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Preliminary communication

Synthesis and stereospecific deuterium-labelling of L-ascorbic acid

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Since the first synthesis of L-ascorbic acid by Reichstein and Grüssner[1] in 1934, several alternative syntheses have been reported[2]. We report here a simple, efficient, synthetic sequence for this biologically important molecule, starting from a readily available fermentation-product, methyl D-*arabino*-hexulosonate[3] (**1**). The key step in this transformation is the inversion of the configuration of C-5, achieved by regioselective protection of hydroxyl groups, and a subsequent oxidation–reduction sequence.

The treatment of methyl ester **1** with 2,2-dimethoxypropane in *N,N*-dimethylformamide, in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate at room temperature, gave a quantitative yield of the 4,5-monoisopropylidene acetal **2**, m.p.†† 116–117°, $[\alpha]_D^{25}$ –124.3° (ethanol). The 2,3-diacetate (**3**) of **2** was obtained in the usual way; m.p. 128–128.5°, $[\alpha]_D^{25}$ –166.2° (ethanol); ^{1}H n.m.r. data ($CDCl_3$): δ 5.2 (d, *J* 7.5 Hz) for H-3. Compound **3** was hydrolyzed to 2,3-diacetate **4**, m.p. 161.5–162.5°, $[\alpha]_D^{25}$ –162.6° (ethanol) in 95% yield (from **1**). Diacetate **4** could be quantitatively reconverted into **3** by treatment with 2,2-dimethoxypropane, thus proving that no acetyl migration occurs during hydrolysis of **3** in aqueous acetic acid to give **4**. Selective monobenzoylation[4] of the equatorial in the presence of the axial hydroxyl group was achieved with benzoyl chloride in dichloromethane–pyridine at –10° to give monobenzoate **5**, m.p. 188–190°, $[\alpha]_D^{25}$ –149.4° (ethanol).

Jones oxidation of monobenzoate **5** gave an unstable ketone **6**, which could be detected as a single spot on a t.l.c. plate of silica gel GF_{245}, but decomposed during chromatography on a column of the same silica gel. Immediate reduction of ketone **6** with sodium borohydride gave the equatorial alcohol **7**, m.p. 175.5–176.5°, $[\alpha]_D^{25}$ –61.1° (ethanol) in 40% yield (from **4**). The stereochemistry of **7** was assigned from its ^{1}H n.m.r. data ($CDCl_3$): δ 5.49 (dd, $J_{3,4}$ 10 Hz, $J_{4,5}$ 8 Hz, H-4). In contrast, **5** showed: δ 5.50 (dd,

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††All compounds for which the m.p. is recorded gave acceptable elemental analyses.

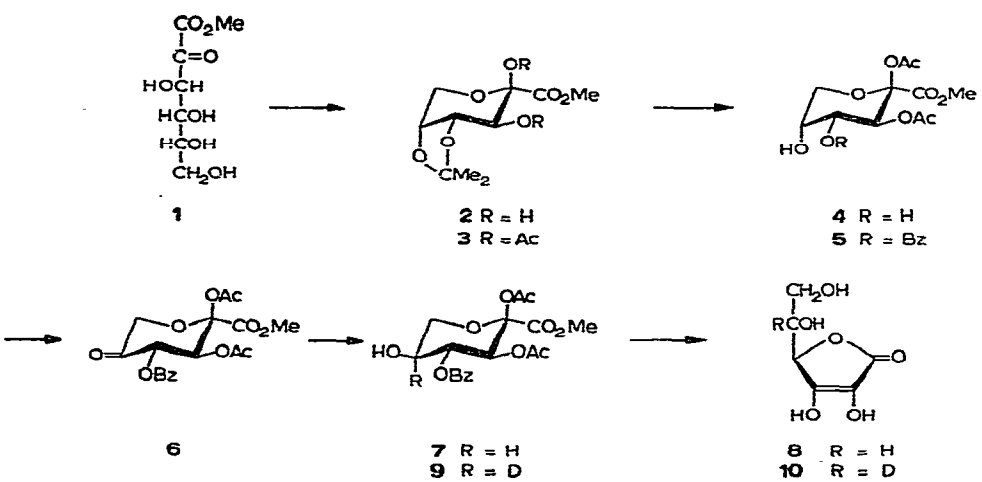
$J_{3,4}$ 10 Hz, $J_{4,5}$ 3 Hz, H-4), which proved the axial–axial and axial–equatorial relationship between H-4 and H-5 in **7** and **5**, respectively. Furthermore, H-3 in **5** appears at δ 5.75, and that in **7** at δ 5.31, in accordance with the 1,3-diaxial disposition of H-3 and OH-5 in **5** exhibiting a deshielding[5] of 0.44 p.p.m.

Deacylation of **7** in 0.2M methanolic sodium methoxide during 10 min under nitrogen at room temperature, and subsequent acidification by methanolic hydrogen chloride, gave L-ascorbic acid (**8**) in excellent yield (overall yield* from **1**, 36%); m.p. 189–191°, $[\alpha]_D^{25}$ +49.1° (*c* 0.53, methanol). The ^{1}H n.m.r. spectrum (D_2O) of synthetic **8** was in complete agreement with that of an authentic specimen of **8**.

Although stereospecific labelling of biologically active compounds with isotopes has been extensively employed in the study of their biochemical behavior, deuterium labelling of L-ascorbic acid had not, to the best of the authors' knowledge, been achieved. Stereospecific introduction of deuterium at C-5 was, therefore, undertaken by using the synthetic sequence already described.

Reduction of ketone **6** with sodium borodeuteride in 1,2-dimethoxyethane afforded the deuterated alcohol **9**, m.p. 174.5–175.5°, $[\alpha]_D^{25}$ –65.0° (ethanol). Its ^{1}H n.m.r. spectrum ($CDCl_3$) disclosed the location of deuterium by showing an AB type of quartet at δ 3.61 and 4.14 ($J_{6,6'}$ 12 Hz) for H-6 and H-6′, and a doublet for H-4 at δ 5.53 (*J* 10 Hz), instead of the doublet of doublets for H-4 in the spectrum of **7**. A diequatorial relationship between OAc-3 and OH-5 was indicated by the H-4 chemical shift of **9**, δ 5.31, which is in good agreement with that of **7**, but not with that of **5**. The equatorial attachment of OH-5 in **9** was firmly established by the dibenzoate chirality rule[6], as shown by the c.d. spectra of the dibenzoates, **11**, m.p. 159–160°, $[\alpha]_D^{25}$ –220° ($CHCl_3$); **12**, m.p. 148–148.5°, $[\alpha]_D^{25}$ –5.1° ($CHCl_3$); and **13**, m.p. 149–150°, $[\alpha]_D^{25}$ –5.3° ($CHCl_3$); see Figs. 1 and 2.

Finally, when **9** was treated as for **7**, it afforded the C-5-deuterated L-ascorbic acid



*Yields were not optimized.

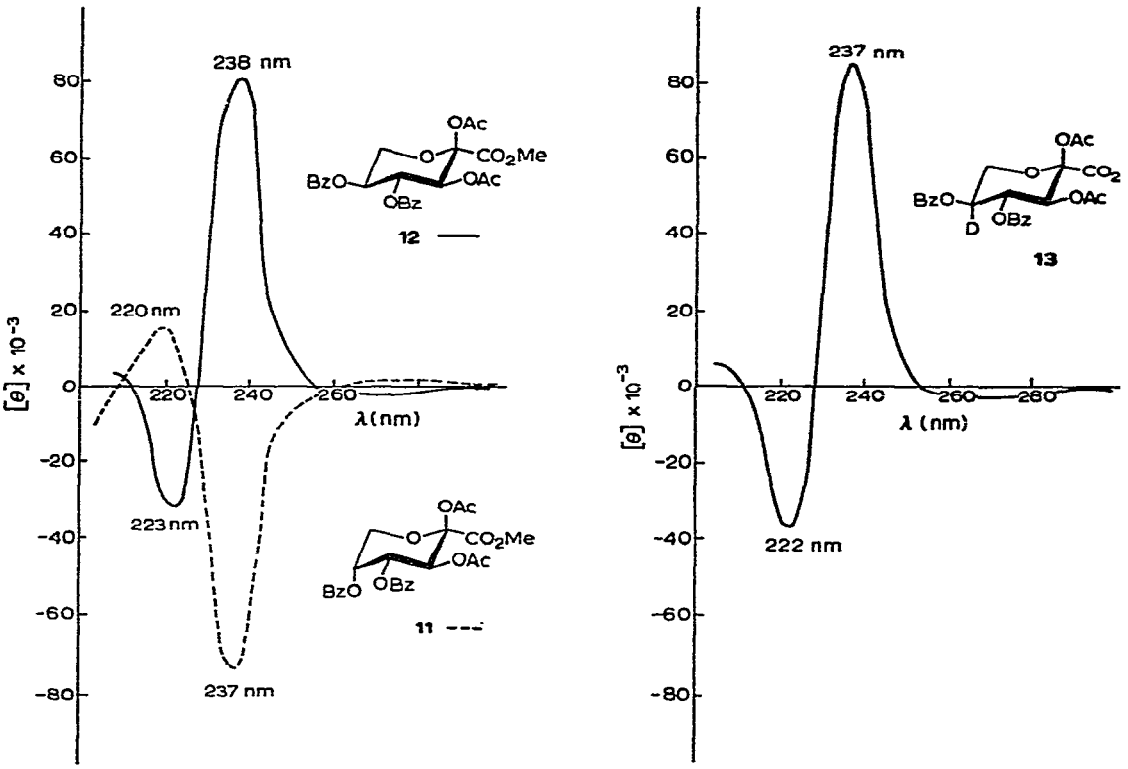


Fig. 1. Circular dichroism of **11** and **12** in methanol. [θ] denotes the molar ellipticity (in degree • cm²/decimole).

Fig. 2. Circular dichroism of **13** in methanol. [θ] denotes the molar ellipticity (in degree • cm²/decimole).

(10), m.p. 168–170°, $[\alpha]_D^{25}$ +43.6° (*c* 0.45, methanol) in 80% yield. Its ^{1}H n.m.r. spectrum (D_2O) showed two singlets at δ 3.78 (2 H) for H-6 and H-6′, and at δ 4.98 (1 H) for H-4, as expected.

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