Carbohydrate Research, 110 (1982) 165–169
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Note

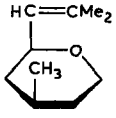
A stereospecific route to (—)-(2*R*, 4*R*)-4-methyl-2-(2-methyl-1-propenyl)tetrahydropyran [(—)-*cis*-rose oxide] from D-glucose

ALAIN LAGRANGE, ALAIN OLESKER, GABOR LUKACS,
Institut de Chimie des Substances Naturelles du C.N.R.S., 91190 Gif-sur-Yvette (France)
AND TON THAT THANG
Équipe de Recherche No 195, C.N.R.S., 8 rue Ecole Normale, Montpellier Cédex 34075 (France)

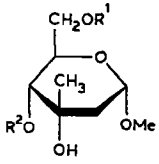
(Received October 21st, 1981; accepted for publication, April 22nd, 1982)

Because of its importance in the perfume industry, there have been several syntheses of *cis*-rose oxide (**1**) as a racemate[1] or as an optically active form[2]. An elegant synthesis of (—)-*cis*-rose oxide starting from D-glucose has been described[3] and we now report another stereospecific synthesis starting from D-glucose.

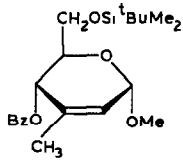
The key step of our approach is based on a reaction discovered by Fraser-Reid and Radatus[4], namely the stereospecific transformation of an isoglucal into a 3-deoxyglucal in the presence of lithium aluminium hydride.



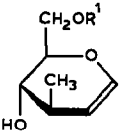
1



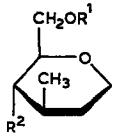
2 $R^1 = R^2 = H$
3 $R^1 = {}^tBuMe_2Si$, $R^2 = H$
4 $R^1 = {}^tBuMe_2Si$, $R^2 = Bz$



5



6 $R^1 = H$
7 $R^1 = {}^tBuMe_2Si$



8 $R^1 = {}^tBuMe_2Si$, $R^2 = OH$
9 $R^1 = {}^tBuMe_2Si$, $R^2 = OCSSMe$
10 $R^1 = {}^tBuMe_2Si$, $R^2 = H$
11 $R^1 = R^2 = H$

Methyl 2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**2**), readily available[5] from D-glucose, was treated with *tert*-butyldimethylsilyl chloride (1.1 equiv.)[6] and imidazole (2.2 equiv.) in *N*,*N*-dimethylformamide at 25° for 14 h to give 98% of the silyl ether **3** as a chromatographically homogeneous syrup. Benzoylation of **3** afforded 97% of syrupy methyl 4-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**4**). Brief treatment of **4** with thionyl chloride at −20° in pyridine gave, after chromatography, 90% of syrupy methyl 4-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-3-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside (**5**). When a solution of **5** in tetrahydrofuran was boiled in the presence of lithium aluminium hydride[4], 95% of crystalline 1,5-anhydro-2,3-dideoxy-3-*C*-methyl-D-*arabino*-hex-1-enitol (**6**) was obtained. The *tert*-butyldimethylsilyl group was lost during the reaction. This result was unexpected, as such protecting groups are generally stable under the reaction conditions used[6]. Treatment of **6** with *tert*-butyldimethylsilyl chloride afforded 86% of syrupy **7**, hydrogenation of which over Pd/C gave a quantitative yield of chromatographically homogeneous, syrupy 1,5-anhydro-6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-3-*C*-methyl-D-*arabino*-hexitol (**8**).

The ^{1}H- and ^{13}C-n.m.r. data for **8** indicated Me-3 to be equatorial, in agreement with the proposed mechanism of the isoglucal–3-deoxyglucal rearrangement[4]. The 250-MHz, ^{1}H-n.m.r. spectrum of **8** contained a triplet at 3.68 p.p.m. (J 10.0 Hz), which was assigned to H-3*a* on the basis of spin-decoupling experiments. In the ^{13}C-n.m.r. spectrum, the chemical shift of C-1 is 78.0 or 75.3 p.p.m. and that of Me-3 is 17.0 p.p.m. If Me-3 were axial, these two signals would be expected at markedly higher fields as a result of the well-known[7] 1,3-diaxial shielding between Me-3 and H-1*a* and H-5*a*. The chemical shift of Me-3 (17.0 p.p.m.) is characteristic of an equatorial methyl substituent shielded only by one *gauche* interaction, *i.e.*, with HO-4. The value of 78.0 or 75.3 p.p.m. for C-1 compares well with that (76.8 p.p.m.) for C-5 in methyl β-D-glucopyranoside, which is an appropriate model compound. After deoxygenation, the signal for Me-3 in **10** appears at 22.5 p.p.m., providing further proof that it is equatorial. An appropriate model compound is *cis*-3-methylcyclohexanol, in which the equatorial Me-3 resonates[7] at 22.8 p.p.m.

The alcohol **8** was converted into the xanthate **9** in quantitative yield, and deoxygenation with tributyltin hydride[8] furnished 61% of syrupy **10**. Treatment of **10** with tetrabutylammonium fluoride in tetrahydrofuran at 25° for 45 min gave, after chromatography, 56% of syrupy 1,5-anhydro-2,3,4-trideoxy-3-*C*-methyl-D-*threo*-hexitol (**11**).

The $[\alpha]_D$ value (+6°) of **11** was close to that (+8.6°) reported by Ogawa[3]. The transformation of **11** into (−)-*cis*-rose oxide **1** in two steps has been reported[3].

EXPERIMENTAL

General. — Solutions were concentrated under diminished pressure. Organic solvents were dried with anhydrous Na_2SO_4. Optical rotations were measured for solutions in $CHCl_3$ at room temperature. ^{1}H-N.m.r. spectra were recorded for

solutions in $CDCl_3$ (internal Me_4Si) with a Varian T-60 or a Cameca 250-MHz spectrometer, and ^{13}C-n.m.r. spectra with a Bruker HX-90 F.T. spectrometer. Chromatography was performed on Silica Gel G (Merck). Melting points are uncorrected.

*Methyl 6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3-*C*-methyl-α-*D*-ribopyranoside* (**3**). — To a solution of **2** (2.26 g) in *N,N*-dimethylformamide (12 mL) were added imidazole (1.76 g) and then *tert*-butyldimethylsilyl chloride (1.95 g), and the mixture was stored at room temperature overnight, poured into water (100 mL), and extracted with toluene (3 × 100 mL). The organic layer was washed with water (6 × 50 mL), dried, and concentrated, to yield syrupy **3** (3.6 g, 98%) which was chromatographically homogeneous. A sample, purified by preparative t.l.c., had $[\alpha]_D$ +44°. ^1H-N.m.r. data: δ 4.70 (bs, 1 H, H-1), 3.30 (s, 3 H, OMe), 2.03 (d, $J_{2,2'}$ 14 Hz, H-2*e*), 1.70 (dd, $J_{2,1}$ 4 Hz, H-2*a*), 1.23 (s, 3 H, Me-3), 0.92 (s, 9 H, ^{t}Bu), and 0.13 (s, 6 H, $SiMe_2$).

Anal. Calc. for $C_{14}H_{30}O_5Si$: C, 54.86; H, 9.87. Found: C, 54.67; H, 10.11.

*Methyl 4-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-3-*C*-methyl-α-*D*-ribo-hexopyranoside* (**4**). — To a solution of **3** (3.6 g) in pyridine (70 mL) at 0° was added benzoyl chloride (1.6 mL), and the mixture was left overnight at room temperature and then partitioned between water (400 mL) and dichloromethane (3 × 200 mL). The organic layer was dried and concentrated, to yield syrupy **4** (4.8 g, 97%). A sample, purified by preparative t.l.c., had $[\alpha]_D$ +59°. Mass spectrum: *m/z* 353 (M^+ − ^{t}Bu). ^1H-N.m.r. data: δ 7.37–7.96 (m, 5 H, Ph), 5.08 (d, 1 H, $J_{4,5}$ 9 Hz, H-4), 4.93 (m, 1 H, H-1), 3.48 (s, 3 H, OMe), 2.08 (m, 2 H, H-2,2'), 1.26 (s, 3 H, Me-3), 0.92 (s, 9 H, ^{t}Bu), and 0.13 (s, 6 H, $SiMe_2$).

Anal. Calc. for $C_{21}H_{34}O_6Si$: C, 61.43; H, 8.35. Found: C, 61.16; H, 8.47.

*Methyl 4-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-3-*C*-methyl-α-*D*-erythro-hex-2-enopyranoside* (**5**). — To a solution of **4** (4.8 g) in pyridine (70 mL) at −20° was added thionyl chloride (13.2 mL) dropwise. After 15 min, the mixture was poured onto ice and extracted with ether (3 × 100 mL). The organic layer was dried and concentrated, to yield a syrupy residue (4.67 g) which was eluted from silica gel with dichloromethane–ethyl acetate (10:1), to afford syrupy, homogeneous **5** (4.1 g, 90%), $[\alpha]_D$ +112°. Mass spectrum: *m/z* 335 (M^+ − ^{t}Bu). N.m.r. data: ^1H, δ 7.3–8.0 (m, 5 H, Ph), 5.72 (m, 2 H, H-2,4), 5.00 (bs, 1 H, H-1), 3.83 (m, 2 H, H-6,6'), 3.57 (s, 3 H, OMe), 1.80 (bs, 3 H, Me-3), 0.92 (s, 9 H, ^{t}Bu), and 0.13 (s, 6 H, $SiMe_2$); ^{13}C, δ 137.6 (C-3), 123.9 (C-2), 95.8 (C-1), 70.5 (C-4), 68.2 (C-5), 63.5 (C-6), 55.6 (OMe), and 18.2 (Me-3) + benzoate and *tert*-butyldimethylsilyl carbons.

Anal. Calc. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.18; H, 8.07.

*1,5-Anhydro-2,3-dideoxy-3-*C*-methyl-*D*-arabino-hex-1-enitol* (**6**). — To a solution of **5** (3.16 g) in dry tetrahydrofuran (100 mL) was added lithium aluminium hydride (0.3 g), and the mixture was heated to reflux for 24 h. Cold water (5 mL) was then added, and the mixture was filtered through Kieselguhr, dried, and concentrated. The residue (1.1 g, 95%) was recrystallised from acetone to give **6**, m.p. 112–113°,

$[\alpha]_D$ −29°. Mass spectrum: *m/z* 144 ($M^{+\cdot}$). ^{1}H-N.m.r. data: δ 6.20 (dd, 1 H, $J_{1,2}$ 6, $J_{1,3}$ 2 Hz, H-1), 4.47 (dd, 1 H, $J_{2,3}$ 2 Hz, H-2), and 1.1 (d, 3 H, $J_{3Me\text{-}3}$ 7 Hz, Me-3).

Anal. Calc. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.17; H, 8.48.

*1,5-Anhydro-6-*O-(tert-*butyldimethylsilyl*)-*2,3-dideoxy-3-*C-*methyl*-D-arabino-*hex-1-enitol* (**7**). — To a solution of **6** (0.65 g) in *N,N*-dimethylformamide (8 mL) were added imidazole (0.9 g) and then *tert*-butyldimethylsilyl chloride (0.74 g). The mixture was stored at room temperature overnight, poured into water (50 mL), and extracted with toluene (3 × 50 mL). The organic layer was washed with water (6 × 50 mL), dried, and concentrated, to yield syrupy **7** (1 g, 86%) which was chromatographically homogeneous. A sample was purified by preparative t.l.c. Mass spectrum: *m/z* 201 (M^+ − ^{t}Bu). ^{1}H-N.m.r. data: δ 6.20 (dd, 1 H, $J_{1,2}$ 6, $J_{1,3}$ 2 Hz, H-1), 4.47 (dd, 1 H, $J_{2,3}$ 2 Hz, H-2), and 1.13 (d, 3 H, $J_{3,Me\text{-}3}$ 7 Hz, Me-3).

Anal. Calc. for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 59.95; H, 10.02.

(−)-(2R,3S,4R)-2-(tert-*Butyldimethylsilyloxymethyl*)-*4-methyltetrahydropyran-3-ol* [*1,5-anhydro-6-*O-(tert-*butyldimethylsilyl*)-*2,3-dideoxy-3-*C-*methyl*-D-arabino-*hexitol*] (**8**). — To a solution of **7** (1 g) in ethyl acetate (100 mL) was added 10% Pd/C (1 g), and the mixture was hydrogenated at normal pressure overnight, filtered through Kieselguhr, and then concentrated. The syrupy residue was chromatographically homogeneous. A sample was purified by t.l.c. (hexane–ethyl acetate, 8:2), to yield syrupy **8** (1 g, 99%), $[\alpha]_D$ −55°. Mass spectrum: *m/z* 203 (M^+ − ^{t}Bu). ^{1}H-N.m.r. data: δ 3.90 (dd, 1 H, $J_{2,3}$ 10, $J_{2,7(7')}$ 3.5 Hz, H-2), 3.82 (dd, 1 H, $J_{6e,6a}$ 12, $J_{6e,5a}$ 4 Hz, H-6*e*), 3.68 (t, 1 H, $J_{3,2} = J_{3,4}$ = 10 Hz, H-3), 3.33 (td, 1 H, $J_{6a,5a}$ 12, $J_{6a,5e}$ 2 Hz, H-6*a*), 3.14 (m, 2 H, H-7,7'), 1.07 (d, 3 H, $J_{4,Me}$ 7 Hz, Me-4), 0.92 (s, 9 H, ^{t}Bu), and 0.13 (s, 6 H, Me_2Si). ^{13}C-N.m.r. data: δ 78.0–75.3 (C-2,3), 66.4 (CH_2OH), 65.3 (C-6), 36.1 (C-4), 32.4 (C-5), and 17.0 (Me-4).

Anal. Calc. for $C_{13}H_{28}O_3Si$: C, 59.59; H, 10.84. Found: C, 60.20; H, 11.15.

(+)-(2R,4R)-*2-*(tert-*Butyldimethylsilyloxymethyl*)-*4-methyltetrahydropyran* [*1,5-anhydro-6-*O-(tert-*butyldimethylsilyl*)-*2,3,4-trideoxy-3-*C-*methyl*-D-threo-*hexitol*] (**10**). — A mixture of **8** (90 mg), dry ether (2 mL), and sodium hydride (15 mg) was boiled under reflux for 3 h. Carbon disulfide (0.06 mL) was then added, and, after 3 h, methyl iodide (0.06 mL). The solution was stored overnight and then diluted with water, and the organic layer was concentrated to yield the xanthate **9** quantitatively. To a solution of toluene (6 mL) containing tributyltin hydride (0.9 mL) heated to reflux under nitrogen was added dropwise a solution of toluene (6 mL) containing **9** (110 mg) and a small amount of α,α-diazobutyronitrile. After 5 h at 120°, the toluene was evaporated and the residue was eluted from silica gel with hexane–ethyl acetate (20:1), to yield syrupy, homogeneous **10** (55 mg, 61%), $[\alpha]_D$ +12°. Mass spectrum: *m/z* 187 (M^+ − ^{t}Bu). ^{1}H-N.m.r. data: δ 4.03 (m, 1 H, H-6*e*), 3.10–3.83 (m, 4 H, H-2,6*a*,7,7'), 0.94 (d, 3 H, $J_{4,Me}$ 7 Hz, Me-4), 0.92 (s, 9 H, ^{t}Bu), and 0.13 (s, 6 H, $SiMe_2$).

Anal. Calc. for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.54. Found: C, 64.33; H, 12.07.

(+)-(2R,4R)-*2-Hydroxymethyl-4-methyltetrahydropyran*(*1,5-anhydro-2,3,4-tri-*

deoxy-3-C-*methyl*-D-threo-*hexitol*) (**11**). — A mixture of tetrahydrofuran (6 mL), tetrabutylammonium fluoride (50 mg), and **10** (0.17 g) was stored at room temperature for 45 min, the solvent was then evaporated, and the residue was eluted from silica gel with hexane–ethyl acetate (1:1), to yield syrupy **11** (50 mg, 56%), $[\alpha]_D$ +6°; lit.[3] $[\alpha]_D$ +8.6°. Mass spectrum: *m/z* 130 ($M^{+\cdot}$). ^{1}H-N.m.r. data: δ 4.00 (dd, 1 H, $J_{6e,6a}$ 12, $J_{6e,5a}$ 4 Hz, H-6*e*), 3.36–3.62 (m, 4 H, H-2,6*a*,7,7′), and 0.92 (d, 3 H, $J_{4,Me}$ 7 Hz, Me-4).

Anal. Calc. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.37; H, 11.09.

REFERENCES

1 Y. R. Naves and P. Ochsner, *Helv. Chim. Acta*, 45 (1962) 397–399; M. Julia and B. Jacquet, *Bull. Soc. Chim. Fr.*, (1963) 1983; H. Ishikawa, S. Ikeda, and T. Mukaiyama, *Chem. Lett.*, (1975) 1051–1054.

2 G. Ohloff, E. Klein, and G. O. Schenck, *Angew. Chem.*, 73 (1961) 578; G. Ohloff and B. Lienhard, *Helv. Chim. Acta*, 48 (1965) 182–189; T. Shono, A. Ikeda, and Y. Kimura, *Tetrahedron Lett.*, (1971) 3599–3602.

3 T. Ogawa, N. Takasaka, and M. Matsui, *Carbohydr. Res.*, 60 (1978) c4–c6.

4 B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.*, 92 (1970) 6661–6663.

5 B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc., C*, (1966) 398–403.

6 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94 (1972) 6190–6191.

7 J. B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 1972.

8 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, (1975) 1574–1585.