Bakers' Yeast Reductions of β-Oxopyrrolidinecarboxylates: Synthesis of (+)-*cis*-(2*R*,3*S*)-3-Hydroxyproline and (−)-(1*S*,5*S*)-Geissman–Waiss Lactone, a Useful Precursor to Pyrrolizidine Alkaloids

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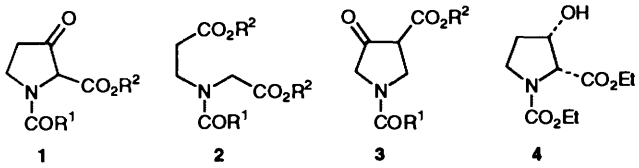
Bakers' yeast reduction of the β-oxo proline derivative **5** leads to the *cis*-hydroxy ester **6** and thence to (+)-*cis*-(2*R*,3*S*)-3-hydroxyproline **7**, with >90% enantiomeric enrichment. Subsequent one-carbon homologation leads to the (−)-Geissman–Waiss lactone **8**, a useful precursor of pyrrolizidine alkaloids.

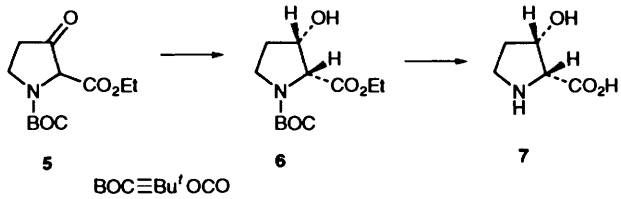
During attempts to apply the Ireland enolate Claisen technology, used in our recent synthesis of (−)-α-kainic acid,[1] to the synthesis of pyrrolizidine alkaloids, we required access to supplies of a homochiral *cis*-3-hydroxyproline. To our surprise, examination of the literature revealed that a practical approach to such a potentially useful compound had not been reported. The only previous asymmetric syntheses [of *cis*-(2*S*,3*R*)- and *trans*-(2*S*,3*S*)-3-hydroxy-L-proline] employed rather small-scale biological methodology, in which the key step was a kinetic enzymic resolution using an aminopeptidase.[2] Both of the above-mentioned prolines occur naturally as components of the antibiotic peptide telomycin, the *trans*-(2*S*,3*S*) isomer also being present in collagen obtained from a sponge.[2] We were attracted by the possibility of using yeast reductions of 3-oxoproline derivatives as a method to access chiral hydroxyprolines. This methodology, although known for many years, has only come to prominence during the past decade or so.[3] Significantly, yeast reductions of both 2-alkoxycarbonylcycloakanones[4] and of 4-oxotetrahydrothiopyran-3-carboxylates[5] have recently been reported to produce the corresponding hydroxy esters with excellent enantiomeric enrichments in both cases. Fortunately, the oxoesters **1** required for our studies are readily available in quantity from various types of Dieckmann cyclisations.[6] We found the original Rapoport route[6a] to be the most convenient even though, under 'aprotic' conditions (Bu^{t}OK, toluene), a 1:1 mixture of the desired regioisomers **1** and the alternative 4-oxo 3-carboxylates **3** are produced from the acyclic precursors **2**. Fortunately, the undesired isomers **3** can be easily separated by extraction into aqueous pH 9.5 buffer.[6a] A more recent approach involving a carbenoid insertion reaction as the key step, while successful, proved less convenient in our hands.[7]



1 **2** **3** **4**

Our first reductions were carried out using the diethyl ester **1** (R^1 = OEt, R^2 = Et) and commercially available dried bakers' yeast. Using a well-established procedure,[8] the reduction afforded a 3-hydroxyproline derivative **4**, but in only 30% isolated yield. Simple solvent extraction gave an essentially pure product which was fortunate as the material proved to be rather sensitive to chromatographic purification. ^{13}C NMR spectroscopy showed it to be a single diastereoisomer and ^1H NMR spectral data suggested it was the *cis* isomer **4** (or its enantiomer), as $J_{2,3}$ was *ca.* 7 Hz. The corresponding *trans* isomer would be expected to show $J_{2,3}$ *ca.* 1.5 Hz.[9] In addition, the ^1H and ^{19}F NMR data of a Mosher's ester derivative (see Experimental section) of the hydroxy ester **4** suggested it to be optically pure, although this has not been proven by comparisons with spectra data of the corresponding racemate. All the foregoing spectra were complicated by the presence of atropisomers but fortunately these did not prevent the relevant assignments from being made and thus establishing the potential of this reduction method. In this particular example, a ^{19}F NMR spectrum of the Mosher derivative obtained in [$^2H_6$]-DMSO at 340 K showed only a single resonance for the trifluoromethyl group. The absolute configuration of the hydroxy ester **4** has not been proven although it probably has the 2*R*,3*S* stereochemistry shown in view of the similarity of the optical rotation value {[α]$_D$ +22.7 (*c* 1.49, CH_2Cl_2)} to that of the corresponding *N*-BOC derivative (*vide infra*).

In view of the rather poor yield obtained from this reduction and the anticipated problems in removing the *N*-ethoxycarbonyl function, we next examined similar reactions of other oxo esters **1**, containing alternative nitrogen protecting groups. We were pleased to find that the corresponding *N*-*tert*-butoxycarbonyl (BOC) derivative **5**, prepared by the same Dieckmann method,[6a] was reduced much more efficiently to give the 3-hydroxyproline derivative **6** in *ca.* 75% yield, again as a single



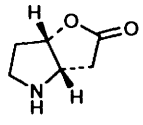
5 **6** **7**

BOC≡Bu^{t}OCO

diastereoisomer {[α]$_D$ +18.2 (*c* 1.45, CH_2Cl_2)} according to ^{13}C NMR data. Both ^1H and ^{19}F NMR spectra of the derived Mosher's ester indicated an enantiomer excess of *ca.* 90% although all of these spectra were complicated by the presence of atropisomers which, for example, prevented an accurate determination of the $J_{2,3}$ coupling constant. An approximate value of 5–6 Hz did, however, indicate that once again, a *cis* enantiomer had been obtained.[9] Both the relative and absolute configurations of the initial reduction product **6** were determined by conversion into the 3-hydroxyproline **7**. Thus, removal of the *N*-BOC group (TFA–CH_2Cl_2) followed by base hydrolysis and ion-exchange chromatography gave a sample of 3-hydroxyproline **7** which clearly had the 2*R*,3*S* absolute configuration shown. The $J_{2,3}$ value in the proton NMR spectrum was 4.0 Hz, consistent with the *cis* stereochemistry

(the corresponding *trans* enantiomers would show $J_{2,3}$ = 1.0 Hz)[9] as was the melting point [240–252 °C (decomp.); lit.,[2c] m.p. 245–255 °C (decomp.), the *trans* isomer shows m.p. 228–235 °C (decomp.)].[2c] Finally, the optical rotation {$[\alpha]_D$ = +85.2 (*c* 1.25, H_2O)} confirmed the absolute configuration as 2*R*,3*S* as the enantiomeric *cis*-(2*S*,3*R*)-3-hydroxy-L-proline is reported to have $[\alpha]_D$ −91.5 ± 1.5 (*c* 0.61, H_2O),[2a] −99 ± 10.0 (*c* 0.2, H_2O)[2b] and −90.3 (*c* 1.0, H_2O).[2c] The corresponding *trans*-(2*S*,3*S*) enantiomer is reported to show $[\alpha]_D$ values between −15.3 and −22.8 under similar conditions.[2] These data suggest a final enantiomeric enrichment of 93% in the hydroxyproline **7**.

The availability of 3-hydroxyproline **7** from this relatively short procedure suggests that it could become a valuable member of the chiral pool in this area. We have illustrated this possibility by a synthesis of the lactone **8**, the (−)-(1*S*,5*S*) enantiomer. Originally the racemate was used as a key intermediate in a synthesis of the natural pyrrolizidine retronecine **9**.[10] This lactone has proven popular as a precursor



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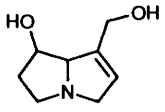

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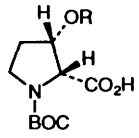
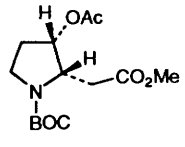


10a R = H
b R = Ac

of many other natural pyrrolizidines,[11] so much so that it is now often referred to as the Geissman–Waiss lactone and has been the subject of a number of synthetic studies aimed at preparing homochiral material.[12] Usually these routes have been designed to produce the (+)-(1*R*,5*R*) enantiomer of lactone **8** as this has the configuration which corresponds to most of the natural alkaloids. Therefore, our preparation of (−)-**8** would allow the synthesis of the non-natural enantiomers of these alkaloids for biological evaluation.

The elaboration of (−)-lactone **8** proceeded in a relatively straightforward manner. Saponification of the initial yeast reduction product afforded, in good yield, the hydroxy acid **10a** which was partly protected as the corresponding acetate **10b**. Subsequent Arndt–Eistert homologation *via* the corresponding acid chloride then led to the acetoxy ester **11**. Attempts to



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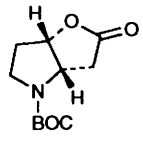

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effect homologation using mixed anhydride intermediates proved unsuccessful as did saponification of the 3-*O*-triisopropylsilyl derivative of the initial reduction product **6**. In both cases, the lack of reactivity is probably due to steric crowding. Finally, the acetoxy ester **11** was treated with methanolic potassium carbonate which was expected to lead to the desired lactone. However, TLC monitoring indicated that, under these conditions, lactone formation was rapidly followed by conversion into the corresponding hydroxy acid. Fortunately, brief exposure of this material to a catalytic amount of toluene-*p*-sulfonic acid in dichloromethane led to the lactone **12**. Alternatively, a final acidification using 3 mol dm^{-3} hydrochloric acid effected both lactonisation and removal of the *N*-BOC group to leave (−)-**8** as its hydrochloride salt. This proved to be identical in all respects, except for the sign of the optical rotation, to (+)-lactone **8**, thereby confirming the assignment of absolute configuration to the reduction product **6**.

Further efforts to exploit the availability of (+)-3-hydroxyproline **7** and its derivatives are in progress. Since this work was first reported,[13] two other groups have illustrated the utility of 3-hydroxyproline **7** in this area during syntheses of (+)-castanospermine[14] and (1*S*,8a*S*)-1-hydroxyindolizidine.[15] In both cases, improvements to the foregoing method of reduction were reported by using an alternative yeast (*Dipodascus sp.*)[14] or bakers' yeast immobilised on calcium alginate[15] respectively.

Experimental

General Details. See ref. 1. *J* Values are given in Hz. $[\alpha]_D$ values are recorded in 10^{-1} deg cm^2 g^{-1}.

Diethyl (+)-3-*Hydroxypyrrolidine*-1,2-*dicarboxylate* **4**.—To the 3-oxopyrrolidinecarboxylate **1** (R^1 = OEt, R^2 = Et) (1.4 g, 6.1 mmol) was added tap water (110 cm^3), sucrose (21 g) and dried bakers' yeast (14 g). The resulting mixture was gently stirred at 30 °C for 24 h and then cooled. Celite (6 g) was added to the resulting mixture which was stirred for 5 min and then filtered. The solid was washed thoroughly with water and the combined filtrates were saturated with sodium chloride and then extracted with diethyl ether (5 × 30 cm^3). The combined extracts were washed with water (2 × 30 cm^3), dried and evaporated to leave the *hydroxy ester* **4** (0.44 g, 31%) as a colourless oil, $[\alpha]_D^{27}$ +22.7 (*c* 1.49, CH_2Cl_2); ν_{max}/cm^{-1} 3430, 1740 and 1708; δ_H 1.30 (6 H, t, *J* 7, 2 × *Me*), 1.95–2.23 (2 H, m, 4-CH_2), 2.81–3.10 (1 H, br s, O*H*), 3.38–3.89 (2 H, m, 5-CH_2), 4.01–4.35 (4 H, m, 2 × OCH_2), 4.43 (1 H, d, *J* 7, 2-C*H*) and 4.67 (1 H, app q, *J* 7, 3-C*H*); δ_C 14.24 (OCH_2CH_3), 14.61 (OCH_2CH_3), 31.9–33.0 (br, 4-CH_2), 44.25 (5-CH_2), 61.21 (OCH_2), 61.46 (OCH_2), 63.78 (2-CH), 71.3–72.6 (br, 3-CH), *ca.* 155.1 (br, CON) and 170.15 (CO_2); *m*/*z* 231 (M^+, 15%, $C_{10}H_{17}NO_5$), 158 (100, $C_7H_{12}NO_3$, M − CO_2Et), 130 (16, $C_5H_8NO_3$), 114 (27, $C_6H_{12}NO$), 86 (89, C_4H_8NO) and 68 (25, C_4H_6N) (Found: M^+, 231.1103. $C_{10}H_{17}NO_5$ requires *M*, 231.1107).

Diethyl 3-[(R)-*Methoxy*(*trifluoromethyl*)*phenylacetoxy*]*pyrrolidine*-1,2-*dicarboxylate*.—To a solution of the foregoing hydroxy ester **4** (0.035 g, 0.15 mmol) in dry tetrachloromethane (0.2 cm^3) and dry pyridine (0.2 cm^3) was added (*R*)-(+)-methoxy(trifluoromethyl)phenylacetyl chloride, prepared by refluxing the corresponding carboxylic acid (0.07 g, 0.3 mmol) with an excess of thionyl chloride (2 cm^3) for 5 h followed by evaporation.[16] The mixture was left at ambient temperature for 16 h and then diluted with water (1 cm^3) and diethyl ether (15 cm^3). The separated diethyl ether solution was washed with 1 mol dm^{-3} aqueous hydrochloric acid (5 cm^3), saturated aqueous sodium hydrogencarbonate (5 cm^3) and water (5 cm^3) and then dried and evaporated. Chromatography of the residue over silica gel eluted with 50% chloroform in light petroleum gave the *Mosher ester* (0.064 g, 95%) as a colourless oil; ν_{max}/cm^{-1} 1758 and 1710; δ_H(400 MHz) 1.08–1.15 (3 H, m, $CHCO_2$-CH_2CH_3), 1.19 (1.7 H, t, *J* 7.1, $NCO_2CH_2CH_3$), 1.27 (1.3 H, t, *J* 7.1, $NCO_2CH_2CH_3$), 2.17–2.36 (2 H, m, 4-CH_2), 3.52 (3 H, s, O*Me*), 3.62–3.69 (2 H, m, 5-CH_2), 3.71–3.81 (1 H, m), 3.96–4.19 (3 H, m), 4.59 (0.57 H, d, *J* 7.0, 2-*H*), 4.63 (0.43 H, d, *J* 7.0, 2′-*H*), 5.66 (1 H, dt, *J* 6.6 and 6.1, 3-*H*), 7.38–7.42 (3 H, m) and 7.48–7.53 (2 H, m); δ_F[$CDCl_3$; 297 K; $CFCl_3$ ghost ref. (0 ppm)] −72.2 (1.7 F) and −72.26 (1.3 F), δ_F[$^2H_6$]DMSO; 340 K; $CFCl_3$ ghost ref. (0 ppm)] −71.28 (CF_3); *m*/*z* 447 (M^+, 1%, $C_{20}H_{24}F_3NO_7$), 374 (100, $C_{17}H_{19}F_3NO_5$, M − CO_2Et), 302 (11, $C_{14}H_{15}F_3NO_3$, M − 2 × CO_2Et), 189 (47, $C_9H_8F_3O$),

105 (11, C_7H_5O) and 68 (65, C_4H_6N) (Found: M^+, 447.1511. $C_{20}H_{24}F_3NO_7$ requires *M*, 447.1505).

3-tert-*Butyl* 1,6-*Diethyl* 3-*Azahexane*-1,4,6-*tricarboxylate* **2** (R^1 = OBu^t; R^2 = Et).—To a stirred solution of di-*tert*-butyl dicarbonate (9.6 g, 44 mmol) in dry dichloromethane (33 cm^3) was added a solution of diethyl 3-azahexane-1,6-dicarboxylate (8.13 g, 40 mmol) and dry triethylamine (5.75 cm^3) in dry dichloromethane (20 cm^3) during 10 min. The resulting solution was stirred at ambient temperature for 2 h, after which time evolution of carbon dioxide had ceased. The solution was washed with 2 mol dm^{-3} aqueous hydrochloric acid (3 × 25 cm^3) and water (25 cm^3) and then dried and evaporated under reduced pressure to leave the title *carbamate* **2** (R^1 = OBu^t; R^2 = Et) (11.9 g, 98%) as a colourless oil, ν_{max}/cm^{-1} 1746 and 1708; δ_H 1.24 (3 H, t, *J* 7, CH_2CH_3), 1.25 (3 H, t, *J* 7, CH_2CH_3), 1.41 and 1.47 [9 H, 2 × s, $C(CH_3)_3$], 2.60 (2 H, t, *J* 7, NCH_2CH_2), 3.53 (2 H, t, *J* 7, NCH_2CH_2), and 3.86–4.30 (6 H, m, 2 × CH_2CH_3 and NCH_2CO_2); *m*/*z* 247 (7%, $C_{10}H_{17}NO_6$, M − C_4H_8), 202 (13, $C_9H_{16}NO_4$, M − BOC), 130 (84, $C_6H_{12}NO_2$), 116 (34, $C_5H_{10}NO_2$), 102 (11, $C_4H_8NO_2$), 84 (34, C_4H_6NO) and 57 (100, C_4H_9) (Found: M^+ − C_4H_8, 247.1058. $C_{10}H_{17}NO_6$ requires 247.1056).

1-*Butyl* 3-*Ethyl* 4-*Oxopyrrolidine*-1,3-*dicarboxylate and* 1-tert-*Butyl* 2-*Ethyl* 3-*Oxopyrrolidine*-1,2-*dicarboxylate* **5**.—To a stirred solution of potassium *tert*-butoxide (5.81 g, 51.8 mmol) in dry toluene (120 cm^3), maintained at 0 °C under dry nitrogen, was added a solution of the foregoing diester **2** (R^1 = OBu^t; R^2 = Et) (11.04 g, 36.4 mmol) in dry toluene (20 cm^3) during 10 min. The solution was stirred for 0.5 h at 0 °C and then quenched with glacial acetic acid (4 cm^3) and a solution of sodium dihydrogen phosphate (22.6 g) in ice-cold water (200 cm^3). The resulting mixture was extracted with chloroform (2 × 150 cm^3) and the combined organic extracts were washed with pH 7 phosphate buffer (2 × 20 cm^3), dried and evaporated to give the two isomers. This mixture was dissolved in toluene (250 cm^3) and the resulting solution extracted with pH 9.5 carbonate buffer (10 × 125 cm^3). The aqueous extracts were brought to pH 3 with concentrated phosphoric acid and extracted with chloroform (5 × 100 cm^3); the combined extracts were dried and evaporated to give the 1,3-*diester* (4.0 g, 43%) as a yellow oil. The toluene fraction was washed with water (20 cm^3), dried and evaporated to give the 1,2-diester **5** (4.2 g, 45%) as a colourless oil; ν_{max}/cm^{-1} 1771, 1745 and 1709; δ_H 1.31 (3 H, t, *J* 7, CH_2CH_3), 1.49 [9 H, s, $C(CH_3)_3$], 2.71 (2 H, t, *J* 7, 4-*H*), 3.69–3.97 (2 H, m, 5-H), 4.28 (2 H, q, *J* 7, CH_2CH_3) and 4.51 (1 H, s, 2-H); *m*/*z* 257 (M^+, 2%, $C_{12}H_{19}NO_5$), 201 (33, $C_8H_{11}NO_5$, M − C_4H_8), 156 (12, $C_6H_6NO_4$), 129 (10, $C_6H_{11}NO_2$), 128 (11, $C_5H_6NO_3$), 116 (11, $C_5H_{10}NO_2$), 100 (12, $C_4H_6NO_2$), 84 (53, C_4H_6NO) and 57 (100, C_4H_9) (Found: M^+, 257.1267. $C_{12}H_{19}NO_5$ requires *M*, 257.1263).

1-tert-*Butyl* 2-*Ethyl* 3-*Hydroxypyrrolidine*-1,2-*dicarboxylate* **6**.—To the foregoing 3-oxopyrrolidine **5** (2.0 g, 7.8 mmol) was added tap water (160 cm^3), sucrose (30 g) and dried bakers' yeast (20 g) and the resulting mixture stirred at 30 °C for 24 h. Celite was added to the mixture which was then filtered and the solid washed with water (20 cm^3); the filtrates were then saturated with sodium chloride and extracted with ether (5 × 100 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried and evaporated to give the *hydroxy ester* **6** (1.51 g, 75%) as a colourless oil, $[\alpha]_D^{27}$ +18.2 (*c* 1.45, CH_2Cl_2), ν_{max}/cm^{-1} 3460, 1734 and 1680; δ_H 1.28 (3 H, t, *J* 7, CH_2CH_3), 1.44 [9 H, s, $C(CH_3)_3$], 1.90–2.19 (2 H, m, 4-H), 3.25–3.81 (3 H, m, 5-H and OH), 4.22 (2 H, q, 7, CH_2CH_3), 4.30–4.44 (1 H, m, 2-H) and 4.46–4.72 (1 H, m, 3-H); δ_C 14.21 and 14.34 (CH_2CH_3), 28.29 and 28.39 [$C(CH_3)_3$], 32.18 and 32.76 (C-4), 43.85 and 44.29 (C-5), 61.16 (CH_2CH_3), 63.47 and 64.00 (C-2), 71.44 and 72.36 (C-3), 80.14 and 80.28 [$C(CH_3)_3$], 153.96 and 154.40 (NCO_2), and 170.45 and 170.61 (CCO_2), *m*/*z* 259 (M^+, < 1%, $C_{12}H_{21}NO_5$), 186 (11, $C_9H_{16}NO_3$, M − CO_2Et), 158 (10, $C_7H_{12}NO_3$, M − BOC), 130 (36, $C_5H_8NO_3$), 88 (96, C_4H_8NO, M − CO_2Et, BOC) and 57 (100, C_4H_9) (Found: M^+, 259.1418. $C_{12}H_{21}NO_5$ requires M, 259.1419). The material was pure according to the ^1H and ^{13}C NMR data and TLC analysis.

1-tert-*Butyl* 2-*Ethyl* 2-[*Methoxy*(*trifluoromethyl*)*phenylacetyl*]*pyrrolidine*-1,2-*dicarboxylate*.—To a solution of the foregoing hydroxy ester **6** (0.05 g, 0.19 mmol) in dry tetrachloromethane (0.2 cm^3) and dry pyridine (0.2 cm^3) was added (*R*)-(+)-methoxy(trifluoromethyl)phenylacetyl chloride, made by refluxing the corresponding acid (0.04 g, 0.4 mmol) with an excess of thionyl chloride (2 cm^3).[16] The reaction mixture was left at room temperature for 16 h, taken up in water (1 cm^3) and diethyl ether (15 cm^3) and washed with 1 mol dm^{-3} hydrochloric acid (5 cm^3), saturated aqueous sodium hydrogen carbonate (5 cm^3) and water (5 cm^3). The diethyl ether was dried and evaporated and the residue chromatographed on silica gel eluting with a 50% solution of chloroform in light petroleum to give the *Mosher ester* (0.088 g, 96%) as a colourless oil, ν_{max}/cm^{-1} 1744 and 1693; δ_H(400 MHz) 1.04–1.16 (3 H, m, CH_2CH_3), 1.39–1.41 [9 H, m, $C(CH_3)_3$], 2.17–2.32 (2 H, m, 4-H), 3.47–3.67 (2 H, m, 5-H), 3.52 (3 H, s, OCH_3), 3.72–3.78 (1 H, m, $CH_aH_bCH_3$), 3.95–4.01 (1 H, m, $CH_aH_bCH_3$), 4.52–4.60 (1 H, m, 2-H), 5.61–5.66 (1 H, m, 3-H), and 7.39–7.51 (5 H, m, C_6H_5); δ_F[$CDCl_3$; 297 K, $CFCl_3$ ghost ref. (0 ppm)] −72.19, *m*/*z* 374 (6%, $C_{17}H_{19}NOF_3$, M − BOC), 346 (15, $C_{15}H_{15}NO_5F_3$), 302 (73, $C_{14}H_{15}NO_3F_3$, M − BOC–CO_2EtO), 189 [32, $C_9H_8OF_3$, C(OMe)(CF_3)Ph], 105 (7, C_7H_5O), 68 (22, C_4H_6N) and 57 (100, C_4H_9). Examination of the remaining column fractions showed that no other isomers were present.

(+)-cis-(2R,3S)-3-*Hydroxyproline* **7**.—To a stirred solution of the foregoing hydroxy ester **6** (0.260 g, 1 mmol) in dry dichloromethane (4 cm^3) was added trifluoroacetic acid (1 cm^3) and the reaction mixture stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the resulting colourless solid dissolved in a solution of potassium hydroxide (0.17 g, 3 mmol) in methanol (3 cm^3) and water (0.5 cm^3) and stirred for 16 h at room temperature. The solvent was evaporated, the residue taken up in water (1 cm^3) and the resulting aqueous solution passed through a column of a strongly acidic ion-exchange resin (Dowex 50W/H) eluting first with water and then with 2 mol dm^{-3} aqueous ammonium hydroxide. The ammonia fraction was concentrated under reduced pressure and the residual solid crystallised from aqueous ethanol to give the *title compound* **7** (0.092 g, 70%) as a colourless solid, m.p. 240–252 °C (decomp.) (lit.,[2c] m.p. 245–255 °C decomp.), $[\alpha]_D^{27}$ +85.2 (*c* 1.25, H_2O) (lit.,[2c] *cis*-(2*S*,3*R*)-3-hydroxyproline has $[\alpha]^D$ −91.5 ± 1.5 (*c* 0.61, H_2O) while *trans*-(2*S*,3*S*)-3-hydroxyproline has $[\alpha]_D$ −22.8 (*c* 1.0, H_2O) and m.p. 228–235 °C decomp.; ν_{max}(KBr)/cm^{-1} 3320 and 1610; δ_H(250 MHz, solvent D_2O, standard H_2O) 2.09–2.14 (1 H, m, 4-H_a), 2.19 (1 H, dt, *J* 9.9 and 4.1, 4-H_b), 3.43–3.49 (1 H, m, 5-H_a), 3.55 (1 H, dt, *J* 7.3 and 4.1, 5-H_b), 4.13 (1 H, d, *J* 4.0, 2-H) and 4.65–4.72 (1 H, m, 3-H); δ_C(solvent D_2O, standard dioxane) 34.37 (C-4), 44.94 (C-5), 68.67 (C-2), 72.03 (C-3) and 171.81 (CO_2); *m*/*z* 87 (36%, $C_3H_5NO_2$), 86 (100, C_4H_8NO, M − CO_2H), 74 (11, $C_2H_4NO_2$), 69 (33, C_3H_3NO), 57 (9, C_3H_5O), 42 (9, C_2H_4N) and 41 (30, C_2H_3N) (Found: C, 45.6; H, 6.9; N, 10.4. Calc. for $C_5H_9NO_3$: C, 45.8; H, 6.9; N, 10.7%).

(2R,3S)-1-tert-*Butoxycarbonyl*-3-*hydroxyproline* **10a**.—The foregoing hydroxy ester **6** (0.260 g, 1 mmol) was stirred in a solution of potassium hydroxide (0.16 g, 3 mmol) in methanol (2 cm^3) and water (1 cm^3) for 16 h at room temperature. The methanol was evaporated, the residue taken up in water (10 cm^3) and the resulting solution washed with diethyl ether (2 × 5 cm^3). The aqueous phase was acidified to pH 3 with 2 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (3 × 5 cm^3). The combined extracts were dried and evaporated to give the *hydroxy acid* **10a** (0.200 g, 86%) as a colourless solid, m.p. 101–103 °C, $[\alpha]_D^{27}$ +55.5 (*c* 1.39, CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3380, 1718 and 1680; δ_H 1.47 [9 H, s, $C(CH_3)_3$], 1.88–2.22 (2 H, m, 4-H), 3.28–3.85 (3 H, m, 5′-H and CHO*H*), 4.30–4.53 (1 H, m, 2-H), 4.55–4.82 (1 H, m, 3-H) and 8.27 (1 H, br s, CO_2H); *m/z* 186 (8%, $C_9H_{16}NO_3$, M − CO_2H), 130 (64, $C_5H_8NO_3$, M − BOC), 113 (17, $C_5H_7NO_2$, M − BOC − OH), 101 (7, $C_5H_9O_2$), 86 (56, C_4H_8NO) and 57 (100, C_4H_9) (Found: C, 51.4; H, 7.4; N, 6.2. $C_{10}H_{17}NO_5$ requires C, 51.9; H, 7.4; N, 6.1%).

(2R,3S)-3-*Acetoxy*-1-tert-*butoxycarbonylproline* **10b**.—To a stirred solution of the foregoing hydroxy acid **10a** (0.190 g, 0.86 mmol) in dry pyridine (2 cm^3) was added acetic anhydride (0.5 cm^3) and the resulting mixture stirred for 2 h at room temperature. The solution was diluted with diethyl ether (20 cm^3) and extracted with saturated aqueous sodium hydrogen carbonate (3 × 5 cm^3). The aqueous phase was acidified to pH 2 with 2 mol dm^{-3} hydrochloric acid and extracted with diethyl ether (3 × 10 cm^3); the combined extracts were dried and evaporated to give the *acetate* **10b** (0.190 g, 85%) as a colourless solid, m.p. 119–121 °C, $[\alpha]_D^{27}$ −6.2 (*c* 0.78, CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450, 1750 and 1695; δ_H 1.46 [9 H, s, $C(CH_3)_3$], 1.76–2.25 (2 H, m, 4-H), 2.05 (3 H, s, $COCH_3$), 3.28–3.80 (2 H, m, 5-H), 4.50 (1 H, d, *J* 7, 2-H), 5.36–5.64 (1 H, m, 3-H) and 9.87 (1 H, br s, CO_2H); *m/z* 172 (13%, $C_7H_{10}NO_4$, M − CO_2 − C_4H_9), 128 (24, $C_6H_{10}NO_2$, M − BOC − CO_2), 113 (15, $C_5H_7NO_2$, M − BOC − OAc), 86 (10, C_4H_8NO), 68 (12, C_4H_6N) and 57 (100, C_4H_9) (Found: C, 52.9; H, 7.1; N, 5.3. $C_{12}H_{19}NO_6$ requires C, 52.7; H, 7.0; N, 5.1%).

(2S,3S)-*Methyl* 3-*Acetoxy*-1-tert-*butoxycarbonylpyrrolidin*-2-*ylacetate* **11**.—To a stirred solution of the foregoing acid **10b** (0.180 g, 0.66 mmol) in dry diethyl ether (3 cm^3), dry DMF (1 μl) and dry pyridine (0.31 cm^3, 3.96 mmol) maintained at 0 °C under nitrogen was added oxalyl chloride (0.17 cm^3, 1.98 mmol). The reaction mixture was stirred for 0.5 h at 0 °C and for 1 h at 20 °C and the precipitated pyridinium hydrochloride then filtered off and washed through with diethyl ether (5 cm^3). The filtrates were treated with an excess of cold ethereal diazomethane and left for 16 h. The solvent was removed, the residue taken up in ether (15 cm^3) and the solution washed with water (5 cm^3), dried and evaporated to give the *diazo ketone* (0.14 g, 71%) as a yellow oil; ν_{max}/cm^{-1} 1730 and 1688; δ_H 1.45 [9 H, s, $C(CH_3)_3$], 2.05 (3 H, s, $COCH_3$), 1.99–2.32 (2 H, m, 4-H), 3.34–3.83 (2 H, m, 5-H), 4.48 (1 H, d, *J* 7, 2-H), 5.34–5.57 (1 H, m, 3-H) and 5.42 (1 H, s, CHN_2); *m/z* 288 (18%, $C_{11}H_{18}NO_4$, M − $COCHN_2$), 186 (5, $C_8H_{12}NO_4$, M − C_4H_9 − CHN_2), 172 (33, $C_7H_{10}NO_4$, M − C_4H_9 − $COCHN_2$), 128 (63, $C_6H_{10}NO_2$, M − $COCHN_2$ − BOC), 68 (8, C_4H_6N) and 57 (100, C_4H_9). To a stirred solution of the foregoing diazo ketone (0.135 g, 0.45 mmol) in dry methanol (2 cm^3) at room temperature was added a solution of silver benzoate (5 mg) in dry triethylamine (0.05 cm^3). The reaction mixture was stirred for 16 h after which it was filtered through Kieselguhr to remove the precipitated silver. The filtrate was concentrated under reduced pressure and the residue taken up in diethyl ether (15 cm^3) and the solution washed with saturated aqueous sodium hydrogen carbonate (2 × 5 cm^3), dried and evaporated to give the *title compound* **11** (0.130 g 66%) as a colourless oil; $[\alpha]_D^{27}$ +27.0 (*c* 1.52, CH_2Cl_2); ν_{max}/cm^{-1} 1750 and 1703; δ_H 1.50 [9 H, s $C(CH_3)_3$], 2.06 (3 H, s, $COCH_3$), 1.88–2.30 (2 H, m, 4-H), 2.74–3.26 (2 H, m, CH_2CO_2), 3.33–3.83 (2 H, m, 5-H), 3.71 (3 H, s, OCH_3), 4.26–4.55 (1 H, m, 2-H) and 5.33–5.61 (1 H, m, 3-H); *m/z* 288 (6%, $C_{11}H_{18}NO_4$, M − CH_2CO_2Me), 186 (15, $C_8H_{12}NO_4$, M − C_4H_9 − OAc), 172 (22, $C_7H_{10}NO_4$, M − C_4H_9 − $CH_2CO_2CH_3$), 141 (45, $C_7H_{11}NO_2$, M − BOC − OAc), 128 (39, $C_6H_{10}NO_2$, M − BOC − $CH_2CO_2CH_3$), 68 (10, C_4H_6N) and 57 (100, C_4H_9) (Found: M^+, 228.1239. $C_{11}H_{18}NO_4$ requires *M*, 228.1236).

(1S,5S)-6-tert-*Butoxycarbonyl*-2-*oxa*-6-*azabicyclo*[3.3.0]*octan*-3-*one* **12**.—To a solution of the foregoing ester **11** (0.040 g, 0.13 mmol) in methanol (2 cm^3) was added an excess of potassium carbonate (0.1 g) and the suspension stirred vigorously for 16 h at room temperature. The methanol was evaporated, the residue taken up in water (5 cm^3) and the solution washed with diethyl ether (2 × 5 cm^3). The aqueous phase was acidified to pH 2 with 2 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (3 × 5 cm^3); the combined extracts were dried and evaporated to give the hydroxy acid as a colourless oil. This was dissolved in dichloromethane (2 cm^3) to which a crystal of toluene-*p*-sulfonic acid was added; the resulting solution was then stirred at room temperature for 2 h. After this it was diluted with dichloromethane (8 cm^3), washed with water (2 × 1 cm^3), dried and evaporated to give the γ-*lactone* **12** (0.027 g, 90%) as a colourless solid, m.p. 106–107 °C, $[\alpha]_D^{27}$ +96.0 (*c* 0.43, CH_2Cl_2); $\nu_{max}(CHCl_3)/cm^{-1}$ 1785 and 1680; δ_H 1.48 [9 H, s, $C(CH_3)_3$], 1.87–2.49 (2 H, m, NCH_2CH_2), 2.70–2.99 (2 H, m, CH_2CO), 3.20–3.98 (2 H, m, NCH_2), 4.37–4.61 (1 H, m, NCH) and 5.02–5.21 (1 H, m, CHO); *m/z* 277 (M^+, 8%, $C_{11}H_{17}NO_4$), 172 (19, $C_7H_{10}NO$, M − C_4H_7), 154 (28, $C_7H_8NO_3$; M − C_4H_9O), 127 (36, $C_6H_9NO_2$, M − BOC), 68 (16, C_4H_6N) and 57 (100, C_4H_9) (Found: C, 58.1; H, 7.6; N, 6.1. $C_{11}H_{17}NO$ requires C, 58.1; H, 7.5; N, 6.2%).

(1S,5S)-2-*Oxa*-6-*azabicyclo*[3.3.0]*octan*-3-*one Hydrochloride* **8·HCl**.—To a solution of the foregoing ester **11** (0.08 g, 0.26 mmol) in methanol (2 cm^3) was added an excess of potassium carbonate (0.1 g) and the resulting suspension stirred vigorously for 16 h at room temperature. The methanol was evaporated and the residue dissolved in ethyl acetate (6 cm^3) to which concentrated hydrochloric acid (2 cm^3) was added. The mixture was stirred at room temperature for 2 h after which it was evaporated and the residue crystallised from ethanol–diethyl ether to give the γ-*lactone hydrochloride* **8·HCl** (0.030 g, 70%) as a colourless solid, m.p. 182–184 °C (lit.,[12b] m.p. 182–184 °C; lit.,[12a] m.p. 185–186 °C), $[\alpha]_D^{27}$ −42.9 (*c* 0.73, MeOH) {lit.,[12b] $[\alpha]_D$ +45.6 (*c* 0.83, MeOH); lit.,[12a] $[\alpha]_D$ +48.5, (*c* 1.5, MeOH)}, $\nu_{max}(KBr)/cm^{-1}$ 1782; δ_H(250 MHz; CD_3OD) 2.20–2.47 (2 H, m, NCH_2CH_2), 2.86 (1 H, d, *J* 19.2, CH_AH_BCO), 3.20 (1 H, dd, *J* 19.3 and 8.5, CH_aH_bCO), 3.34–3.52 (2 H, m, NCH_2), 4.44–4.66 (1 H, m, NCH), and 5.23–5.35 (1 H, m, CHO); *m/z* 127 (70, $C_6H_9NO_2$, M − HCl), 85 (100, C_3H_7NO), 71 (17, C_4H_9N), 68 (14, C_4H_6N), 56 (90, C_3H_6N) and (23, C_2H_5N).

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