Carbohydrate Research, 125 (1984) 318–322
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

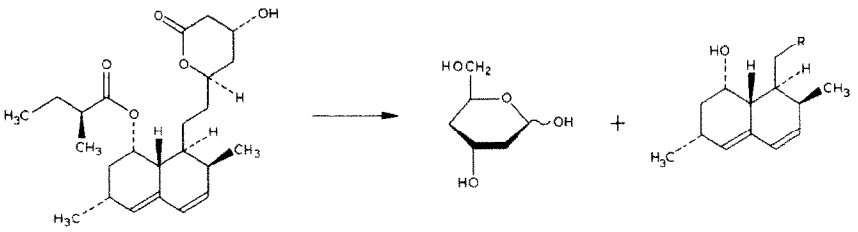
Synthesis of 2,4-dideoxy-D-*erythro*-hexopyranose. An intermediate for synthesis of the lactone moiety of inhibitors of hydroxymethylglutaryl-coenzyme A reductase

PAK-TSUN HO AND SHARON CHUNG

Guelph-Waterloo Center for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1 (Canada)

(Received February 8th, 1983; accepted for publication, August 1st, 1983)

Mevinolin **1** and its related analogs are potent inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase[1,2] and have recently been found, in clinical trials, to lower significantly serum cholesterol levels in animals and human beings[3,4]. Syntheses of 2,4-dideoxy-D-*erythro*-hexopyranose (**2**) and its derivatives are of considerable current interest[5], because this deoxy sugar is an important intermediate for the lactone moiety of the cholesterol-lowering agent. This prompts us to report our results for the synthesis of **2**.

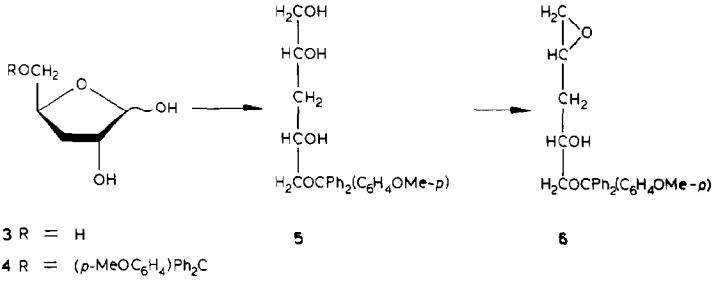


1 2

3-Deoxy-D-*erythro*-pentose **3** possesses a suitable skeleton, as well as two correct asymmetric centers, and requires only the insertion of a methylene unit between C-1 and C-2 in **3** (carbohydrate numbering). It can be easily prepared in large quantities from D-glucose by known procedures[6]. Treatment with *p*-anisylchlorodiphenylmethane in pyridine gave 5-*O*-(*p*-anisyldiphenylmethyl)-3-deoxy-D-*erythro*-pentofuranose (**4**) in quantitative yield, and **5** was obtained in 96% yield by reduction with sodium borohydride in ethanol. Selective mono-*p*-toluenesulfonylation of CH_2OH-1 of **5** afforded an unstable mono-*p*-toluenesulfonate which could not be isolated. Therefore, the crude product was immediately treated with a slight excess of potassium hydroxide in methanol at $-10°$ to give the desired hydroxy

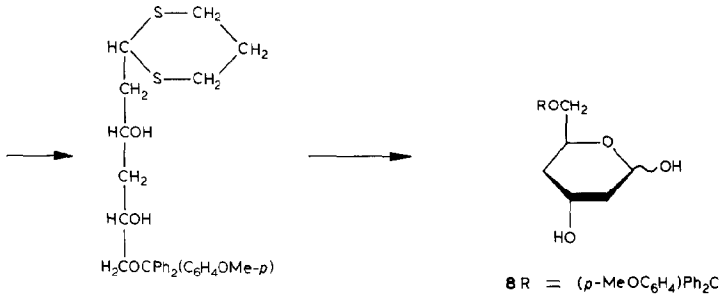
0008-6215/84/$ 03.00

epoxide **6** in 60–65% overall yield, the ^{1}H-n.m.r. spectrum of which was completely in agreement with the assigned structure.



3 R = H
4 R = (*p*-MeOC$_6$H$_4$)Ph$_2$C

5 **6**



7

8 R = (*p*-MeOC$_6$H$_4$)Ph$_2$C
2 R = H

Incorporation of a carbonyl group or its equivalent was achieved by treatment of **6** with the lithium anion of 1,3-dithiane in oxolane at −70°. Protection of the secondary hydroxyl group was not necessary because opening of the epoxide ring by an intramolecular, nucleophilic attack by the secondary hydroxyl group is not favored[7]. The desired 5-*O*-(*p*-anisyldiphenylmethyl)-1,3-dideoxy-1-C-(1,3-dithian-2-yl)-D-*erythro*-pentitol (**7**) was obtained as the sole product in 78% yield; the ^{1}H-n.m.r. signal at δ 4.25 agreed with the assigned structure. Finally, treatment of **7** with *N*-bromosuccinimide in aqueous acetone in the presence of 2,6-dimethylpyridine, followed by aqueous acetic acid, gave, in 76% yield, 2,4-dideoxy-D-*erythro*-hexopyranose (**2**).

EXPERIMENTAL

General. — Melting points were determined in capillary tubes with a Büchi model SMP-20 apparatus and are uncorrected. Optical rotations were measured with a Carl Zeiss model LEP nun 370740 polarimeter at room temperature. Infrared spectra were recorded for chloroform solutions. ^{1}H-N.m.r. spectra were recorded with a Bruker WP-80 spectrometer using tetramethylsilane as an internal reference, and high-resolution mass spectra with a VG 7070F spectrometer. Thin-

layer and preparative-layer chromatographies were performed on silica gel containing a fluorescent indicator (Merck G_{254}).

5-O-(p-Anisyldiphenylmethyl)-3-deoxy-D-erythro-*pentofuranose* (**4**). — A mixture of 3-deoxy-D-*erythro*-pentose (**3**, 5.36 g, 40 mmol) and *p*-anisylchlorodiphenylmethane (13.6 g, 44 mmol) in pyridine (50 mL) was stirred overnight at room temperature. The mixture was diluted with dichloromethane and washed with cold, 10% aqueous hydrochloric acid, then with aqueous sodium hydrogencarbonate solution, and finally with water. After being dried (anhydrous magnesium sulfate), the solution was evaporated to give **4** as a foam in quantitative yield; $[\alpha]_D^{25}$ +56° (*c* 0.5, chloroform); $\nu_{max}^{CHCl_3}$ 3500 and 3380 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 5.31 (d) and 5.20 (s) (1 H, H-1), 4.21 (m, 2 H, H-2 and -4), 3.34 (s, 3 H, OCH_3), 3.12 (m, 2 H, H_2-5), and 1.92 (t, 2 H, H_2-3).

Anal. Calc. for $C_{25}H_{26}O_5$: C, 74.21; H, 6.44; Found: C, 74.23; H, 6.43.

5-O-(p-Anisyldiphenylmethyl)-3-deoxy-D-erythro-*pentitol* (**5**). — A solution of **4** (750 mg) in ethanol (20 mL) was cooled to 0°, and sodium borohydride (250 mg) was added with stirring. After 1 h, acetic acid was added dropwise until the solution became neutral (pH 7). Evaporation of the solvent to dryness gave a residue which was extracted with chloroform. Removal of the solvent gave **5** as a homogeneous syrup (735 mg, 98%); $[\alpha]_D^{25}$ −21° (*c* 0.42, chloroform); $\nu_{max}^{CHCl_3}$ 3500 and 3382 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 3.95 (m, 2 H, H-2 and -4), 3.75 (s, 3 H, OCH_3), 3.31 (d, 2 H, H-1), 3.12 (d, 2 H, H-5), and 1.54 (t, 2 H, H-3).

Anal. Calc. for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.54; H, 7.02.

1,2-Anhydro-5-O-(p-anisyldiphenylmethyl)-D-erythro-*pentitol* (**6**). — To a stirred solution of **5** (980 mg, 2.4 mmol) in anhydrous pyridine (7 mL) was added at −10° *p*-toluenesulfonyl chloride (477 mg, 2.5 mmol). The mixture was stirred for 12 h at −10°, and then for 10 h at room temperature. The solvent was removed *in vacuo*. The crude product was treated with methanolic potassium hydroxide (pH 9) in methanol (15 mL) for 3 h at −5°, after which time *p*-toluenesulfonic acid was added until the solution was neutral (pH 7). Evaporation of the solvent at room temperature and standard processing gave a crude product which was purified by chromatography on silica gel with 2.5% methanol in dichloromethane as the eluent. Pure **6** was obtained as a chromatographically homogeneous syrup (580 mg, 64%); $[\alpha]_D^{25}$ +6.1° (*c* 0.84, chloroform); $\nu_{max}^{CHCl_3}$ 3550 and 3380 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 3.99 (m, 1 H, H-4), 3.85 (s, 3 H, OCH_3), 3.19 (d, 2 H, H_2-5), 2.94 (m, 1 H, H-2), 2.61 (t, 1 H, H-1), 2.38 (q, 1 H, H-1), and 1.69 (t, 2 H, H_2-3).

Anal. Calc. for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 77.01; H, 6.75.

5-O-(p-Anisyldiphenylmethyl)-1,3-dideoxy-1-C-(1,3-dithian-2-yl)-D-erythro-*pentitol* (**7**). — A solution of the epoxide **6** (460 mg, 1.2 mmol) in oxolane (10 mL) was added dropwise, at −70°, to a solution of the lithium anion of 1,3-dithiane [prepared by treatment of 1,3-dithiane (300 mg, 3 mmol) with 1-butyllithium (3 mmol) in oxolane (10 mL) under argon]. The mixture was stirred at −70° overnight, and then aqueous sodium hydrogencarbonate solution (5 mL) was added. The mixture was extracted with dichloromethane (3 × 70 mL), and the extracts were

washed with water and dried (anhydrous magnesium sulfate). After removal of the solvent, chromatography of the crude product on silica gel with 2.5% methanol in chloroform as the eluent yielded **7** as a chromatographically homogeneous syrup (470 mg; 78%); $[\alpha]_D^{25}$ +8.9° (*c* 0.81, chloroform); $\nu_{max}^{CHCl_3}$ 3550 and 3360 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 4.25 (t, 1 H, -S-CH-S-), 4.05 (m, 2 H, H-2 and -4), 3.80 (s, 3 H, OCH_3), 3.12 (d, 2 H, H_2-5), 2.89 [m, 4 H, (-CH_2-S-)$_2$], and 2.60 (m, 6 H).

Anal. Calc. for $C_{29}H_{34}O_4S_2$: C, 68.20, H, 6.71. Found: C, 68.27; H, 6.76.

2,4-Dideoxy-D-erythro-*hexopyranose* (**2**). — A solution of **7** (510 mg, 1 mmol) in acetone (4 mL) was added dropwise, at room temperature, to a stirred solution of *N*-bromosuccinimide (1.06 g, 6 mmol) and 2,6-dimethylpyridine (1 g) in 80% aqueous acetone (10 mL). Stirring was continued for 20 min until the starting material disappeared. The mixture was diluted with dichloromethane, and the solution washed with 2% hydrochloric acid until the solution became neutral. Evaporation of the solvent gave a crude material which was purified by chromatography on silica gel with 5% methanol in chloroform as the eluent. Pure **8** was obtained as a homogeneous syrup (356 mg, 85%); $[\alpha]_D^{25}$ +61.3° (*c* 0.45, chloroform); $\nu_{max}^{CHCl_3}$ 3500–3400 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 4.32 (broad t, 1 H, H-1), 4.10–3.9 (m, 2 H, H-3 and -5), 3.80 (s, 3 H, OCH_3), 3.15 (d, 2 H, H_2-6), and 1.70 (m, 4 H, H-2 and -4).

Anal. Calc. for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.32; H, 6.81.

A solution of **8** (356 mg) in 80% aqueous acetic acid (3 mL) was stirred at room temperature for 3 h, after which time removal of the solvent gave a crude material that was purified by chromatography on silica gel with 10% methanol in dichloromethane as the eluent. Compound **2** was obtained as a syrup (112 mg, 90%); $[\alpha]_D^{25}$ +98° (*c* 1.1, methanol); $\nu_{max}^{CHCl_3}$ 3610–3420 cm^{-1} (OH); ^{1}H-n.m.r. ($CDCl_3$): δ 4.30 (broad t, 1 H, H-1), 4.12–3.82 (m, 4 H, H-3, -5, and H_2-6), and 1.58 (m, 4 H, H_2-2 and -4).

Anal. Calc. for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.69; H, 8.09.

ACKNOWLEDGMENT

The authors thank the National Sciences and Engineering Research Council of Canada for financial support.

REFERENCES

1 A. W. ALBERTS, J. CHEN, G. KURON, V. HUNT, J. HUFF, C. HOFFMAN, J. ROTHROCK, M. LOPEZ, H. JOSHUA, E. HARRIS, A. PATCHETT, R. MONAGHAN, S. CURRIE, E. STAPLEY, G. A. SCHONBERG, O. HENSENS, J. HIRSHFIELD, K. HOOGSTEEN, J. LIESCH, AND J. SPRINGER, *Proc. Natl. Acad. Sci. U.S.A.*, 77 (1980) 3957–3961.

2 A. G. BROWN, T. C. SMALE, T. J. KING, R. H. HASENKAMP, AND R. H. THOMPSON, *J. Chem. Soc., Perkin Trans. 1*, (1976) 1165–1170.

3 M. KUROBA, Y. TSUJITA, K. TANZAWA, AND A. ENDO, *Lipids*, 14 (1979) 585–589.

4 A. YAMAMOTO, H. SUDO, AND A. ENDO, *Atherosclerosis*, 35 (1980) 259–263.

5 J. D PRUGH AND A. A. DEANA, *Tetrahedron Lett.*, 23 (1982) 281–284; Y. L. YANG AND J R. FALCK, *Tetrahedron Lett.*, 23 (1982) 4305–4308 and references cited therein
6 P. SZABÓ AND L. SZABÓ, *J. Chem. Soc.*, (1965) 2944–2947; D. H R. BARTON AND S. W. MCCOMBIE, *J. Chem Soc., Perkin Trans I*, (1975) 1574–1581.
7 J. E. BALDWIN, *J. Chem. Soc., Chem. Commun.*, (1976) 734–736.
8 B.-T. GROBEL AND D. SEEBACH, *Synthesis*, (1977) 357–418.