 115.07 (C 0.48, $CHCl_3$); 11 + 22.80 (C 1.2, $CHCl_3$). All new compounds gave satisfactory NMR spectral data, microanalyses and/or mass spectra.

(17) (a) The sodium salt of the methylene precursor of 12a was formed at room temperature in DMF. With 12b,c, dimsyl sodium in Me_2SO was used; (b) B. M. Trost and A. J. Bridges, J. Org. Chem., 40, 2014 (1975).

(18) TLC suggested these reactions were complete in a few minutes. However, they were allowed to react at room temperature for 2.5 hours.

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