Chiral synthesis of the necic acid components, crobarbatic acid and integerrinecic acid lactone

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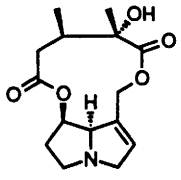
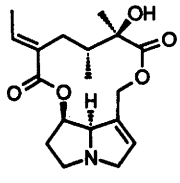
Samarium(II) diiodide-promoted regioselective fragmentation of the γ-halogeno esters 12 and 13 afforded the olefins 14 and 20, respectively, which were converted into the necic acid components, crobarbatic acid and a known advanced intermediate of integerrinecic acid lactone, of macropyrrolizidine alkaloids.

Introduction

Pyrrolizidine alkaloids,[1] a large class of natural products, exhibit interesting biological properties such as hepatotoxic and carcinogenic activities.[2] Much effort involving White's extensive work has, therefore, been devoted to developing new methods and strategies for their synthesis.[3] Some of these alkaloids occur in nature as macrocyclic compounds having 11-, 12-, 13- and 14-membered rings through the diester linkage between the necine base and necic acid.



Crobarbatine



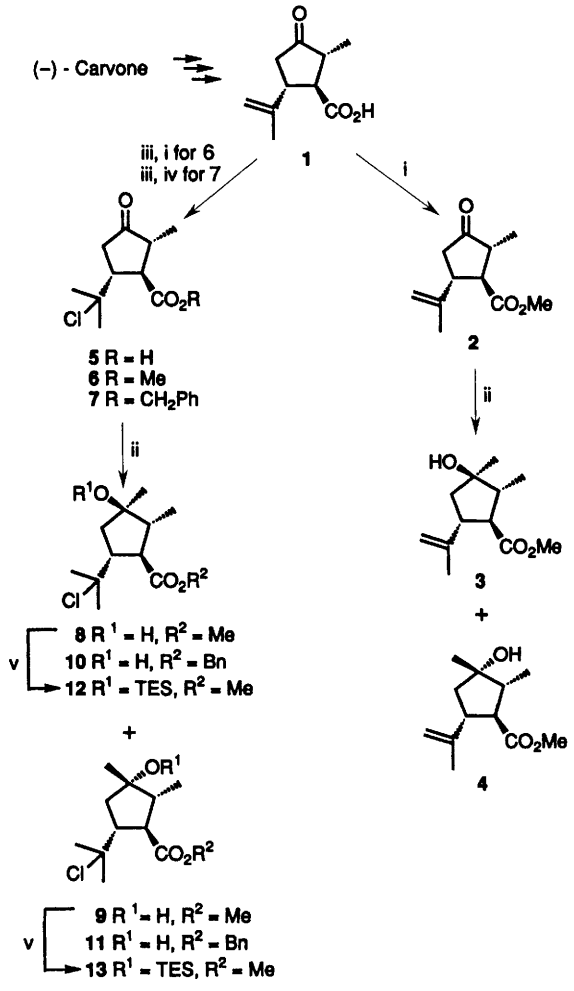
Integerrimine

Results and discussion

In our continuing work on the synthesis of pyrrolizidine alkaloids,[4] we were interested in the chiral synthesis of (+)-crobarbatic acid and (+)-integerrinecic acid lactone, the necic acid components of the 11- and 12-membered pyrrolizidine alkaloids, crobarbatine and integerrimine, respectively. A challenging feature in the synthesis of the necic acid components is the construction of two stereogenic vicinal methyls and a tertiary hydroxy group. This was achieved using the cyclic ketone **5**, easily prepared from (−)-carvone, as a starting material.

The synthesis of crobarbatic acid was established as follows. (see Schemes 1 and 2).

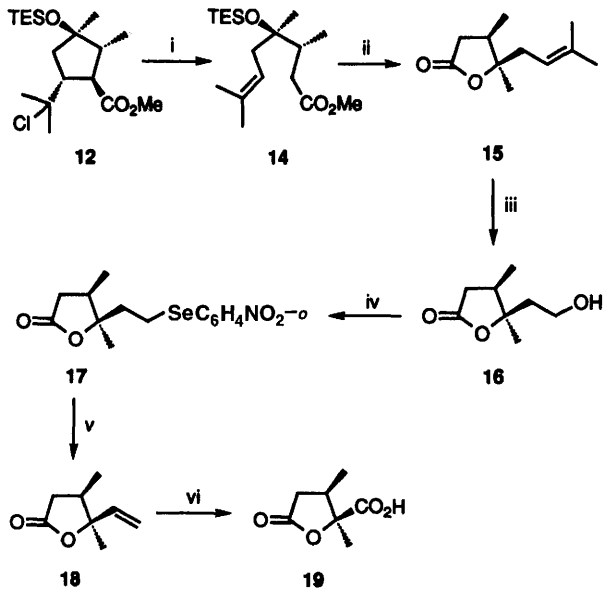
Reaction of the cyclopentanone **2**,[5] prepared from the acid **1**,[6] with methyllithium afforded the tertiary alcohols **3** and **4** in 86% yield. No stereoselectivity of the products was observed. However, the use of methyl γ-chloro ester **6** gave the tertiary alcohols **8** and **9** in 62 and 20% yield, respectively. Methylation of the corresponding benzyl ester **7** further improved this stereoselectivity. After conversion of the adducts **10** and **11** into the methyl esters in two steps the ratio of the alcohols **8** and **9** increased to ~5:1 in 69% yield. The stereochemistry of the products was determined on the basis of their NMR spectra. The signals for the secondary methyl group of compound **3** appeared at δ 0.97 and at δ_C 10.80 in the ^{1}H and ^{13}C NMR spectra, respectively, whereas the signals for the corresponding methyl group of compound **4** were shifted downfield to δ 1.04 in ^{1}H and at δ_C 16.39 in ^{13}C NMR spectra due to the presence of the *cis*-hydroxy group. Also, the signals of the secondary methyl



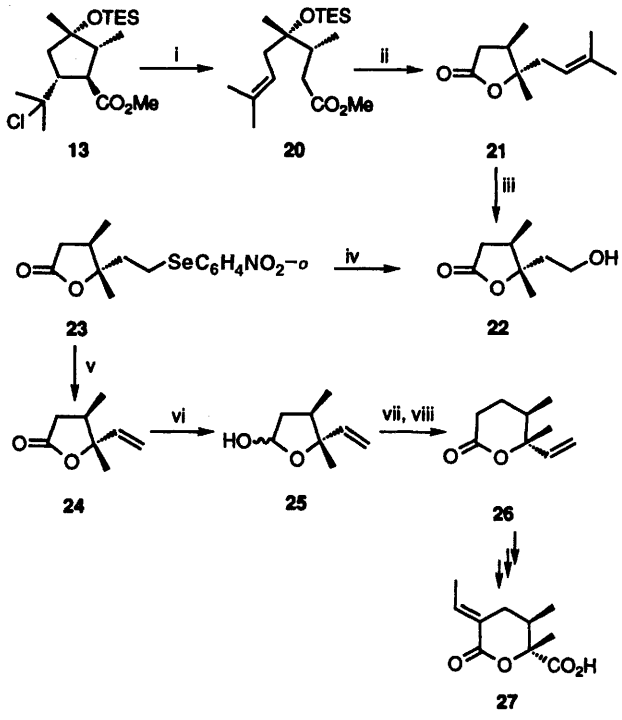
Scheme 1 *Reagents and conditions:* i, K_2CO_3, MeI, DMF, room temp.; ii, MeLi, THF, −78 °C; iii, conc. HCl, Bu_4NBr, MeCN, room temp.; iv, K_2CO_3, $PhCH_2Br$, DMF, room temp.; v, TESOTf, 2,6-lutidine, CH_2Cl_2, room temp.

group of compounds **8** and **9** appeared at δ 0.97 and 1.04 in their ^{1}H NMR spectra, respectively. These results supported the view that the major adduct **8** has two methyl groups in a *cis* configuration.

The tertiary hydroxy group of the major product **8** was protected as the triethylsilyl (TES) ether **12** in 96% yield. Previously we developed[7] the samarium(II) diiodide-promoted carbon–carbon bond cleavage of γ-halogeno carbonyl compounds to give the regioselective fragmentation to olefinic carbonyl compounds. The samarium(II) diiodide-promoted



Scheme 2 *Reagents and conditions:* i, SmI_2, THF–HMPA, room temp.; ii, TBAF, THF, room temp.; iii, O_3, EtOH, −78 °C; then $NaBH_4$; iv, *o*-nitrophenyl selenocyanate, Bu_3P, THF, room temp.; v, MCPBA, CH_2Cl_2, 0 °C; vi, $RuCl_3$, $NaIO_4$, MeCN–CCl_4–water



Scheme 3 *Reagents and conditions:* i, SmI_2, THF–HMPA, room temp.; ii, TBAF, THF, room temp.; iii, O_3, EtOH, −78 °C; then $NaBH_4$; iv, *o*-nitrophenyl selenocyanate, Bu_3P, THF, room temp.; v, MCPBA, CH_2Cl_2, 0 °C; vi, DIBAH, THF, −78 °C; vii, BuLi, 2-trimethylsilyl-1,3-dithiane, THF, −15 °C; viii, PTSA, CH_2Cl_2, room temp.

cleavage of the tertiary silyl ether **12** gave the desired product **14** in 94% yield (Scheme 2). Removal of the silyl group of ester compound **14** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) and consequential lactonization gave the γ-lactone **15** in quantitative yield. Ozonolysis of the lactone **15** in ethanol, followed by reduction with sodium boranuide, afforded the alcohol **16** in 97% yield. Dehydration of the alcohol **16** to alkene **18** proved to be problematic. However, oxidative elimination of the selenide **17** derived from the alcohol **16** according to Grieco's procedure,[8] with *m*-chloroperbenzoic acid (MCPBA) furnished the olefin **18** in 87% yield after two steps. Finally, treatment of the olefin **18** with ruthenium tetraoxide under Sharpless's condition[9] provided the crobarbatic acid **19**, mp 182–184.5 °C [lit.,[10] 181.5–183 °C], in 96% yield, whose spectroscopic data including its specific optical rotation, $[\alpha]_D$ +3.45 (H_2O) {lit.,[11] $[\alpha]_D$ +3.93 (H_2O)}, were identical with those reported.[11]

We next examined the synthesis of integerrinecic acid lactone starting from the tertiary alcohol **9** by adapting the above synthetic route. Samarium(II) diiodide-promoted fragmentation of the silyl ether **13** followed by deprotection of the OH group of the ester **20** gave the γ-lactone **21**, in 79% yield, which was further converted into the olefin **24** *via* the alcohol **22** and the selenide **23**, in 79% overall yield from compound **21**. Diisobutylaluminium hydride (DIBAH) reduction of lactone **24** in THF gave the lactol **25**, which on treatment with 2-lithio-2-trimethylsilyl-1,3-dithiane and subsequent acid hydrolysis with toluene-*p*-sulfonic acid (PTSA) in dichloromethane furnished the δ-lactone **26** in 69% yield, whose spectroscopic data including its specific optical rotation, {$[\alpha]_D$ +17.7 ($CHCl_3$); lit.,[11] $[\alpha]_D$ +17.7 ($CHCl_3$)}, were identical with those reported.[11] This lactone has previously been converted into integerrinecic acid lactone **27** by White *et al.*[11] Therefore the above constitutes a formal synthesis of integerrinecic acid lactone (see Scheme 3).

In conclusion, we have developed a new synthetic pathway to crobarbatic acid and integerrinecic acid lactone which should be applicable to the synthesis of other necic acids.

Experimental

General methods

Mps were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX 270 instrument (270 MHz), and chemical shifts are reported in ppm on the δ-scale from internal Me_4Si. *J* Values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. All new compounds described in the Experimental section were homogeneous on TLC.

Methyl (1*S*,2*R*,3*R*,5*R*)-3-hydroxy-5-isopropenyl-2,3-dimethylcyclopentanecarboxylate 3 and methyl (1*S*,2*R*,3*S*,5*R*)-3-hydroxy-5-isopropenyl-2,3-dimethylcyclopentanecarboxylate 4

To a stirred solution of the ester **2** (572 mg, 2.92 mmol) in dry THF (6 cm^3) was added a 1.16 mol dm^{-3} hexane solution of methyllithium (3.16 cm^3, 3.5 mmol) at −78 °C under argon and the resulting solution was stirred at the same temperature for a further 30 min. The mixture was treated with saturated aq. ammonium chloride and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with hexane–ethyl acetate (10:1, v/v) gave the ester **3** (257 mg, 42%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ 0.97 (3 H, d, *J* 6.7, Me), 1.30 (3 H, s, Me), 1.73 (3 H, s, Me), 1.77 (1 H, dd, *J* 7.3 and 14.0, 4-H), 1.89–2.01 (1 H, m, 2-H), 2.14 (1 H, dd, *J* 11.0 and 14.0, 4-H), 2.69 (1 H, t, *J* 11.0, 1-H), 2.83–2.94 (1 H, m, 5-H), 3.69 (3 H, s, Me), 4.71 (1 H, br s, olefinic proton) and 4.78 (1 H, s, olefinic proton); δ_C 10.80 (q), 19.88 (q), 26.99 (q), 45.64 (t), 48.04 (d), 49.12 (d), 51.55 (q), 54.46 (d), 79.11 (s), 110.47 (t), 146.14 (s) and 175.88 (s). Further elution with the same solvent system afforded the ester **4** (270 mg, 44%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ 1.04 (3 H, d, *J* 7.3, Me), 1.22 (3 H, s, Me), 1.71 (3 H, s, Me), 1.66–1.77 (1 H, m, 4-H), 1.91–2.03 (1 H, m, 2-H), 2.13–2.24 (1 H, m, 4-H), 2.38 (1 H, dd, *J* 6.7 and 10.4, 1-H), 2.40 (1 H, br s, OH), 3.04–3.14 (1 H, m, 5-H), 3.70 (3 H, s, Me), 4.74 (1 H, s, olefinic proton) and 4.77 (1 H, s, olefinic proton); δ_C 16.39 (q), 20.58 (q), 24.10 (q), 45.29 (t),

47.69 (d), 49.99 (d), 51.92 (q), 55.54 (d), 80.26 (s), 110.30 (t), 145.64 (s) and 176.82 (s).

(1*R*,2*R*,5*R*)-5-(1-Chloro-1-methylethyl)-2-methyl-3-oxocyclopentanecarboxylic acid 5

A mixture of the acid **1** (10.0 g, 54.95 mmol) and TBABr (5.0 g, 15.51 mmol) in acetonitrile (200 cm^3) was stirred at ambient temperature for 15 min. To this solution was added conc. hydrochloric acid (100 cm^3) and the resulting solution was further stirred for 12 h. After evaporation off of the organic solvent, the aqueous layer was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was purified by column chromatography on silica gel with hexane–ethyl acetate (8:1, v/v) as eluent to give the *acid* **5** (11.2 g, 93%) as a solid, mp 118–120 °C; $[\alpha]_D$ −96.58 (*c* 0.8, $CHCl_3$) (Found: C, 54.85; H, 6.95. $C_{10}H_{15}ClO_3$ requires C, 54.95; H, 6.90%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ 1.22 (3 H, d, *J* 6.7, Me), 1.59 and 1.63 (each 3 H, each s, 2 × Me), 2.41–2.89 (5 H, m, 1-, 2- and 5-H and 4-H_2) and 8.50–9.00 (1 H, br s, CO_2H) (Found: M^+, 218.0708. $C_{10}H_{15}ClO_3$ requires M, 218.0708).

Methyl (1*R*,2*R*,5*R*)-5-(1-chloro-1-methylethyl)-2-methyl-3-oxocyclopentanecarboxylate 6

To a stirred solution of the acid **5** (15.0 g, 68.65 mmol) and potassium carbonate (14 g, 0.1 mol) in dimethylformamide (DMF) (150 cm^3) was added iodomethane (6 cm^3, 42.25 mmol) slowly at 0 °C and the resulting solution was stirred for another 12 h at room temperature. The mixture was treated with saturated aq. ammonium chloride and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (8:1, v/v) gave the *ester* **6** (15.0 g, 94%) as an oil; $[\alpha]_D$ −83.34 (*c* 1.4 $CHCl_3$) (Found: C, 55.75; H, 7.25. $C_{11}H_{17}ClO_3{\cdot}0.25H_2O$ requires C, 56.0; H, 7.35%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ 1.14 (3 H, d, *J* 6.7, Me), 1.56 and 1.57 (each 3 H, each s, 2 × Me), 2.38–2.90 (5 H, m, 1-, 2- and 5-H and 4-H_2) and 3.77 (3 H, s, Me) (Found: M^+, 232.0856. $C_{11}H_{17}ClO_3$ requires M, 232.0859).

Benzyl (1*R*,2*R*,5*R*)-5-(1-chloro-1-methylethyl)-2-methyl-3-oxocyclopentanecarboxylate 7

To a stirred solution of the acid **5** (1.21 g, 5.54 mmol) and potassium carbonate (0.93 g, 6.74 mmol) in DMF (36 cm^3) was added benzyl bromide (1.13 g, 6.43 mmol) at ambient temperature and the resulting solution was stirred for another 12 h at the same temperature. The mixture was treated with saturated aq. ammonium chloride and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) gave the *ester* **7** (1.53 g, 90%) as an oil; $[\alpha]_D$ −52.31 (*c* 1.2, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ 1.13 (3 H, d, *J* 6.7, Me), 1.48 and 1.54 (each 3 H, each s, 2 × Me), 2.38–2.87 (5 H, m, 1-, 2- and 5-H and 4-H_2), 5.14–5.24 (2 H, m, CH_2Ph) and 7.35–739 (5 H, m, ArH) (Found: M^+, 308.1173. $C_{17}H_{21}ClO_3$ requires M, 308.1168).

Methyl (1*R*,2*R*,3*R*,5*R*)-5-(1-chloro-1-methylethyl)-3-hydroxy-2,3-dimethylcylopentanecarboxylate 8 and methyl (1*R*,2*R*,3*S*,5*R*)-5-(1-chloro-1-methylethyl)-3-hydroxy-2,3-dimethylcylopentanecarboxylate 9

To a stirred solution of the ketone **7** (15.0 g, 64.52 mmol) in dry THF (300 cm^3) in the presence of 4 Å molecular sieves (1 g) was added a 1.16 mol dm^{-3} solution of methyllithium in diethyl ether (78.2 cm^3, 86.0 mmol) at −78 °C under argon. The solution was further stirred at the same temperature for 30 min and treated with saturated aq. ammonium chloride solution. The mixture was extracted with ethyl acetate and the extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue. which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) gave the *ester* **8** (10.0 g, 62%) as an oil; $[\alpha]_D$ − 12.51 (*c* 0.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3540, 2900 and 1720; δ 0.97 (3 H, d, *J* 6.7, Me), 1.26 (3 H, s, Me), 1.51 and 1.55 (each 3 H, each s, 2 × Me), 1.84–1.96 (2 H, m, 2- and 4-H), 2.12–2.21 (1 H, m, 4-H), 2.66–2.75 (2 H, m, 1- and 5-H) and 3.72 (3 H, s, Me) (Found: M^+, 248.1164. $C_{12}H_{21}ClO_3$ requires M, 248.1179). Further elution with the same solvent system afforded the *ester* **9** (3.24 g, 20%) as an oil; $[\alpha]_D$ −12.77 (*c* 0.9, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 2900 and 1720; δ 1.04 (3 H, d, *J* 7.3, Me), 1.24 (3 H, s, Me), 1.53 and 1.55 (each 3 H, each s, 2 × Me), 1.86–2.00 (2 H, m, 2- and 4-H), 2.07–2.13 (1 H, m, 5-H), 2.63 (1 H, dd, *J* 3.1 and 7.3, 4-H), 2.80 (1 H, dt, *J* 7.3 and 15.8, 1-H) and 3.73 (3 H, s, Me) (Found: M^+, 248.1185. $C_{12}H_{21}ClO_3$ requires M, 248.1179).

Benzyl (1*R*,2*R*,3*R*,5*R*)-5-(1-chloro-1-methylethyl)-3-hydroxy-2,3-dimethylcyclopentanecarboxylate 10 and benzyl (1*R*,2*R*,3*S*,5*R*)-5-(1-chloro-1-methylethyl)-3-hydroxy-2,3-dimethylcyclopentanecarboxylate 11

Addition of a methyl group to the ketone **7** (1.34 g, 4.34 mmol) with a 1.16 mol dm^{-3} solution of methyllithium (4.82 cm^3, 5.59 mmol) was carried out by the same procedure as described above to give the benzyl esters **10** (810 mg, 58%) and **11** (165 mg, 12%) as an oil. Compound **10**; $[\alpha]_D$ −10.31 (*c* 1.1, $CHCl_3$) (Found: C, 66.35; H, 7.85; M^+, 324.1483. $C_{18}H_{25}ClO_3$ requires C, 66.70; H, 7.75%; M, 324.1491); $\nu_{max}(CHCl_3)/cm^{-1}$ 1735; δ 0.96 (3 H d, *J* 6.7, Me), 1.24 (3 H, s, Me), 1.44 and 1.52 (each 3 H, each s, 2 × Me), 1.81–1.97 (2 H, m, 1- and 5-H), 2.10–2.25 (1 H, m, 2-H), 2.68–2.79 (2 H, m, 4-H_2), 5.13–5.20 (2 H, m, CH_2Ph) and 7.31–7.39 (5 H, m, ArH). Compound **11**; $[\alpha]_D$ −6.36 (*c* 0.6, $CHCl_3$) (Found: C, 66.4; H, 7.80; M^+, 324.1490); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720; δ 1.03 (3 H, d, *J* 7.3, Me), 1.23 (3 H, s, Me), 1.46 and 1.52 (each 3 H, each s, 2 × Me), 1.85–2.00 (2 H, m, 1- and 5-H), 2.04–2.17 (1 H, m, 2-H), 2.63–2.86 (2 H, m, 4-H_2), 5.12 (1 H, d, *J* 12.2, C*H*HPh), 5.18 (1 H, *J* 12.2, C*H*HPh) and 7.32–7.38 (5 H, m, ArH).

Conversion of the benzyl ester 10 into the methyl ester 8

A solution of the benzyl ester **10** (0.52 g, 1.60 mmol) in ethanol (50 cm^3) in the presence of 10% palladium on carbon (70 mg) was stirred under hydrogen at ambient temperature for 12 h. An insoluble material was filtered off and the filtrate was concentrated to give a residue, which was taken up with DMF (50 cm^3). To this solution were added potassium carbonate (440 mg, 3.19 mmol) and iodomethane (0.20 cm^3, 3.19 mmol) and the resulting mixture was stirred at room temperature for a further 2 h. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate and the extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (4:1, v/v) gave the methyl ester **8** (379 mg, 95%) which was identical with the authentic sample obtained above. Conversion of benzyl ester **11** into methyl ester **9** was also carried out in 96% yield by using the same procedure as above.

Methyl (1*R*,2*R*,3*R*,5*R*)-5-(1-chloro-1-methylethyl)-2,3-dimethyl-3-(triethylsiloxy)cyclopentanecarboxylate 12

To a stirred solution of the alcohol **8** (650 mg, 2.62 mmol) and (2,6-lutidine) (1.36 cm^3, 11.27 mmol) in dichloromethane (15 cm^3) was added triethylsilyl triflate (TESOTf) (1.35 cm^3, 5.13 mmol) at ambient temperature under argon and the resulting solution was stirred for another 1 h. The mixture was treated with brine and extracted. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which

was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (10:1, v/v) gave the *silyl ether* (911 mg, 96%) as an oil; $[\alpha]_D$ +24.77 (*c* 0.7, $CHCl_3$) (Found: C, 59.45; H, 9.65. $C_{18}H_{35}ClO_3Si$ requires C, 59.55; H, 9.70%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; δ 0.59 (6 H, q, *J* 7.3, 3 × $SiCH_2$), 0.90–1.00 (12 H, m, 3 × $SiCH_2Me$ and 2-Me), 1.21 (3 H, s, Me), 1.53 and 1.55 (each 3 H, each s, 2 × Me), 1.75–2.08 (3 H, m, 2-, 4- and 5-H), 2.65–2.80 (2 H, m, 1- and 4-H) and 3.69 (3 H, s, Me) [Found: *m/z*: 333.1621. $C_{16}H_{30}ClO_3Si$ (M^+ − 29) requires *m/z* 333.1621].

Methyl (1*R*,2*R*,3*S*,5*R*)-5-(1-chloro-1-methylethyl)-2,3-dimethyl-3-(triethylsiloxy)cyclopentanecarboxylate 13

Silylation of the alcohol **11** (3.24 g, 13.04 mmol) with TESOTf (7.2 cm^3, 27.27 mmol) and 2,6-lutidine (7.23 cm^3, 59.75 mmol) by the same procedure as described above gave the *silyl ether* **13** (4.73 g, 100%) as an oil; $[\alpha]_D$ −21.87 (*c* 0.9, $CHCl_3$) (Found: C, 59.8; H, 9.75%), $\nu_{max}(CHCl_3)/cm^{-1}$ 1735; δ 0.59 (6 H, q, *J* 7.3, 3 × $SiCH_2$), 0.90–1.00 (12 H, m, 3 × $SiCH_2Me$ and 2-Me), 1.21 (3 H, s, 4-Me), 1.53 and 1.55 (each 3 H, each s, 2 × Me), 1.78–2.02 (2 H, m, 4-H_2), 2.20–2.26 (1 H, m, 5-H), 2.44 (1 H, dd, *J* 7.3 and 9.2, 2-H), 2.89 (1 H, dd, *J* 9.2 and 11.0, 2-H) and 3.69 (3 H, s, Me) [Found: *m/z*; 333.1643. $C_{16}H_{30}ClO_3Si$ (M^+ − 29) requires *m/z* 333.1621].

Methyl (3*R*,4*R*)-3,4,7-trimethyl-4-(triethylsiloxy)oct-6-enoate 14

To a stirred suspension of samarium metal (27 g, 0.18 mol) and 4 Å molecular sieves (2 g) in dry THF (490 cm^3) was added diiodomethane (48.7 g, 0.18 mol) at ambient temperature and the resulting solution was stirred for another 30 min. Hexamethylphosphoric triamide (HMPA) (122 cm^3) was added to the solution and the mixture was stirred for 15 min. To this solution was added a solution of the chloride **12** (13.47 g, 37.16 mmol) in dry THF (135 cm^3) and the mixture was stirred for a further 10 min and then treated with saturated aq. sodium hydrogen carbonate (2 cm^3). Celite (~ 50 g) and an excess of diethyl ether were added and the insoluble material was filtered off by filtration through a Celite pad. The filtrate was treated with water and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–dichloromethane (9:1, v/v) gave the *olefin* **14** (11.43 g, 94%) as an oil; $[\alpha]_D$ +16.50 (*c* 1.3, $CHCl_3$) (Found: C, 65.6; H, 10.8. $C_{18}H_{36}O_3Si$ requires C, 65.80; H, 11.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2870, 1730 and 905; δ 0.54–0.62 (6 H, m, 3 × $SiCH_2$), 0.81–0.98 (12 H, m, 3 × $SiCH_2Me$ and 3-Me), 1.12 (3 H, s, Me), 1.60 and 1.71 (each 3 H, each s, 2 × Me), 1.89–2.27 (4 H, m, 2-H_2, 3- and 5-H), 2.63 (1 H, d, *J* 12.8 , 5-H), 3.67 (3 H, s, Me) and 5.16–5.22 (1 H, m, 6-H) [Found: *m/z* 299.2033. $C_{16}H_{31}O_3Si$ (M^+ − 29) requires *m/z*, 299.2041].

(3*R*,4*R*)-3,4-Dimethyl-4-(3-methylbut-2-enyl)-γ-butyrolactone 15

A solution of the silyl ether **14** (11.4 g, 34.76 mmol) and TBAF (65 cm^3, 65 mmol) in THF (150 cm^3) was stirred at ambient temperature for 16 h. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) gave the *olefin* **15** (6.33 g, 100%) as an oil; $[\alpha]_D$ −4.19 (*c* 1.1, $CHCl_3$) (Found: C, 71.2; H, 9.9; M^+ 182.1306. $C_{11}H_{18}O_2 \cdot 0.2H_2O$ requires C, 71.10; H, 10.00%; M, 182.1306); $\nu_{max}(CHCl_3)/cm^{-1}$ 2900 and 1750; δ 1.04 (3 H, d, *J* 6.7, Me), 1.23 (3 H, s, Me), 1.63 and 1.74 (each 3 H, each s, 2 × Me), 2.25 (1 H, dd, *J* 10.4 and 16.5, 2-H), 2.34–2.46 (3 H, m, 3-H and 4-CH_2), 2.43 (1 H, dd, *J* 7.9 and 16.5, 2-H) and 5.16–5.22 (1 H, m, olefinic proton).

(3*R*,4*R*)-4-(2-Hydroxyethyl)-3,4-dimethyl-γ-butyrolactone 16

A stirred solution of the ketone **15** (24 mg, 0.13 mmol) in ethanol (30 cm^3) was saturated with ozone at −78 °C. The solution was stirred for 10 min, the ozone was removed by exchange with argon and the mixture treated with sodium boranuide (8 mg, 0.22 mmol), then was warmed to room temperature. Acetone (1 cm^3) was added to this solution and the mixture was stirred for another 15 min at room temperature. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) gave the *alcohol* **16** (20 mg, 97%) as an oil; $[\alpha]_D$ −24.9 (*c* 0.2, $CHCl_3$) (Found: C, 59.85; H, 8.9; M^+, 158.0955. $C_8H_{14}O_3 \cdot 0.2H_2O$ requires C, 59.60; H, 9.00%; M, 158.0943); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 2900 and 1750; δ 1.08 (3 H, d, *J* 6.7, Me), 1.32 (3 H, s, Me), 1.93–2.01 (2 H, m, CH_2CH_2OH), 2.27 (1 H, dd, *J* 10.4 and 16.5, 2-H), 2.49 (1 H, ddq, *J* 6.7, 7.9 and 10.4, 3-H), 2.64 (1 H, dd, *J* 7.9 and 16.5, 2-H) and 3.85 (2 H, dt, *J* 5.5 and 11.0, CH_2OH).

(3*R*,4*R*)-3,4-Dimethyl-4-[2-(*o*-nitrophenylselanyl)ethyl]-γ-butyrolactone 17

To a stirred solution of the alcohol **16** (1.84 g, 11.65 mmol) and *o*-nitrophenyl selenocyanate (4.9 g, 21.6 mmol) in THF (35 cm^3) was added dropwise tributylphosphine (8.0 cm^3, 39.7 mmol) at room temperature and the resulting mixture was stirred at the same temperature for a further 2 h. After evaporation off of the solvent, the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) afforded the selenide **17** (4.0 g, 100%) as a pale yellow oil; $[\alpha]_D$ +6.33 (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2940 and 1770; δ 1.10 (3 H, d, *J* 6.7, Me), 1.33 (3 H, s, Me), 1.99–2.20 (2 H, m, 2- and 3-H), 2.28–2.48 (2 H, m, CH_2CH_2Se), 2.67 (1 H, dd, *J* 7.9 and 16.5, 2-H), 2.92–3.12 (2 H, m, CH_2Se), 7.31–7.37 (1 H, m, ArH), 7.52–7.60 (2 H, m, ArH) and 8.29–8.33 (1 H, m, ArH).

(3*R*,4*R*)-3,4-Dimethyl-4-vinyl-γ-butyrolactone 18

To a stirred solution of the selenide **17** (489 mg, 1.40 mmol) in dichloromethane (9.6 cm^3) was added MCPBA (0.63 g, 2.6 mmol) at 0 °C and the resulting solution was stirred for a further 30 min at the same temperature. The mixture was washed successively with 10% aq. sodium thiosulfate and saturated aq. sodium hydrogen carbonate, and dried over Na_2SO_4. Evaporation of the mixture gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (8:1, v/v) gave the olefin **18** (171 mg, 87%) as an oil; $[\alpha]_D$ −7.78 (*c* 0.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1765; δ 1.07 (3 H, d, *J* 6.7, Me), 1.35 (3 H, s, Me), 2.24 (1 H, dd, *J* 10.4 and 16.5, 2-H), 2.42 (1 H, ddq, *J* 6.7, 7.9 and 10.4, 3-H), 2.68 (1 H, dd, *J* 7.9 and 16.5, 2-H), 5.17 (1 H, d, *J* 10.4, CH=CH*H*), 5.30 (1 H, d, *J* 17.1, CH=C*H*H) and 5.93 (1 H, dd, *J* 10.4 and 17.1, C*H*=CH_2) [Found: *m/z*, 125.0586. $C_7H_9O_2$ (M^+ − 15) requires *m/z*, 125.0601].

Crobarbatic acid 19

To a stirred solution of the olefin **18** (84 mg, 0.6 mmol) in a mixture of tetrachloromethane (1.2 cm^3), acetonitrile (1.2 cm^3) and water (1.8 cm^3) was added sodium periodate (0.52 g, 2.4 mmol) at ambient temperature. Ruthenium trichloride hydrate (270 mg, 2.2 mol equiv.) was then added to this solution at the same temperature and the resulting mixture was stirred for a further 30 min. The mixture was extracted with dichloromethane and the extract was washed with brine and and dried over Na_2SO_4. Evaporation off of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (3:1, v/v) gave the acid **19** (91 mg, 96%) as a solid; mp 182–184.5 °C; $[\alpha]_D$ +3.45 (*c* 0.4, water); δ 1.11 (3 H, d, *J* 6.7, Me), 1.46 (3 H, s, Me), 2.15–2.25 (1 H, m, 3-H) and 2.71–2.81 (2 H, m, 2-H_2).

Methyl (3*R*,4*S*)-3,4,7-trimethyl-4-(triethylsiloxy)oct-6-enoate 20
A regioselective carbon–carbon bond fragmentation of the ester **13** (16.5 g, 45.52 mmol) with samarium diiodide, using the same procedure as for the preparation of the olefin **14**, afforded the *olefin* **20** (14.33 g, 96%) as an oil; $[\alpha]_D$ −1.32 (*c* 1.1, $CHCl_3$) (Found: C, 65.45; H, 11.0. $C_{18}H_{36}O_3Si$ requires C, 65.80; H, 11.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2900 and 1710; δ 0.59 (6 H, q, *J* 7.9, 3 × $SiCH_2$), 0.90–0.98 (12 H, m, 3 × $SiCH_2Me$ and 3-Me), 1.18 (3 H, s, Me), 1.61 and 1.71 (each 3 H, each s, 2 × Me), 1.99–2.24 (4 H, m, 2- and 5-H_2), 2.60–2.67 (1 H, m, 3-H), 3.67 (3 H, s, Me) and 5.13–5.18 (1 H, m, 6-H) [Found: *m*/*z*, 299.2083. $C_{16}H_{31}O_3Si$ (M^+ − 29) requires *m*/*z*, 299.2080].

(3*R*,4*S*)-3,4-Dimethyl-4-(3-methylbut-2-enyl)-γ-butyrolactone 21
The *lactone* **21** (2.54 g, 79%) was obtained as an oil from the olefin **20** (5.82 g, 17.74 mmol) by the same procedure as for the preparation of epimer **15**; $[\alpha]_D$ +37.90 (*c* 1.0, $CHCl_3$) (Found: C, 70.7; H, 10.0; M^+, 182.1306. $C_{11}H_{18}O_2{\cdot}0.25H_2O$ requires C, 70.75; H, 10.0%; M, 182.1306); $\nu_{max}(CHCl_3)/cm^{-1}$ 2920 and 1760; δ 1.10 (3 H, d, *J* 7.3, Me), 1.36 (3 H, s, Me), 1.62 and 1.74 (each 3 H, each s, 2 × Me), 2.24–2.42 (4 H, m, 2-, 3-H and CH_2CH=), 2.61–2.70 (1 H, dd, *J* 7.3 and 15.9, 2-H) and 5.17–5.22 (1 H, m, olefinic proton).

(3*R*,4*S*)-4-(2-Hydroxyethyl)-3,4-dimethyl-γ-butyrolactone 22
Ozonolysis of the olefin **21** (2.45 g, 13.46 mmol) by the same procedure as for the preparation of compound **16** afforded the alcohol **22** (1.72 g, 81%) as an oil; $[\alpha]_D$ −0.10 (*c* 1.1, $CHCl_3$) (Found: C, 60.1; H, 8.95; M^+, 158.0952. $C_8H_{14}O_3{\cdot}0.13H_2O$ requires C, 59.90; H, 8.95%; M, 158.0943); $\nu_{max}(CHCl_3)/cm^{-1}$ 2925 and 1765; δ 1.09 (3 H, d, *J* 6.7, Me), 1.44 (3 H, s, Me), 1.68–1.97 (2 H, m, 2-H_2), 2.25–2.45 (2 H, m, CH_2CH_2OH), 2.56–2.71 (1 H, m, 3-H) and 3.83–3.88 (2 H, m, CH_2OH).

(3*R*,4*S*)-3,4-Dimethyl-4-[2-(*o*-nitrophenylselanyl)ethyl]-γ-butyrolactone 23
Reaction of the alcohol **22** (1.48 g, 9.37 mmol) with *o*-nitrophenyl selenocyanate (4.17 g, 18.37 mmol) was carried out using the same procedure as for the preparation of compound **17** to afford the selenide **23** (3.18 g, 99%) as a pale yellow oil; $[\alpha]_D$ −46.26 (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1765, 1595 and 1335; δ 1.07 (3 H, d, *J* 6.7, Me), 1.50 (3 H, s, Me), 1.81–2.06 (2 H, m, CH_2CH_2Se), 2.25 (1 H, dd, *J* 10.4 and 17.1, 2-H), 2.40–2.50 (1 H, m, 3-H), 2.69 (1 H, dd, *J* 7.9 and 17.1, 2-H), 2.93 (1 H, dt, *J* 6.1 and 12.2, CHHSe), 3.09 (1 H, dt, *J* 7.3 and 12.2, CHHSe), 7.32–7.36 (1 H, m, ArH), 7.50–7.58 (2 H, m, ArH) and 8.29–8.33 (1 H, m, ArH).

(3*R*,4*S*)-3,4-Dimethyl-4-vinyl-γ-butyrolactone 24
Oxidative elimination of the selenide **23** (3.16 g, 9.20 mmol) with MCPBA (5.72 g, 23.61 mmol) was carried out by the same procedure as for the preparation of compound **18** to give the *olefin* **24** (1.28 g, 99%) as an oil; $[\alpha]_D$ −21.18 (*c* 0.9, $CHCl_3$) (Found: C, 67.95; H, 8.7; M^+, 140.0831. $C_8H_{12}O_2{\cdot}0.1H_2O$ requires C, 67.70; H, 8.65%; M, 140.0836); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 and 1605; δ 1.05 (3 H, d, *J* 6.7, Me), 1.49 (3 H, s, Me), 2.20 (1 H, dd, *J* 11.0 and 16.5, 2-H), 2.32–2.46 (1 H, m, 3-H), 2.58 (1 H, dd, *J* 7.3 and 16.5, 2-H), 5.22 (1 H, d, *J* 10.4, CH=CHH), 5.30 (1 H, d, *J* 17.1, CH=CHH) and 5.93 (1 H, dd, *J* 10.4 and 17.1, $CH{=}CH_2$).

(4*R*,5*S*)-4,5-Dimethyl-5-vinyltetrahydrofuran-2-ol 25
To a stirrred solution of the lactone **24** (241 mg, 1.72 mmol) in dry THF (9.8 cm^3) was added dropwise a 0.91 mol dm^{-3} hexane solution of DIBAH (4.0 cm^3, 3.72 mmol) at −78 °C and the resulting mixture was stirred for a further 40 min. After treatment with saturated aq. ammonium chloride, the mixture was extracted with ethyl acetate and the extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (3:1, v/v) gave a diastereoisomeric mixture of the lactol **25** (244 mg, 99%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 2930 and 1610; δ 0.94 and 0.97 (each 1.5 H, each d, *J* 6.7, Me), 1.30 and 1.46 (each 1.5 H, each s, Me), 1.50–2.43 (3 H, m, 3-H_2 and 4-H), 3.50 and 3.95 (each 0.5 H, each m, 2-H), 5.10 and 5.30 (each 1 H, each m, CH=CH_2), 5.69 (0.5 H, dd, *J* 10.4 and 17.1, C*H*=CH_2) and 5.95 (0.5 H, dd, *J* 10.4 and 17.1, C*H*=CH_2) [Found: *m*/*z*, 124.0885. $C_8H_{12}O$ (M^+ − 18) requires *m*/*z*, 124.0905].

(5*R*,6*S*)-5,6-Dimethyl-6-vinyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one 26
To a stirred solution of 2-trimethylsilyl-1,3-dithiane (2.37 cm^3, 11.41 mmol) in THF (11.2 cm^3) was added a 1.64 mol dm^{-3} hexane solution of butyllithium (6.30 cm^3, 9.78 mmol) at −15 °C under argon. After the mixture had been stirred for 30 min at the same temperature, a solution of the lactol **25** (232 mg, 1.63 mmol) in THF (3.4 cm^3) was added dropwise and the mixture was stirred for a further 20 min. The mixture was treated with saturated aq. ammonium chloride and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was taken up with dichloromethane (20 cm^3). A catalytic amount of PTSA was added to the solution and the mixture was stirred for 1 h at room temperature. The solution was basified with saturated aq. sodium hydrogen carbonate and extracted with dichloromethane. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–dichloromethane (4:1, v/v) gave the δ-lactone **26** (174 mg, 69%) as an oil; $[\alpha]_D$ +17.70 (*c* 0.7, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2900, and 1735; δ 1.04 (3 H, d, *J* 7.3, Me), 1.47 (3 H, s, Me), 1.86–2.23 (3 H, m, 3-H_2 and 5-H), 2.44–2.60 (2 H, m, 4-H_2), 5.16–5.32 (2 H, m, CH=CH_2) and 5.88 (1 H, dd, *J* 10.4 and 17.1, C*H*=CH_2) (Found: M^+, 154.0982. Calc. for $C_9H_{14}O_2$: M, 154.0992).

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