First synthesis of L-ascorbic acid (vitamin C) from a non-carbohydrate source

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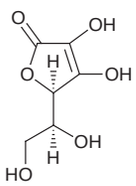
The enantiopure *cis*-1,2-dihydrocatechol 2, which is obtained by microbial oxidation of chlorobenzene, has been converted, *via* 3,5-*O*-benzylidene-L-gulonolactone (8), into L-ascorbic acid (1).

L-Ascorbic acid (vitamin C, **1**), a biologically significant



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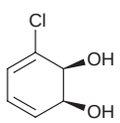

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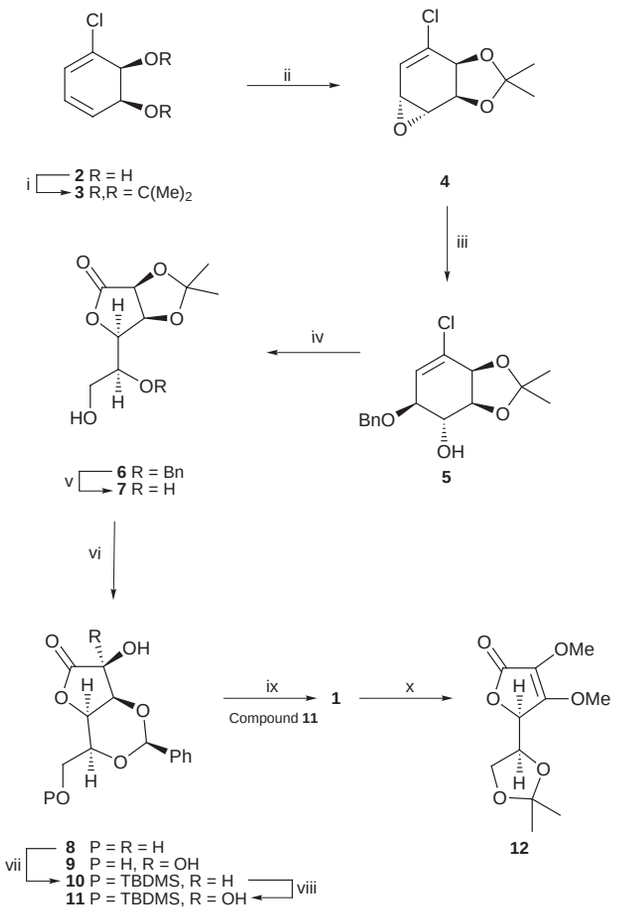
reducing agent, is implicated in a variety of key physiological processes[1] including, for example, the production of collagen.[2] It is also considered to be important in the prevention of various chronic diseases such as cancer, cerebral apoplexy, diabetes, atopic dermatitis, myocardial infarction and AIDS.[3] The compound has been the subject of many synthetic studies[4,5] and is produced commercially from D-glucitol *via* a six step reaction sequence including an initial microbiological oxidation process.[6] In connection with other work, we required access to certain ^{17}O-, ^{13}C- and/or ^{2}H-labelled samples of L-ascorbic acid and none of the existing syntheses, all of which involve the use of carbohydrate-based starting materials, seemed suitable for our purposes. Consequently, we now report the first total synthesis of the title compound from non-carbohydrate sources.[7,8] The reaction sequence described herein should be especially amenable to the preparation of labelled ascorbates which could be used for probing their *in vivo* functions.

The present synthesis (Scheme 1) employs enantiopure (>99% ee) *cis*-1,2-dihydrocatechol **2**† (obtained by microbial oxidation of chlorobenzene) as starting material and was inspired by the seminal contributions of Hudlicky and coworkers who have pioneered the use of such microbial oxidation products in the chemoenzymatic synthesis of, *inter alia*, various monosaccharides.[7,9] Thus, the known[10] acetonide derivative, **3**, of diol **2** was converted into the previously reported[10,11] mono-epoxide **4** by standard methods. Reaction of this last compound with benzyl alcohol and a catalytic amount of trifluoromethanesulfonic acid (TfOH) afforded a stereochemically pure nucleophilic ring-cleavage product which, by analogy with related reactions of this epoxide,[11] is assigned structure **5**‡ {50%, mp 93–94 °C, $[a]_D$ +23.2 (*c* 0.2, $CHCl_3$)}.[12] Confirmation of this assignment followed from the conversion of compound **5** into the known[13] 2,3-*O*-isopropylidene-L-gulono-1,4-lactone (**7**). Thus, subjection of chloroalkene **5** to reaction with ozone in methanol and subsequent *in situ* reduction of the intermediate hydroperoxide with sodium cyanoborohydride at pH 3 gave the L-gulonolactone derivative **6** {74%, mp 120–122 °C, $[a]_D$ +53.4 (*c* 0.8, $CHCl_3$)}. Compound **6** could not be de-benzylated under standard conditions but by using transfer hydrogenolysis techniques[14] (with sonication) conversion into compound **7** {53%; mp 143–146 °C; lit.,[13] mp



Scheme 1 *Reagents and conditions*: (i) $(CH_3O)_2C(CH_3)_2$ (1.5 mol equiv.), CH_2Cl_2, *p*-TsOH (1.5 mol%), 20 °C, 0.33 h; (ii) MCPBA, $NaHCO_3$, CH_2Cl_2, 18 °C, 5 h; (iii) $C_6H_5CH_2OH$ (1.05 mole equiv.), TfOH (5 mol%), CH_2Cl_2, 20 °C, 0.25 h; (iv) O_3 (excess), CH_3OH, −78 °C ⟶ 20 °C then HCl (2 M solution in CH_3OH), $NaBH_3CN$ (8 mole equiv.), 20 °C, 3 h; (v) cyclohexa-1,4-diene (10 mole equiv.), 10% Pd on C, CH_3CH_2OH, sonication, 18 °C, 8 h; (vi) C_6H_5CHO (4 mole equiv.), TfOH (5 mol%), 18 °C, 4 h; (vii) TBDMSCl (1.1 mole equiv.), imidazole (3.0 mole equiv.), DMAP (3 mol%), THF, 0 °C ⟶ 18 °C, 19 h; (viii) Dess–Martin periodinane (1.1 mole equiv.), CH_2Cl_2, 18 °C, 1.5 h; (ix) CH_3CO_2H–H_2O (7 : 3), 70–75 °C, 4 h; (x) CH_3COCl (5 mol%), $(CH_3)_2CO$, 18 °C, 2 h then K_2CO_3 (5 mole equiv.), $(CH_3O)_2SO_2$ (5 mole equiv.), 56 °C, 3 h.

143–146 °C; $[a]_D$ +74 (*c* 0.5, EtOH); lit.,[13] $[a]_D$ +30 (*c* 2, EtOH)§} was achieved. Reaction of acetonide **7** with neat benzaldehyde and TfOH as catalyst resulted in a *trans*-acetalisation reaction and formation of the benzylidene acetal **8** {47%; mp 188–190 °C; lit.,[5b] mp 188–189 °C; $[a]_D$ +57 (*c* 1.0, DMF); lit.,[5b] $[a]_D$ +61.1 (DMF)} which was identical, in all respects, with an authentic sample[5,15] prepared (in <10% yield) from commercially available L-gulonic-γ-lactone. Theoretically, the acquisition of acetal **8** constitutes a formal total synthesis of

L-ascorbic acid since Crawford and Breitenbach[5] have converted the former compound into the latter *via* sequential oxidation and acetal hydrolysis steps. However, despite numerous attempts we were not able to effect the previously reported[5] manganese dioxide[16]-promoted oxidation of compound **8** to compound **9**. In order to examine alternate oxidants, the primary hydroxy group of diol **8** was protected as the corresponding TBDMS-ether so as to give compound **10** {74%; mp 176 °C; $[\alpha]_D$ +55.5 (*c* 0.4, $CHCl_3$)}. After extensive experimentation with a variety of potential oxidants it was established that the Dess–Martin periodinane[17] effects smooth conversion of compound **10** into a variable mixture of ketone hydrate **11** and a regioisomer which is presumed to derive from silyl-group migration. Acetic acid promoted hydrolysis of this unstable mixture then provided L-ascorbic acid (**1**) in 66% yield (from compound **10**). For the purposes of comprehensive spectroscopic characterisation, compound (**1**) was converted, *via* a simple one-pot procedure,[18] into the stable derivative (**12**) {80%, mp 99–100 °C; lit.,[18] mp 100–101 °C; $[\alpha]_D$ +9.1 (*c* 0.6, $CHCl_3$); $[\alpha]_D$ (authentic sample) +9.3 (*c* 0.6, $CHCl_3$)}. This latter material was identical, in all respects, with an authentic sample prepared from commercial L-ascorbic acid.

Experimental

Compound 6

A solution of chloroalkene **5** (100 mg, 0.32 mmol) in methanol (15 cm^3) was cooled to −78 °C and a stream of ozone was bubbled through the solution until a blue colouration persisted. The solution was then purged with dioxygen for 0.25 h before being allowed to warm to room temperature. The resulting solution was concentrated to about one-third of the original volume then treated with one drop of methyl orange indicator followed by sufficient HCl (2 M solution in methanol) to establish pH 3. Sodium cyanoborohydride (160 mg, 2.5 mmol) was added in four roughly equal portions over a period of 3 h while ensuring pH 3 was maintained by appropriate additions of HCl. The reaction was quenched with acetone (10 cm^3) then filtered through Celite™ and the filtrate concentrated under reduced pressure to give a light yellow oil. Subjection of this material to flash chromatography[19] (1 : 1 hexane–ethyl acetate elution) and concentration of the appropriate fractions (R_f 0.2 in 3 : 2 hexane–ethyl acetate) afforded a white solid. Recrystallisation (CH_2Cl_2–hexane) of this material then gave the *title compound* **6** (73 mg, 74%) as white needles, mp 118–120 °C (Found: $M^{+\cdot}$ 308.1262; C, 62.0; H, 6.6. $C_{16}H_{20}O_6$ requires $M^{+\cdot}$ 308.1260; C, 62.3; H, 6.5%); ν_{max} (KBr)/cm^{-1} 3473 and 1788; δ_H (300 MHz, $CDCl_3$) 7.42–7.28 (5H, complex m), 4.85 (1H, d, *J* 11.4 Hz), 4.80 (2H, broadened s), 4.68 (1H, m), 4.64 (1H, d, *J* 11.4 Hz), 3.91 (1H, dd, *J* 12.1 and 2.7 Hz), 3.84 (1H, dt, *J* 8.2 and 3.1 Hz), 3.77 (1H, dd, *J* 12.1 and 3.1 Hz), 2.04 (1H, br s), 1.45 (3H, s, CH_3), 1.37 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 173.8 (C), 137.6 (C), 128.5 (CH), 128.0 (CH), 127.9(7) (CH), 114.1 (C), 80.3 (CH), 78.7 (CH), 75.9 (CH), 75.8 (CH), 73.4 (CH_2), 61.3 (CH_2), 26.7 (CH_3), 25.8 (CH_3); *m*/*z* (EI, 70 eV) 308 (8%), 250 [5, $(M - CH_3COCH_3)^{+\cdot}$] and 91 (100, $C_7H_7^+$).

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Notes and references

† Available commercially from Genencor International Inc., 925 Page Mill Road, Palo Alto, CA 94304-1013, USA.

‡ All new compounds had spectroscopic data (IR, ^1H and ^{13}C NMR, *m*/*z*) consistent with the assigned structure. Satisfactory combustion analysis data were obtained for new compounds.

§ The specific rotation recorded for an authentic sample of compound (**7**) {$[\alpha]_D$ +74 (*c* 0.5, EtOH)} matched that obtained on our material thus suggesting that the value recorded in the literature[13] may be in error.

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