Synthesis of (2*R*)-2-bromodehydroquinic acid and (2*R*)-2-fluorodehydroquinic acid†

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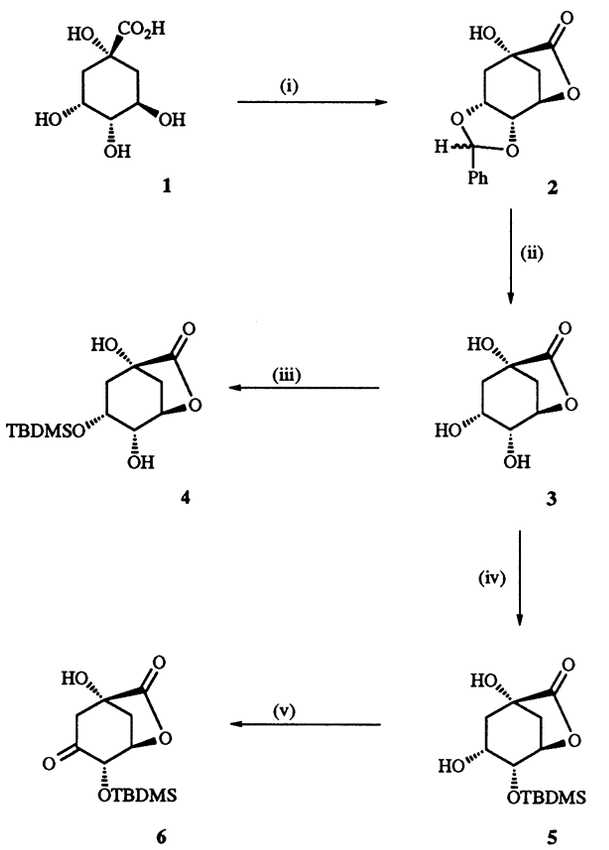
(2*R*)-2-Bromodehydroquinic acid and (2*R*)-2-fluorodehydroquinic acid† have each been synthesised in six steps from quinic acid *via* the common intermediate 6. The syntheses exploit the selective protection of the 4-hydroxy group of the quinic acid lactone 3 with *tert*-butyldimethylsilyl chloride.

The shikimate pathway to the aromatic amino acids[1] is a target for herbicides and antimicrobial agents. The broad spectrum post-emergence herbicide glyphosate acts by inhibiting 5-enolpyruvyl shikimate 3-phosphate (EPSP) synthase,[2] and recently the antimicrobial action has been demonstrated for (6*S*)-6-fluoroshikimic acid.[3] Interest in this pathway has resulted in the synthesis of many analogues of pathway intermediates, especially derivatives of shikimic acid.

We are interested in dehydroquinic acid analogues substituted at C-2 as potential inhibitors of 3-dehydroquinate dehydratase. Here we describe the synthesis of (2*R*)-2-bromodehydroquinic acid **8** and (2*R*)-2-fluorodehydroquinic acid **10**.† These are the first syntheses of 2-substituted dehydroquinic acid derivatives. Bartlett and co-workers have recently reported the synthesis of the corresponding 2-bromoshikimic acid[4] and 2-fluoroshikimic acid.[5] (2*R*)- and (2*S*)-2-Hydroxyquinic acids and (2*R*)-2-bromoquinic acid have also been synthesised.[6]

Quinic acid was used as an inexpensive chiral advanced intermediate. The required transformations are selective oxidation at C-3 and introduction of the halogenic substituent at C-2. However to achieve this it is necessary to protect the other functionality present in quinic acid (Scheme 1). The first step involves the quadruple protection of quinic acid **1** in the toluene-*p*-sulfonic acid catalysed reaction with benzaldehyde.[7] Azeotropic removal of the water gave the benzylidene acetal **2** as a 2.2:1 mixture of diastereoisomers in 79% yield. The major isomer was isolated after recrystallisation from diethyl ether. The benzylidene centre was shown to have the *R*-configuration by observation of NOEs from H-4 and H-5 to the benzylidene hydrogen in the ^{1}H NMR spectrum. The benzylidene protecting group was removed by catalytic hydrogenation over 10% palladium on charcoal to give quinic acid lactone **3** in 93% yield. It is possible to convert **1** directly into **3**[8] but the two step procedure used has been found to be experimentally preferable.

The selective protection of the C-4 hydroxy group of **3** was achieved using *tert*-butyldimethylsilyl (TBDMS) chloride. Reaction of **3** with TBDMS chloride in *N*,*N*-dimethylformamide (DMF) at 0 °C for 6 h gave a mixture of the mono-protected compounds **4** and **5** in a ratio of 97:3 (combined yield 82%). However if the reaction was carried out at 90 °C, the selectivity was reversed and the product ratio was then 1:2 in favour of the required C-4 silyl ether (combined yield 84%). Submission of the kinetic product **4** to the higher temperature conditions resulted in it being converted to a mixture of **4** and **5**.



Scheme 1 *Reagents, conditions and yields:* (i) PhCHO, 4-TsOH, toluene, reflux (74%); (ii) H_2, [10%]Pd/C, AcOH, room temp. (94%); (iii) TBDMSCl, DMAP, Et_3N, Bu_4NI, 0 °C (79%); (iv) TBDMSCl, DMAP, Et_3N, Bu_4NI, 90 °C (54%); (v) PDC, 4 Å molecular sieves, CH_2Cl_2, room temp. (87%)

The structure of **5** was assigned after careful NMR spectroscopic studies. The ^{1}H NMR spectrum recorded under rigorously dry conditions showed an 11.3 Hz coupling between 5-H and a hydroxy proton. Furthermore NOE difference spectroscopy indicated significant enhancements of 3-H and 5-H and in the TBDMS protons upon irradiation of 4-H. Conversely, irradiation of 5-H resulted in enhancement of 4-H, 6eq-H and the C-5 hydroxy proton. Irradiation of 3-H resulted in enhancement of 4-H, 2eq-H, 2ax-H and the TBDMS protons. These observations and subsequent chemical transformations con-

† IUPAC names: (1*S*,2*R*,4*S*,5*R*)-2-bromo-1,4,5-trihydroxy-3-oxocyclohexanecarboxylic acid and (1*S*,2*R*,4*S*,5*R*)-2-fluoro-1,4,5-trihydroxy-3-oxocyclohexanecarboxylic acid, respectively.

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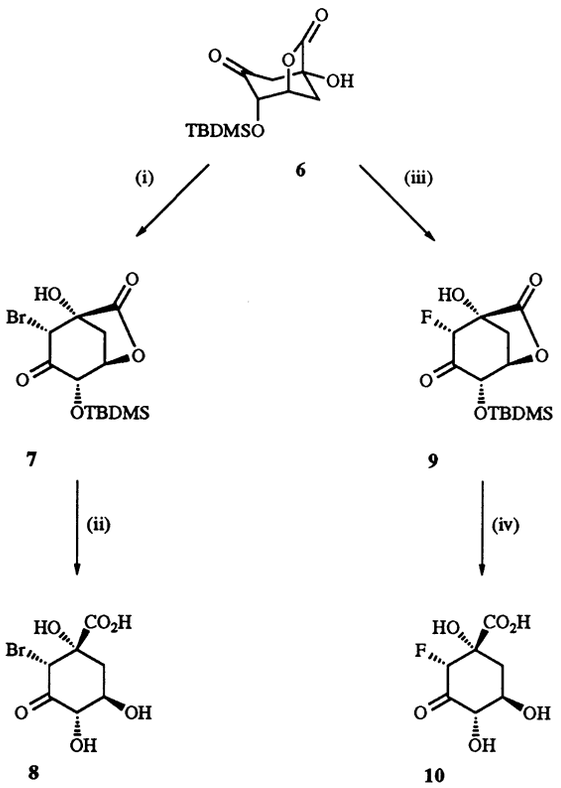

Scheme 2 *Reagents, conditions and yields:* (i) Br_2·dioxane, Et_2O, room temp. (89%); (ii) AcOH, THF, H_2O, 40 °C (95%); (iii) (*a*) TMSOTf, Et_3N, toluene, reflux (*b*) Selectfluor®, DMF, room temp. (89%); (iv) AcOH, H_2O, 50 °C (90%)

firmed the location of the silyl group in **5** and hence the corresponding location in **4**.

The secondary hydroxy group in **5** was readily oxidised using either pyridinium chlorochromate (PCC), tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide (TPAP–MNO) or pyridinium dichromate (PDC) in the presence of 4 Å activated molecular sieves. The latter reaction proceeded in the highest yield (87%) to give the ketone **6**. This compound is acid-sensitive and so was purified by recrystallisation from hexane.

Ketone **6** is the key intermediate in the synthesis of both (2*R*)-2-bromodehydroquinic acid **8** and (2*R*)-2-fluorodehydroquinic acid **10** (Scheme 2). For the synthesis of (2*R*)-2-bromodehydroquinic acid, the bromine is introduced stereoselectively using dioxane dibromide[10] to afford the axially-brominated derivative **7** (89%). In the NMR spectrum of **7** the axial bromine causes a downfield shift in the signal for the hydrogen 1,3-diaxial to it (2ax-H) from δ 2.86 in **6** to δ 3.33. The isolation of a single diastereoisomer of **7** is presumed to be due to preferential bromination on the side of the ketone **6** opposite to the bridging lactone group.

The TBDMS protecting group of **7** was removed and the lactone opened by mild acid hydrolysis (HOAc–H_2O–THF) at 40 °C to give the required (2*R*)-2-bromodehydroquinic acid **8** in 95% yield. The equatorial position of the bromine was confirmed by NMR spectroscopy. Irradiation of 2-H led to enhancement of the signals for 4-H (6%) and 6ax-H (4%). Correspondingly, irradiation of 4-H enhanced the signals for 2-H (6%) and 6ax-H (3%). The configuration at C-2 (C-6 in compound **7**) is unchanged in going from **7** to **8**, it is simply the cleaving of the lactone which allows the ring to flip to the other chair conformation.

(2*R*)-2-Fluorodehydroquinic acid **10** was synthesised from the protected ketone **6** in two steps. The silyl enol ether was made using trimethylsilyl trifluoromethanesulfonate and reacted directly with Selectfluor®[9] in DMF to give the protected fluoro ketone **9** in 89% yield. This was deprotected in aqueous acetic acid to give **10** (90%). The equatorial position of the fluorine was confirmed by NMR spectroscopy. The fluorine has a geminal coupling to 2-H of 47 Hz and a W-coupling to 6eq-H of 8 Hz. Irradiation of 2-H led to enhancement of the signals for 4-H (6%) and 6ax-H (4%). Correspondingly, irradiation of 4-H enhanced the signals for 2-H (6%) and 6ax-H (3%).

(2*R*)-2-Bromodehydroquinic acid and (2*R*)-2-fluorodehydroquinic acid are stable in either water or acetone at 4 °C. However, upon heating to over 80 °C quantitative dehydrohalogenation and aromatisation yield 3,4,5-trihydroxybenzoic acid.

The syntheses of (2*R*)-2-bromodehydroquinic acid **8** and (2*R*)-2-fluorodehydroquinic acid **10** are both short and high-yielding, especially in light of the problems encountered in the synthesis of the related 2-bromoshikimic acid[4] and 2-fluoroshikimic acid.[5] Preliminary studies show that both **8** and **10** are inhibitors for dehydroquinate dehydratase, the third enzyme on the shikimate pathway. Full details of these biological studies will be published elsewhere.

Experimental

General

NMR Spectra were recorded on either a Bruker WM-250, WM-400, DPX-250 or DPX-500 NMR spectrometer in deuteriated solvents, with tetramethylsilane as an internal standard. *J* Values are given in Hz. Melting points were determined on a Buchi 510 or Reichert melting points apparatus and are uncorrected. IR Spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer or a 1710 Fourier Transform spectrometer as Nujol mulls unless otherwise indicated. Mass spectra were recorded on a Kratos MS890 double-focussing magnetic sector apparatus (for EI, CI and FAB). Optical rotations were measured on an AA-10 automatic polarimeter (Optical Activity Ltd.); $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. All organic solvents were freshly distilled prior to use. Dichloromethane, triethylamine, toluene and hexane were dried over calcium hydride. Methanol was dried over potassium carbonate. Diethyl ether was dried over lithium aluminium hydride. Analytical thin layer chromatography was carried out on commercial Kieselgel 60 0.25 mm silica plates. Spots were visualised by UV absorbance at 254 nm, iodine, potasium permanganate(VII) or cerium molybdate solution. Flash chromatography was carried out using 230–400 mesh Kieselgel 60 silica. The carboxylic acids were purified by HPLC on a preparative (300 mm × 16 mm) Bio-Rad Aminex Ion Exclusion HPX-87H Organic Acids column, eluting with aqueous formic acid (50 mM) at a flow rate of 1.2 cm^3 min^{-1} with the UV detector set at 277 nm.

(1*S*,3*R*,4*R*,5*R*)-4,5-Benzylidenedioxy-1-hydroxycyclohexane-1,3-carbolactone 2

A mixture of (−)-quinic acid **1** (4.94 g, 25.7 mmol), distilled benzaldehyde (3.9 cm^3, 38.6 mmol) and toluene-*p*-sulfonic acid (253 mg, 1.3 mmol) was heated at reflux in toluene (50 cm^3) in an apparatus fitted with a Dean–Stark trap for 22 h. The solution was allowed to cool and the toluene evaporated at reduced pressure. The oily residue was taken up in diethyl ether and decanted from the solid. The crude mixture was purified by column chromatography on silica gel eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:1) to give the benzylidene carbolactones **2** (5.31 g, 79%) as a mixture of diastereoisomers at the benzylic carbon, in a ratio of 2.2:1. On cooling, the viscous oil crystallised. Recrystallisation from diethyl ether gave the major diastereoisomer (with the *R* configuration at the benzylic centre) of carbolactone **2** as white needles, mp 100–101 °C (lit.,[7] 95 °C); R_F 0.46 [ethyl acetate–light petroleum (bp 40–60 °C), 1:1] (Found: C, 63.9; H, 5.4. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3540 (free OH), 3420 (H-bonded OH), 1800 (C=O) and 1470 (Ar C–C); δ_H(250 MHz; $CDCl_3$) 7.51–7.36 (5 H, m, Ph), 5.75 (1 H, s, $PhCHO_2$), 4.81 (1 H, dd, *J*

6.1 and 2.1, 3-H), 4.52 (1 H, td, *J* 7.0 and 2.7, 5-H), 4.37 (1 H, dt, *J* 7.0 and 2.1, 4-H), 2.91 (1 H, br s, OH), 2.78 (1 H, d, *J* 11.9, 2ax-H), 2.46 (1 H, ddd, *J* 15.1, 7.0 and 2.1, 6eq-H), 2.36 (1 H, dd, *J* 15.1 and 2.7, 6ax-H) and 2.34 (1 H, ddt, *J* 11.9, 6.1 and 2.1, 2eq-H); δ_C(62 MHz; $CDCl_3$) 178.9, 135.4, 129.9, 128.6, 126.6, 103.7, 75.5, 72.9, 72.7, 71.4, 37.7 and 34.4; *m/z* (EI^+) 262 (M^+), 261 [$(M - H)^+$] and 105 [$(PhCO)^+$] (Found: M^+, 262.0820. $C_{14}H_{14}O_5$ requires *M*, 262.0841).

(1*S*,3*R*,4*R*,5*R*)-1,4,5-Trihydroxycyclohexane-1,3-carbolactone 3

To 500 mg of palladium on charcoal (10%) under a hydrogen atmosphere was added glacial acetic acid (10 cm^3). After 10 min a solution of the acetal **2** (5 g, 19.0 mol) in glacial acetic acid (40 cm^3) was added. The system was evacuated and kept under a hydrogen atmosphere until reduction was complete as judged by TLC (48 h). The hydrogen was evacuated, the suspension filtered over Celite and washed with acetic acid (50 cm^3) and methanol (50 cm^3). The solvent was removed under reduced pressure and the product was recrystallised from acetic acid to afford 3.09 g (94%) of the hydroxylactone **3** as white prisms, mp 184–185 °C (lit.,[8] 185–189 °C); ν_{max}/cm^{-1} 3000–3560 (OH) and 1780 (C=O); δ_H(250 MHz; CD_3OD) 4.91 (3 H, br s, OH), 4.75 (1 H, dd, *J* 4.9 and 6.0, 3-H), 4.02 (1 H, dd, *J* 4.5 and 4.9, 4-H), 3.74 (1 H, ddd, *J* 4.5, 6.6 and 11.3, 5-H), 2.51 (1 H, d, *J* 11.5, 2ax-H), 2.26 (1 H, ddd, *J* 2.9, 6.0 and 11.5, 2eq-H), 2.07 (1 H, ddd, *J* 6.6, 2.9 and 11.6, 6eq-H) and 1.91 (1 H, dd, *J* 11.3 and 11.6, 6ax-H); δ_C(62 MHz; CD_3OD) 179.5, 77.6, 73.1, 67.3, 66.8, 40.0 and 37.8.

Selective monosilylation of the trihydroxylactone 3

Method A. To a stirred solution of the hydroxylactone **3** (1.83 g, 10.52 mmol), 4-dimethylaminopyridine (DMAP) (180 mg, 1.47 mmol) and butylammonium iodide (194 mg, 0.53 mmol) in dry DMF (17 cm^3) and dry triethylamine (1.8 cm^3, 12.62 mmol) at 0 °C under argon was added 1.82 g (12.1 mmol) of *tert*-butyldimethylsilyl chloride. The solution was stirred at this temperature for 30 min and then 5 h at room temp. The resultant suspension was diluted with ethyl acetate (100 cm^3) and filtered over Celite. The solution was washed successively with 1 M HCl (100 cm^3) and brine (3 × 100 cm^3), dried ($MgSO_4$), filtered and evaporated. The crude product (yellow solid) was purified by column chromatography on silica gel eluting with diethyl ether–hexane (1:1) to yield 2.40 g (79%) of *monosilyl ether* **4** and 82 mg (3%) of *monosilyl ether* **5** as white needles.

Method B. To a stirred solution of the hydroxylactone **3** (1.02 g, 5.86 mmol), DMAP (100 mg, 0.82 mmol) and butylammonium iodide (108 mg, 0.29 mmol) in dry DMF (9.6 cm^3) and dry triethylamine (0.98 cm^3, 7.03 mmol) at room temp. under argon was added 1.01 g (6.73 mmol) of *tert*-butyldimethylsilyl chloride. The resultant solution was heated at 90 °C for 24 h, and after cooling was diluted with ethyl acetate (100 cm^3) and filtered over Celite. The solution was washed successively with 1 M HCl (100 cm^3) and brine (3 × 100 cm^3), dried ($MgSO_4$), filtered and evaporated. The crude product was purified by column chromatography on silica gel eluting with diethyl ether–hexane (1:1 to 3:1) to yield 918 mg (54%) of *monosilyl ether* **5** and 505 mg (30%) of *monosilyl ether* **4** as white needles.

(1*R*,3*R*,4*S*,5*R*)-5-*tert*-Butyldimethylsiloxy-1,4-dihydroxycyclohexane-1,3-carbolactone 4. Mp 95–96 °C (from hexane) (Found: C, 54.12; H, 8.45. $C_{13}H_{24}SiO_5$ requires C, 54.17; H, 8.33%); $[\alpha]_D^{20}$ −34 (*c* 1.1 in CH_3OH); ν_{max}/cm^{-1} 3300 (br, OH) and 1780 (C=O); δ_H(250 MHz; $CDCl_3$) 4.85 (1 H, dd, *J* 6.0 and 4.7, 3-H), 3.95 (1 H, dd, *J* 4.5 and 4.7, 4-H), 3.86 (1 H, ddd, *J* 4.5, 7.2 and 11.6, 5-H), 3.00 (1 H, s, OH), 2.96 (1 H, s, OH), 2.59 (1 H, d, *J* 11.6, 2ax-H), 2.28 (1 H, ddd, *J* 2.6, 6.0 and 11.6, 6eq-H), 1.89–2.06 (2 H, m, 6ax-H and 2eq-H), 0.88 [9 H, s, $C(CH_3)_3$] and 0.08 [6 H, s, $Si(CH_3)_2$]; δ_C(62 MHz; $CDCl_3$) 178.1, 76.3, 71.7, 67.0, 65.6, 40.1, 36.4, 25.6, 17.9, −4.7 and −5.0.

(1*S*,3*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsiloxy-1,5-dihydroxycyclohexane-1,3-carbolactone 5. Mp 154–155 °C (from hexane) (Found: C, 54.21; H, 8.39. $C_{13}H_{24}O_5Si$ requires C, 54.17; H, 8.33%); $[\alpha]_D^{20}$ −24 (*c* 0.4 in CH_3OH); ν_{max}/cm^{-1} 3480 (OH), 3380 (OH) and 1800 (C=O); δ_H(250 MHz; $CDCl_3$) 4.65 (1 H, dd, *J* 6.0 and 4.2, 3-H), 4.08 (1 H, dd, *J* 4.8 and 4.2, 4-H), 3.80 (1 H, dddd, *J* 4.9, 6.6, 11.1 and 11.3, 5-H), 2.99 (1 H, s, 1-OH), 2.50 (1 H, d, *J* 11.4, 2ax-H), 2.29 (1 H, ddd, *J* 2.9, 6.0 and 11.4, 2eq-H), 2.17 (1 H, ddd, *J* 2.9, 6.6 and 12.0, 6eq-H), 2.09 (1 H, d, *J* 11.3, 5-OH), 1.83 (1 H, dd, *J* 12.0 and 11.1, 6ax-H), 0.92 [9 H, s, $C(CH_3)_3$], 0.15 (3 H, s, $SiCH_3$) and 0.12 (3 H, s, $SiCH_3$); δ_C(62 MHz; $CDCl_3$) 177.9 (C), 76.3 (CH), 71.9 (C), 67.0 (CH), 65.8 (CH), 40.7 (CH_2), 36.4 (CH_2), 25.6 [$C(CH_3)_3$], 17.9 (C), −4.7 ($SiCH_3$) and −5.0 ($SiCH_3$).

(1*R*,3*R*,4*S*)-4-*tert*-Butyldimethylsiloxy-1-hydroxy-5-oxocyclohexane-1,3-carbolactone 6

To a stirred suspension of the alcohol **5** (232 mg, 0.81 mmol) and 4 Å activated molecular sieves (300 mg) in dry dichloromethane (6 cm^3) was added pyridinium dichromate (606 mg, 1.61 mmol). The resultant suspension was stirred at room temp. for 2 h and then diluted with diethyl ether (60 cm^3) and filtered over Celite. The solution was washed successively with HCl (5%, 2 × 50 cm^3) and brine (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated. The product was recrystallised from hexane to afford 201 mg of the *ketone* **6** as white crystals (87%), mp 92–93 °C (Found: C, 54.46; H, 7.84. $C_{13}H_{22}SiO_5$ requires C, 54.54; H, 7.69%); $[\alpha]_D^{20}$ −46 (*c* 0.4 in CH_3OH); ν_{max}/cm^{-1} 3350–3500 (OH), 1810 (C=O) and 1730 (C=O); δ_H(62 MHz; $CDCl_3$) 4.78 (1 H, dd, *J* 3.9 and 6.2, 3-H), 4.05 (1 H, ddd, *J* 0.6, 1.1 and 3.9, 4-H), 3.10 (1 H, d, *J* 16.2, 6ax-H), 2.95 (1 H, s, OH), 2.86 (1 H, d, *J* 12.1, 2ax-H), 2.78 (1 H, ddd, *J* 1.1, 3.1 and 16.2, 6eq-H), 2.66 (1 H, dddd, *J* 0.6, 3.1, 6.2 and 12.1, 2eq-H), 0.95 [9 H, s, $C(CH_3)_3$], 0.20 (3 H, s, $SiCH_3$) and 0.16 (3 H, s, $SiCH_3$); δ_C(250 MHz; $CDCl_3$) 202.7 (C), 177.0 (C), 75.1 (CH), 71.4 (C), 70.6 (CH), 50.0 (CH_2), 35.8 (CH_2), 25.5 [$C(CH_3)_3$], 16.0 (C), −4.7 ($SiCH_3$) and −5.3 ($SiCH_3$); *m/z* (FAB+ve) 287 (MH^+) (Found: MH^+, 287.1328. $C_{13}H_{23}SiO_5$ requires *M*, 287.1315).

(1*S*,3*R*,4*S*,6*R*)-6-Bromo-4-*tert*-butyldimethylsiloxy-1-hydroxy-5-oxocyclohexane-1,3-carbolactone 7

To a stirred solution of the ketone **6** (328 mg, 1.15 mmol) in dry diethyl ether (30 cm^3) under argon was added freshly made dioxane dibromide[10] (313 mg, 1.26 mmol). The red solution was stirred at room temp. until decoloration (2 h), diluted with diethyl ether (30 cm^3) and washed successively with aqueous sodium metabisulfite (5%, 30 cm^3), aqueous sodium hydrogen carbonate (5%, 30 cm^3) and water (30 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated. The product was recrystallised from hexane to afford the *bromo ketone* **7** as white needles (371 mg, 89%), mp 124–125 °C (Found: C, 42.68; H, 5.78. $C_{13}H_{21}BrSiO_5$ requires C, 42.74; H, 5.75%); $[\alpha]_D^{20}$ −203 (*c* 0.4 in CH_3OH); ν_{max}/cm^{-1} 3540 (OH), 1820 (C=O) and 1725 (C=O); λ_{max}(EtOH)/nm 238 and 339 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 832 and 117); δ_H(250 MHz; $CDCl_3$) 4.79 (1 H, dd, *J* 4.1 and 6.3, 3-H), 4.35 (1 H, dd, *J* 1.2 and 2.5, 6-H), 4.19 (1 H, ddd, *J* 0.9, 1.2 and 4.1, 4-H), 3.78 (1 H, s, OH), 3.33 (1 H, d, *J* 12.7, 2ax-H), 2.55 (1 H, dddd, *J* 0.9, 2.5, 6.3 and 12.7, 2eq-H), 0.95 [9 H, s, $C(CH_3)_3$], 0.26 (3 H, s, $SiCH_3$) and 0.19 (3 H, s, $SiCH_3$); δ_C(100 MHz; $CDCl_3$) 198.3 (C), 172.8 (C), 76.4 (CH), 74.7 (C), 74.0 (CH), 71.0 (CH), 51.9 (CH), 32.7 (CH_2), 25.3 [$C(CH_3)_3$], 17.9 (C), −5.3 ($SiCH_3$) and −5.5 ($SiCH_3$); *m/z* (FAB+ve) 365 (MH^+) (Found: MH^+, 365.0420. $C_{13}H_{22}BrSiO_5$ requires *M*, 365.0420).

(1*S*,2*R*,4*S*,5*R*)-2-Bromo-1,4,5-trihydroxy-3-oxocyclohexanecarboxylic acid [(2*R*)-2-bromodehydroquinic acid] 8

To a solution of the bromo ketone **7** (400 mg, 1.10 mmol) in acetic acid (4 cm^3) was added water (1 cm^3) and the solution stirred at 40 °C for 72 h. The solution was lyophilised and the residue partitioned between ethyl acetate (25 cm^3) and water (25 cm^3). The aqueous phase was washed with ethyl acetate (25 cm^3) and lyophilised to give the crude product. Recrystallisation

from ethyl acetate–hexane (50:50) yielded 2-*bromodehydroquinic acid* **8** (280 mg, 95%), mp 112–114 °C (decomp.) (Found: C, 31.39; H, 3.31. $C_7H_9BrO_6$ requires C, 31.23; H, 3.35%); $[\alpha]_D^{20}$ −36 (*c* 1.1 in CH_3OH); ν_{max}/cm^{-1} 3420 (OH), 3280 (OH), 1740 (C=O) and 1700 (C=O); δ_H(250 MHz; [$^2H_6$]acetone) 5.55 (1 H, d, *J* 0.9, 2-H), 4.80 (3 H, br s, OH), 4.40 (1 H, dd, *J* 0.9 and 9.2, 4-H), 3.96 (1 H, ddd, *J* 5.6, 9.2 and 10.8, 5-H) and 2.38–2.48 (2 H, m, 6-H); δ_C(62 MHz; [$^2H_6$]acetone) 197.8 (CH), 173.1 (C), 81.9 (CH), 77.9 (CH), 72.3 (CH), 61.7 (CH) and 40.9 (CH_2); *m/z* (CI, NH_4^+) 268, 266, 252, 250, 188 and 172.

(1*S*,3*R*,4*S*,6*R*)-6-Fluoro-4-(*tert*-butyldimethylsiloxy)-1-hydroxy-5-oxocyclohexane-1,3-carbolactone 9

To a stirred solution of the ketone **6** (47 mg, 0.16 mmol) in dry toluene (1.2 cm^3) under argon was added successively dry triethylamine (100 µl, 0.74 mmol) and then trimethylsilyl trifluoromethanesulfonate (95 µl, 0.49 mmol). The resultant mixture was refluxed for 2 h. After cooling at room temp. hexane was added (10 cm^3) and the organic layer was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), filtered and evaporated. To the crude product dissolved in 1.6 cm^3 of dry DMF under argon was added 58 mg (0.16 mmol) of Selectfluor® and the resultant mixture was stirred for 8 h. The reaction mixture was extracted with diethyl ether (3 × 10 cm^3), dried ($MgSO_4$) and evaporated to give a pale yellow solid. Recrystallisation from hexane yielded the *protected fluoro ketone* as white needles (40 mg, 89%), $[\alpha]_D^{20}$ −49 (*c* 0.5 in CH_3OH); ν_{max}(KBr)/cm^{-1} 3430 (OH), 1812 (C=O) and 1753 (C=O); δ_H(400 MHz; $CDCl_3$) 5.21 (1 H, d, J_{H-F} 48.4, 6-H), 4.67 (1 H, dd, *J* 6.2 and 4.4), 4.25 (1 H, dt, *J* 1.5 and 4.2), 2.91 (1 H, d, *J* 12.9), 2.76 (2 H, m), 0.87 [9 H, s, $C(CH_3)_3$], 0.14 (3 H, s, $SiCH_3$) and 0.10 (3 H, s, $SiCH_3$); δ_F(250 MHz; $CDCl_3$) −205 (1 F, ddd, J_{H-F} 49, 4 and 3); δ_C(100 MHz; $CDCl_3$) 197.2 (C, J_{C-F} 13.0), 172.4 (C), 96.7 (CH, J_{C-F} 204.7), 74.6 (C, J_{C-F} 18.0), 73.8 (CH), 73.1 (CH), 34.0 (CH_2), 25.4 [$C(CH_3)_3$], 17.9 (C), −5.0 ($SiCH_3$) and −5.2 ($SiCH_3$); *m/z* (FAB+ve) 305 (MH^+) and 287 ($MH^+ - F$) (Found: MH^+, 305.1221. $C_{13}H_{22}SiO_5F$ requires *M*, 305.1209).

(1*S*,3*R*,4*S*,6*R*)-2-Fluoro-1,4,5-trihydroxy-3-oxocyclohexanecarboxylic acid [(2*R*)-2-fluorodehydroquinic acid] 10

A stirred solution of the protected fluoro ketone **9** (25 mg, 82.24 nmol) in 2 cm^3 of a solution acetic acid–water (4:1) was heated at 50 °C for 48 h. The solvent was removed and the crude product was partitioned in 10 cm^3 of ethyl acetate–water (1:1). The aqueous layer was washed with ethyl acetate (3 × 10 cm^3) and then lyophilised. The crude product was purified by HPLC using the Organic Acids column, eluting with aqueous formic acid (50 mM) to yield 2-*fluorodehydroquinic acid* **11** (15 mg, 90%) as a white hygroscopic solid, t_r 15 min (flow rate 1.2 cm^3 min^{-1}); $\lambda_{max}(H_2O)$/nm 191 and 270; $[\alpha]_D^{20}$ −30 (*c* 0.1 in water); ν_{max}(KBr)/cm^{-1} 3420 (OH), 1750 (C=O) and 1720 (C=O); δ_H(500 MHz; D_2O) 5.64 (1 H, dd, J_{H-F} 46.3 and 0.8, 2-H), 4.34 (1 H, d, *J* 9.4, 4-H), 3.85 (1 H, m, 5-H) and 2.30–2.18 (2 H, m, 6-H); δ_F(235 MHz; $CDCl_3$) −207 (1 F, dd, J_{H-F} 47 and 8); δ_C(100 MHz; D_2O) 206.1 (C, J_{C-F} 14), 178.3 (C), 96.9 (CH, J_{C-F} 195), 81.7 (CH), 77.8 (C), 74.0 (CH) and 39.3 (CH_2, J_{C-F} 6); *m/z* (ESI) 231 (MNa^+) (Found: MNa^+, 231.0278. $C_7H_9O_6FNa$ requires *M*, 231.0278).

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