Macrocyclic Pyrrolizidine Alkaloids. Synthesis and Stereochemistry of (+)-Dicrotaline (13β-Hydroxy-13α-methyl-1,2-didehydrocrotalanine) and (+)-13-*epi*-Dicrotaline [1]

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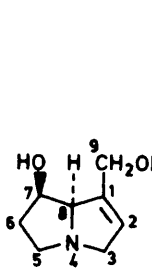
Treatment of (+)-retronecine (1) with the trimethylsilyl ether of 3-hydroxy-3-methylglutaric anhydride gave a mixture of the 7- and 9-monoesters of (+)-retronecine (1). Lactonisation of this mixture was achieved using the corresponding pyridine-2-thiol esters to give (+)-dicrotaline (13β-hydroxy-13α-methyl-1,2-didehydrocrotalanine) (2) and (+)-13-*epi*-dicrotaline (3). The absolute configuration at C-13 in both compounds was established by a sequence of selective reactions on each epimer to yield optically active mevalonolactone.

More than 200 pyrrolizidine alkaloids have been characterised.[2] These alkaloids are important for their widespread occurrence, and because they exhibit a broad range of biological activities, particularly hepatotoxicity.[3] Many of these alkaloids contain (+)-retronecine (1) as the base portion (' necine '). In order to exhibit hepatotoxicity, the necine must contain a 1,2-double bond, and it must also be esterified at C-9.[4] The most toxic pyrrolizidine alkaloids are those in which a necine diol is linked to a diacid to form a macrocyclic dilactone. About 20 of these dilactones are known which contain substituted glutaric acids esterified to (+)-retronecine giving rise to 11-membered macrocycles, as in dicrotaline (2).

Most of the synthetic work in pyrrolizidine alkaloids has been directed towards the necines,[2,5] including retronecine (1).[6] The total synthesis of natural macrocyclic pyrrolizidine dilactones has been the outstanding challenge in this area. The first step in the resolution of this problem was taken by Robins and Sakdarat when they constructed an unnatural 11-membered dilactone with (+)-retronecine.[7] Treatment of 3,3-dimethylglutaric anhydride with (+)-retronecine (1) gave a mixture of the 7- and 9-monoesters of (+)-retronecine. Lactonisation was achieved by the Corey–Nicolaou double activation method using the pyridine-2-thiol esters.[8] The pyrrolizidine alkaloid analogue, 13,13-dimethyl-1,2-dide-



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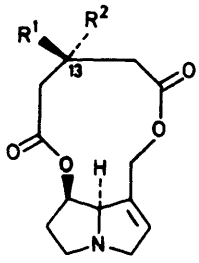
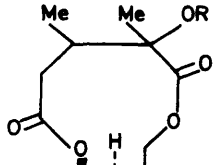
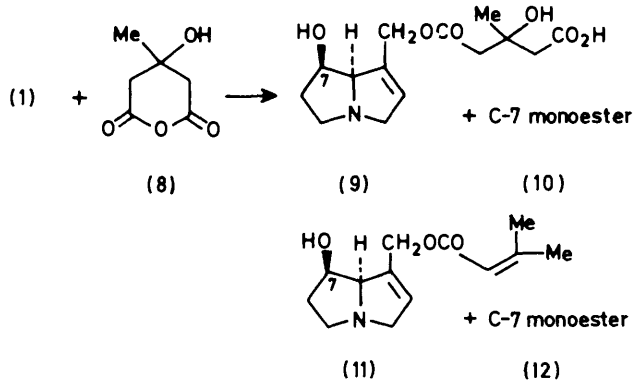


(2) R^1 = OH, R^2 = Me
(3) R^1 = Me, R^2 = OH
(4) R^1 = R^2 = Me
(5) R^1 = OAc, R^2 = Me

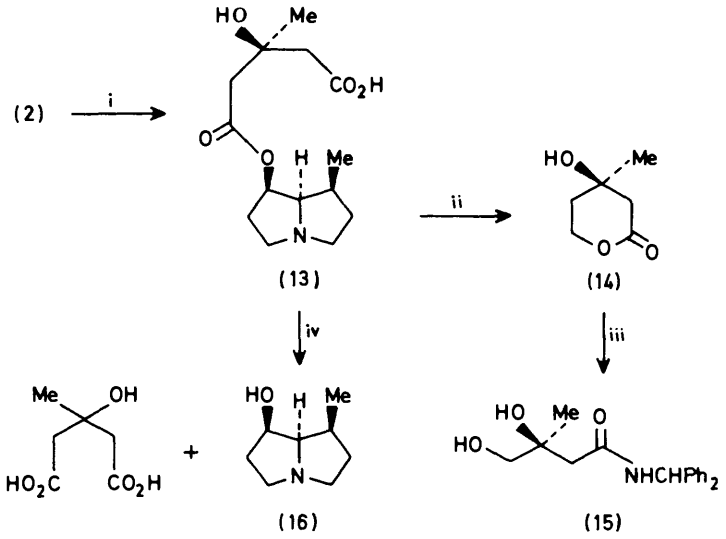




Scheme 1.

dicrotaline (2) was typical for a macrocyclic pyrrolizidine diester. In particular, the ion at *m/z* 136 is characteristic for pyrrolizidine diesters.[3] The key feature in the ^{1}H n.m.r. spectrum of dicrotaline is an AB system due to the non-equivalent protons at C-9. The chemical shift difference between these protons is 1.24 p.p.m. This is the largest value so far observed for an 11-membered macrocyclic diester of (+)-retronecine, but it is the same value as that recorded for the related pyrrolizidine alkaloid analogue (4).[10]

The second component of the cyclisation reaction, obtained in 36% overall yield, R_F 0.61, was identified as (+)-13-*epi*-dicrotaline (3). This material could not be crystallised and was characterised as the hydrochloride salt. The mass spectrum of the epimer (3) was very similar to dicrotaline, while the major difference in the ^{1}H n.m.r. spectrum of (3) was the



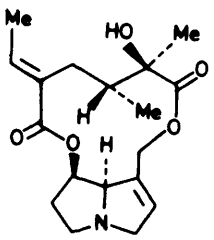
Scheme 2. *Reagents:* i, H_2–PtO_2–AcOH; ii, Na–liq. NH_3; iii, Ph_2CHNH_2; iv, $Ba(OH)_2$

product. The major component of this mixture was separated by preparative t.l.c. (31% yield) and was shown to be a mixture of the diastereoisomeric 9- (11) and 7- (12) senecioate monoesters of (+)-retronecine by the following spectral data. A molecular ion at *m/z* 237 in the mass spectrum indicated the loss of carbon dioxide and water from the starting monoesters [(9) and (10)]. The presence of the α,β-unsaturated ester was apparent from bands at 1 700 and 1 650 cm^{-1} in the i.r. spectrum, and from $\lambda_{max.}$ at 220 nm (ε 10 900) in the u.v. spectrum. The two methyl groups attached to unsaturated carbon were observed in the ^{1}H n.m.r. spectrum at δ 1.90 and 2.18.

The facile decarboxylation and dehydration observed led us to protect the t-hydroxy group in the anhydride (8) by formation of the trimethylsilyl ether. Reaction of the protected anhydride with (+)-retronecine gave the expected mixture of 9- and 7-monoesters, which was cyclised in chloroform using the pyridine-2-thiol esters. The crude products were purified by acid–base recycling, which also removed the trimethylsilyl protecting group. The two main components (75% yield), present in *ca.* equal amounts, were separated by preparative t.l.c. The less polar component, R_F 0.68, obtained in 32% overall yield was shown to be (+)-dicrotaline by comparison with authentic material (undepressed mixed m.p. and almost identical [α], i.r., ^{1}H, and ^{13}C n.m.r., and mass spectra). The fragmentation pattern observed in the mass spectrum of smaller chemical shift difference of 0.98 p.p.m. for the protons at C-9.

In order to establish the absolute configuration at C-13 in (+)-dicrotaline (2) and (+)-13-*epi*-dicrotaline (3), a sequence of two selective reactions was carried out on each epimer to yield optically active samples of mevalonolactone (Scheme 2). Thus, hydrogenolysis of the allylic ester in (+)-dicrotaline (2) gave the retronecanyl ester (13). The structure of this monoester was established by basic hydrolysis of part of the sample to (−)-retronecanol (16) and 3-hydroxy-3-methylglutaric acid. [A comparison sample of (−)-retronecanol was prepared by hydrogenolysis of (+)-retronecine (1).] The retronecanyl ester (13) was reduced with sodium in liquid ammonia or lithium borohydride [15] to give (*R*)-(−)-mevalonolactone (14), characterised as its benzhydrylamide (1,1-diphenylmethylamide) (15).[16] Since both these reducing agents are known to reduce esters in the presence of acids, it follows that the stereochemistry at C-13 in dicrotaline is *S*.

The optical purity of the benzyhydrylamide (15) of (*R*)-(−)-mevalonolactone obtained by degradation of (+)-dicrotaline was shown to be >98% as follows. In its ^{1}H n.m.r. spectrum, the racemic benzhydrylamide of mevalonolactone shows doubling of the signals on addition of the chiral shift reagent Eu(hfc)$_3$. Previous determinations of the optical purity of the benzhydrylamide (15) have utilised the benzhydrylic proton,[17] but we found that on addition of *ca.* 0.1 equivalent of Eu(hfc)$_3$



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the methyl signals of the diastereoisomeric complexes were well separated in the ^{1}H n.m.r. spectrum recorded at 90 MHz. The sample of amide (15) from the degradation of (+)-dicrotaline (2) displayed only one signal in this region of the ^{1}H n.m.r. spectrum at δ 1.82 in the presence of Eu(hfc)$_3$. Addition of 4% of the racemic material (15) and rerunning of the spectrum gave an extra detectable signal at δ 1.88. Thus, the limit of detection of the enantiomeric amide is *ca.* 2%, and no detectable racemisation has occurred during the degradation sequence performed on (+)-dicrotaline (2).

In a similar manner, (+)-13-*epi*-dicrotaline (3) was degraded

Natural (+)-*Dicrotaline* (13β-*Hydroxy*-13α-*methyl*-1,2-*didehydrocrotalanine*) (2).—Finely ground seeds (5 g) of *Crotalaria dura* were extracted repeatedly with methanol until the extracts were colourless. The combined methanol extracts were concentrated, and the residue was dissolved in 2% citric acid (10 ml). The acidic solution was washed with chloroform (4 × 10 ml), and basified with conc. ammonia (2 ml). The basic solution was extracted with chloroform (4 × 10 ml). The chloroform extracts were dried, filtered, and concentrated to a colourless oil, which contained one major component, R_F 0.68. Separation of this component by preparative t.l.c. yielded *dicrotaline* (2) (24 mg, 0.48%) as crystals, m.p. 134—135 °C (CH_3CN); $[\alpha]_D^{18}$ +8.1° (*c.* 1.18 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 690, 3 610, 1 730, 1 445, 1 260, 1 168, and 1 075 cm^{-1}; δ_H (360 MHz) 1.41 (3 H, s, Me), 2.10 (1 H, m, 6-H), 2.19 (1 H, dd, *J* 6 and 14 Hz, 6-H), 2.43 (2 H, ABq, *J* 16 Hz, 12-H$_2$ or 14-H$_2$), 2.56 (1 H, m, 5-H), 2.58 (2 H, ABq, *J* 12 Hz, 12-H$_2$ or 14-H$_2$), 3.31 (1 H, t, *J* 6 Hz, 5-H), 3.43 (1 H, m, 3-H), 3.82 (1 H, brs, OH), 3.92 (1 H, d, *J* 14 Hz, 3-H), 4.18 (1 H, d, *J* 12 Hz, 9-*H*), 4.34 (1 H, brs, 8-H), 4.99 (1 H, brs, 7-H), 5.41 (1 H, d, *J* 12 Hz, 9-H), and 5.92 (1 H, brs, 2-H); δ_C (90 MHz) 29.0 (Me), 34.0 (C-6), 43.8 and 47.1 (C-12 and C-14), 53.4 (C-5), 60.7 (C-9), 62.0 (C-3), 71.0 (C-13), 75.7 and 76.7 (C-7 and C-8), 131.0 (C-2), 132.4 (C-1), and 170.0 and 172.2 p.p.m. (2 ×

the 9- and 7-monoesters [(9) and (10)] of (+)-retronecine (97 mg, 0.325 mmol) in dry dimethylformamide (15 ml) under argon, and the mixture was stirred for 24 h. The resulting solution was diluted with dry dimethylformamide (10 ml), and added over 6 h by syringe to dimethylformamide (15 ml) heated at reflux under argon. Heating at reflux was continued for a further 20 h. The cooled solution was concentrated to an oil, which was dissolved in 1M-H_2SO_4 (10 ml). The acidic solution was washed with chloroform (2 × 10 ml), and basified with conc. ammonia (10 ml). The basic solution was extracted with chloroform (4 × 20 ml). The combined chloroform extracts were dried, filtered, and concentrated to give an oil which contained one major component, R_F 0.3. Purification of this component by preparative t.l.c. gave a mixture of 9- and 7-O-(3-*methylbut*-2-*enoyl*)*retronecine* [(11) and (12)] as an oil (24 mg, 31%); $\lambda_{max.}$ (EtOH) 220 nm (ε 10 900); $\nu_{max.}$ ($CHCl_3$) 3 450, 1 720, 1 700, and 1 650 cm^{-1}; δ_H 1.90 (3 H, s, Me), 2.18 (3 H, s, Me), 1.84—4.4 (complex), 5.70 ($\frac{1}{3}$ H, m, 2-H of C-7 ester), and 5.82 ($\frac{2}{3}$ H, m, 2-H of C-9 ester); *m/z* 237 (M^+), 155, 154, 138, 137, 117, 111, 106, 94, 93, 83, and 80 (Found: M^+, 237.1367. $C_{13}H_{19}NO_3$ requires *M*, 237.1360).

3-*Methyl*-3-*trimethylsilyloxyglutaric Anhydride*.—Solutions of chlorotrimethylsilane (108 mg, 1 mmol) in dry diethyl ether (1 ml) and pyridine (79 mg, 1 mmol) in dry diethyl ether (1 ml) were added to a solution of 3-hydroxy-3-methylglutaric anhydride (8) (144 mg, 1 mmol) in dry diethyl ether (10 ml). The mixture was kept at room temperature for 10 h. The precipitated pyridinium chloride was filtered off, and the filtrate was concentrated to give 3-*methyl*-3-*trimethylsilyloxyglutaric anhydride* in quantitative yield as a colourless oil, $\nu_{max.}$ (film), 1 800, 1 750, 1 250, and 1 070 cm^{-1}; δ_H (C_5D_5N) 0.10 (9 H, s, Me_3Si), 1.32 (3 H, s, Me), and 3.13 (4 H, ABq, *J* 16 Hz, 2 × CH_2) (Found: M^+, 168.0818. $C_9H_{16}OSi$ requires *M*, 216.0813).

7- *and* 9-O-(*Hydrogen* 3-*Methyl*-3-*trimethylsilyloxyglutaryl*)*retronecine*.—Solutions of 3-methyl-3-trimethylsilyloxyglutaric anhydride (216 mg, 1 mmol) in chloroform (5 ml) and (+)-retronecine (1) (155 mg, 1 mmol) in chloroform (5 ml) were mixed and stirred at room temperature for 12 h. The precipitated oil was a 1 : 1 mixture of 7- and 9-O-(*hydrogen* 3-*methyl*-3-*trimethylsilyloxyglutaryl*)*retronecine* (370 mg, 100%); $\nu_{max.}$ (film) 1 737 cm^{-1}; δ (C_5D_5N) 0.1 (9 H, s, Me_3Si), 1.35 (3 H, s, Me), complex signals for retronecine, 4.7 (0.5 H, s, 9-H of C-9 ester), 5.1 (0.5 H, m, 7-H of C-7 ester), and 5.7 (1 H, s, 2-H of C-7 and C-9 esters); *m/z* 371 (M^+), 356, 155, 139, 138, 137, 120, 95, 94, and 80 (Found: M^+, 371.1752. $C_{17}H_{29}NO_6Si$ requires *M*, 371.1756). A small portion of this mixture of monoesters was stirred in methanolic ammonia solution for 4 h. Removal of the solvent gave 7- and 9-*O*-(hydrogen 3-hydroxy-3-methylglutaryl)retronecine [(10) and (9)] with similar spectroscopic and chromatographic properties to the mixture prepared previously.

Dicrotaline (2) *and* 13-*epi*-*Dicrotaline* (3).—A suspension of 7- and 9-*O*-(hydrogen 3-methyl-3-trimethylsilyloxyglutaryl)-retronecine (148 mg, 0.4 mmol) in chloroform (25 ml) was stirred vigorously under argon. After 4 h, triphenylphosphine (262 mg, 1 mmol) and 2,2′-dithiodipyridine (220 mg, 1 mmol) were added to this suspension, and vigorous stirring was continued for 8 h. The resulting homogeneous solution was added dropwise by syringe during 4 h to chloroform (30 ml) heated at reflux under argon. When the addition was complete, heating at reflux was continued for 8 h. The cooled solution was concentrated to a clear red gum which was subjected to acid–base recycling [as described for compounds (11) and (12)] to give an oil, which contained two major components in equal amounts at R_F 0.61 and 0.68. These compounds were separated by preparative t.l.c.

The less polar component was dicrotaline (2) (36 mg, 32%), obtained as crystals, m.p. 134—135 °C (CH_3CN); undepressed mixed m.p. with natural (+)-dicrotaline; $[\alpha]_D^{18}$ +8.0° (*c* 1.0 in $CHCl_3$); i.r., δ_H, δ_C, and mass spectral data were almost identical with natural (+)-dicrotaline (Found: M^+, 281.1238. $C_{14}H_{19}NO_5$ requires *M*, 281.1263). The hydrochloride had m.p. 211—212 °C (decomp.); undepressed mixed m.p. with the hydrochloride of natural (+)-dicrotaline; $[\alpha]_D^{20}$ +25.2° (*c* 0.20 in H_2O) (Found: C, 52.85; H, 6.3; N, 4.65. $C_{14}H_{20}ClNO_5$ requires C, 52.91; H, 6.34; N, 4.41%).

The more polar component of the cyclisation mixture was 13-epi-*dicrotaline* (3), obtained as an oil (41 mg, 36%), $[\alpha]_D^{18}$ +43.3° (*c* 0.72 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 700, 2 915, 2 830, 1 730, 1 600, 1 260, and 1 170 cm^{-1}; δ_H (360 MHz) 1.42 (3 H, s, Me), 2.09 (2 H, complex, 6-H_2), 2.51 (2 H, ABq, *J* 15 Hz, 12-H_2 or 14-H_2), 2.54 (2 H, ABq, *J* 14 Hz, 12-H_2 or 14-H_2), 2.62 (1 H, m, 5-H), 3.34 (1 H, t, *J* 7 Hz, 5-H), 3.44 (1 H, d, *J* 15 Hz, 3-H), 3.94 (1 H, d, *J* 15 Hz, 3-H), 4.20 (1 H, d, *J* 12 Hz, 9-H), 4.40 (1 H, brs, 8-H), 5.15 (1 H, d, *J* 12 Hz, 9-H), 5.35 (1 H, brs, 7-H), and 5.92 (1 H, brs, 2-H); δ_C (90 MHz) 29.4 (Me), 33.8 (C-6), 44.5 and 46.7 (C-12 and C-14), 53.7 (C-5), 59.7 (C-9), 61.7 (C-3), 70.7 (C-13), 74.7 and 77.4 (C-7 and C-8), 131.9 (C-2), 132.5 (C-1), and 169.6 and 172.5 (2 × C=O); *m/z* 281 (M^+), 238, 222, 179, 137, 136, 120, 119, 94, 93, and 80 (Found: M^+, 281.1254. $C_{14}H_{19}NO_5$ requires *M*, 281.1263). The *hydrochloride* had m.p. 158—161 °C (decomp.), $[\alpha]_D^{20}$ +29.6° (*c* 0.1 in H_2O) (Found: C, 53.15; H, 6.45; N, 4.1. $C_{14}H_{20}ClNO_5$ requires C, 52.91; H, 6.34; N, 4.41%).

Assignment of Stereochemistry at C-13 *of Dicrotaline* (2). 7-O-[*Hydrogen* (3S)-3-*Hydroxy*-3-*methylglutaryl*]*retronecanol* (13).—Platinum oxide (5 mg) was added to a solution of (+)-dicrotaline (2) (50 mg, 0.18 mmol) in acetic acid (10 ml), and the mixture was stirred for 24 h under hydrogen. The catalyst was filtered off, and the filtrate was concentrated to give 7-O-[*hydrogen* (3S)-3-*hydroxy*-3-*methylglutaryl*]*retronecanol* (13) as an oil, (51 mg, 100%), $\nu_{max.}$ (film) 3 200 and 1 730 cm^{-1}; δ (CD_3OD) 1.14 (3 H, d, *J* 7 Hz, Me), 1.33 (3 H, s, MeCO), 5.37 (1 H, m, 7-H), plus complex signals for retronecanol; *m/z* 285 (M^+) (Found: M^+, 285.1557. $C_{14}H_{23}NO_5$ requires *M*, 285.1570).

3-*Hydroxy*-3-*methylglutaric Acid and* (−)-*Retronecanol* (16).—A solution of the retronecanyl ester (13) (285 mg, 0.1 mmol) in 1M-barium hydroxide (1 ml) was heated at reflux for 1 h. The cooled solution was diluted with water (4 ml), and solid carbon dioxide was added. Barium carbonate was filtered off and the filtrate was acidified to pH 3 with 1M-hydrochloric acid. The acidic solution was extracted continuously with diethyl ether for 24 h. The ethereal extracts were dried, filtered, and concentrated to yield 3-hydroxy-3-methylglutaric acid as crystals (12 mg, 74%), m.p. 108—109 °C (diethyl ether–light petroleum). This material was identical (i.r., ^1H n.m.r., and undepressed mixed m.p.) with a synthetic sample of 3-hydroxy-3-methylglutaric acid.

The acidic solution (above) was basified with conc. ammonia (1 ml) and continuously extracted with diethyl ether for 3 days. The ether extracts were dried, filtered, and concentrated to give (−)-retronecanol (10 mg, 70%) as crystals, m.p. 95—96 °C (light petroleum) (lit.,[21] m.p. 94 °C); $[\alpha]_D^{20}$ −91° (*c* 1 in EtOH) (Found: C, 68.15; H, 10.8; N, 10.0%. $C_8H_{15}NO$ requires C, 68.04; H, 10.70; N, 9.91%). This sample of (−)-isoretronecanol was identical ([α], i.r., ^1H n.m.r., and mass spectra, undepressed mixed m.p.) with a sample prepared by hydrogenolysis of (+)-retronecine (1).

(R)-*Mevalonolactone* (14).—Liquid ammonia (10 ml) was added to a vigorously stirred solution of 7-O-[hydrogen (3*S*)-3-hydroxy-3-methylglutaryl]retronecanol (13) (28.5 mg, 1 mmol) in methanol (1 ml). A small piece of sodium was suspended in the solution until the mixture was dark blue. The sodium was then removed, and the solvents allowed to evaporate. The residue was dissolved in 1M-hydrochloric acid (10 ml), and the acidic solution was extracted with dichloromethane for 48 h. The organic extracts were dried, filtered, and concentrated to yield (*R*)-mevalonolactone as an oil (10 mg, 76%); $[\alpha]_D^{20}$ −20° (*c* 0.14 in EtOH) (lit.,[22] −23°); δ 1.35 (3 H, s, Me), 1.90 (2 H, m, 4-H_2), 2.45 and 2.70 (2 H, ABq, *J* 18 Hz, 2-H_2), 3.45 (1 H, brs, OH), and 4.47 (2 H, m, 5-H_2). The i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic sample of (+)-mevalonolactone.

Alternative reduction of the retronecanyl ester (13) with lithium borohydride [15] in tetrahydrofuran gave (*R*)-(−)-mevalonolactone (40%).

The benzhydrylamide [16] of (*R*)-mevalonolactone had m.p. 99—100 °C (lit.,[22] m.p. 98—99 °C); $[\alpha]_D^{20}$ −2.7° (*c* 0.5 in EtOH); (lit.,[22] −2.7°); δ 1.30 (3 H, s, Me), 1.60 (2 H, m, CH_2), 2.17 and 2.49 (2 H, ABq, *J* 12 Hz, CH_2), 3.71 (2 H, m, CH_2OH), 6.12 and 6.20 (1 H, 2s, benzylic H, rotamers), and 7.18 (10 7-H), and 5.96 (1 H, brs, 2-H); δ_C 22.5 (CH_3CO), 26.5 (CH_3COH), 34.6 (C-6), 42.3 and 44.6 (C-12 and C-14), 54.3 (C-5), 60.8 (C-3), 62.5 (C-9), 76.1 and 77.7 (C-7 and C-8), 80.3 (C-13), 132.3 (C-2), 134.1 (C-1), 169.6, 170.4, and 171.1 p.p.m. (3 × C=O); *m/z* 323 (M^+), 220, 167, 136, 119, 93, and 83 (Found: M^+, 323.1357. $C_{16}H_{21}NO_6$ requires 323.1368).

(S)-*Mevalonolactone*.—The 13β-acetoxycrotalanine (5) was hydrogenolysed as described above to give 7-*O*-hydrogen [(3*S*)-3-acetoxy-3-methylglutaryl]retronecanol as an oil in quantitative yield. A solution of this monoester (37.1 mg, 0.11 mmol) in tetrahydrofuran (5 ml) was treated with 1M-diborane in tetrahydrofuran (0.25 ml, 0.25 mmol) at 0 °C for 5 min, and 1 h at room temperature. Methanol (0.5 ml) was added and the solution was concentrated. The residue was hydrolysed with barium hydroxide (160 mg, 0.5 mmol) in water (15 ml) for 12 h at room temperature. The solution was acidified with 1M-hydrochloric acid (Congo Red) and extracted continuously with chloroform for 4 days. The chloroform extracts were dried, filtered, and concentrated to give (*S*)-(+)-mevalonolactone as an oil (11.1 mg, 78%). The benzhydrylamide had m.p. 99—100 °C, $[\alpha]_D^{18}$ +2.4° (*c* 0.34 in EtOH). Addition of Eu(hfc)$_3$ gave a small amount of doubled

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