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(-)-QUINIC ACID IN ORGANIC SYNTHESIS. 1. A FACILE SYNTHESIS OF 2-CROTONYLOXYMETHYL-(4*R*,5*R*,6*R*)-4,5,6-TRIHYDROXYCYCLOHEX-2-ENONE.

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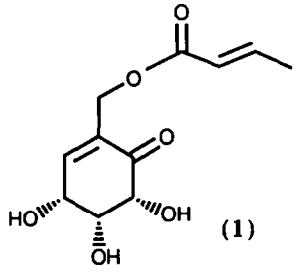
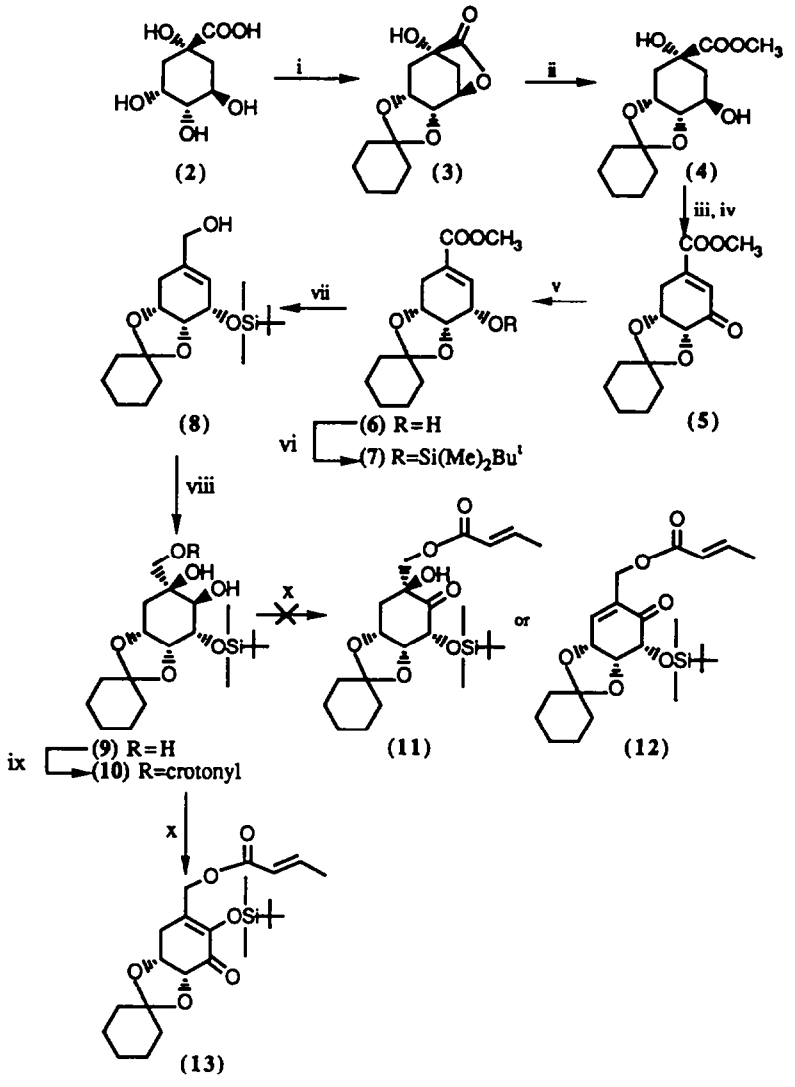
Abstract—The glyoxalase I inhibitor COTC {2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone}(**1**) has been synthesised from (-)-quinic acid in thirteen steps; an interesting rearrangement involving a silyl migration upon oxidation of (**10**) is also described.

Recently, the use of glyoxalase I inhibitors as potential anticancer agents has been reviewed.[1] COTC (**1**), isolated and characterised in 1975 as a glyoxalase I inhibitor from cultures of *Streptomyces griseosporeus*, has been shown to display cytotoxic and cancerostatic activity with low toxicity,[2,3] and to act synergistically with aclarubicin, an anticancer drug.[4] The absolute configuration of (**1**) was assigned by an *X*-ray analysis[3] of its bromo-derivative and confirmed by synthesis.[5,6] We are interested in its mechanism of tumour inhibition, but were unable to obtain an authentic sample of COTC. This paper describes our synthesis of COTC (**1**) and also reports an interesting rearrangement involving a silyl migration upon oxidation of (**10**). A preliminary account on part of this work has appeared.[7]



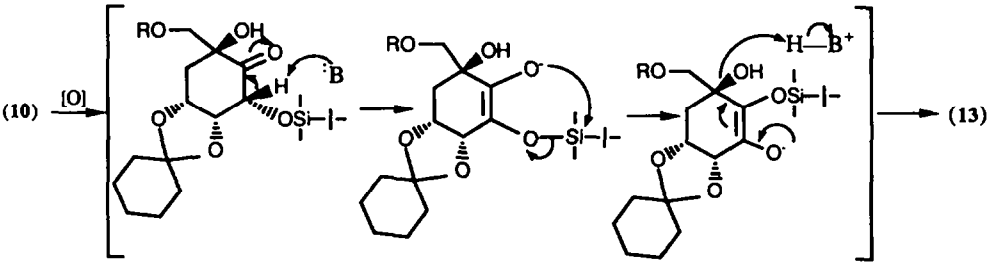
(**1**)

Our initial approach for the synthesis of COTC is shown in Scheme 1. Thus acetalisation of quinic acid (**2**) with cyclohexanone in the presence of Dowex 50WX8 (H^+) ion exchange resin proceeded with concomitant lactonisation, affording the known acetal (**3**)[8] in 79% yield. The lactone ring in (**3**) was cleaved with sodium methoxide in methanol to give the methyl ester (**4**) (96%). Swern oxidation of the free secondary alcohol in (**4**) followed by β-elimination with phosphoryl chloride—pyridine provided the enone (**5**) in an overall yield of 76%. Hydride reduction of the keto group in (**5**) with $NaBH_4$ occurred at the less hindered β-face, furnishing exclusively the desired α-alcohol (**6**), which was protected as the silyl ether (**7**) in 78% overall yield. The ester group in (**7**) was reduced with di-isobutylaluminium hydride (DIBAL-H) to the alcohol (**8**) in 96% yield. Hydroxylation of the double bond in (**8**) proceeded smoothly at the less



Scheme 1. *Reagents and conditions*: i. cyclohexanone, benzene, *N,N*-dimethylformamide (DMF), Dowex 50WX8 resin, reflux, (79%); ii. NaOMe/MeOH, 0°C, (96%); iii. dimethyl sulphoxide (DMSO), oxalyl chloride, triethylamine, CH_2Cl_2 ; iv. $POCl_3$, pyridine, room temp., (76%); v. $NaBH_4$, MeOH, 0°C, (82%); vi. $Me_2(Bu^t)SiCl$, imidazole, *N,N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., (96%); vii. DIBAL-H, tetrahydrofuran (THF), 0°C, (96%); viii. OsO_4, trimethylamine-*N*-oxide, Bu^tOH, H_2O, pyridine, reflux, (82%); ix. crotonic acid,1,3-dicyclohexylcarbodiimide (DCC), 3 Å molecular sieves, DMAP, CH_2Cl_2, (81%); x. DMSO, trifluoroacetic anhydride (TFAA), triethylamine, CH_2Cl_2, (80%).

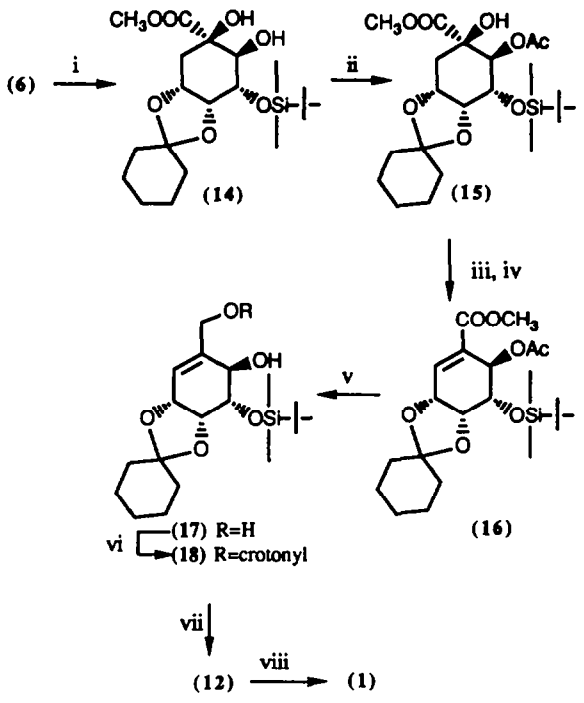
esterification of the primary alcohol in (9) with crotonic acid furnished the ester (10) in 81% yield. It was envisaged that oxidation of the secondary alcohol in (10) would yield the hydroxy-ketone (11) which then would undergo a facile elimination to the desired enone (12). Thus Swern or pyridinium chlorochromate oxidation of (10) gave a strong chromophore initially thought to be the enone (12) since the mass spectral and combustion data were consistent with the molecular formula of $C_{23}H_{36}O_6Si$. In addition, the presence of an enone carbonyl group was indicated by the i.r. absorption band at 1690 cm^{-1}. However, the ^1H n.m.r. spectrum of the chromophore showed only one β-olefinic proton (crotonyl), two methine protons and also the continued existence of the two high-field methylene protons. The alternate structure (13) was therefore assigned to the oxidation product of diol (10), an assignment supported by the u.v. spectral data: $\lambda_{max.}$ 271 nm ($\varepsilon_{max.}$ 18.5 × 10^3); the $\lambda_{max.}$ calculated[9] for an α-hydroxy-β,β-disubstituted cyclohex-2-enone is 274 nm. The mechanism for the formation of (13) is speculated to involve a facile silyl migration (Fig. 1) and the driving force believed to be the release of the steric compression between the bulky silyl ether and the cyclohexylidene blocking group.



R=crotonyl

Fig. 1

In order to avoid the undesirable rearrangement, it was decided that the double bond of the enone moiety be introduced first before oxidation. This change of strategy gratifyingly proved successful. Thus hydroxylation of the aforementioned enoate (6) gave the diol (14) in 82% yield. The stereochemistry of the newly formed secondary alcohol was indicated from the ^1H n.m.r. spectrum ($J_{3,4}$ = 9.8 Hz). This alcohol was selectively acetylated at room temperature to give a quantitative yield of the monoacetate (15). Esterification of the tertiary alcohol in (15) with triflic anhydride followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) —triethylamine mediated β-elimination afforded the enoate (16) in 61% overall yield. DIBAL-H reduction of the diester (16) in tetrahydrofuran (THF) at 0°C afforded the diol (17) (75%) which then was esterified selectively at the primary alcohol with crotonic anhydride to the crotonyl ester (18). Oxidation of the allylic alcohol (18) with pyridinium chlorochromate in CH_2Cl_2 at room temperature gave cleanly the enone (12) which then was hydrolysed to COTC (1) in an overall yield of 80%, m.p. 178—179°C; $[\alpha]_D$ - 106.4° (c 0.6, MeOH) {lit.[2] m.p. 181°C; $[\alpha]_D$ - 109° (c 1.5, MeOH)}. Thus COTC (1) was prepared in thirteen stages from (-)-quinic acid (2) in an overall yield of 13%.



Scheme 2. *Reagents and conditions*: i. OsO_4, trimethylamine-*N*-oxide, Bu^{t}OH, H_2O, pyridine, reflux, (82%); ii. $(MeCO)_2O$ (Ac_2O), pyridine, DMAP, CH_2Cl_2, (100%); iii. $(CF_3CO)_2O$, pyridine, DMAP, CH_2Cl_2, (86%); iv. triethylamine, 1.8-diazabicylo-[5,4,0]undec-7-ene (DBU), CH_2Cl_2, (71%); v. DIBAL-H, THF, 0°C, (75%); vi. crotonic anhydride, pyridine, DMAP, CH_2Cl_2, (95%); vii. pyridinium chlorochromate, 3 Å molecular sieves, CH_2Cl_2, (80%); viii. 50% aq. CF_3COOH, room temp. (100%).

Experimental

M.p.s were recorded on a Kofler block. ^1H N.m.r. spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Infra red (i.r.) spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrophotometer. Mass spectra were recorded on a Kratos MS25 instrument. Ultraviolet (u.v.) spectra were recorded on a Shimadzu UV-260 UV/VIS Spectrophotometer as solutions in ethanol. Optical rotations were measured on an AA-100 polarimeter using CH_2Cl_2 as solvent unless otherwise stated. T.l.c. was performed on glass plates precoated with Merck silica $60F_{254}$, and compounds were visualised with a spray of 5% w/v dodeca-molybdophosphoric acid in ethanol and subsequent heating. Dry and flash chromatography were performed on silica gel. THF was distilled from sodium and benzophenone under dry nitrogen. CH_2Cl_2 was distilled from P_2O_5 under dry nitrogen. Pyridine was distilled from barium oxide. Petroleum ether (b.p. 40—60°C) was used as solvent unless otherwise stated.

3,4-O-Cyclohexylidenequinic acid-1,5-lactone (3).

Quinic acid (2) (25 g, 130 mmol), DMF (105 ml), benzene (100 ml) and cyclohexanone (88 ml) were refluxed together with stirring in a Dean and Stark apparatus for 3 h. Water was removed and the mixture was cooled briefly. Dowex 50WX8 resin (H^+, 25 g) was added and mixture was refluxed for a further 24 h. The resin was removed by filtration and washed with ethyl acetate (50 ml). The combined filtrate was washed with ice-cold $NaHCO_3$ (15% w/v, 2 X 50 ml), water (2 X 100 ml), dried ($MgSO_4$), and filtered. Solvent was removed from the filtrate to afford a yellow sticky solid. The solid was washed extensively with petroleum ether (100 ml) and the *title compound* (3) (26 g, 79%) was obtained as a white solid, m.p. 142—143°C (lit.,[8] m.p. 139—141°C); R_F 0.23 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ -30.31° (*c* 4.22, MeOH) {lit.,[8] $[\alpha]_D$ -33° (*c* 1.05, $CHCl_3$)}; $\nu_{max.}$ 3425 (OH) and 1795 cm^{-1} (lactone C=O); δ 1.41 (2H, b), 1.56 (4H, b), 1.68 (4H, m), 2.18 (1H, dd, *J* 14 and 3 Hz), 2.32 (2H, m), 2.66 (1H, d, *J* 10 Hz), 2.84 (1H, b), 4.30 (1H, ddd, *J* 6, 2.5 and 1.25 Hz), 4.48 (1H, td, *J* 10 and 2.5 Hz), 4.74 (1H, dd, *J* 6 and 2.5 Hz); *m/z* (CI, NH_3) 272 (100%, MNH_4^+) (Found: C, 61.2; H, 7.1. $C_{13}H_{18}O_5$ requires C, 61.5; H, 7.1%).

Methyl 3,4-O-cyclohexylidenequinate (4)

To a solution of lactone (3) (26 g, 102.6 mmol) in methanol (150 ml) was added dropwise a solution of sodium methoxide [prepared from adding sodium hydride (60% in oil, 4.7 g) to methanol (100 ml)] over 20 min at 0°C. The mixture was stirred for 1 h and then the solvent was removed *in vacuo* to a small volume (70 ml). The pH of the resultant solution was adjusted to 5 with acetic acid. The mixture was diluted with CH_2Cl_2 (100 ml) and washed with water (2 X 10 ml), brine (2 X 10 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate *in vacuo*, followed by dry column chromatography (hexane—EtOAc) gave the *title compound* (4) [17 g, 96% (based on recovery of the starting lactone)] as a white solid. Recrystallization from petroleum ether-diethyl ether (1:1 v/v) afforded colourless needles, m.p. 81—82°C; R_F 0.51 [petroleum ether-diethyl ether (1:3 v/v)]; $[\alpha]_D$ -40.46° (*c* 5.20); $\nu_{max.}$ 3454 (OH) and 1736 cm^{-1} (ester C=O); δ 1.40 (2H, b), 1.56 (4H, m), 1.70 (4H, m), 1.75-2.40 (4H, m), 3.77 (3H, s), 3.97 (1H, t, *J* 6.5 Hz), 4.09 (1H, ddd, *J* 11, 6.5 and 4.5 Hz), 4.47 (1H, dt, *J* 7.5 and 4.5 Hz); *m/z* (EI) 286 (35.6%, M^+) (Found: C, 58.3; H, 7.8. $C_{14}H_{22}O_6$ requires C, 58.7; H, 7.7%).

Methyl 4,5-O-cyclohexylidene-3-dehydro-4-epishikimate (5)

To a stirred solution of DMSO (4.2 ml, 59.3 mmol) in dry CH_2Cl_2 (10 ml) at -60°C under nitrogen was added dropwise oxalyl chloride (2.8 ml, 32.1 mmol). The mixture was stirred for 10 min, then removed from the cold bath for 3 min and recooled to -60°C. The diol (4) (6.04 g, 21.1 mmol) in dry CH_2Cl_2 (40 ml) was added in one delivery and this mixture was stirred at -60°C for 40 min. Triethylamine (16 ml, 115 mmol) was added dropwise and the light yellow solution was stirred at -60°C for a further 10 min. The mixture was allowed to warm up to room temp. and poured into saturated aqueous NH_4Cl (50 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 20 ml). The combined extracts were washed with water (2 X 100 ml), brine (2 X 100 ml), dried ($MgSO_4$), and filtered. Solvent removal gave an oil which was passed through a short column of silica gel and eluted with EtOAc. Concentration of the eluant afforded a colourless oil (5.2 g).

The oil was dissolved in pyridine (15 ml) and phosphoryl chloride (4.1 ml) was added slowly. The mixture was stirred overnight at room temp., poured into ice-cold saturated aqueous NH_4Cl

(50 ml) and extracted with CH_2Cl_2 (5 X 20 ml). The combined extracts were washed with brine (2 X 50 ml), dried ($MgSO_4$), and filtered. Solvent removal gave a deep red oil. Fractionation by flash chromatography [petroleum ether-diethyl ether (5:1 v/v)] afforded the *enone* (**5**) (4.26 g, 76%) as a white solid, m.p. 90—91°C; R_F 0.56 [petroleum ether-diethyl ether (5:1 v/v)]; $[\alpha]_D$ -43.96° (*c* 2.12); $\nu_{max.}$ 1722 (ester C=O) and 1682 cm^{-1} (ketone C=O); δ 1.2-1.8 (10H, m), 2.86 (1H, ddd, *J* 20, 5 and 3 Hz), 3.24 (1H, db, *J* 20 Hz), 3.86 (3H, s), 4.31 (1H, d, *J* 5 Hz), 4.69 (1H, td, *J* 5 and 2 Hz), 6.84 (1H, d, *J* 3 Hz); *m/z* (CI, NH_3) 267 (100%, MH^+) (Found: C, 63.4; H, 7.0. $C_{14}H_{18}O_5$ requires C, 63.2; H, 6.8%).

(1R,2R,3S)-1,2-O-cyclohexylidene-5-methoxycarbonyl-4-cyclohexen-1,2,3-triol (**6**)

To a stirred solution of the enone (**5**) (0.8 g, 3 mmol) in methanol (15 ml) at 0°C was added sodium borohydride (0.6 g, 15 mmol) in batches over 30 min. The mixture was stirred for 1.5 h at 0°C and quenched with saturated aqueous NH_4Cl (5 ml). The aqueous phase was extracted with CH_2Cl_2 (2 X 10 ml). The combined extracts were dried ($MgSO_4$), filtered, and the filtrate concentrated *in vacuo*. Fractionation by flash chromatography [petroleum ether-diethyl ether (1:4 v/v)] afforded the *alcohol* (**6**) (0.66 g, 82%) as a white solid, m.p. 70—71°C; R_F 0.36 [petroleum ether-diethyl ether (1:5 v/v)]; $[\alpha]_D$ +49.17° (*c* 2.40); $\nu_{max.}$ 3466 (OH) and 1717 cm^{-1} (ester C=O); δ 1.36 (2H, b), 1.52 (8H, m), 1.94 (1H, ddd, *J* 16.5, 7.5 and 4 Hz), 3.04 (1H, dd, *J* 16.5 and 2 Hz), 3.76 (3H, s), 4.05 (1H, m), 4.52 (1H, ddd, *J* 7.5, 5 and 1.5 Hz), 4.64 (1H, ddd, *J* 7.5, 4 and 2.5 Hz), 6.92 (1H, m); *m/z* (EI) 268 (27.3%, M^+) (Found: C, 62.9; H, 7.7. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%).

(1R,2R,3S)-3-O-tert-butyldimethylsilyl-1,2-O-cyclohexylidene-5-methoxycarbonyl-4-cyclohexen-1,2,3-triol (**7**)

To a solution of the alcohol (**6**) (100 mg, 0.37 mmol), imidazole (50.8 mg, 0.75 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (1.8 ml) was added *tert*-butyldimethylsilyl chloride (67.8 mg, 0.44 mmol) at room temp. The mixture was stirred for 14 h and poured into saturated aqueous NH_4Cl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (2:1 v/v)] afforded the *title compound* (**7**) (0.13 g, 96%) as a white solid, m.p. 54—55°C; R_F 0.76 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ +21.51° (*c* 2.38); $\nu_{max.}$ 1712 cm^{-1} (ester C=O); δ 0.02 (3H, s), 0.15 (3H, s), 0.92 (9H, s), 1.36 (2H, b), 1.56 (8H, b), 1.90 (1H, ddd, *J* 16.5, 7 and 4 Hz), 2.99 (1H, dd, *J* 16.5 and 1.5 Hz), 3.75 (3H, s), 4.17 (1H, m), 4.42 (1H, ddd, *J* 7.5, 5 and 1.5 Hz), 4.57 (1H, ddd, *J* 7.5, 4 and 2 Hz), 6.91 (1H, m); *m/z* (EI) 382 (3.6%, M^+) (Found: M^+ 382.2174 $C_{20}H_{34}O_5Si$ requires M^+ 382.2175).

(1R,2R,3S)-3-O-tert-Butyldimethylsilyl-1,2-O-cyclohexylidene-5-hydroxymethyl-4-cyclohexen-1,2,3-triol (**8**)

To a solution of the ester (**7**) (1.2 g, 2.68 mmol) in dry THF (5 ml) was added dropwise a 1.0 M solution of DIBAL-H in THF (5.9 ml, 5.9 mmol) over 30 min at -20°C. The mixture was stirred for 1 h at 0°C, quenched with the saturated aqueous NH_4Cl (5 ml) and filtered. The aqueous phase was extracted with CH_2Cl_2 (4 X 10 ml). The combined extracts were washed with brine (2 X 5 ml) and dried ($MgSO_4$), and filtered. Solvent removal gave a light brown oil which was flash chromatographed [petroleum ether-diethyl ether (1:1 v/v)] to give the *title compound* (**8**) (1.02 g, 96%) as a colourless oil, R_F 0.66 [petroleum ether-diethyl ether (1:3 v/v)]; $[\alpha]_D$ -2.43° (*c* 4.28); $\nu_{max.}$ 3452 cm^{-1} (OH); δ 0.11 (6H, s), 0.92 (9H, s), 1.36 (2H, b), 1.56 (8H, b), 1.92 (1H, m), 2.37 (1H,

dd, *J* 20 and 2 Hz), 4.02 (2H, s), 4.13 (1H, b), 4.36 (1H, ddd, *J* 7.5, 5 and 1.5 Hz), 4.50 (1H, ddd, *J* 7.5, 4 and 2 Hz), 5.71 (1H, b); *m/z* (CI, NH_3) 372 (9.4%, MNH_4^+) (Found: C, 64.7; H, 10.1. $C_{19}H_{34}O_4Si$ requires C, 64.4; H, 9.6%).

(1S,2S,3S,4R,5R)-3-O-tert-Butyldimethylsilyl-4,5-O-cyclohexylidene-1-hydroxymethyl-cyclohexan-1,2,3,4,5-pentaol (**9**)

A solution of the alcohol (**8**) (0.73 g, 2.05 mmol), trimethylamine-*N*-oxide (0.32 g, 2.83 mmol), pyridine (0.9 ml, 12.6 mmol), water (0.2 ml, 11.1 mmol), *tert*-butanol (5 ml) and a catalytic amount of OsO_4 was refluxed with stirring for 12 h under nitrogen. After cooling, saturated aqueous $Na_2S_2O_3$ (5 ml) was added and the mixture was passed through a short column of silica gel and washed with ethyl acetate (20 ml). The eluant was concentrated *in vacuo* and the residue was extracted with CH_2Cl_2 (4 X 15 ml). The combined extracts were washed with the saturate aqueous $Na_2S_2O_3$ (2 X 10 ml), brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Removal of solvent followed by flash chromatography [petroleum ether-diethyl ether (1:4 v/v)] afforded the *title compound* (**9**)(0.65 g, 82%) as a white solid, m.p. 104—105°C; R_F 0.35 [petroleum ether-diethyl ether (1:4 v/v)]; $[\alpha]_D$ -33.23° (*c* 1.24); $\nu_{max.}$ 3420 cm^{-1} (OH); δ 0.17 (3H, s), 0.18 (3H, s), 0.95 (9H, s), 1.40 (2H, b), 1.59 (8H, b), 1.55-1.80 (3H, m), 1.88 (1H, db, *J* 6.5 Hz), 1.92 (1H, dd, *J* 15 and 6.5 Hz), 3.41 (1H, d, *J* 11.5 Hz), 3.72 (1H, d, *J* 11.5 Hz), 3.89 (1H, d, *J* 10 Hz), 4.08 (1H, dd, *J* 10 and 4 Hz), 4.32 (1H, t, *J* 4 Hz), 4.40 (1H, m); *m/z* (CI, NH_3) 389 (100%, MH^+) (Found: C, 58.4; H, 9.5. $C_{19}H_{36}O_6Si$ requires C, 58.7; H, 9.3%).

(1S,2S,3S,4R,5R)-3-O-tert-Butyldimethylsilyl-1-crotonyloxymethyl-4,5-O-cyclohexylidene-cyclohexan-1,2,3,4,5-pentaol (**10**)

To a solution of the triol (**9**) (0.8 g, 2.05 mmol), crotonic acid (0.6 g, 7.0 mmol), 3Å molecular sieve powder (1.1 g) and a catalytic amount of DMAP in dry CH_2Cl_2 (10 ml) was added dropwise a solution of DCC (1 g, 4.74 mmol) in CH_2Cl_2 (5 ml) at room temp. The reaction mixture was stirred for 24 h and filtered through a pad of Celite. The solution was poured into the saturated aqueous NH_4Cl (5 ml) and extracted with CH_2Cl_2 (3 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (1:1 v/v)] afforded the *title compound* (**10**) (0.76 g, 81%) as a colorless oil, R_F 0.35 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ -13.02° (*c* 1.72); $\nu_{max.}$ 3458 (OH) and 1728 cm^{-1} (ester C=O); δ 0.11 (3H, s), 0.12 (3H, s), 0.92 (9H, s), 1.36 (2H, b), 1.53 (8H, b), 1.62-1.80 (3H, m), 1.98 (3H, dd, *J* 7 and 1.5 Hz), 2.01 (1H, d, *J* 6.5 Hz), 2.05 (1H, d, *J* 7.5 Hz), 3.77 (1H, d, *J* 9.5 Hz), 4.0-4.2 (3H, m), 4.32 (1H, ddd, *J* 17, 6 and 4 Hz), 5.86 (1H, dq, *J* 17 and 2 Hz), 7.01 (1H, dq, *J* 17 and 7 Hz); *m/z*(EI) 456 (3.4%, M^+) (Found: M^+ 456.2341 $C_{23}H_{40}O_7Si$ requires M^+ 456.2343).

(5R,6R)-2-tert-Butyldimethylsilyloxy-3-crotonyloxymethyl-5,6-O-cyclohexylidene-5,6-dihydroxycyclohex-2-enone. (**13**)

To a stirred solution of DMSO (0.3 ml, 4.2 mmol) in dry CH_2Cl_2 (18 ml) at -60°C under nitrogen was added dropwise TFAA (0.54 ml, 4.0 mmol). The resulting colourless solution was stirred for 10 min at -60°C, and then a solution of the diol (**10**) (0.6 g, 1.3 mmol) in dry CH_2Cl_2 (0.5 ml) was added in dropwise. The mixture was stirred at -60°C for 1.5 h. Triethylamine (1.2 ml, 8.8 mmol) was then added dropwise and the light yellow solution was stirred at -60°C for a further 1.5 h, warmed up to room temp. and poured into aqueous HCl (2 M, 20 ml). The aqueous phase was

extracted with CH_2Cl_2 (3 X 50 ml). The combined extracts were washed with water (2 X 10 ml), brine (2 X 10 ml), dried ($MgSO_4$), and filtered. Solvent removal gave a yellow oil which was flash chromatographed [hexane-ethyl acetate (4:1 v/v)] to give the *title compound* (13) (0.46 g, 80%) as a colourless oil, R_F 0.63 [hexane-ethyl acetate (3:1 v/v)]; $[\alpha]_D$ -6.85° (*c* 2.16); UV $\lambda_{max.}$ 271 nm (ε_{max} 1.85 X 10^3); $\nu_{max.}$ 1727 (ester C=O) and 1690 cm^{-1} (ketone C=O); δ 0.18 (3H, s), 0.20 (3H, s), 0.94 (9H, s), 1.2-1.7 (10H, m), 1.92 (3H, dd, *J* 6.5 and 1.5 Hz), 2.78 (1H, dd, *J* 20 and 4.5 Hz), 2.88 (1H, d,*J* 20 Hz), 4.32 (1H, d, *J* 5 Hz), 4.57 (1H, b), 4.88 (1H, d, *J* 15 Hz), 5.09 (1H, d, *J* 15 Hz), 5.88 (1H, dd, *J* 16 and 1.5 Hz), 7.04 (1H, dq, *J* 16 and 6.5 Hz); *m/z* (CI, NH_3) 454 (100%, MNH_4^+) (Found: C, 62.9; H, 8.4. $C_{23}H_{36}O_6Si$ requires C, 63.4; H, 8.3%).

(*1*R,*2*R,*3*S,*4*S,*5*R)-*3*-O-tert-*Butyldimethylsilyl-1,2*-O-*cyclohexylidene-5-methoxycarbonyl-cyclohexane-1,2,3,4,5-pentol* (14)

A solution of the ester (6) (2.9 g, 7.6 mmol), trimethylamine-*N*-oxide (1.2 g, 10.6 mmol), pyridine (3.3 ml, 45.6 mmol), water (0.7 ml, 38 mmol), *tert*-butanol (20 ml) and a catalytic amount of OsO_4 was refluxed with stirring for 12 h under nitrogen. After cooling, saturated aqueous $Na_2S_2O_3$ (5 ml) was added and the mixture was passed through a short column of silica gel and washed with ethyl acetate (40 ml). The eluate was concentrated *in vacuo* and the residue extracted with CH_2Cl_2 (4 X 20 ml). The combined extracts were washed with the saturate aqueous $Na_2S_2O_3$ (2 X 10 ml), brine (2 X 10 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (1:1 v/v)] provided the *title compound* (14) (2.6 g, 82%) as a white solid, m.p. 97—99°C; R_F 0.32 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ -18.57° (*c* 1.12); $\nu_{max.}$ 3481 (OH) and 1740 cm^{-1} (ester C=O); δ 0.13 (3H, s), 0.16 (3H, s), 0.92 (9H, s), 1.4-2.2 (12H, m), 2.34 (1H, t, *J* 8 Hz), 3.83 (3H, s), 4.07 (1H, dd, *J* 10 and 4 Hz), 4.15 (1H, d, *J* 15 Hz), 4.34 (2H, m); *m/z* (EI) 416 (1.5%, M^+) (Found: C, 57.8; H, 8.8. $C_{20}H_{36}O_7Si$ requires C, 57.7; H, 8.7%).

(*1*R,*2*S,*3*S,*4*R,*5*R)-*2*-O-*Acetyl-3*-O-tert-*butyldimethylsilyl-4,5*-O-*cyclohexylidene-1-methoxycarbonyl-cyclohexan-1,2,3,4,5-pentaol* (15)

To a mixture of the diol (14) (100 mg, 0.24 mmol), pyridine (39 μl, 0.48 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (1.8 ml) was added acetic anhydride (57 μl, 0.60 mmol) at room temp. The mixture was stirred for 12 h and poured into the saturated aqueous NH_4Cl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (1:1 v/v)]] provided the *title compound* (15) (0.11 g, 100%) as a white solid, m.p. 124—126°C; R_F 0.53 [petroleum ether-diethyl ether (1:1 v/v)]; $[\alpha]_D$ -43.18° (*c* 2.20); $\nu_{max.}$ 3482 (OH) and 1712 cm^{-1} (ester C=O); δ 0.05 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 1.4-2.2 (12H, m), 2.03 (3H, s), 3.75 (3H, s), 4.26 (1H, dd, *J* 9.5 and 4 Hz), 4.34 (2H, m), 5.41 (1H, d, *J* 9.5 Hz); *m/z* (CI, NH_3) 476 (64.7%, MNH_4^+) (Found: C, 57.8; H, 8.6. $C_{22}H_{38}O_8Si$ requires C, 57.6; H, 8.3%).

(*1*R,*2*R,*3*S,*4*R)-*4*-O-*Acetal-3*-O-tert-*butyldimethylsilyl-1,2*-O-*cyclohexylidene-5-methoxycarbonyl-5-cyclohexen-1,2,3,4-tetraol* (16)

To a mixture of the alcohol (15) (0.3 g, 0.66 mmol), pyridine (0.16 ml, 2.0 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (3.5 ml) was added triflic anhydride (0.26 ml, 1.52 mmol) at -78°C. The mixture was stirred for 1 h at -78°C and allowed to warm up to 0°C. After 12 h, the mixture

was poured into the saturated aqueous NH_4Cl (5 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (1:1 v/v)] afforded the triflate ester (0.4 g, 86%) as a white solid. To a solution of the triflate ester (0.4 g) in dry CH_2Cl_2 (5 ml) was added triethylamine (0.19 ml) and DBU (0.1 ml) at 0°C. After 6 h, the mixture was poured into the saturated aqueous NH_4Cl (3 ml). The aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with brine (2 X 5 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (3:1 v/v)] gave the *title compound* (**16**) (0.24 g, 71%) as a white solid, m.p. 82—84°C; R_F 0.45 [petroleum ether-diethyl ether (3:1 v/v)]; $[\alpha]_D$ -39.55° (*c* 0.89); $\nu_{max.}$ 1754 (deconjugated ester C=O) and 1728 cm^{-1} (conjugated ester C=O); δ 0.09 (3H, s), 0.11 (3H, s), 0.87 (9H, s), 1.2-1.8 (10H, m), 2.03 (3H, s), 3.77 (3H, s), 3.99 (1H, dd, *J* 7.5 and 3 Hz), 4.37 (1H, dd, *J* 5.2 and 3 Hz), 4.68 (1H, m), 5.97 (1H, dt, *J* 7.5 and 3 Hz), 6.82 (1H, m); *m/z* (EI) 440 (4.8%, M^+) (Found: C, 60.4; H, 8.3. $C_{22}H_{36}O_6Si$ requires C, 60.0; H, 8.2%).

(1R,2R,3S,4R)-3-O-tert-Butyldimethylsilyl-1,2-O-cyclohexylidene-5-hydroxymethyl-5-cyclohexen-1,2,3,4-tetraol (**17**)

To a solution of the ester (**16**) (25 mg, 0.06 mmol) in dry THF (0.5 ml) was added dropwise a 1.0 M solution of DIBAL-H in THF (0.18 ml, 0.18 mmol) over 10 min at -20°C. The mixture was stirred for 1 h at 0°C, quenched with the saturated aqueous NH_4Cl (2 ml) and filtrated. The aqueous phase was extracted with CH_2Cl_2 (4 X 5 ml). The combined extracts were washed with brine (2 X 2 ml), dried ($MgSO_4$), and filtered. Solvent removal gave a light brown oil which was flash chromatographed [petroleum ether-diethyl ether (1:2 v/v)] to yield the *title compound* (**17**) (16 mg, 75%) as a white solid, m.p. 65—67°C; R_F 0.46 [petroleum ether-diethyl ether (1:2 v/v)]; $[\alpha]_D$ -56.33° (*c* 0.98); $\nu_{max.}$ 3419 cm^{-1} (OH); δ 0.13 (3H, s), 0.15 (3H, s), 0.94 (9H, s), 1.2-1.7 (10H, m), 3.76 (1H, dd, *J* 8.5 and 2.5 Hz), 4.15 (1H, d, *J* 13 Hz), 4.29 (1H, d, *J* 13 Hz), 4.38 (1H, ddd, *J* 5.5, 2.5 and 0.8 Hz), 4.54 (1H, dt, *J* 8.5 and 2.5 Hz), 4.60 (1H, m), 5.56 (1H, m); *m/z* (EI) 370 (10.4%, M^+) (Found: C, 61.9; H, 9.5. $C_{19}H_{34}O_5Si$ requires C, 61.6; H, 9.2%).

(1R,2R,3S,4R)-3-O-tert-Butyldimethylsilyl-5-crotonyloxymethyl-1,2-O-cyclohexylidene-5-cyclohexen-1,2,3,4-tetraol (**18**)

To a mixture of the diol (**17**) (0.1 g, 0.3 mmol), pyridine (50 µl, 0.6 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (1 ml) was added crotonic anhydride (45 µl, 0.33 mmol) at room temp. The mixture was stirred for 12 h and poured into the saturated aqueous NH_4Cl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (3 X 5 ml). The combined extracts were washed with brine (3 X 2 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (2:1 v/v)] afforded the *title compound* (**18**) (0.13 g, 95%) as a colourless oil, R_F 0.36 [petroleum ether-diethyl ether (2:1 v/v)]; $[\alpha]_D$ -31.15° (*c* 2.62); $\nu_{max.}$ 3488 (OH) and 1724 cm^{-1} (conjugated ester C=O); δ 0.16 (3H, s), 0.17 (3H, s), 0.94 (9H, s), 1.2-1.7 (10H, m), 1.90 (3H, dd, *J* 8.5 and 1.5 Hz), 3.76 (1H, dd, *J* 8.5 and 2.5 Hz), 4.37 (1H, ddd, *J* 4, 1.5 and 0.8 Hz), 4.43 (1H, d, *J* 8.5 Hz), 4.62 (1H, b), 4.66 (1H, dd, *J* 12 and 0.8 Hz), 4.92 (1H, dd, *J* 12 and 0.8 Hz), 5.61 (1H, b), 5.88 (1H, dq, *J* 16 and 1.5 Hz)), 7.02 (1H, dq, *J* 16 and 8.5 Hz); *m/z* (CI, NH_3) 456 (6.4%, MNH_4^+) (Found: C, 63.3; H, 9.0. $C_{23}H_{38}O_6Si$ requires C, 63.0; H, 8.7%).

(4R,5R,6R)-6-O-tert-Butyldimethylsilyl-2-crotonyloxymethyl-4,5-O-cyclohexylidene-4,5,6-trihydroxycyclohex-2-enone (12)

To a mixture of the alcohol (18) (0.2 g, 0.5 mmol) and molecular sieve 3Å powder (0.1 g) in dry CH_2Cl_2 (5 ml) was added pyridinium chlorochromate (0.15 g, 0.7 mmol) in one portion at room temp. The mixture was stirred for 12 h, diluted with diethyl ether (5 ml) and passed through a pad of Celite. The residue was washed with diethyl ether (20 ml). The combined solution were washed with brine (2 X 2 ml), dried ($MgSO_4$), and filtered. Concentration of the filtrate followed by flash chromatography [petroleum ether-diethyl ether (3:1 v/v)] furnished the *title compound* (12) (0.16 g, 80%) as a colourless oil, R_F 0.48 [petroleum ether-diethyl ether (3:1 v/v)]; $[\alpha]_D$ -28.31° (*c* 2.43); $\nu_{max.}$ 1727 (conjugated ester C=O) and 1712 cm^{-1} (conjugated ketone C=O); δ 0.09 (3H, s), 0.20 (3H, s), 0.92 (9H, s), 11.2-1.7 (10H, m), 1.89 (3H, dd, *J* 7 and 1.5 Hz), 4.48 (1H, d, *J* 3 Hz), 4.67 (1H, m), 4.77 (1H, dt, *J* 14 and 1.5 Hz), 4.88 (1H, dt, *J* 14 and 1.5 Hz), 5.86 (1H, dq, *J* 16 and 1.5 Hz), 6.47 (1H, b), 6.98 (1H, dq, *J* 16 and 7 Hz); *m/z* (CI, NH_3) 436 (24.2%, M^+) (Found: C, 63.6; H, 8.6. $C_{23}H_{36}O_6Si$ requires C, 63.3; H, 8.3%).

2-Crotonyloxymethyl-(4R,5R,6R)-4,5,6-trihydroxycyclohex-2-enone (1)

Ice-cold aqueous CF_3COOH (8 ml, 1:1 v/v) was added to the compound (12) (50 mg) and the mixture was stirred at room temp. for 4 h. Removal of solvent gave an oil which was twice concentrated from the solution on absolute ethanol, giving a reddish solid. Recrystallization from $CHCl_3$/MeOH at -5°C gave colourless needles (1) (27.8 mg, 100%), m.p. 178—179°C (lit[2]. 180°C); R_F 0.29 (ethyl acetate); $[\alpha]_D$ -106.3° (*c* 0.58, MeOH) [lit[2]. -109° (*c* 1.5, MeOH)]; $\nu_{max.}$ 3418 (OH), 1713 (conjugated ester C=O) and 1688 cm^{-1}(enone C=O); δ (DMSO) 1.98 (3H, dd, *J* 6.8 and 1.5 Hz), 4.23 (1H, m), 4.31 (1H, dd, *J* 7.5 and 2 Hz), 4.67 (1H, m), 4.75 (1H, dt, *J* 13.5 and 1.5 Hz), 4.84 (1H, dt, *J* 13.5 and 1.5 Hz), 5.19 (1H, d, *J* 3.8 Hz), 5.32 (1H, d, *J* 7.5 Hz), 5.48 (1H, d, *J* 8.3 Hz), 6.02 (1H, dq, *J* 15.2 and 1.8 Hz), 6.72 (1H, b), 7.05 (1H, dq, *J* 15.2 and 6.8 Hz); *m/z* (CI, NH_3) 260 (100%, MNH_4^+).

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