Stereocontrolled Synthesis of Necine Bases, (+)-Heliotridine and (+)-Retronecine[1]

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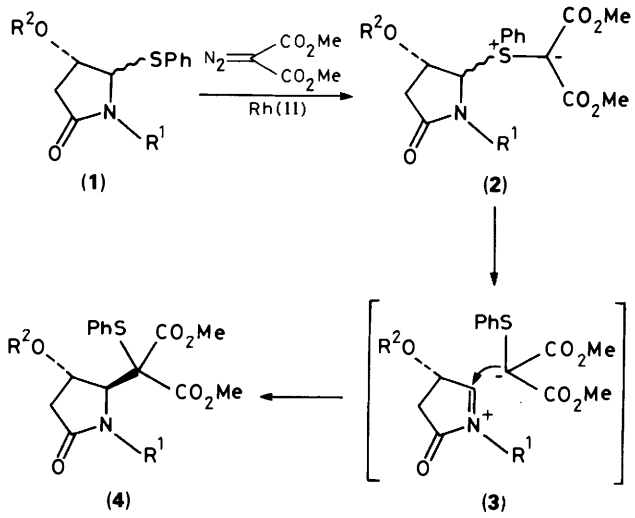
Synthesis of pyrrolizidine alkaloids, (+)-heliotridine and (+)-retronecine from (*S*)-malic acid was achieved by utilizing an intermolecular carbenoid displacement reaction as a key step.

The development of versatile methods for forming a new carbon–carbon bond at the α-position to nitrogen under mild conditions is a central goal in alkaloid synthesis.

Recently we developed[2] a novel carbon–carbon bond-forming reaction at the 4-position of azetidin-2-one by using the rearrangement of sulphur ylides obtained from divalent sulphur and carbenoids. This method which, in essence, facilitates the introduction of a functionalized carbon unit, was expected to have broad utility in the synthesis of natural products. We have now applied[3] this procedure intramolecularly to the synthesis of the pyrrolizidine alkaloids, (±)-trachelanthamidine, (±)-isoretronecanol, and (±)-supinidine.

As an extension of this work, we were interested in the stereoselective synthesis of the necine bases, heliotridine and retronecine in natural enantiomeric form. We planned to synthesize both alkaloids from the same chiral source since they are diastereoisomers with respect to the secondary alcohol group, inversion of the alcohol function of one isomer leading to the synthesis of the other. We decided to adopt an intermolecular carbenoid displacement reaction of the optically active sulphide (**1**) derived from readily available (*S*)-malic acid with α-diazomalonate in the presence of rhodium acetate as a catalyst in order to control the stereochemistry at the position previously occupied by the sulphide group as a natural form. Our choice was dictated by the expectation that nucleophilic attack on the acyliminium salt (**3**) generated from the ylide (**2**) would occur from the less hindered side to give predominantly a 2,3-*trans*-pyrrolidone derivative (**4**) (see Scheme 1).

Thus the requisite starting material (**11**) was synthesized as follows.

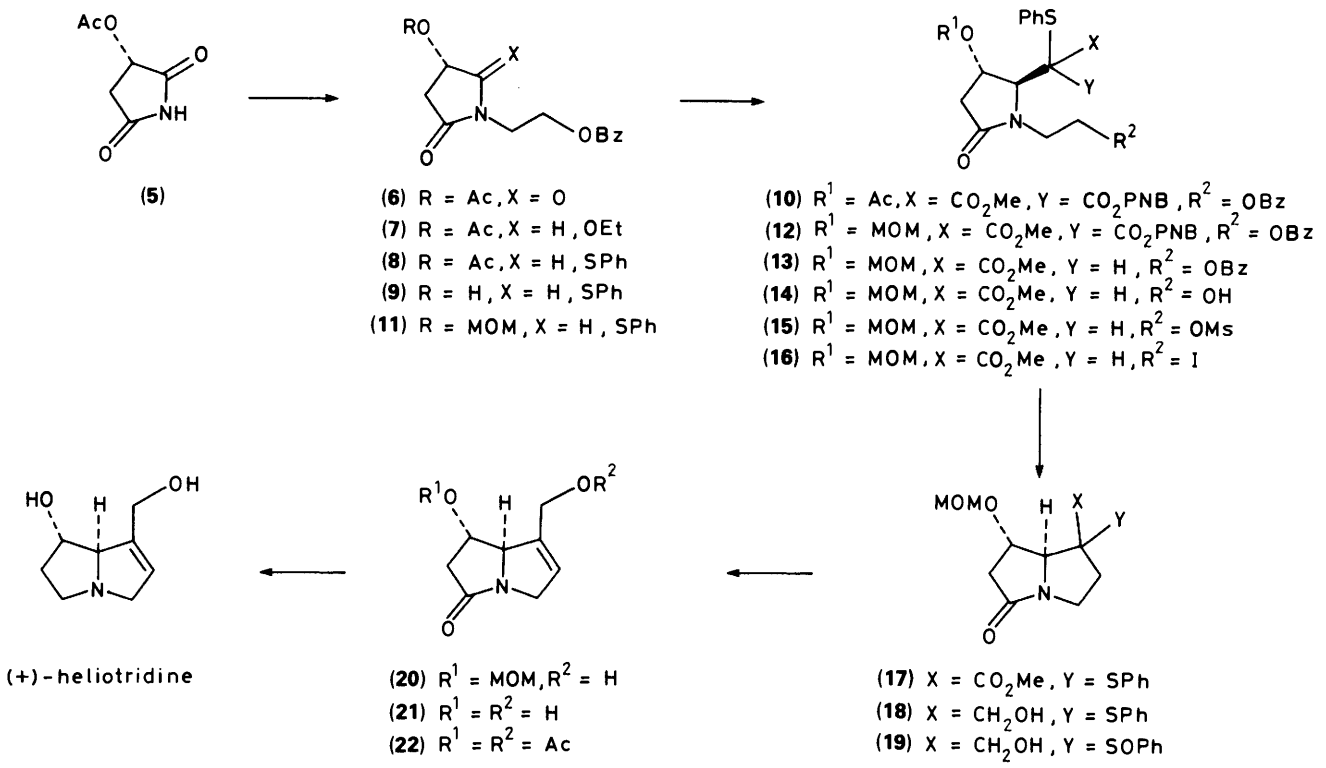


Scheme 1.

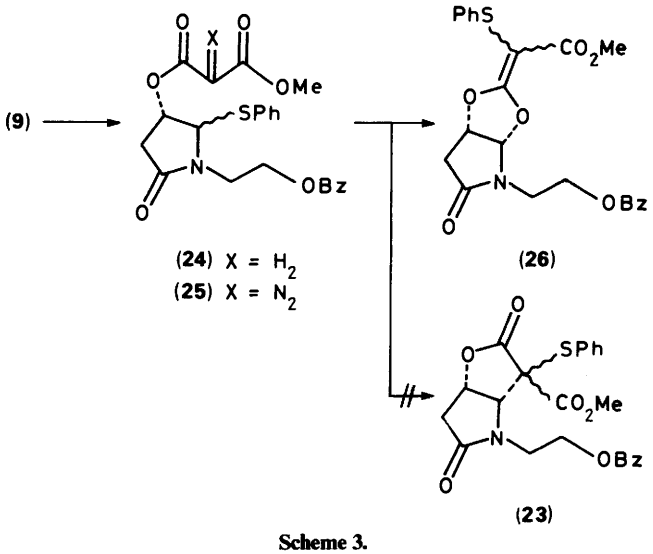
Results and Discussion

(*S*)-Malic acid was converted by a known procedure into the imide (**5**)[4] and this upon *N*-alkylation with ethylene glycol monobenzoate under Mitsunobu reaction condition[5] afforded the *N*-alkylated compound (**6**) (95.5% yield). Reduction of (**6**) with sodium borohydride, followed by treatment with ethanolic hydrogen chloride[6] provided the ethoxy derivative (**7**), which without purification was further treated with thiophenol in the presence of toluene-*p*-sulphonic acid to give the acetoxy sulphide (**8**) (27.7% yield) and the hydroxy sulphide (**9**) (48.7% yield). Acetylation of the latter with acetic anhydride gave the former compound quantitatively. With this starting material in our hands, we first investigated the synthesis of (+)-heliotridine. Intermolecular carbenoid displacement reaction of the sulphide (**8**) with methyl *p*-nitrobenzyl α-diazomalonate in the presence of a catalytic quantity of rhodium acetate in refluxing benzene afforded the carbon-introduced product (**10**) (84.7% yield) to which a 2,3-*trans* stereochemical relationship was assigned on the basis of nmr results. Since, however, the acetyl group of (**10**) was found to be an inconvenient protecting group for the secondary alcohol in its conversion into the natural product, the acetate (**8**) was selectively hydrolysed with sodium carbonate in methanol to give the alcohol (**9**) (79.7% yield). Protection of this with methoxymethyl chloride in dichloromethane in the presence of di-isopropylethylamine and 4-dimethylaminopyridine yielded the methoxymethyl ether (MOM) (**11**) as a diastereoisomeric mixture (α:β SPh = 1:8) (86.1% yield). The major *trans*-sulphide was subjected to an intermolecular carbenoid displacement reaction with methyl *p*-nitrobenzyl α-diazomalonate in refluxing benzene using rhodium acetate as a catalyst to furnish (**12**) (82.6% yield). Although the relative stereochemistry for the 2 and 3 positions of this could not be determined at this stage it was assumed to be *trans* on the basis of the earlier result; the product was therefore used in the next reaction. Catalytic hydrogenation of (**12**) over palladium–carbon in methanol provided the ester (**13**), which on treatment with potassium carbonate in methanol afforded the alcohol (**14**) [58.4% yield from (**12**)]. This compound was then converted into the corresponding iodide (**16**) *via* the methanesulphonate (**15**) by successive treatment with methanesulphonyl chloride and triethylamine and then with sodium iodide. Intramolecular alkylation of (**16**) with lithium hexamethyldisilazide in dry tetrahydrofuran gave the bicyclic ester (**17**) as a mixture of diastereoisomers [46.6% yield from (**15**)]. Since the basic skeleton of (+)-heliotridine was constructed stereoselectively, we focussed our attention on the transformation of (**17**) into the natural product by manipulation of the sulphide group. In order to introduce a 1,2-didehydro system, an oxidative elimination of the sulphide was employed as follows. The ester group of (**17**) was selectively reduced with lithium aluminium hydride in dry tetrahydrofuran at 0 °C to

† Deceased on 11th October 1988.



Scheme 2. PNB = p-$O_2NC_6H_4CH_2$; Ms = $MeSO_2$; MOM = $MeOCH_2$.

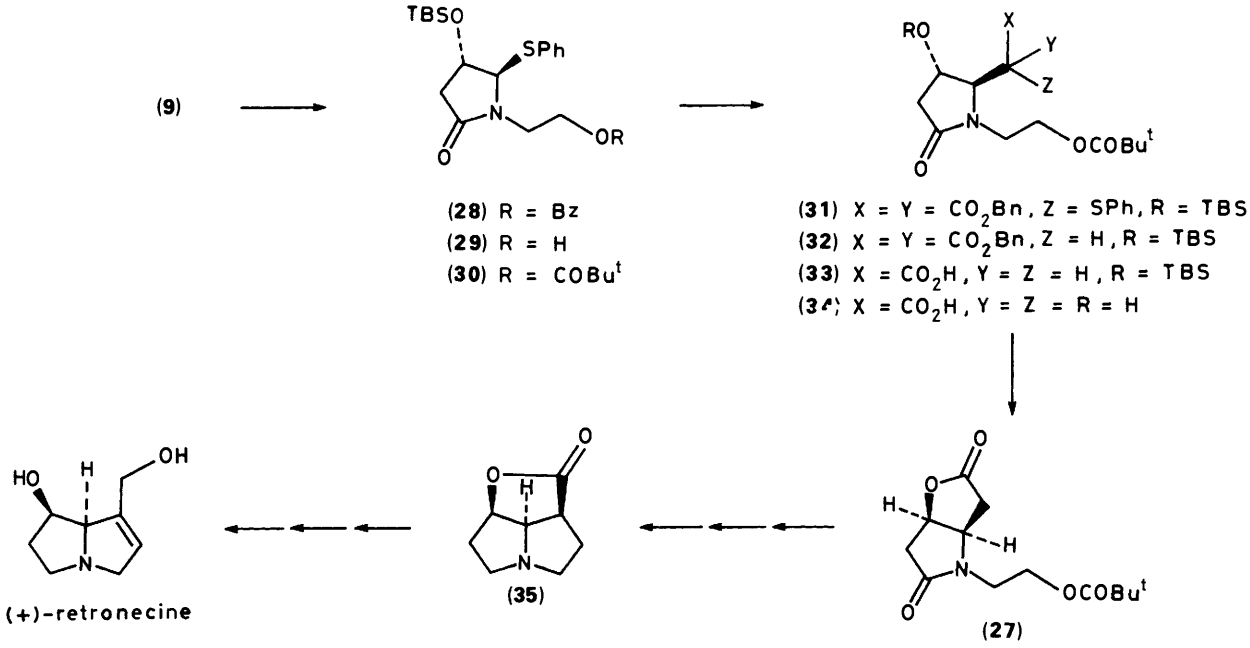


Scheme 3.

give the alcohol (**18**), which on oxidation with *m*-chloroperbenzoic acid in dichloromethane furnished the sulphoxide (**19**) [67.0% yield from (**17**)]. Heating of (**19**) in refluxing toluene for 45 min afforded the olefin (**20**), which was further subjected to hydrolysis with hydrochloric acid to give the diol (**21**). Acetylation of (**21**) with acetic anhydride in chloroform in the presence of triethylamine provided the diacetate (**22**), whose spectroscopic data[7] and specific optical rotation,[8] $[\alpha]_D^{25}$ +34.4° (*c* 2.2, $CHCl_3$) {lit.,[7] $[\alpha]_D^{25}$ +36.2° (*c* 1.1, $CHCl_3$)} were identical with those reported. Since this amide (**22**) had already been converted[7] into (+)-heliotridine by a lithium aluminium hydride reduction, this synthesis constitutes its total synthesis.

On the basis of our previous work,[2b] we also attempted the synthesis of (−)-retronecine, the antipode of the natural enantiomer, by employing an intramolecular carbenoid displacement reaction, which would be expected to give a carbon-introduced product with a *cis* stereochemical relationship for the 2 and 3 positions of the pyrrolidone ring (**23**). Condensation of the alcohol (**9**) with monomethyl malonate in ethyl acetate in the presence of dicylohexylcarbodi-imide at ambient temperature furnished the ester (**25**) as a mixture of diastereoisomers (66.4% yield). A diazo exchange reaction of (**24**) with toluene-*p*-sulphonyl azide and triethylamine in acetonitrile gave the diazo compound (**25**) (71% yield) which underwent an intramolecular carbenoid displacement reaction with rhodium acetate as catalyst to afford the oxygen-introduced product (**26**) rather than the expected compound (**23**). A similar result has already been observed[9] in our earlier studies on intramolecular *C*-glycosylation reaction.

Since (+)-retronecine, an epimeric isomer of the secondary alcohol of (+)-heliotridine, was recently synthesized[10] from (*R*)-malic acid *via* the lactone (**27**) as a key intermediate, we decided to investigate its synthesis from the sulphide (**9**) by employing a similar strategy to that described above, where an inversion of a secondary alcohol would be required in some stage of the synthesis. Silylation of the alcohol (**9**) with t-butyldimethylsilyl chloride in dry tetrahydrofuran in the presence of triethylamine afforded the silyl ether (**28**), which was then subjected to an ester exchange reaction by hydrolysis with potassium carbonate in methanol, followed by treatment of the resulting alcohol (**29**) with pivaloyl chloride and pyridine in ether to give (**30**) [54.5% yield from (**9**)]. An intermolecular carbenoid displacement reaction of (**30**) with dibenzyl α-diazomalonate in the presence of a catalytic amount of rhodium acetate in refluxing benzene provided (**31**), which on reductive desulphurization with Raney nickel in ethanol furnished (**32**) [67.2% yield from (**30**)]. Hydrogenolysis of (**32**) over palladium on carbon in methanol, followed by decarboxylation in refluxing benzene gave the acid (**33**) (83.2% yield). After



Scheme 4. Bn = CH_2Ph; TBS = Bu^tMe_2Si.

deprotection of the silyl group of the acid (**33**) by exposure to tetrabutylammonium fluoride in tetrahydrofuran at room temperature, the resulting hydroxy acid (**34**) was subjected to the Mitsunobu reaction.[11] In this, intramolecular inversion of the secondary alcohol by treatment with diethyl azodicarboxylate in tetrahydrofuran in the presence of triphenylphosphine provided the lactone (**27**) with the desired stereochemistry [49.3% yield from (**33**)]. The specific optical rotation of the lactone (**27**) obtained $[\alpha]_D^{26}$ + 55.2° (*c* 0.69, $CHCl_3$) {lit., $[\alpha]_D^{17}$ + 48.8° (*c* 0.53, $CHCl_3$)} and its m.p.[10] [112–113 °C (from benzene–hexane); lit., m.p. 109–110 °C] correlated with those reported.[10]

The lactone (**27**) has already been transformed[10] into (+)-retronecine *via* compound (**35**).

Experimental

IR spectra were obtained with a Hitachi 260-10 spectrophotometer, NMR spectra with JEOL PMX-60, JEOL JNM FX-100, and JEOL GSX-270 instruments (tetramethylsilane as an internal standard reference), and mass spectra with a JEOL JMS D-300 spectrometer. M.p.s were determined with a Yanagimoto micro apparatus and are uncorrected. Optical rotations were performed with JASCO DIP-360.

(3S)-3-*Acetoxy*-1-(2-*benzoyloxyethyl*)*pyrrolidine*-2,5-*dione* (**6**).—A mixture of (3*S*)-3-acetoxypyrrolidine-2,5-dione (**5**) (24.7 g), 2-benzoyloxyethanol (25.9 g), triphenylphosphine (41.2 g), and dry tetrahydrofuran (500 ml) was cooled in an ice-bath. Diethyl azodicarboxylate (24.8 g) was added to the above cooled mixture, and the bath was removed. The mixture was stirred for 4 h at ambient temperature after which the solvent was evaporated. The residue was diluted with ethyl acetate (100 ml) and hexane (200 ml). The precipitated triphenylphosphine oxide was filtered off, and the filtrate was concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded a solid, which was recrystallized from chloroform–hexane to yield the imide (**6**) (45.9 g, 95.5%) as colourless needles, m.p. 75–76 °C; $[\alpha]_D^{26}$ −10.2° (*c* 2 in $CHCl_3$) (Found: C, 59.1; H, 4.95; N, 4.5. $C_{15}H_{15}NO_6$ requires C, 59.1; H, 4.95; N, 4.6%); $\nu_{max.}(CHCl_3)$ 1 720 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 2.13 (3 H, s, Ac), 2.69 (1 H, dd, *J* 19 and 5 Hz), 3.19 (1 H, dd, *J* 19 and 9 Hz), 3.96 (2 H, br t, *J* 5 Hz), 4.50 (2 H, br t, *J* 5 Hz), 5.45 (1 H, dd, *J* 9 and 5 Hz), 7.30–7.65 (3 H, m, ArH), and 7.92–8.17 (2 H, m, ArH); *m/z* 305 (M^+).

(2RS,3S)-3-*Acetoxy*-1-(2-*benzoyloxyethyl*)-2-*phenylthiopyrrolidin*-5-*one* (**8**) *and* (2RS,3S)-1-(2-*Benzoyloxyethyl*)-3-*hydroxy*-2-*phenylthiopyrrolidin*-5-*one* (**9**).—Sodium borohydride (1.4 g) was added to a solution of the imide (**6**) (5.7 g) in dry ethanol (250 ml) at −10 °C, and the mixture was stirred for 15 min at the same temperature. After acidification of the solution (pH 3) by addition of ethanolic hydrogen chloride, the mixture was further stirred at ambient temperature for 2 h. It was then carefully basified with 1M ethanolic sodium hydroxide to pH 9, and diluted with water. Extraction with chloroform gave (2*RS*,3*R*)-3-acetoxy-1-(2-benzoyloxyethyl)-2-ethoxypyrrolidin-5-one (**7**) as an oil. This was dissolved in thiophenol (30 ml), and a catalytic amount of toluene-*p*-sulphonic acid was added to the solution. The mixture was stirred for 2 h at room temperature and then extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded the title compound (**8**) (2 g, 27.7%) as a colourless oil, $\nu_{max}(CHCl_3)$ 1 710 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.78 and 2.10 (total 3 H, each s, OAc), 1.60–2.67 (2 H, m, CH_2), 3.21–4.79 (4 H, m, CH_2 × 2), 4.93 and 5.18–5.56 (total 2 H, 2-H + 3-H), 7.18–7.75 (8 H, m, ArH), and 7.83–8.20 (2 H, m, ArH); *m/z* 355 (M^+ − 44) and 290 (M^+ − 109). Further elution with hexane–ethyl acetate (1:1, v/v) gave the title compound (**9**) (3.25 g, 48.7%) as a colourless oil (Found: C, 63.9; H, 5.3; N, 3.9. $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.35; N, 3.9%); $\nu_{max}(CHCl_3)$ 1 710 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.71–2.35 (2 H, m, CH_2), 3.26–4.71 (5 H, m), 4.85 and 5.08 (total 1 H, s and d, *J* 6 Hz, 2-H), 7.08–7.62 (8 H, m, ArH), and 7.73–8.15 (2 H, m, ArH); *m/z* 359 (M^+ + 2), and 248 (M^+ − 109).

Deacetylation of the Acetate (**8**).—To a stirred solution of the acetate (**8**) (11.3 g) in methanol (600 ml) in an ice-bath was added sodium carbonate (300 mg). After being stirred for 2 h at

0 °C, the mixture was poured into water and extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded the starting acetate (**8**) (1.2 g, 10.8%), and further elution with hexane–ethyl acetate (1:1, v/v) yielded the alcohol (**9**) (8.1 g, 79.7%), which was identical with the authentic sample obtained above.

(2S,3S)-3-*Acetoxy*-1-(2-*benzoyloxyethyl*)-2-(*methoxycarbonyl*-p-*nitrobenzyloxycarbonylphenylthio*)*methylpyrrolidin*-5-*one* (**10**).—A solution of methyl *p*-nitrobenzyl diazomalonate (1.93 g) in dry benzene (100 ml) was added dropwise over 1 h to a refluxing solution of compound (**8**) (1.79 g) in dry benzene (100 ml) in the presence of a catalytic amount of rhodium acetate. The mixture was stirred for an additional 1 h at the same temperature after which the solvent was removed. The residue was chromatographed on silica gel using benzene–ethyl acetate (8:2, v/v) as eluant to furnish (**10**) (2.32 g, 84.7%) as an oil; $\nu_{max}(CHCl_3)$ 1 730 and 1 700 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 2.24 (1 H, dd, *J* 18.5 and 4.5 Hz), 2.72–2.85 (1 H, m), 3.17–3.36 (1 H, m), 3.96–4.16 (2 H, m), 4.30–4.40 (1 H, m), 4.55 (1 H, s, 2-H), 5.10–5.24 (2 H, m, CH_2Ar), 5.28 (1 H, br t, *J* 5.5 Hz, 3-H), and 8.24 (2 H, d, *J* 9 Hz, ArH); *m/z* 611 ($M^+ + 1$).

(2R,3S)- *and* (2S,3S)-1-(2-*Benzoyloxyethyl*)-3-*methoxymethoxy*-2-*phenylthiopyrrolidin*-5-*one* (**11**).—A solution of the alcohol (**9**) (5.45 g), chloromethyl methyl ether (11.6 ml), diisopropylethylamine (27.3 ml), and a catalytic amount of 4-dimethylaminopyridine in dichloromethane (200 ml) was stirred for 2 days at room temperature. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded the title compound (2*R*,3*S*)-(**11**) (4.69 g, 76.6%) as a colourless oil, $[\alpha]_D^{24}$ −18.9° (*c* 3 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 710 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 2.07 (2 H, br d, *J* 4 Hz, CH_2), 3.19 (3 H, s, OMe), 3.00–4.88 (5 H, m), 4.49 (2 H, s, OCH_2O), 5.01 (1 H, s, 2-H), 7.15–7.72 (8 H, m, ArH), and 7.82–8.23 (2 H, m, ArH); *m/z* 340 ($M^+ - 61$) and 292 ($M^+ - 109$). Further elution with same solvent gave (2*S*,3*S*)-(**11**) (578 mg, 9.45%) as a colourless oil, $[\alpha]_D^{26}$ −24.1° (*c* 3 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 710 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.91 (1 H, dd, *J* 17 and 8 Hz), 2.30 (1 H, dd, *J* 17 and 8 Hz), 3.36 (3 H, s, OMe), 3.15–4.83 (5 H, m), 4.65 (2 H, s, OCH_2O), 5.22 (1 H, d, *J* 6 Hz, 2-H), 7.20–7.68 (8 H, m, ArH), and 7.81–8.20 (2 H, s, ArH); *m/z* 340 ($M^+ - 61$) and 292 ($M^+ - 109$).

(2S,3S)-1-(2-*Benzoyloxyethyl*)-3-*methoxymethoxy*-2-(*methoxycarbonyl*-p-*nitrobenzyloxycarbonylphenylthio*)*methylpyrrolidin*-5-*one* (**12**).—A solution of methyl *p*-nitrobenzyl diazomalonate (246 mg) in dry benzene (19 ml) was added over 1 h to a refluxing solution of (2*R*,3*S*)-sulphide (**11**) (295 mg) in dry benzene (15 ml) in the presence of a catalytic amount of rhodium acetate. The mixture was further stirred for 2 h after which the solvent was removed. The residue was chromatographed on silica gel with hexane–ethyl acetate (8:2, v/v) as eluant to afford the starting sulphide (**11**) (29 mg, 9.8%); further elution with hexane–ethyl acetate (7:3, v/v) gave (**12**) (395 mg, 82.6%) as a pale yellow oil, $\nu_{max}(CHCl_3)$ 1 700 cm^{-1} (CO); δ_H(400 MHz, $CDCl_3$) 2.35 (1 H, dd, *J* 18 and 1.5 Hz, 4-H), 2.55–2.68 (1 H, m, 4-H), 3.27 (3 H, s, OMe), 4.13–4.22 (1 H, m), 4.31–4.38 (1 H, m), 4.50 (1 H, d, *J* 7 Hz), 4.53–4.62 (1 H, m), 4.64 (1 H, s), 4.67–4.74 (1 H, m), 4.95–5.16 (2 H, m), 7.23–7.60 (10 H, m), 8.02–8.07 (2 H, m, ArH), and 8.16–8.23 (2 H, m, ArH); *m/z* 621 ($M^+ - 31$) and 591 ($M^+ - 61$) (Found: $M^+ - 61$, 591.1429. $C_{30}H_{27}N_2O_9S$ requires $M^+ - 61$, 591.1435).

(2S,3S)-1-(2-*Benzoyloxyethyl*)-3-*methoxymethoxy*-2-(*methoxycarbonylphenylthio*)*methylpyrrolidin*-5-*one* (**13**).—A solution of the malonate (**12**) (217 mg) in methanol (50 ml) in the presence of 10% palladium on carbon (200 mg) was stirred at room temperature under an atmosphere of hydrogen for 18 h. The catalyst was then filtered off, and the filtrate was concentrated to leave an oil, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (8:2, v/v) gave (**13**) (119 mg, 75.6%) as a colourless oil, $[\alpha]_D^{21}$ 2.16° (*c* 2 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 690 cm^{-1} (CO); δ_H(400 MHz, $CDCl_3$) 2.00–3.00 (2 H, m, CH_2), 3.22 and 3.32 (total 3 H, each s, OMe), 3.62 and 3.68 (total 3 H, each s, OMe), 3.43–5.20 (8 H, m), 7.16–7.78 (8 H, m, ArH), and 7.91–8.25 (2 H, m, ArH); *m/z* 442 ($M^+ - 31$) and 412 ($M^+ - 61$) (Found: $M^+ - 61$, 412.1227. $C_{22}H_{22}NO_5S$ requires $M^+ - 61$, 412.1227.

(2S,3S)-1-(2-*Hydroxyethyl*)-3-*methoxymethoxy*-5-(*methoxycarbonylphenylthio*)*methylpyrrolidin*-5-*one* (**14**).—Potassium carbonate (222 mg) was added to a stirred solution of the benzoate (**13**) (1.55 g), in methanol (70 ml), and the mixture was stirred for 2 h at room temperature. The mixture was then poured into water and extracted with dichloromethane. The organic solvent was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (6:4, v/v) afforded starting material (**13**) (165 mg, 10.6%), and further elution with ethyl acetate gave (**14**) (935 mg, 77.3%) as a mixture of diastereoisomers, $[\alpha]_D^{24}$ −15.4° (*c* 4 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 670 and 1 720 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.92–3.30 (2 H, m, CH_2), 3.28 and 3.35 (total 3 H, each s, OMe), 3.57 and 3.66 (total 3 H, each s, OMe), 3.41–3.98 (4 H, m), 4.02–4.51 (3 H, m), 4.55 and 4.60 (total 2 H, each s, OCH_2O), and 7.03–7.58 (5 H, m, ArH) (Found: M^+, 369.1236. $C_{17}H_{23}NO_6S$ requires M^+, 369.1244).

(2S,3S)-1-(2-*Methylsulphonyloxyethyl*)-3-*methoxymethoxy*-2-(*methoxycarbonylphenylthio*)*methylpyrrolidin*-5-*one* (**15**).—Triethylamine (0.38 ml) was added to a solution of the alcohol (**14**) (914 mg) and methanesulphonyl chloride (0.21 ml) in dry dichloromethane (30 ml) at room temperature. After being stirred for 10 min, the mixture was poured into water and extracted with dichloromethane. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (6:4, v/v) afforded (**15**) (1.05 g, 94.4%) as mixture of diastereoisomers, $\nu_{max}(CHCl_3)$ 1 680 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 3.00 (3 H, s, SO_2Me), 3.43 and 3.48 (total 3 H, each s, OMe), 3.75 and 3.87 (total 3 H, each s, OMe), 4.77 and 4.83 (total 2 H, each s, OCH_2O), and 7.55 (5 H, br s, ArH).

Methyl (1RS,7S,8S)-7-*Methoxymethoxy*-5-*oxo*-1-*phenylthiohexahydro*-1H-*pyrrolidine*-1-*carboxylate* (**17**).—A mixture of (**15**) (63 mg), sodium iodide (105 mg), and acetone (10 ml) was heated at reflux for 4 h. After cooling, the mixture was diluted with water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to give the iodide (**16**), which was dissolved in dry tetrahydrofuran (10 ml). A solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (0.13 ml) and 1.6M butyl-lithium hexane solution (0.086 ml) in dry tetrahydrofuran] was added to the above solution at −78 °C. The reaction temperature was gradually warmed up to 0 °C, and the mixture was stirred at 0 °C for 5 h. The reaction was quenched by addition of water and the mixture was extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (6:4, v/v) provided (**17**) (23 mg, 46.6%) as a mixture of diastereoisomers, $[\alpha]_D^{23}$ 11.6° (*c* 2 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 660 cm^{-1} (CO); δ_H(400 MHz, $CDCl_3$) 2.00 (1 H, ddd, *J* 14.5, 8, and 1.5 Hz, 3-H), 2.22–2.38 (1 H, m), 2.58–2.80 (1 H, m), 3.03 (1 H, dd, *J* 18 and 8.5 Hz), 3.16 (1 H, dd,

J 11 and 9.5 Hz), 3.42 (3 H, s, OMe), 3.57–3.66 (1 H, m), 3.78 (3 H, s, OMe), 4.02 and 4.20 (total 1 H, each d, *J* 3.5 Hz and 2.5 Hz), 4.37–4.42 and 4.68–4.74 (total 1 H, each m), 4.69 (1 H, d, *J* 7 Hz), 4.79 (1 H, d, *J* 7 Hz), 7.32–7.56 (5 H, m, ArH) (Found: M^+, 351.1144. $C_{17}H_{21}NO_5S$ requires M^+, 351.1141).

(1RS,7S,8S)-1-*Hydroxymethyl*-7-*methoxymethoxy*-1-*phenylthiohexahydro*-1H-*pyrrolizin*-5-*one* (**18**).—Lithium aluminium hydride (22 mg) was added to a stirred solution of the ester (**17**) (323 mg) in dry ether at 0 °C. After being stirred for 2 h, 10% aqueous sodium hydroxide was added dropwise to the mixture until the aluminium compound was entirely precipitated. The mixture was filtered through a Celite pad and the filtrate was dried (Na_2SO_4), and concentrated to give a residue, which was chromatographed on silica gel with hexane–ethyl acetate (4:6–2:8, v/v) as eluant to afford (**18**) (226 mg, 76.1%) as a mixture of diastereoisomers, $[\alpha]_D^{25}$ 97.1° (*c* 1 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 3 400 (OH) and 1 670 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 3.44 (3 H, s, OMe), 4.05 (1 H, d, *J* 3 Hz), 4.70 (2 H, s), and 7.41 (5 H, br s, ArH) (Found: M^+, 323.1190. $C_{16}H_{21}NO_4S$ requires M^+, 323.1190).

(1RS,7S,8S)-1-*Hydroxymethyl*-7-*methoxymethoxy*-1-*phenylsulphinylhexahydro*-1H-*pyrrolizin*-5-*one* (**19**).—80% *m*-Chloroperbenzoic acid (173 mg) was added to a two-phase solution of the sulphide (**18**) (226 mg) in dichloromethane and aqueous sodium hydrogen carbonate (5 ml) at 0 °C, and the mixture was further stirred for 30 min at the same temperature. The mixture was then poured into water and extracted with dichloromethane. The organic layer was washed with aqueous sodium sulphite, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate furnished the sulphoxide (**19**) (209 mg, 88.1%) as a mixture of diastereoisomers, $\nu_{max}(CHCl_3)$ 1 680 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 3.50 (3 H, s, OMe), 4.88 (2 H, d, *J* 2.5 Hz), 5.38 (1 H, br s), and 7.77 (5 H, br s, ArH).

(7S,8R)-7-*Hydroxy*-1-*hydroxymethyl*-5,6,7,8-*tetrahydro*-3H-*pyrrolizin*-5-*one* (**21**).—A solution of the sulphoxide (**19**) (209 mg) in toluene (10 ml) was heated under reflux for 45 min after which the solvent was removed. The residue was chromatographed on silica gel using benzene–ethyl acetate (7:3, v/v) as eluant to afford (7*S*,8*R*)-1-hydroxymethyl-7-methoxymethoxy-5,6,7,8-tetrahydro-3*H*-pyrrolizin-5-one (**20**) as an oil, $[\alpha]_D^{26}$ 20.2° (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 680 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 3.48 (3 H, s, OMe), 4.79 (2 H, s, OCH_2O), and 5.85 (1 H, br s, 2-H); *m*/*z* 213 (M^+). This oil was dissolved in methanol (10 ml) and conc. hydrochloric acid (0.02 ml) was added to the solution. The mixture was heated under reflux for 2 h and then diluted with ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to provide a residue, which was subjected to column chromatography on silica gel. Elution with chloroform–methanol (5:5, v/v) gave the diol (**21**) (35 mg, 33.6%); δ_H(60 MHz, $CDCl_3$ + CD_3OD) 2.58–2.86 (2 H, m), 3.42 (2 H, br s), 4.38 (5 H, br s), and 5.79 (1 H, br s); *m*/*z* 169 (M^+).

(7S,8R)-7-*Acetoxy*-1-*acetoxymethyl*-5,6,7,8-*tetrahydro*-3H-*pyrrolizin*-5-*one* (**22**).—Triethylamine (0.1 ml) was added to a stirred solution of the diol (**21**) (30 mg) and acetic anhydride (0.08 ml) in chloroform (2 ml). After being stirred for 2 h at ambient temperature, the mixture was diluted with chloroform. The organic layer was separated, washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to provide a residue. This was chromatographed on silica gel using hexane–ethyl acetate as eluant giving the diacetate (**22**) (44 mg, 98%) as a colourless oil, $[\alpha]_D^{25}$ 34.4° (*c* 2.2 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 740 and 1 700 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 2.06 (3 H, s, Ac), 2.11 (3 H, s, Ac), 2.71 (1 H, dd, *J* 17 and 9 Hz), 2.89 (1 H, dd, *J* 17 and 9 Hz), 3.70 (1 H, br d, *J* 14.5 Hz), 4.28–4.90 (3 H, m), 5.29 (1 H, dt, *J* 8.5 and 6 Hz), and 5.88 (1 H, br s); *m*/*z* 254 (M^+), 211 (M^+ − 43), and 193 (M^+ − 61) (Found: M^+ −43, 211.0851. $C_{10}H_{13}NO_4$ requires M^+ − 43, 211.0845).

(2RS,3S)-1-(2-*Benzoyloxyethyl*)-3-(3-*methoxy*-1,3-*dioxopropoxy*)-2-*phenylthiopyrrolidin*-5-*one* (**24**).—Dicyclohexylcarbodi-imide (524 mg) was added to a solution of compound (**9**) (756 mg) and monomethyl malonate (275 mg) in ethyl acetate (20 ml) at room temperature. After being stirred overnight, the mixture was filtered to remove insoluble material, and the filtrate was concentrated to give a residue. This was chromatographed on silica gel using benzene–ethyl acetate (9:1, v/v) as eluant to afford the title malonate (**24**) (643 mg, 66.4%), $\nu_{max}(CHCl_3)$ 1 700 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.79–2.49 (2 H, m, CH_2), 3.18 and 3.49 (total 2 H, each s, CH_2), 3.70 and 3.82 (total 3 H, each s, OMe), 3.94–4.98 (4 H, m, CH_2 × 2), 5.11 and 5.30–5.72 (total 2 H, s and m, 2-H and 3-H), 7.32–7.85 (8 H, m, ArH), and 7.99–8.35 (2 H, m, ArH); *m*/*z* 348 (M^+ −109). Further elution with benzene–ethyl acetate (1:1, v/v) gave the starting alcohol (**9**) (154 mg, 20.4%).

(2RS,3S)-1-(2-*Benzoyloxyethyl*)-3-(3-*methoxy*-2-*diazo*-1,3-*dioxopropoxy*)-2-*phenylthiopyrrolidin*-5-*one* (**25**).—Triethylamine (0.4 ml) was added to a stirred solution of the malonate (**24**) (630 mg) and toluene-*p*-sulphonyl azide (544 mg) in dry acetonitrile (15 ml) at 0 °C. Stirring was continued overnight at ambient temperature after which the mixture was diluted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel using benzene–ethyl acetate (85:15, v/v) as eluant to provide the diazo compound (**25**) (474 mg, 71.0%) as a mixture of diastereoisomers, $\nu_{max}(CHCl_3)$ 2 140 (N_2) and 1 700 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 1.93–2.50 (2 H, m, CH_2), 3.70 and 3.84 (total 3 H, each s, OMe), 3.95–4.80 (4 H, m, CH_2 × 2), 5.06 and 5.29–5.73 (total 2 H, s and m, 2-H and 3-H), 7.18–7.73 (8 H, m, ArH), 7.85–8.21 (2 H, m, ArH); *m*/*z* 374 (M^+ − 109).

(1S,5S)-8-(2-*Benzoyloxyethyl*)-3-(*methoxycarbonylphenylthio*)*methylene*-2,4-*dioxa*-8-*azobicyclo*[3.3.0]*octan*-7-*one* (**26**).—A solution of the diazo compound (**25**) (474 mg) in dry benzene (10 ml) was added over 1 h to a refluxing suspension of a catalytic quantity of rhodium acetate in dry benzene (20 ml), and the resulting mixture was further stirred for 1 h at the same temperature. After evaporation of the solvent, the residue was chromatographed on silica gel using hexane–ethyl acetate (1:1, v/v) as eluant to afford (**26**) (206 mg, 46.2%) as a mixture of olefinic isomers, $\nu_{max}(CHCl_3)$ 1 580 (C=C) and 1 700 cm^{-1} (CO); δ_H(400 MHz, $CDCl_3$) 2.74–3.02 (2 H, m, CH_2), 3.70 (3 H, s, OMe), 3.75–3.82 (1 H, m), 4.01–4.10 (1 H, m), 4.43–4.50 (1 H, m), 4.68–4.75 (1 H, m), 5.26 and 5.49 (total 1 H, dt and t, *J* 6 and 4 Hz, and *J* 6 Hz), 7.07–7.60 (8 H, m, ArH), and 7.95–8.05 (2 H, m, ArH) (Found: M^+, 455.1030. $C_{24}H_{21}NO_7S$ requires M^+, 455.1037).

(2R,3S)- *and* (2S,3S)-1-(2-*Benzoyloxymethyl*)-3-*t*-*butyldimethylsilyloxy*-2-*phenylthiopyrrolidin*-5-*one* (**28**).—Triethylamine (7.3 ml) was added to a solution of the alcohol (**9**) (15.5 g) and t-butyldimethylchlorosilane (9.8 g) in dry tetrahydrofuran (300 ml), and the resulting mixture was stirred at room temperature for 5 h. It was then poured into water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–

ethyl acetate (8:2, v/v) afforded (2*R*,3*S*)-(**28**) (13.5 g, 65.9%) as a colourless oil, $[\alpha]_D^{25}$ −11.8° (*c* 2.7 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 700 cm^{-1} (CO); δ_H(270 MHz, $CDCl_3$) −0.05 (3 H, s, Me), 0.00 (3 H, s, Me), 0.80 (9 H, s, Bu^t), 2.16 (1 H, dd, *J* 17 and 2 Hz), 2.26 (1 H, dd, *J* 17 and 5 Hz), 3.73 (1 H, ddd, *J* 14.5, 6.5, and 4.5 Hz), 4.30 (1 H, ddd, *J* 14.5, 6, and 4 Hz), 4.46–4.55 (2 H, m), 4.67 (1 H, ddd, *J* 11.5, 6, and 4 Hz), 4.87 (1 H, s, 2-H), 7.34–7.67 (8 H, m, ArH), and 8.06–8.09 (2 H, m, ArH); *m/z* 456 (M^+ − 15), 414 (M^+ − 57), and 362 (M^+ − 109) (Found: M^+ − 15, 456.1679. $C_{24}H_{30}NO_4SSi$ requires M^+ − 15, 456.1664). Further elution with hexane–ethyl acetate (7:3, v/v) gave (2*S*,3*S*)-(**28**) (4.43 g, 21.6%) as a colourless oil, $\nu_{max}(CHCl_3)$ 1 700 cm^{-1} (CO); δ_H(270 MHz, $CDCl_3$) −0.04 (3 H, s, Me), 0.00 (3 H, s, Me), 0.80 (9 H, s, Bu^t), 1.94 (1 H, dd, *J* 16.5 and 7.5 Hz), 2.23 (1 H, dd, *J* 16.5 and 7.5 Hz), 3.36 (1 H, ddd, *J* 14.5, 6.5, and 3.5 Hz), 4.03 (1 H, ddd, *J* 14.5, 6.5, and 4.5 Hz), 4.13 (1 H, ddd, *J* 11.5, 6.5, and 4.5 Hz), 4.30 (1 H, ddd, *J* 11.5, 6.5, and 3.5 Hz), 4.49 (1 H, dt, *J* 7.4 and 6 Hz, 3-H), 5.63 (1 H, d, *J* 6 Hz, 2-H), 7.13–7.48 (8 H, m, ArH), and 7.82–7.86 (2 H, m, ArH); *m/z* 456 (M^+ − 15), 414 (M^+ − 57), and 362 (M^+ − 109).

(2R,3S)-1-(2-*Hydroxyethyl*)-3-*t*-*butyldimethylsilyloxy*-2-*phenylthiopyrrolidin*-5-*one* (**29**).—A mixture of the benzoate (2*R*,3*S*)-(**28**) (8.05 g), potassium carbonate (1.18 g), and methanol (70 ml) was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was treated with water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to give a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) furnished the alcohol (**29**) (5.27 g, 84.0%) as a colourless oil, $\nu_{max}(CHCl_3)$ 1 670 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 0.00 (6 H, s, Me × 2), 1.88 (9 H, s, Bu^t), 2.51–2.32 (2 H, m, CH_2), 2.78–3.05 (1 H, br s), 3.38–4.18 (3 H, m), 4.60 (1 H, br t, *J* 3 Hz, 3-H), 4.83 (1 H, s, 2-H), and 7.52 (5 H, br s, ArH); *m/z* 352 (M^+ − 15) and 310 (M^+ − 57) (Found: M^+ − 15, 352.1410. $C_{17}H_{26}NO_3SSi$ requires M^+ − 15, 352.1403).

(2R,3S)-3-*t*-*Butyldimethylsilyloxy*-2-*phenylthio*-1-(2-*trimethylacetoxyethyl*)*pyrrolidin*-5-*one* (**30**).—Trimethylacetyl chloride (2.05 g) was added to a solution of the alcohol (**29**) (5.2 g) and pyridine (10 ml) in dry ether (100 ml) at 0 °C, and the resulting mixture was stirred at ambient temperature for 12 h. The mixture was diluted with dichloromethane and the organic layer was separated, washed with 2% hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4) and evaporated. The residue was then subjected to column chromatography on silica gel with benzene–ethyl acetate (9:1, v/v) as eluant to afford a solid. This crystallised from benzene–hexane to afford (**30**) (6.29 g, 98.5%) as needles, m.p. 88–88.5 °C; $[\alpha]_D^{25}$ −18.1° (*c* 2.12 in $CHCl_3$) (Found: C, 61.3; H, 8.4; N, 3.2. $C_{23}H_{37}NO_4SSi$ requires C, 61.15; H, 8.25; N, 3.1%); $\nu_{max}(CHCl_3)$ 1 680 cm^{-1} (CO); δ_H(60 MHz, $CDCl_3$) 0.00 (6 H, s, Me × 2), 0.85 (9 H, s, Bu^t), 1.20 (9 H, s, Bu^t), 2.11 (2 H, d, *J* 4 Hz), 3.34–4.58 (5 H, m), 4.78 (1 H, s, 2-H), and 7.45 (5 H, s, ArH); *m/z* 436 (M^+ − 15) and 394 (M^+ − 57).

(2R,3S)-3-*t*-*Butyldimethylsilyloxy*-2-*bis*(*benzyloxycarbonyl*)-*methyl*-1-(2-*trimethylacetoxyethyl*)*pyrrolidin*-5-*one* (**32**).—A solution of dibenzyl diazomalonate (3.2 g) in dry benzene (50 ml) was added dropwise over 1 h to a refluxing solution of (2*R*,3*R*)-(**30**) (1.22 g) and a catalytic amount of rhodium acetate in dry benzene (50 ml). The mixture was further heated under reflux for an additional 2 h. After removal of the solvent, the residue was chromatographed on silica gel with hexane–ethyl acetate (8:2, v/v) as eluant to afford an inseparable mixture of the malonate (**31**) and starting material (**30**) as an oil. This mixture was then treated with Raney nickel (W-2) (500 mg) in refluxing ethanol (100 ml) for 4 h. After the mixture had cooled, insoluble material was filtered off and the filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel with benzene–ethyl acetate (9:1, v/v) as eluant to afford (**32**) (1.13 g, 67.2%) as a colourless oil, $[\alpha]_D^{24}$ 6.41° (*c* 3.34 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 690 cm^{-1} (CO); δ_H(60 MHz, CCl_4) 0.00 (6 H, s, Me × 2), 0.81 (9 H, s, Bu^t), 1.05 (9 H, s, Bu^t), 1.58–3.10 (3 H, m), 3.51–4.58 (6 H, m), 5.02 (4 H, d, *J* 4 Hz), and 7.16 (10 H, s, ArH); *m/z* 610 (M^+ − 15) and 568 (M^+ − 57); (Found: M^+ − 15, 610.2835. $C_{33}H_{44}NO_8Si$ requires M^+ − 15, 610.2835).

(2R,3S)-3-*t*-*Butyldimethylsilyloxy*-2-*carboxymethyl*-1-(2-*trimethylacetoxyethyl*)*pyrrolidin*-5-*one* (**33**).—The malonate (**32**) (897 mg) was hydrogenated with 10% palladium on carbon (300 mg) in methanol (50 ml) at room temperature under an atmosphere of hydrogen overnight. The mixture was filtered to remove an insoluble material after which the filtrate was concentrated to give an oil. This was dissolved in toluene and the solution was heated at reflux for 2 h. The solvent was then removed to yield a solid which crystallised from benzene–hexane to afford the acid (**33**) (479 mg, 83.2%) as colourless needles, m.p. 154.5–156 °C; $[\alpha]_D^{25}$ 19.3° (*c* 1.08 in $CHCl_3$) (Found: C, 56.6; H, 9.0; N, 3.5. $C_{19}H_{35}NO_6Si$ requires C, 56.85; H, 8.8; N, 3.5%); $\nu_{max}(CHCl_3)$ 1 720 and 1 680 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 0.07 (6 H, s, Me × 2), 0.87 (9 H, s, Bu^t), 1.20 (9 H, s, Bu^t), 2.44 (1 H, dd, *J* 22 and 8 Hz), 2.48–2.84 (3 H, m), 2.95–3.28 (1 H, m), 3.80–4.39 (6 H, m), and 6.39 (1 H, br s); *m/z* 402 (M^+ + 1), 386 (M^+ − 15), and 344 (M^+ − 57).

(2R,3S)-2-*Carboxymethyl*-3-*hydroxy*-1-(2-*trimethylacetoxyethyl*)*pyrrolidin*-5-*one* (**34**).—A 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.44 ml) was added to a stirred solution of compound (**33**) (91 mg) in tetrahydrofuran (5 ml) and water (0.05 ml). The mixture was further stirred at room temperature for 2 h after which the solvent was removed. The residue was then treated with benzene and extracted with aqueous sodium hydrogen carbonate. The aqueous layer was acidified with 10% hydrochloric acid, and re-extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give the acid (**34**) (51 mg, 78.3%) as a colourless oil [$\nu_{max}(CHCl_3)$ 1 690 cm^{-1} (CO); δ_H(100 MHz, $CDCl_3$) 1.19 (9 H, s, Bu^t), 2.19–3.28 (6 H, m), and 3.65–4.51 (5 H, m); *m/z* 269 (M^+ − 18)] which without further purification was used to next reaction.

(1R,5S)-2-(2-*Trimethylacetoxyethyl*)-2-*aza*-6-*oxabicyclo*-[3.3.0]*octane*-3,7-*dione* (**27**).—Diethyl azodicarboxylate (93 mg) was added to a stirred solution of the acid (**34**) (154 mg) and triphenylphosphine (155 mg) in dry tetrahydrofuran (50 ml) and the mixture was stirred at room temperature overnight. It was then poured into water and extracted with dichloromethane. The organic layer was dried (Na_2SO_4), and evaporated to give a residue, which was subjected to column chromatography on silica gel with hexane–ethyl acetate (2:8, v/v) as eluant to afford a solid. This crystallised from benzene–hexane to provide the lactone (**27**) (91 mg, 63.0%) as colourless needles, m.p. 112–113 °C; $[\alpha]_D^{26}$ 55.2° (*c* 0.69 in $CHCl_3$) (Found: C, 58.05; H, 7.15; N, 5.15. $C_{13}H_{19}NO_5$ requires C, 58.0; H, 7.1 N, 5.2%); $\nu_{max}(CHCl_3)$ 1 770 and 1 690 cm^{-1} (CO); δ_H(270 MHz, $CDCl_3$) 1.13 (9 H, s, Bu^t), 2.67–2.72 (4 H, m), 2.99–3.09 (1 H, m), 3.92–4.06 (2 H, m), 4.25–4.34 (1 H, m), 4.47 (1 H, dt, *J* 5.5 and 3.5 Hz), and 5.05 (1 H, dt, *J* 5 and 2.5 Hz); *m/z* 269 (M^+).

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