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The synthesis of (−)-*cis*- and (−)-*trans*-crobarbatic acid

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Abstract

The synthesis of both *cis*- and *trans*-crobarbatic acid is reported. The five-step sequence proceeds in high yield and with control of both relative and absolute stereochemistry. The key step in the synthesis is the Birch reductive alkylation of a chiral furoic acid which sets the absolute stereochemistry of the products. The stereochemistry of the compounds described was proven unambiguously by X-ray crystallography on one synthetic intermediate and on *trans*-crobarbatic acid. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The pyrrolizidine alkaloids are widespread in nature and can be found in many different plant species;[1] several of these alkaloids have interesting pharmacological properties such as hepatotoxicity and carcinogenic activity.[1] Pyrrolizidine alkaloids have been implicated in the poisoning of livestock and are thought to be used by both plants and insects as protection against predators.[2] In terms of structure, pyrrolizidine alkaloids consist of two halves, joined through ester linkages. Cleavage of the esters under standard conditions gives a pyrrolidizine diol (known as a necine base) and a diacid (necic acid). In view of the interesting structure and manifold biological activity of these alkaloids, we aim to undertake the synthesis of several of them using a flexible strategy. And, as the parent necine base (retronecine) is common to many of these alkaloids and is available from natural sources,[3] we wish to concentrate on the necic acid moiety.

trans-Crobarbatic acid is the hydrolysis product of the alkaloid crobarbatine and represents the cyclised form of the necic acid of this alkaloid.[4] Although the relative stereochemistry of crobarbatic acid obtained from natural sources is known, the absolute configuration and specific rotation are not;[5] consequently, the

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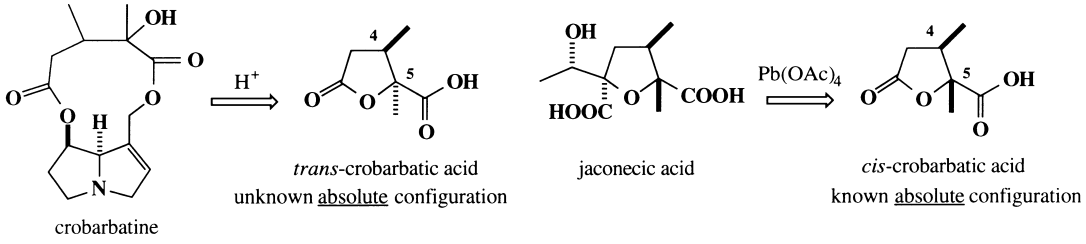
identity of crobarbatine is ambiguous with respect to the necic acid moiety (Scheme 1). The *cis*-isomer of crobarbatic acid was originally isolated from the degradation of jaconecic acid with lead tetraacetate; the absolute stereochemistry of the material thus produced was proven to be as shown.[6]



Scheme 1.

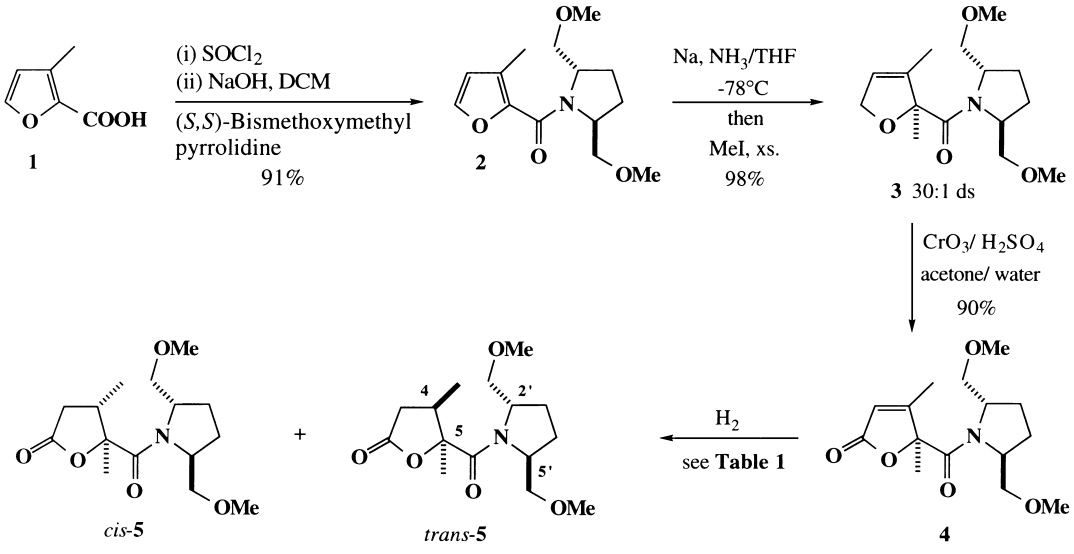
We decided to embark on a synthesis of crobarbatic acid using recently developed methodology involving the Birch reduction of furans.[7] Our route was designed to be short and also to be flexible enough to produce any stereoisomer of the target at will.

2. Results and discussion

The synthesis began with commercially available 3-methyl-2-furoic acid **1** which was coupled to (*S*,*S*)-bis(methoxymethyl)pyrrolidine under standard conditions (Scheme 2). The amide **2** was then subjected to a Birch reductive alkylation reaction (quenching with methyl iodide) under our previously reported conditions. This reaction proceeded in excellent yield and gave **3** with a 30:1 level of diastereoselectivity. The diastereoselectivity of this step was assessed by GC in comparison with an authentic (1:1) mixture of diastereoisomers; we were sure of the relative stereochemistry of the adduct from previous studies. The ^{1}H NMR spectrum of **3** clearly shows a multiplet attributable to one vinyl proton at δ 5.4 and does not contain any resonances pertaining to a furan nucleus at δ 6–7. Allylic oxidation of **3** took place with Jones' reagent to give the lactone **4** in good yield (Scheme 2). The identity of **4** was most clear from IR spectroscopy (C=O at 1765 and 1627 cm^{-1}). The lactone was then hydrogenated with the aim of investigating the stereoselectivity of the process (Table 1).

Reduction with either platinum or rhodium catalysts essentially gave a 1:1 mixture of the two diastereoisomers (Table 1); an increase in pressure did little to alter the ratio. This lack of selectivity was, as expected, based upon steric considerations. Fortunately, the two diastereoisomers were easily separable on a silica column and a reasonable yield of *trans*-**5** (50%) was thus obtained. Changing the metal catalyst to palladium resulted in an immediate shift in the selectivity of the reaction, with *cis*-**5** now being the preferred product. An increase in pressure improved the ratio and enabled the isolation of *cis*-**5** in good (83%) yield. The sense of the diastereoselectivity obtained with palladium is unusual;[8] we presume that the stereoselectivity originates from association between the polar amide group and the metal surface, forming the *cis*-isomer preferentially.[9] The literature contains some examples of polar groups directing heterogeneous hydrogenation with palladium catalysis, although homogeneous catalysis with Crabtree's catalyst [Ir(cod)py(PCy$_3$)]PF$_6$ is more commonly used in conjunction with amide directing groups.[10]

The spectroscopic data obtained from *cis*- and *trans*-**5** clearly showed that reduction of the alkene had occurred, IR of both isomers showed C=O at 1621 and 1785 cm^{-1}, while ^{1}H NMR revealed a (3H) doublet for the C-4 methyl group at δ 1.28 (*cis*) and 1.05 (*trans*). The relative stereochemistry of these two diastereoisomers was assigned by X-ray crystallography (Fig. 1).



Scheme 2.

Table 1
Ratio of *cis*:*trans*-**5** was determined by GC on the crude reaction mixture

Catalyst	H_2 pressure	Ratio (*cis*:*trans*-**5**)	Isolated yield of **5** (%)
PtO_2	1 atm	46:54	46 (*cis*) 46 (*trans*)
5% Rh/C	1 atm	48:52	45 (*cis*) 50 (*trans*)
10% $Pd(OH)_2/C$	1 atm	81:19	—
10% $Pd(OH)_2/C$	55 psi	92:8	83 (*cis*)

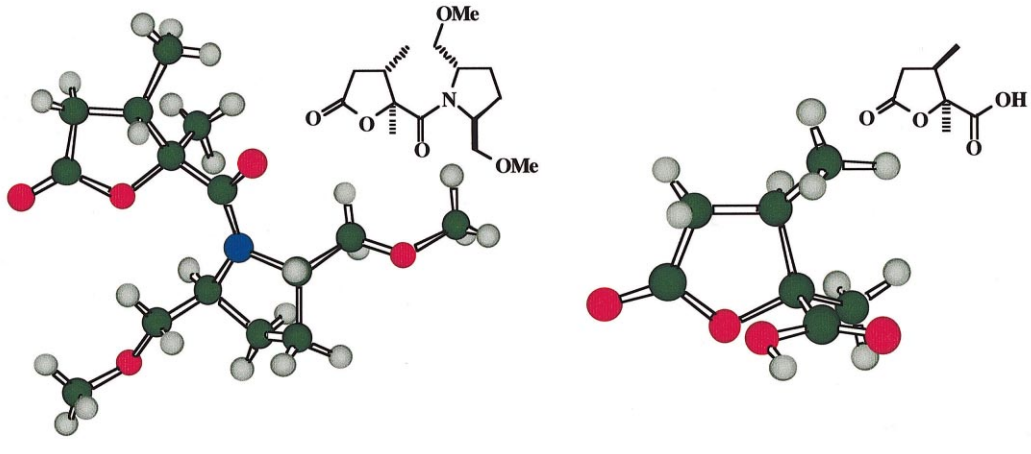
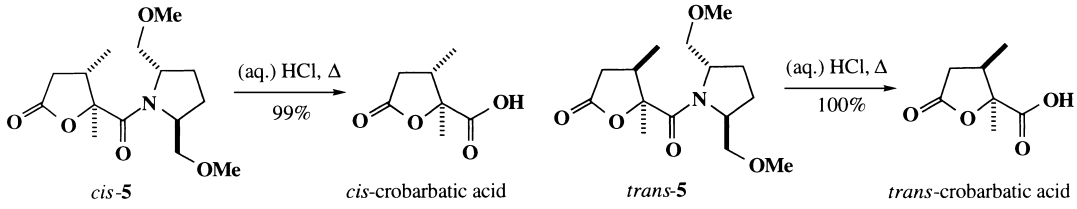


Figure 1. X-Ray crystal structures of *cis*-**5** and *trans*-crobarbatic acid

All that remained to complete the synthesis was removal of the chiral auxiliary. This was accomplished by heating *cis*-**5** and *trans*-**5** (separately) in aqueous acid in a high yielding protocol (Scheme 3). We know that the Birch reduction proceeded with 30:1 stereoselectivity and, as racemisation under this sequence is extremely unlikely,[7] both isomers of crobarbatic acid are formed in ≥94% ee.



Scheme 3.

The structure of *cis*-**5** and *trans*-crobarbatic acid was proven unambiguously by X-ray crystallography (Fig. 1). As we know the absolute stereochemistry of the amine auxiliary used in this sequence, these two structures prove the relative and absolute stereochemistry of all the compounds shown in Schemes 2 and 3.

Although we have prepared the antipode of *cis*-crobarbatic acid, compared to the material originally isolated, the amine auxiliary is commercially available as either enantiomer and so (+)-*cis*-crobarbatic acid could be produced with ease using this sequence.

The *trans*-crobarbatic acid displayed spectroscopic and physical data that was very similar to that reported in the literature.[5] We found that the ^{1}H NMR spectra of the *cis*- and *trans*-acids did not show much distinction between them; however, as the two ^{13}C NMR spectra differed enough, a definite correlation (all peaks within ±0.5 ppm) could be made with our data for the *trans*-acid and that reported by Meinwald.[5]

There has been only one report in the literature that correlates the absolute stereochemistry of *trans*-crobarbatic acid with the sign of its specific rotation: Honda and co-workers prepared the (4*R*,5*S*) enantiomer and reported a specific rotation, $[\alpha]_D$ +3.45 (*c*=0.4 in H_2O).[11] However, we have also prepared the (4*R*,5*S*) enantiomer and found that its rotation, $[\alpha]_D$ −3.7 (*c*=1.4 in H_2O), was of an opposite sign to that reported earlier. It is worth pointing out, however, that arguments based on such small rotations are weak ones and that we did find some variation in rotation of *trans*-crobarbatic acid at varying concentrations {although each rotation measured was always negative, e.g. $[\alpha]_D$ −8.0 (*c*=0.2 in H_2O)}.

To conclude, we have prepared *cis*- and *trans*-crobarbatic acid in five steps with an overall yield of 66% for the *cis*-isomer and 40% for the *trans*-isomer. This chemistry fulfils our objective of being able to prepare any stereoisomer of crobarbatic acid and allows the preparation of substantial quantities of material for further synthetic studies.

3. Experimental

Proton nuclear magnetic resonance spectra (NMR) were recorded on a Bruker AC300/Varian XL300 at 300 MHz. ^{13}C Nuclear magnetic resonance spectra were recorded on an AC300/Varian XL300 at 75 MHz. Spectra were recorded in deuterated chloroform unless otherwise indicated. Peak multiplicities are abbreviated as follows: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m). Chemical shifts are quoted in parts per million (ppm), downfield from Me_4Si. Coupling constants (*J*) are quoted in hertz. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FTIR as evaporated films: points of

maximum absorption (ν_{max}) are recorded. Optical rotations were recorded on an Optical Activity Ltd AA-100 polarimeter and $[\alpha]_D$ values (all reported at 21°C) are given in units of 10^{-1} deg cm^2 g^{-1}; concentration *c* in units of g/100 ml. Mass spectra were recorded on a Kratos Concept or a Fisson VG Trio 2000; chemical ionisation (CI) was performed using NH_3. Gas chromatography (GC) was carried out using a CP-Chirasil DEXCB column (25 m×0.32 mm, 0.28 μ) controlled by a Shimadzu Cromatopac R4AX unit.

All reactions were carried out under an atmosphere of dry nitrogen. All solvents and reagents requiring purification were purified using standard laboratory techniques according to methods published in *Purification of Laboratory Chemicals* by Perrin, Armarego and Perrin, Pergamon Press, 1966. Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as an indicator. Dichloromethane (DCM) was distilled over calcium hydride. Petroleum ether (boiling range 40–60°C) was distilled prior to use. Ammonia was distilled from sodium metal and ferric chloride. (+)-Bis(methoxymethyl)pyrrolidine was purchased from Oxford Asymmetry.

3.1. (2′S,5′S)-2-(Bismethoxymethylpyrrolidinyl)carbonyl-3-methylfuran ***2***

Thionyl chloride (12 ml, xs) was added to **1** (2.39 g, 19.0 mmol) and the resulting dark mixture heated at reflux for 3 h. Excess thionyl chloride was then removed under reduced pressure, azeotroping with toluene. To the brown liquid was added dichloromethane (10 ml), and this solution was then added dropwise to a stirred mixture of (*S*,*S*)-bis(methoxymethyl)pyrrolidine (3.32 g, 21.0 mmol), 2 M aq. sodium hydroxide (40 ml, 80 mmol) and dichloromethane (40 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The dichloromethane was then removed under reduced pressure, and the residue extracted into ethyl acetate (4×75 ml). The combined organics were then dried ($MgSO_4$) and evaporated to dryness under reduced pressure to yield a brown oil. The crude product was purified by column chromatography on silica, eluting with 25% ethyl acetate/petrol to give the title compound as a pale yellow oil (4.6 g, 91%). $[\alpha]_D$ −123.8 (*c*=0.64 in EtOH); found: M^+ 267.1478, $C_{14}H_{21}NO_4$ requires M^+, 267.1471; ν_{max}/cm^{-1} 1617 (C=O); δ_H (300 MHz) 7.25 (1H, d, *J* 1.5, OC*H*=CH), 6.25 (1H, d, *J* 1.5, OCH=C*H*), 4.74–4.64 (1H, m, CONC*H*), 4.48–4.37 (1H, m, CONC*H*), 3.48 (1H, dd, *J* 9.0 and 3.0, $CH_{2A}OCH_3$), 3.35–3.23 (1H, m, $CH_{2B}OCH_3$), 3.26 (3H, s, CH_2OCH_3), 3.12 (3H, s, CH_2OCH_3), 3.04–2.88 (2H, m, CH_2OCH_3), 2.25 (3H, s, C=CCH_3) and 2.20–1.79 (4H, m, CH_2CH_2); δ_C (75 MHz, $CDCl_3$) 159.5, 142.9, 141.5, 128.5, 114.8, 73.7, 71.8, 58.9, 58.8, 57.4, 57.0, 27.3, 23.9 and 11.5; *m/z* (CI) 268 ($M+H^+$, 100%).

3.2. (2S,2′S,5′S)-2-(Bismethoxymethylpyrrolidinyl)carbonyl-2,3-dimethyl-2,5-dihydrofuran ***3***

A solution of **2** (1.0 g, 3.7 mmol) in THF (15 ml) was added to ammonia (200 ml) at −78°C under N_2. Freshly cut sodium (258 mg, 11 mmol) was then added, and the mixture stirred at −78°C for 30 min, during which time the solution became blue. Isoprene was then added dropwise to disperse the blue colour, followed immediately by methyl iodide (700 μl, 11 mmol), which resulted in the yellow solution becoming colourless. After stirring for a further 40 min, the reaction was quenched by the addition of solid ammonium chloride (0.5 g) and the stoppers removed from the reaction flask to allow evaporaton of ammonia. The residual tetrahydrofuran was removed under reduced pressure and the crude product was purified by column chromatography on silica, eluting with 25% ethyl acetate/petrol to afford the title compound as a yellow oil (1.04 g, 98%). $[\alpha]_D$ −107.1 (*c*=2.0 in EtOH); found: $M+H^+$, 284.1853. $C_{15}H_{25}NO_4$ requires $M+H^+$, 284.1862; ν_{max}/cm^{-1} 1621 (C=O); δ_H (300 MHz) 5.48–5.45 (1H, m, C*H*=CCH_3), 4.67 (1H, m, NC*H*), 4.57–4.53 (2H, m, OCH_2CH=C), 4.23 (1H, m, NC*H*), 3.45 (1H,

dd, *J* 9.0 and 3.0, CH_{2A}OCH$_3$), 3.30–3.09 (2H, m, CH_2OCH$_3$), 3.27 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 2.97 (1H, t, *J* 9.0, CH_{2B}OCH$_3$), 2.12–1.74 (7H, m, C=CCH_3, CH_2CH_2) and 1.44 (3H, s, OCCH_3); δ_C (75 MHz) 172.1, 140.9, 120.3, 93.3, 74.0, 73.0, 71.3, 58.7, 58.6, 57.9, 57.6, 27.3, 25.9, 23.3 and 12.7; *m/z* (CI) 284 (M+H$^+$, 100%).

*3.3. (5*S,*2′*S,*5′*S*)-5-(Bismethoxymethylpyrrolidinyl)carbonyl-4,5-dimethyl-5*H*-furan-2-one **4***

To a solution of **3** (500 mg, 1.76 mmol) in acetone (10 ml) at room temperature, was added chromium dioxide (2 M in 2 M aq. sulfuric acid, 2.7 ml, 5.3 mmol) and the brown solution was stirred at room temperature overnight. Acetone was then removed under reduced pressure and the residue dissolved in ethyl acetate (50 ml), and washed with 2 M aq. hydrochloric acid (5 ml) then 5% aq. sodium bicarbonate (5 ml) then evaporated under reduced pressure. The crude bright orange material was purified by column chromatography on silica, eluting with 30% ethyl acetate/petrol to give the title compound as a colourless oil (470 mg, 90%). $[\alpha]_D$ −176.0 (*c*=1.89 in EtOH); found: M+H$^+$, 298.1663, $C_{15}H_{23}NO_5$ requires M+H$^+$, 298.1654; ν_{max}/cm^{-1} 1765 (C=O) and 1627 (C=O); δ_H (300 MHz) 5.84 (1H, m, *J* 1.5, C*H*=CCH$_3$), 4.83 (1H, m, NC*H*), 4.38–4.28 (1H, m, NC*H*), 3.51 (1H, dd, *J* 9.0 and 2.5, CH_{2A}OCH$_3$), 3.37 (3H, s, CH$_2$OCH_3), 3.23 (3H, s, CH$_2$OCH_3), 3.44–3.12 (2H, m, CH_2OCH$_3$), 3.00 (1H, m, CH_{2B}OCH$_3$), 2.29 (3H, d, *J* 1.5, CH=CCH_3), 2.28–1.80 (4H, m, CH_2CH_2) and 1.74 (3H, s, OCCH_3); δ_C (75 MHz) 171.6, 171.3, 168.3, 116.1, 90.0, 73.9, 71.4, 58.9, 58.5, 58.4, 57.6, 27.2, 26.6, 24.0, 14.8; *m/z* (CI) 298 (M+H$^+$, 100%).

*3.4. (4*S,*5*S,*2′*S,*5′*S*)-5-(Bismethoxymethylpyrrolidinyl)carbonyl-4,5-dimethyldihydrofuran-2-one* cis-***5*** *and (4*R,*5*S,*2′*S,*5′*S*)-5-(bismethoxymethylpyrrolidinyl)carbonyl-4,5-dimethyldihydrofuran-2-one* trans-***5***

Compound **4** (490 mg, 1.6 mmol) and rhodium (5% on carbon, 50 mg) were stirred in ethanol (40 ml) and acetic acid (5 ml) under 1 atm of hydrogen overnight. The catalyst was removed by filtration through Celite, and the solution evaporated to dryness under reduced pressure to give the crude product as a yellow oil. Column purification on silica, eluting with 20% ethyl acetate/petrol afforded the two diastereoisomers, (−)-*cis*-**5**: 223 mg (45%) and (−)-*trans*-**5**: 246 mg (50%), both as colourless oils.

Compound (−)-*cis*-**5** crystallised on standing at −10°C: $[\alpha]_D$ −38.4 (*c*=1.8 in EtOH); found: C, 60.30; H, 8.46; N, 4.54%, $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%. Found M+H$^+$, 300.1813, $C_{15}H_{25}NO_5$ requires M+H$^+$, 300.1811; ν_{max}/cm^{-1} 1784 (C=O) and 1621 (C=O); δ_H (300 MHz) 4.73 (1H, m, NC*H*), 4.30 (1H, m, NC*H*), 3.51 (1H, dd, *J* 9.0 and 2.5, CH_{2A}OCH$_3$), 3.43–3.24 (8H, m, CH_2OCH$_3$ and 2×CH$_2$OCH_3), 3.22–3.14 (1H, m, CH_{2B}OCH$_3$), 3.12–2.98 (1H, m, CH$_2$C*H*CH$_3$), 2.62 (1H, dd, *J* 17.5, 9.0, COCH_{2A}), 2.20 (1H, dd, *J* 17.5 and 10.0, COCH_B), 2.27–1.78 (4H, m, CH_2CH_2), 1.50 (3H, s, OC(CH_3)) and 1.28 (3H, d, *J* 7.0, CHCH_3); δ_C (75 MHz) 174.8, 172.4, 88.4, 74.5, 71.3, 58.8, 58.7, 58.2, 57.4, 36.6, 35.6, 27.4, 24.2, 21.5 and 15.7; *m/z* (CI) 300 (M+H$^+$, 100%).

Compound (−)-*trans*-**5**: $[\alpha]_D$ −64.9 (*c*=0.8 in EtOH); found: M+H$^+$, 300.1811, $C_{15}H_{25}NO_5$ requires M+H$^+$, 300.1811; ν_{max}/cm^{-1} 2976 (C–H), 1785 (C=O) and 1621 (C=O); δ_H (300 MHz) 4.51 (1H, m, NC*H*), 4.24 (1H, m, NC*H*), 3.47 (1H, dd, *J* 9.0 and 2.5, CH_{2A}OCH$_3$), 3.38–3.14 (9H, m, CH_{2B}OCH$_3$, CH_2OCH$_3$ and 2×CH$_2$OCH_3), 2.81 (1H, dd, *J* 17.5 and 8.0, COCH_{2B}), 2.69–2.57 (1H, m, C*H*CH$_3$), 2.13 (1H, d, *J* 17.5, COCH_{2A}), 2.08–1.74 (4H, m, CH_2CH_2), 1.54 (3H, s, OCCH_3) and 1.05 (3H, d, *J* 7.0, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 175.1, 169.5, 89.5, 74.9, 71.0, 58.7, 57.2, 38.4, 35.8, 27.3, 27.0, 24.0 and 17.3; *m/z* (CI) 300 (M+H$^+$, 100%).

Compound **4** (446 mg, 1.5 mmol) was dissolved in ethanol (10 ml) and acetic acid (1 ml) and 10% palladium hydroxide (50 mg) was added. The mixture was shaken at 55 psi of hydrogen overnight, and

the catalyst was filtered off through Celite. The solvent was removed under reduced pressure to give the crude product as an orange oil. Column purification on silica, eluting with 20% ethyl acetate/petrol afforded (−)-*cis*-**5** as a colourless oil (372 mg, 83%).

3.5. *(4*S,*5*S*)*-cis-*Crobarbatic acid*

Compound (−)-*cis*-**5** (125 mg, 0.42 mmol) was heated at reflux for 4 h in 6 M aq. hydrochloric acid (2 ml). The reaction mixture was extracted into ethyl acetate (4×25 ml) and the combined organics dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the crude product as a white solid. Recrystallisation from dichloromethane/petrol afforded colourless crystals (65 mg, 99%). M.p. 65–66.5°C [lit.[6b] 65–67°C (racemic)]; $[\alpha]_D$ −2.81 (*c*=1.78 in H_2O), found: M+NH_4^+ 176.0920, $C_7H_{10}O_4$ requires M+NH_4^+, 176.0922; ν_{max}/cm^{-1} 3497 (br, OH), 2979 (C–H), 1783, 1756 (C=O); δ_H (300 MHz) 9.05 (1H, brs, CO_2H), 2.85–2.70 (2H, m, CH_2), 2.24 (1H, m, $CHCH_3$), 1.53 (3H, s, $OCCH_3$), 1.15 (3H, d, *J* 7.0, CCH_3); δ_H (300 MHz, D_2O) 2.80–2.68 (2H, m, CH_2), 2.33 (1H, m, $CHCH_3$), 1.43 (3H, s, CCH_3), 1.05 (3H, d, *J* 6.5, $CHCH_3$); δ_C (75 MHz, $CDCl_3$) 176.5, 175.4, 85.9, 36.7, 36.0, 17.9, 14.9; δ_C (75 MHz, D_2O) 179.1, 175.6, 87.8, 36.5, 35.5, 17.2, 13.7; *m/z* (CI) 113 (M−CO_2H^+, 100%); *m/z* (EI) 176 (M+NH_4^+, 100%).

3.6. *(4*R,*5*S*)*-trans-*Crobarbatic acid*

Compound (−)-*trans*-**5** (350 mg, 1.17 mmol) was heated at reflux for 4 h in 6 M aq. hydrochloric acid (4 ml). The reaction mixture was extracted into ethyl acetate (4×30 ml) and the combined organics dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the title compound as pale pink crystals (185 mg, 100%). M.p. 170–180°C (lit.[6b] 181.5–183°C, (+)-enantiomorph); $[\alpha]_D$ −8.0 (*c*=0.2 in H_2O, 22°C); $[\alpha]_D$ −3.7 (*c*=1.4 in H_2O) (lit.[11] $[\alpha]_D$ +3.45 (*c*=0.4 in H_2O); found: M+NH_4^+ 176.0923, $C_7H_{10}O_4$ requires M+NH_4^+ 176.0923; ν_{max}/cm^{-1} 3531 (br, OH), 2972, 2940 (C–H), 1783, 1765 (C=O) δ_H (300 MHz) 7.80 (1H, brs, CO_2H), 2.66–2.35 (3H, m, $COCH_2CH$), 1.56 (3H, s, $OCCH_3$), 1.07 (3H, d, *J* 6.0, $CHCH_3$); δ_H (300 MHz, D_2O) 2.71 (1H, dd, *J* 17.5 and 8.0, $COCH_{2A}CCH_3$), 2.62–2.47 (1H, m, CH_2CHCH_3), 2.33 (1H, dd, *J* 17.5 and 10.0, $COCH_{2B}CCH_3$), 1.51 (3H, s, $OCCH_3$) and 0.96 (3H, d, *J* 7.0, $CHCH_3$); δ_C (75 MHz) 175.8, 172.9, 87.2, 40.6, 35.8, 21.8, 14.3; δ_C (75 MHz, D_2O)[5] 179.9, 174.0, 89.1, 39.5, 35.5, 21.0 and 13.7; *m/z* (CI) 176 (M+NH_4^+, 100%).

Acknowledgements

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