1,2-Asymmetric Induction in Intramolecular Michael Reaction. A Novel and Enantioselective Route to (+)-Geissman Lactone[1]

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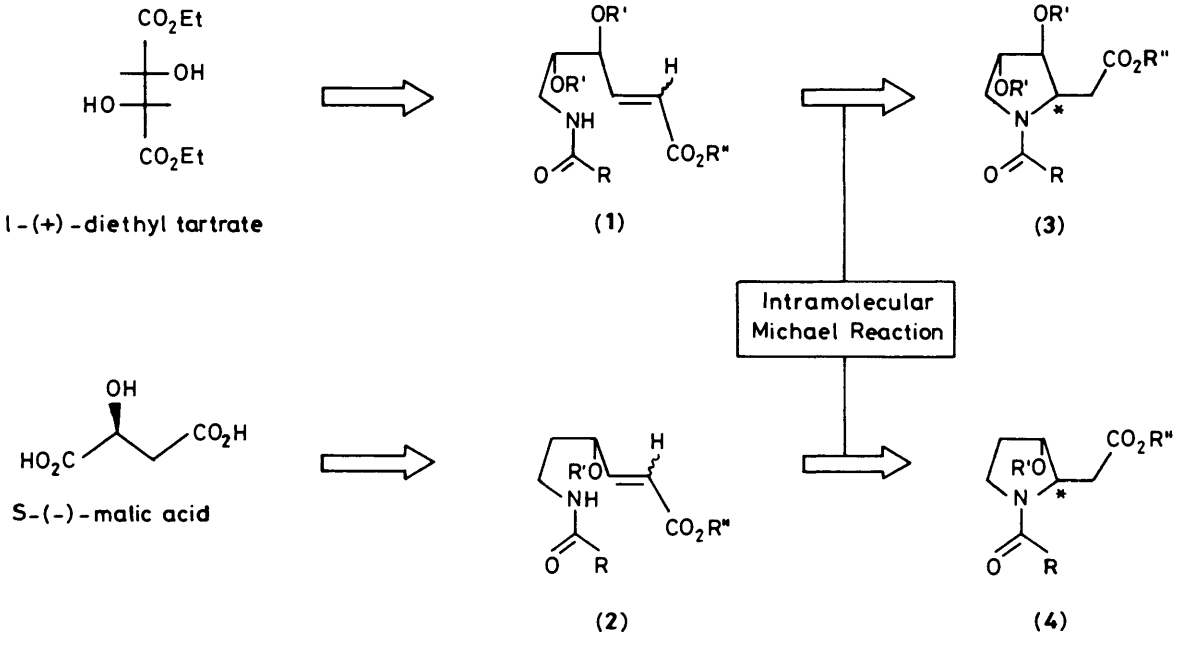
The Horner-Emmons reaction of the hemiacetal (**19**), derived from L-(+)-diethyl tartrate, was found to give the pyrrolidine (**21**) *via* an intramolecular Michael reaction as a mixture of diastereoisomers which, after treatment with ethanethiol and boron trifluoride–diethyl ether, was converted into the lactone (**22**) and the ester (**23**). The lactone (**22**), a minor component, could then be transformed into the Geissman lactone (**10**), a potential precursor for retronecine synthesis, *via* a three-step sequence. Alternatively, the hemiacetal (**41**), prepared from *S*-(−)-malic acid, was converted into the *Z*-α,β-unsaturated ester (**49**) whose intramolecular Michael reaction followed by cleavage of the corresponding methoxymethyl ether afforded the pyrrolidine (**51**) as a major product in a highly diastereoselective manner. The three-step conversion of (**51**) into (−)-ethyl 3-oxo-2-oxa-6-azabicyclo[3.3.0]octane-6-carboxylate (**32**) provided an efficient and stereocontrolled route to the Geissman lactone in optically active form.

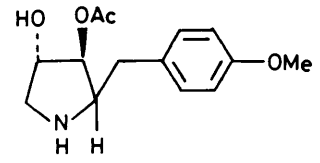
The intramolecular Michael reaction[2] is a powerful synthetic tool particularly for the synthesis of nitrogen heterocycles.[3] In the latter, two features of the Michael reaction are important: (i) the accessibility of the substrates and (ii) the nucleophilicity of the nitrogen atom shown towards the Michael acceptor. While the 1,2-asymmetric induction *via* an intramolecular Michael reaction[4,5] during the pyrrolidine ring-forming process has potential as a way of controlling chirality, practical examples are few. Our interest was, therefore, in 1,2-asymmetric induction of substrates with an oxygen function at the γ-carbon of the Michael acceptor in order to achieve stereochemical selectivity. Scheme 1 summarises our synthetic strategy. The substrates of general structure (**1**) and (**2**) are derived from L-(+)-diethyl tartrate and *S*-(−)-malic acid, inexpensive chiral starting materials available commercially. In each case cyclisation should proceed smoothly according to the 5-*exo*-*trig* mode of Baldwin's rule.[6]

Since the products (**3**) and (**4**) contain functional groups which may be manipulated into more complex products, this reaction should also provide an important method for the construction of complex, physiologically active natural products, *e.g.* anisomycin (**5**),[7] swainsonine (**6**),[8] retronecine (**7**),[9] heliotridine (**8**),[9] and hastanecine (**9**).[9]

Herein we now present experimental details of the intramolecular Michael reaction-based 1,2-asymmetric induction and a use of the strategy in the synthesis of the optically active Geissman lactone (**10**),[10] a potential intermediate for the synthesis of retronecine.[11]



Scheme 1.



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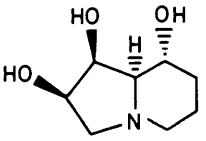

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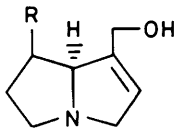
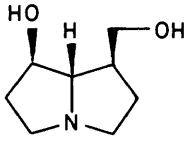


(7) R = β-OH

(8) R = α-OH



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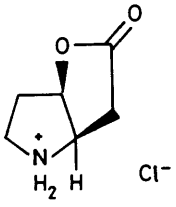

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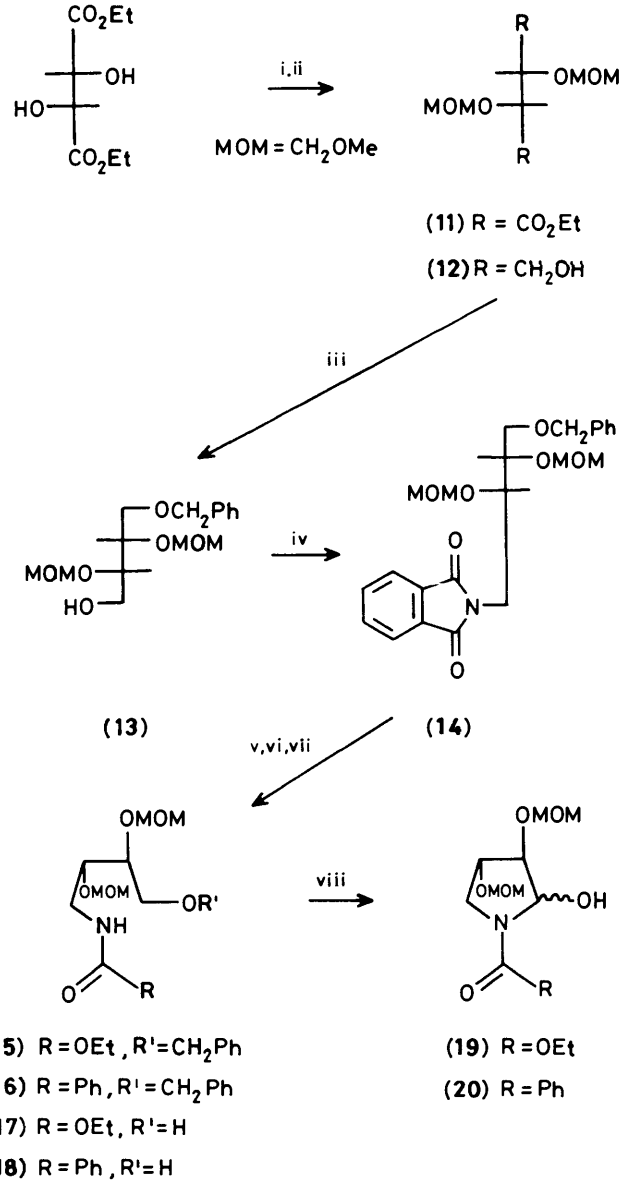


Scheme 2. *Reagents:* i, $CH_2(OMe)_2$, P_2O_5; ii, $LiAlH_4$; iii, $PhCH_2Br$, NaH; iv, phthalimide, Ph_3P, diethyl azodicarboxylate; v, $NH_2NH_2 \cdot H_2O$, EtOH; vi, $ClCO_2Et$, NEt_3, or PhCOCl, NEt_3; vii, H_2, 10% Pd–C; viii, $(COCl)_2$, Me_2SO, NEt_3

Results and Discussion

1,2-*Asymmetric Induction of the Substrates Derived from* L-(+)-*Diethyl Tartrate and a Synthesis of* (+)-*Geissman Lactone.*—Preparation of the key compounds (**19**) and (**20**) from L-(+)-diethyl tartrate was effected uneventfully by the sequence of reactions depicted in Scheme 2. The diol was protected as its methoxymethyl derivative by the method of Fujita and Fuji[12] followed by lithium aluminium hydride reduction and monobenzylation of the resulting diol (**12**) with benzyl bromide and sodium hydride to give the alcohol (**13**). Introduction of an amino functionality was accomplished by the sequential well-established Mitsunobu reaction[13] and Ing-Manske hydrazinolysis[14] of the resulting phthalimide (**14**). Acylation of the crude primary amine thus obtained with ethyl chloroformate or benzoyl chloride in the presence of triethylamine gave the carbamate (**15**) and the amide (**16**), which *via* hydrogenolysis and Swern oxidation[15] of the resulting primary alcohol moiety gave a mixture of the diastereoisomeric hemiacetals, (**19**) and (**20**) in 67 and 59% overall yield from the tartrate, respectively.

Treatment of the hemiacetal (**19**) with triethyl phosphonoacetate (3.4 equiv.) and sodium hydride (3.9 equiv.) in dimethoxyethane (DME) at room temperature for 39 h gave the pyrrolidinyl ester (**21**) as an inseparable diastereoisomeric mixture (70% yield). Examination of the ^1H n.m.r. spectrum of (**21**) showed a complete absence of vinyl protons, thus confirming that the initial reaction product, an α,β-unsaturated ester, had undergone a spontaneous Michael addition. Cleavage of the MOMO ether (**21**) with ethanethiol and boron trifluoride–diethyl ether[16] afforded a 74% yield of a readily separable 1:1.6 mixture of the lactone (**22**) and the ester (**23**). Both compounds were spectroscopically characterised as their acetates, (**26**) and (**27**). Similarly, Horner-Emmons reaction of the hemiacetal (**20**) and deprotection of the MOMO ether (**20a**) afforded an inseparable mixture of lactone (**24**) and ester (**25**), which was then acetylated to give a separable mixture of (**28**) and (**29**) in the ratio of 1:1 in 54% overall yield.

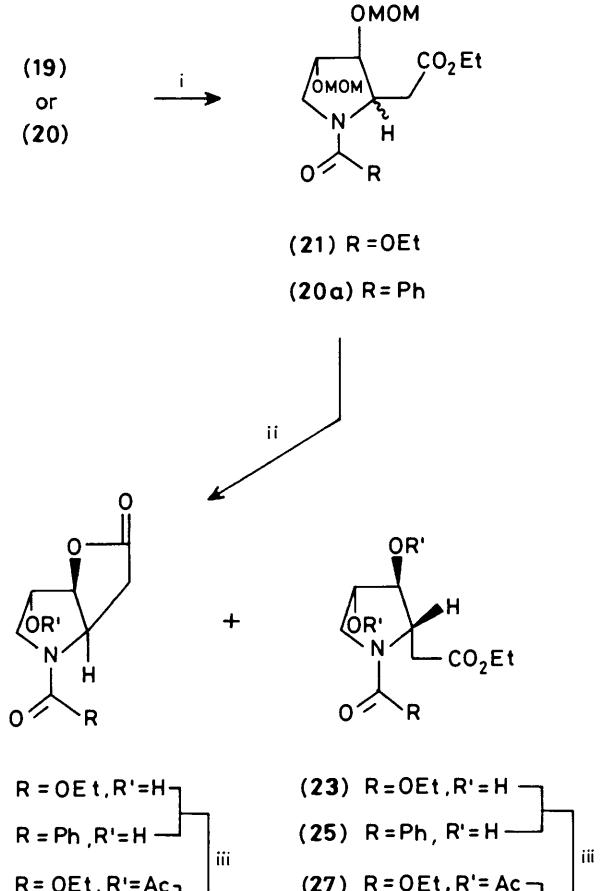
Prolonging the reaction time in the Horner-Emmons reaction, to allow for Michael-retro Michael equilibration, resulted in no change of the product distribution but caused a slight decomposition. Treatment of (**19**) with triethyl phosphonoacetate using potassium hydride[17] as base for 17 h led, after the same treatment as above, to the formation of (**22**) and (**23**) (71% yield), in a ratio of 1:3.4.

These results suggested that the 2*S*-isomer of (**21**) was the kinetic product. A preference for the formation of the 2*S*-isomer in the cyclisation can be rationalised by considering the transition state. The preferred conformation is assumed to be **A** (over **B**).[18] Therefore, attack of the nitrogen nucleophile would take place preferentially from the *si*-face to yield (**30**).

Conversion of the hydroxy lactone (**22**) into the Geissman lactone involved treatment of (**22**) with thiocarbonyldiimidazole[19] to afford the ester (**31**) which was then reduced with

Table 1. The conversion of hemiacetals (**19**) or (**20**) into (**22**) or (**24**) and (**23**) or (**25**).

	Hemiacetal	Base	Reaction time (h)	Ratio of (**22**):(**23**) or (**28**):(**29**)*	Overall yield from (**19**) or (**20**) (%)
(a)	(**19**)	NaH	39	1:1.6	52
(b)	(**19**)	KH	17	1:3.4	71
(c)	(**20**)	NaH	34	1:1*	54



Scheme 3. *Reagents:* i, $(EtO)_2POCH_2CO_2Et$, base, DME, room temperature; ii, EtSH, $BF_3{\cdot}OEt_2$; iii, Ac_2O, pyridine

tributyltin hydride[11c] to give the deoxygenated lactone (**32**) whose spectral data (i.r., ^1H n.m.r.) and the t.l.c. behaviour were indistinguishable from those of an authentic sample of the racemate.[11a] Finally, de-ethoxycarbonylation following the method of Ruegner and Benn furnished the Geissman lactone, m.p. 185—186.5 °C (lit.,[11b] 185—186 °C). The synthetic sample of (**10**) showed $[\alpha]_D^{24.8}$ +48.8° (*c* 0.2, MeOH) {lit.,[11b] $[\alpha]_D$ +48.5° (*c* 1.5, MeOH}, confirming that all the conversions proceed in an enantioselective manner.

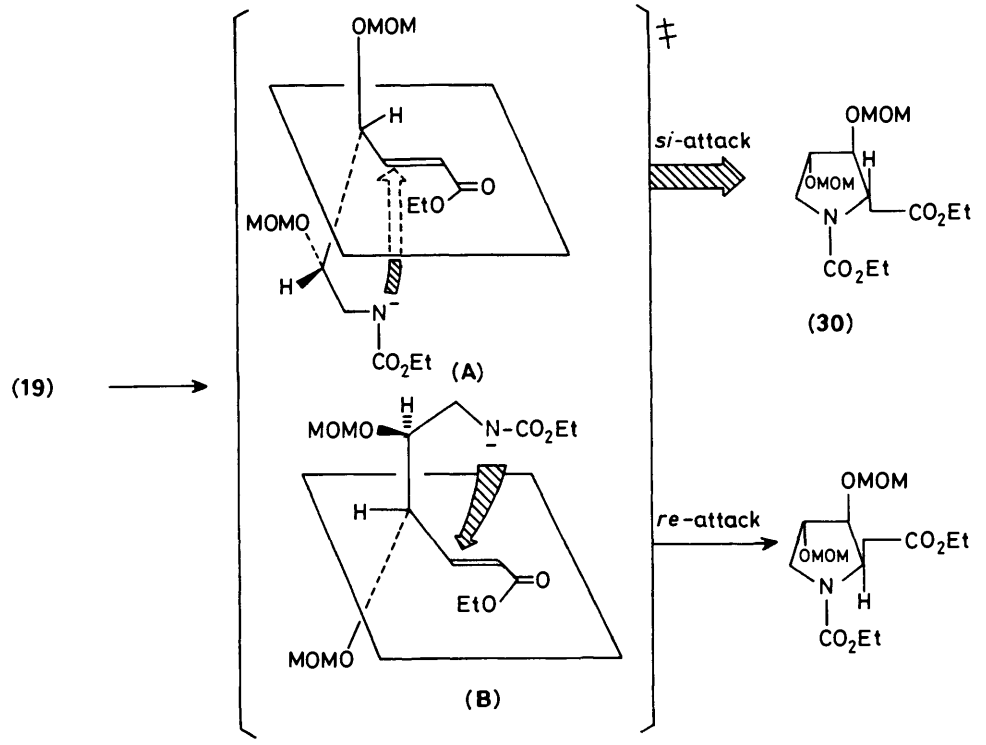
1,2-*Asymmetric Induction of the Substrates derived from* S-(−)-*Malic Acid and a Highly Diastereoselective Synthesis of* (**32**).—Treatment of (**19**) with Horner-Emmons reagent provided, *via* intramolecular ring closure, predominantly the 2*S*-isomer (**30**); this occurred as a result of a kinetically controlled, preferential *si*-face attack on the Michael acceptor by the nitrogen nucleophile. From these observations, it was expected that the intramolecular Michael reaction of a substrate, which contains the γ-oxygen function with reverse absolute configuration, should result in the predominant formation of the 2*R*-isomer. The 2*R*-isomer thus obtained could then be converted into the (+)-Geissman lactone by lactonisation with inversion at C-3. We therefore chose *S*-(−)-malic acid, the less expensive enantiomer available commercially, as a starting material. Reduction of the malic acid by the method of Hanessian[20] gave the triol (**33**) whose vicinal diol was then selectively protected as an acetal to afford (**34**).[21] The primary alcohol was then transformed into the urethane (**36**) *via* the same three-step sequence as in the previous case. Deprotection followed by the selective protection of the primary alcohol moiety with the dimethyl-t-butylsilyl group of the resulting diol (**37**) afforded (**38**). Treatment of the secondary alcohol with chloromethyl methyl ether and di-isopropylethylamine gave the corresponding MOMO ether (**39**), which upon treatment with tetrabutylammonium fluoride afforded (**40**) in 86% overall yield from the malic acid. Swern oxidation of (**40**) proceeded smoothly to furnish the hemiacetal (**41**) as a mixture of two diastereoisomers, quantitatively.

On treatment with triethyl phosphonoacetate (2.3 equiv.) and sodium hydride (2.5 equiv.) in DME at room temperature for 13 h, the diastereoisomeric hemiacetal (**41**) was converted into the cyclised product (**42**) as an inseparable diastereoisomeric mixture. Cleavage of the MOMO function afforded a chromatographically separable 1:1.4 mixture of the lactone (**43**) and the hydroxy ester (**44**) in 69% yield from (**41**). The spectral properties and the t.l.c. behaviour of (**43**) were identical with those of (**32**), although the sign of optical rotation was reversed; this indicated that (**43**) was the enantiomer of (**32**). The structure of the ester (**44**) was confirmed by the spectral properties of its acetate (**45**). Attempted reaction using potassium hydride as a base in the presence of a catalytic amount of 18-crown-6 for 95 min gave (**43**) and (**44**) in a ratio of 1:1.4 (65% overall yield). These results indicate that the intramolecular Michael process is rapid and that the cyclic product equilibrates under the reaction conditions. It was thought that if the intermediate unsaturated ester (**46**) could be isolated and treated with base for a short period of time then greater selectivity may result. Thus, treatment of (**41**) with triethyl phosphonoacetate (2.3 equiv.) and potassium hydride (3 equiv.) in DME at 0 °C for 45 min afforded the unsaturated ester (**46**) as an inseparable *E*/*Z* mixture in a ratio of 4:1 [from the ^1H n.m.r. in 92% yield (Method A)]. Alternatively, treatment of (**41**) with ethoxycarbonylmethylenetriphenylphosphorane (1.1 equiv.) in refluxing acetonitrile for 1 week gave (**46**), a 3:1 mixture of *E* and *Z* olefinic isomers in 90% yield (Method B). The results of diastereoselectivity in the Michael reaction are shown in Table 2.

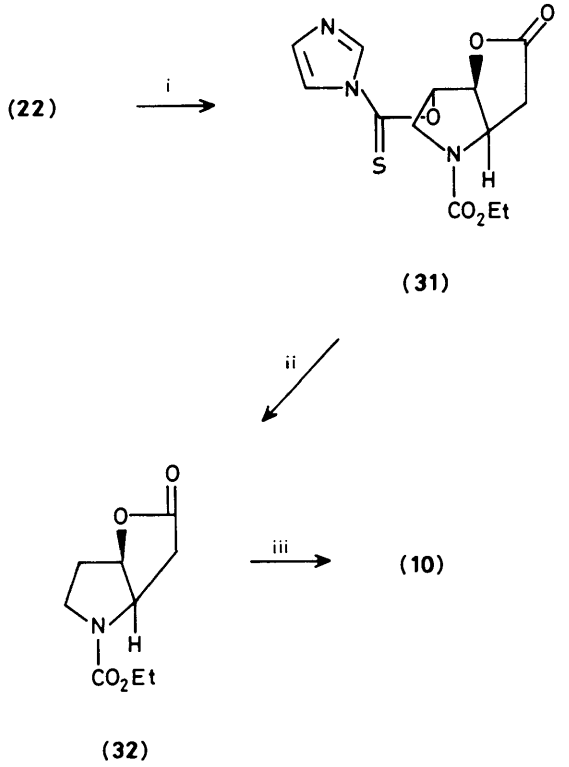
Optimum conditions for cyclisation to give the cyclic ester (**42**) involved the use of potassium hydride in DME at 0 °C for 34 min. The expected preferential formation of the 2*R*-isomer of (**42**) *via re*-face attack [see transition state (**C**) in Scheme 8] was confirmed by the results.

The molecular models suggest that because of the high degree of steric and electronic repulsion between the ester group and MOMO function in the transition state (**D**) ring closure leads to 2*S*-isomer *via si*-face attack (Scheme 9); the Michael reaction of the *Z*-olefinic isomer (**47a**) should, therefore, preferentially, give the 2*R*-isomer.

Thus, treatment of (**41**) with trimethyl phosphonoacetate[22] (2.0 equiv.) and potassium disilazide (2.0 equiv.) in the presence of 18-crown-6 (3.0 equiv.) at −78 °C—room temperature for 3.5 h gave an inseparable 1:2 (from ^1H n.m.r.) mixture of *E* and *Z* isomers of the unsaturated ester (**48**) (71% yield). Analogous



Scheme 4.



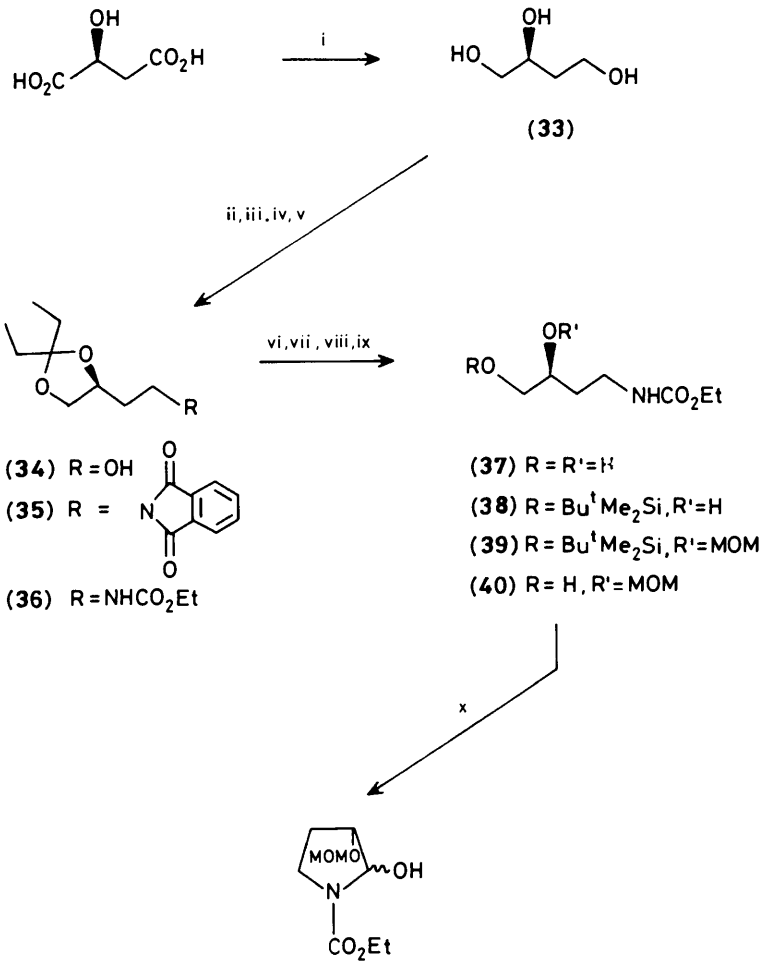
Scheme 5. *Reagents:* i, $(Imidazole)_2CS$; ii, Bu_3SnH; iii, $Ba(OH)_2 \cdot 8H_2O$ then HCl

treatment of the mixture afforded a 1:7.8 mixture of (**43**) and (**51**) (92% yield). Encouraged by this result, we examined the *Z*-olefination of the hemiacetal (**41**) and found that a modification of Still's method[23] gave exclusive formation of the *Z*-isomer. Under olefination conditions (see Experimental section) (**41**) gave (**49**) (55%), which was then cyclised; MOMO cleavage of the product then afforded (**43**) and (**51**) in a ratio of 1:39 (47% yield).

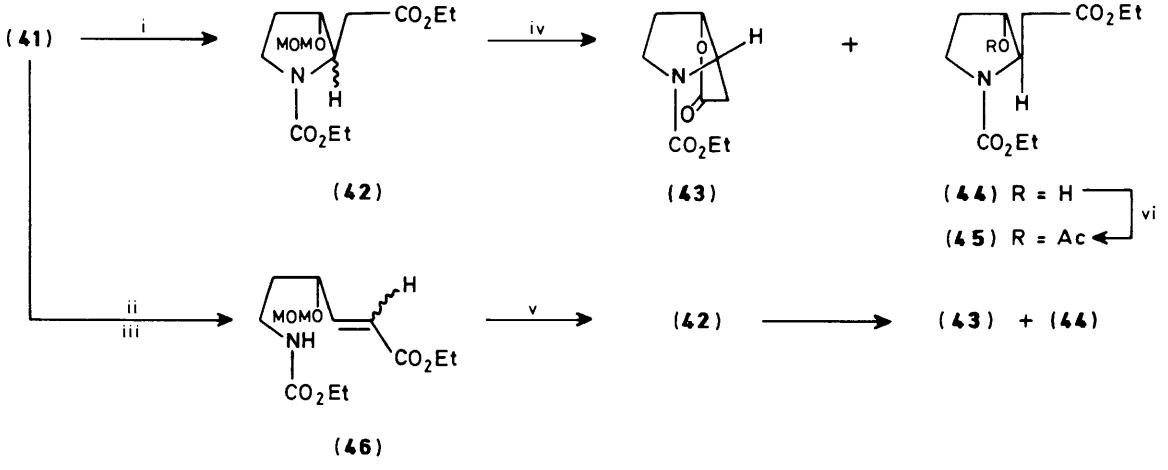
The stage was now set for us to examine the feasibility of the conversion of the major hydroxy esters (**44**) and (**51**) into the Geissman lactone. Independent treatment of (**44**) and (**51**) with methanesulphonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine gave the corresponding methanesulphonates (**52**) and (**53**) which were then hydrolysed with lithium hydroxide in aqueous dioxane to afford the carboxylic acid (**54**). Finally, (**54**) was exposed without purification to potassium carbonate and a catalytic amount of 18-crown-6 in acetonitrile to afford the desired lactone (**32**) in 86 and 82% overall yield from (**44**) and (**51**), respectively. The spectroscopic properties including optical rotation (see Experimental section) were identical with those of a sample prepared previously, confirming that the lactonisation proceeded with the anticipated complete inversion of configuration at the alcohol centre.

Experimental

General Methods.—M.p.s were determined on a Yanako micro-melting point apparatus and are uncorrected. I.r. spectra were measured with a Hitachi 260-10 recording spectrophotometer, n.m.r. spectra with JEOL JNM-PMX-60, JEOL PS-100, and JEOL JNM-GX-400 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra were taken on a Hitachi M-52G spectrometer and JEOL-TMS-OISG-2 spectrometer. All reactions were carried out under dry nitrogen. Column chromatography was carried out with silica gel (Wako gel C-200). The phrase 'residue upon work-up' refers to the residue when the organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. All new compounds described in the Experimental section were homogeneous on t.l.c.



Scheme 6. *Reagents:* i, $B(OMe)_3$, $BH_3{\cdot}SMe_2$, MeOH; ii, $Et_2C(OMe)_2$, *p*-$MeC_6H_4SO_3H$; iii, phthalimide, Ph_3P, diethyl azodicarboxylate; iv, $NH_2NH_2{\cdot}H_2O$, EtOH; v, $ClCO_2Et$, NEt_3; vi, 6N-HCl, THF; vii, Bu^tMe_2SiCl, imidazole, 4-dimethylaminopyridine; viii, $ClCH_2OMe$, Pr^i_2NEt; ix, Bu^n_4NF; x, $(COCl)_2$, Me_2SO, NEt_3

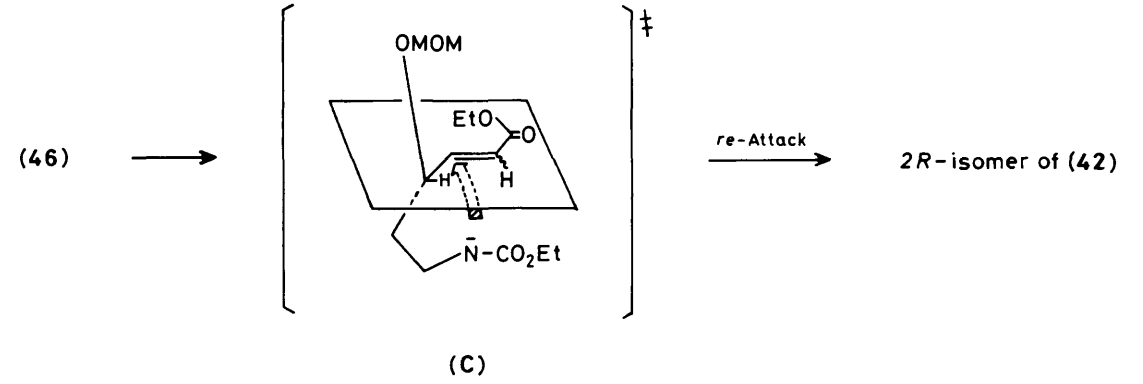


Scheme 7. *Reagents:* i, NaH or KH, $(EtO)_2POCH_2CO_2Et$; ii, (Method A) $(EtO)_2POCH_2CO_2Et$, KH, DME, 0 °C; iii, (Method B) $Ph_3P{=}CHCO_2Et$, MeCN, reflux; iv, EtSH, $BF_3{\cdot}OEt_2$; v, base, 0 °C; vi, Ac_2O, pyridine

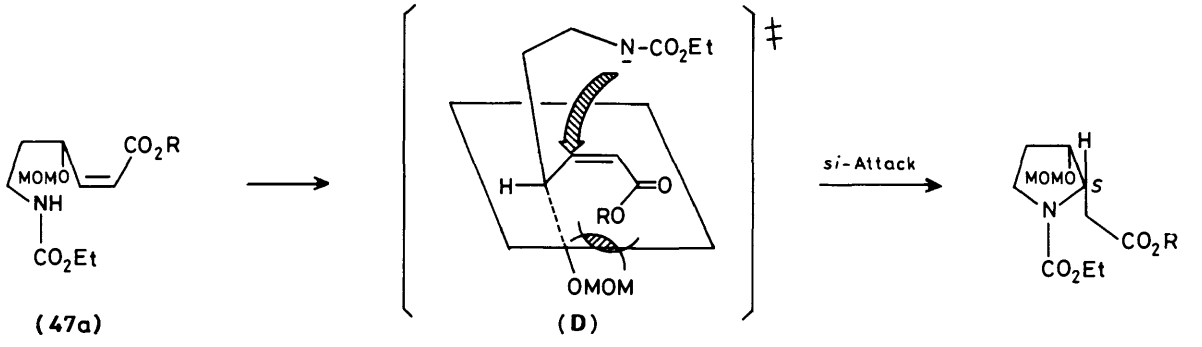
(+)-(2R,3R)-*Diethyl* 2,3-*Bismethoxymethoxybutanedioate* (**11**).—A solution of L-(+)-diethyl tartrate (50 g, 0.24 mol) in anhydrous chloroform (2 l) was stirred with dimethoxymethane (194 g, 2.54 mol) and phosphorus pentaoxide (171 g, 1.21 mol) at room temperature for 2.5 h. Saturated aqueous sodium carbonate was added to the mixture and the organic layer separated; the aqueous layer was then extracted with chloroform. The combined organic phases were washed with

Table 2. The intramolecular Michael reaction of (**46**)

	Method for (**46**)	Base	Additive	Reaction time (min)	Solvent	Ratio of (**43**):(**44**)	Yield of (**43**) + (**44**) from (**46**) (%)
(i)	B	NaH		45	DME	1:1.9	83
(ii)	B	KH	18-crown-6 (cat.)	16	THF	1:2.1	86
(iii)	A	KH	18-crown-6 (cat.)	34	DME	1:5.0	82



Scheme 8.

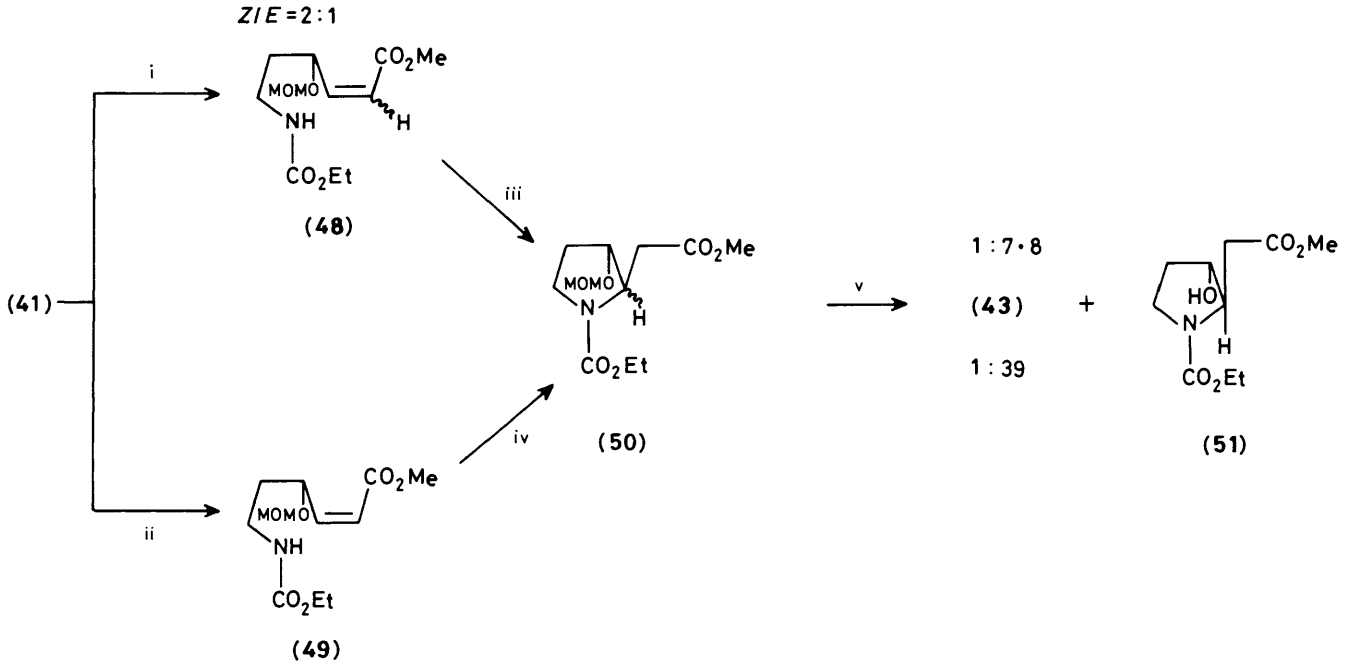


Scheme 9.

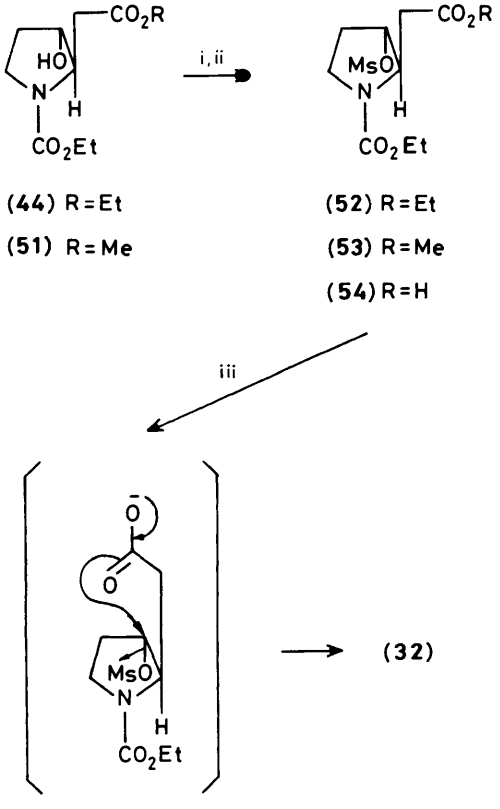
saturated brine. The residue upon work-up was the crude *ester* (**11**) (79 g, 100%) as a pale yellow oil, which was used in the next reaction without further purification. An analytical sample of (**11**) was obtained by column chromatography using hexane–ethyl acetate (3:2, v/v) as an oil (Found: C, 48.7; H, 7.45. $C_{12}H_{22}O_8$ requires C, 49.0; H, 7.55%); $[\alpha]_D^{27}$ +141.0° (*c* 1.55, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 750 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.33 (6 H, t, *J* 7.0 Hz, OCH_2Me × 2), 3.30 (6 H, s, OMe × 2), 4.20 (4 H, q, *J* 7.0 Hz, OCH_2Me × 2), and 4.53—4.83 (6 H, m); *m/z* 263 (M^+ − OMe).

(−)-(2S,3S)-2,3-*Bis*(*methoxymethoxy*)*butane*-1,4-*diol* (**12**).—To a stirred suspension of lithium aluminium hydride (23 g, 0.61 mol) in anhydrous tetrahydrofuran (THF) (600 ml) was added dropwise a solution of the ester (**11**) (79 g, 0.24 mol) in anhydrous THF (500 ml) at 0 °C. Stirring was continued for 1 h, when the mixture was quenched with 30% aqueous sodium hydroxide at 0 °C. After filtration through Celite, the filtrate was concentrated to give the residue which was submitted to vacuum distillation, b.p. 125—147 °C at 0.2—0.3 mmHg, to give the *diol* (**12**) (43 g, 85%) as an oil. With time crystals formed and recrystallisation from benzene–hexane gave needles, m.p. 64 °C (Found: C, 45.45; H, 8.35. $C_8H_{18}O_6$ requires C, 45.7; H, 8.65%); $[\alpha]_D^{25}$ −41.3° (*c* 1.32, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 400 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.40 (8 H, br s, OMe × 2 and OH × 2, two of these D_2O disappeared), 3.70 (6 H, br s, CH_2OH × 2 and *CH* × 2), and 4.70 (4 H, s, OCH_2O × 2).

(−)-(2S,3S)-4-*Benzyloxy*-2,3-*bis*(*methoxymethoxy*)*butan*-1-*ol* (**13**).—To a stirred suspension of sodium hydride (60% in oil; 2.14 g, 53.5 mmol) in anhydrous dimethylformamide (DMF) was added dropwise a solution of the diol (**12**) (10.6 g, 50.5 mmol) in anhydrous DMF (40 ml) at −40—−20 °C. Stirring was continued for 0.5 h, when a solution of benzyl bromide (8.9 g, 52.0 mmol) in anhydrous DMF (40 ml) was added dropwise to the mixture. The mixture was stirred at −20 °C—room temperature for 10 h, after which the solvent was evaporated off, the residue extracted with methylene dichloride, and the organic



Scheme 10. *Reagents:* i, $(MeO)_2POCH_2CO_2Me$, $KN(TMS)_2$, 18-crown-6, THF, 3.5 h; ii, $(CF_3CH_2O)_2POCH_2CO_2Me$, KH, DME, 3 h; iii, KH, 18-crown-6, DME, 0 °C, 21 min; iv, KH, 18-crown-6, DME, 0 °C, 9 min; v, EtSH, BF_3·OEt_2



Scheme 11. *Reagents:* i, $MeSO_2Cl$, NEt_3, 4-DMAP; ii, LiOH, dioxane, H_2O; iii, K_2CO_3, 18-crown-6(cat.), MeCN

phase washed with saturated brine. The residue upon work-up was the crude *alcohol* (**13**) (15 g, 99%) as the yellow oil which was used for the next reaction without further purification. An analytical sample of (**13**) as an oil was obtained by column chromatography using hexane–ethyl acetate (2:3, v/v) as an eluant (Found: C, 60.0; H, 8.05. $C_{15}H_{24}O_6$ requires C, 59.8; H, 7.85%); $[\alpha]_D^{26}$ −2.51° (*c* 1.08, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.00 (1 H, br s, OH, D_2O disappeared), 3.35 (6 H, s, OMe × 2), 4.50 (2 H, s, OCH_2Ph), 4.66 (4 H, m, OCH_2O × 2), and 7.30 (5 H, s, ArH); *m/z* 300 (M^+).

(−)-(2S,3S)-N-(4-*Benzyloxy*-2,3-*bis*(*methoxymethoxy*)*butyl*-*phthalimide* (**14**): *General.*—To a stirred solution of the alcohol (**13**) (528 mg, 1.76 mmol) in anhydrous THF (5 ml) was added phthalimide (388 mg, 2.64 mmol), triphenylphosphine (542 mg, 2.07 mmol), and diethyl azodicarboxylate (365 mg, 2.11 mmol) at 0 °C. The mixture was stirred for 10 min at room temperature after which the solvent was evaporated off and the residue chromatographed using hexane–ethyl acetate (7:3, v/v) as an eluant to afford the *phthalimide* (**14**) (692 mg, 92%) as an oil, $[\alpha]_D^{28}$ −43.3° (*c* 1.38, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 710 and 1 770 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.10 and 3.43 (3 H, each, s, OMe), 4.53 and 4.56 (2 H, each, s, OCH_2O), 4.76 (2 H, s, CH_2Ph), 7.27 (5 H, s, ArH), and 7.74 (4 H, m, ArH) (Found: M^+ − OEt, 384.1444. $C_{21}H_{22}NO_6$ requires *M* − OEt, 384.1445).

(−)-(2S,3S)-*Ethyl* 1-*Amino*-4-*benzyloxy*-2,3-*bis*(*methoxy*-*methoxy*)*butane*-N-*carboxylate* (**15**).—A solution of the phthalimide (**14**) (3.18 g, 7.40 mmol) and 90% hydrazine hydrate (1.17 g, 21.1 mmol) in ethanol (60 ml) was heated under reflux for 2.5 h. After filtration, the filtrate was evaporated to give the crude amine which was taken up with anhydrous methylene dichloride (60 ml). To the solution, triethylamine (3.80 g, 37.6 mmol) and ethyl chloroformate (4.09 g, 37.6 mmol) were added at 0 °C. The mixture was stirred for 17 h at room temperature, after which it was diluted with water and the organic layer separated. The aqueous layer was extracted with methylene dichloride, and the combined organic phases were washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (3:2, v/v) as eluant to afford the *title compound* (**15**) (2.44 g, 89%) as an oil (Found: C, 58.15; H, 7.6; N, 3.55. $C_{18}H_{29}NO_7$ requires C, 58.2; H, 7.85; N, 3.75%); $[\alpha]_D^{27}$ −0.58° (*c* 0.96, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 400 and 1 710 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.6 Hz, OCH_2Me), 3.36

(6 H, s, OMe × 2), and 7.25 (5 H, br s, ArH); *m/z* 340 (M^+ − OMe).

(−)-(2S,3S)-N-*Benzoyl*-4-*benzyloxy*-2,3-*dimethoxymethoxybutylamine* (**16**).—A solution of the crude amine, prepared from the phthalimide (**14**) (8.62 g, 20 mmol) and 85% hydrazine hydrate (3.31 g, 56 mmol) by the same procedure as described above, in anhydrous methylene dichloride (30 ml) was treated with triethylamine (6.05 g, 60 mmol) and benzoyl chloride (4.21 g, 30 mmol) to afford the amine (**16**) (6.35 g, 79%), after column chromatography using hexane–ethyl acetate (3:2, v/v) as an eluant, as a pale yellow oil, $[\alpha]_D^{25}$ −17.9° (*c* 1.44, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 400 and 1 660 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 3.33 and 3.36 (3 H each, s, OMe), 4.46 (2 H, s, CH_2Ph), 7.20 (5 H, s, ArH), 7.36 (3 H, m, ArH), and 7.66 (2 H, m, ArH) (Found: M^+, 403.2023. $C_{22}H_{29}NO_6$ requires *M*, 403.1995).

(−)-(2S,3S)-*Ethyl* 1-*Amino*-2,3-*bis*(*methoxymethoxy*)-4-*hydroxybutane*-N-*carboxylate* (**17**).—A solution of the carbamate (**15**) (3.35 g, 9.0 mmol) in anhydrous ethanol (90 ml) was hydrogenated over 10% palladium–carbon (660 mg) under a pressure of 6 kg/cm^2 at room temperature for 22 h. After filtration through Celite, the filtrate was concentrated to give the residue which was chromatographed using hexane–ethyl acetate (2:3, v/v) as an eluant to afford the *alcohol* (**17**) (2.46 g, 97%) as needles after recrystallisation from ether–hexane, m.p. 50—52 °C (Found: C, 47.05; H, 8.1; N, 5.05. $C_{11}H_{23}NO_7$ requires C, 46.95; H, 8.25; N, 5.0%); $[\alpha]_D^{24}$ −27.0° (*c* 1.33, $CHCl_3$); $\nu_{max.}(CHCl_3)$; 3 450 and 1 710 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.23 (3 H, t, *J* 7.6 Hz, OCH_2Me), 2.96 (1 H, br s, OH, D_2O disappeared), 3.42 (6 H, s, OMe × 2), 4.10 (2 H, q, *J* 7.6 Hz, OCH_2Me), 4.67 and 4.71 (2 H each, s, OCH_2O), and 5.24 (1 H, br s, NH); *m/z* 250 (M^+ − OMe).

(−)-(2S,3S)-N-*Benzoyl*-4-*hydroxy*-2,3-*bis*(*methoxymethoxy*)-*butylamine* (**18**).—The benzoate (**16**) (1.80 g, 3.79 mmol) was hydrogenated over 10% palladium–carbon (500 mg) for 84 h under atmospheric pressure. After column chromatography using hexane–ethyl acetate (1:4, v/v) as eluant, the *alcohol* (**18**) (1.33 g, 100%) was obtained as an oil (Found: C, 57.7; H, 7.3; N, 4.4. $C_{15}H_{23}NO_6$ requires C, 57.5; H, 7.4; N, 4.45%); $[\alpha]_D^{25}$ − 43.5° (*c* 1.56, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 440 and 1 660 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 2.93 (1 H, br s, OH, D_2O disappeared), 3.40 and 3.43 (3 H each, s, OMe), 4.75 (4 H, s, OCH_2O × 2), 7.43 (3 H, m, ArH), and 7.76 (2 H, m, ArH); *m/z* 282 (M^+ − OMe).

Swern Oxidation of (**17**): *General.*—To a stirred solution of oxalyl chloride (1.0 g, 7.9 mmol) in anhydrous methylene dichloride (34 ml) was added dropwise a solution of dimethyl sulphoxide (DMSO) (1.23 g, 15.8 mmol) in anhydrous methylene dichloride (2 ml) at −78 °C. To the mixture was added dropwise a solution of the alcohol (**17**) (2.02 g, 7.20 mmol) in anhydrous methylene dichloride (4 ml) and stirring was continued for 15 min. Triethylamine (3.63 g, 36 mmol) was then added dropwise at the same temperature. The mixture was stirred for 0.5 h at room temperature after which it was diluted with water and the aqueous layer separated and extracted with methylene dichloride. The combined organic phases were washed with saturated brine and the residue upon work-up was chromatographed using hexane–ethyl acetate (2:3, v/v) as an eluant to afford the hemiacetal (**19**) (2.02 g, 100%), a mixture of two diastereoisomers, as an oil; $\nu_{max.}(CHCl_3)$ 3 500 and 1 690 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.6 Hz, OCH_2Me), 3.37 and 3.46 (3 H each, s, OMe), 4.69 and 4.75 (2 H each, s, OCH_2O), and 5.13—5.56 (2 H, m, NCHOH, one of these D_2O disappeared) (Found: M^+ − OH, 262.1252. $C_{11}H_{20}NO_6$ requires *M* − OH, 262.1289).

Swern Oxidation of (**18**).—According to the procedure for (**17**), the *hemiacetal* (**20**) (96%) was obtained by column chromatography using hexane–ethyl acetate (1:1, v/v) as eluant; $\nu_{max.}(CHCl_3)$ 3 525 and 1 635 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 3.36 (6 H, br s, OMe × 2), 4.64 (4 H, br s, OCH_2O × 2), and 7.26—7.96 (5 H, m, ArH) (Found: M^+ − OH, 294.1352. $C_{15}H_{20}NO_5$ requires *M* − OH, 294.1342).

Sequential Horner-Emmons and Michael Reaction of (**19**).—*Method* (*a*) *Using sodium hydride.* To a stirred suspension of sodium hydride (60% in oil; 88 mg, 2.21 mmol) in anhydrous dimethoxyethane (DME) (4 ml) were added dropwise and sequentially at room temperature triethyl phosphonoacetate (435 mg, 1.95 mmol) and the hemiacetal (**19**) (158 mg, 0.566 mmol) in ahydrous DME (1 ml). After being stirred for 39 h, the mixture was quenched with saturated aqueous ammonium chloride, and the solvent was evaporated off to give the residue which was extracted with methylene dichloride. The extract was washed with saturated brine and the residue upon work-up was chromatographed using hexane–ethyl acetate (7:3, v/v) as eluant to afford the *ester* (**21**) (139 mg, 70%), a mixture of two diasteroisomers, as an oil (Found: C, 51.55; H, 7.95; N, 3.9. $C_{15}H_{27}NO_8$ requires C, 51.55; H, 7.8; N, 4.0%); $\nu_{max.}(CHCl_3)$ 1 725 and 1 690 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.18 (6 H, t, *J* 7.6 Hz, OCH_2Me × 2), 3.27 and 3.30 (3 H each, s, OMe), 3.40—3.64 (2 H, m, CH_2N), 3.84—4.24 (6 H, m), and 4.40—4.80 (4 H, m); *m/z* 318 (M^+ − OMe).

Method (*b*) *Using potassium hydride.* According to the procedure described above (except the reaction time, see Table 1), the ester (**21**) (78%) was obtained as a mixture of two diasteroisomers.

(−)-(1S,5R,8S)-*Ethyl* 8-*Hydroxy*-3-*oxo*-2-*oxa*-6-*azabicyclo*-[3.3.0]*octane*-6-*carboxylate* (**22**) *and* (+)-(2S,3S,4S)-*Ethyl* 2-(*Ethoxycarbonyl*)*methyl*-3,4-*dihydroxypyrrolidine*-1-*carboxylate* (**23**): *General.*—A stirred solution of the ester (**21**) (139 mg, 0.39 mmol), prepared by method (a), in anhydrous methylene dichloride (1.5 ml) was added dropwise to a mixture of ethanethiol (126 mg, 1.99 mmol) and boron trifluoride–diethyl ether (289 mg, 1.99 mmol) at room temperature. The mixture was stirred for 10 min after which the solvent and the excess reagents were evaporated off to give a residue which was chromatographed using hexane–ethyl acetate (2:3, v/v) as eluant to afford the *lactone* (**22**) (24 mg, 28%) as an oil, $[\alpha]_D^{23}$ − 64.8° (*c* 2.19, MeOH); $\nu_{max.}(CHCl_3)$ 3 380, 1 790, and 1 695 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.6 Hz, OCH_2Me), 1.38 (1 H, br s, O*H*, D_2O disappeared), 2.68—2.82 (2 H, m, OCH_2O), 3.30—3.72 (2 H, m, CH_2N), 4.16 (2 H, q, *J* 7.6 Hz, OCH_2Me) (Found: M^+, 215.0804. $C_9H_{13}NO_5$ requires *M*, 215.0794). From the later fractions, the *ester* (**23**) (48 mg, 46%) was obtained as an oil, $[\alpha]_D^{24}$ +48.3° (*c* 0.77, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 400 and 1 700 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.26 and 1.27 (3 H each, t, *J* 7.6 Hz, OCH_2Me), 2.39 (1 H, br s, O*H*, D_2O disappeared), and 4.14 and 4.15 (2 H each, q, *J* 7.6 Hz, OCH_2Me) (Found: M^+ − H_2O, 243.1102. $C_{11}H_{17}NO_5$ requires *M* − H_2O, 243.1105).

(b) The ester (**21**) (1.50 g, 4.3 mmol), prepared by method (b), was similarly converted into the lactone (**22**) (190 mg, 21%) and the ester (**23**) (790 mg, 70%).

Sequential Horner-Emmons and Michael Reaction of (**20**).—According to the procedure for [(**19**), method (a)], the hemiacetal (**20**) (1.27 g, 4.09 mmol) was converted into the *ester* (**20a**) (1.11 g, 71%) as a pale yellow oil, a mixture of two diastereoisomers, which was purified by column chromatography using hexane–ethyl acetate (13:7, v/v) as eluant (Found: C, 60.0; H, 7.2; N, 3.7. $C_{19}H_{27}NO_7$ requires C, 59.85; H, 7.15; N, 3.65%); $\nu_{max.}(CHCl_3)$ 1 720 and 1 620 cm^{-1}; δ_H (100 MHz;

$CDCl_3$) 1.31 (3 H, t, *J* 8.0 Hz, $-OCH_2Me$), and 7.39 (5 H, m, ArH); *m/z* 381 (M^+).

(+)-(2S,3S,4S)-*Ethyl* 3,4-*Diacetoxy*-N-*benzoyl*-2-*methylpyrrolidine*-2-*carboxylate* (**29**) *and* (−)-(1S,5R,8S)-*Methyl* N-*Benzoyl*-3-*oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-8-*carboxylate* (**28**).—According to the general procedure for (**22**) and (**23**), the ester (**20a**) (1.05 g, 2.76 mmol) was converted into an inseparable mixture (817 mg) of the lactone (**24**) and the ester (**25**), which without further purification was treated with acetic anhydride (8 ml) and pyridine (8 ml) at room temperature for 10 h. After evaporation of the excess reagents, the residue was chromatographed using hexane–ethyl acetate (3:2, v/v) as eluant to afford the *ester* (**29**) (395 mg, 38%) as a pale yellow oil, $[\alpha]_D^{23}$ +88.3° (*c* 1.47, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 750 and 1 630 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.19 (3 H, t, *J* 8.0 Hz, OCH_2Me), 2.02 (6 H, s, OCOMe × 2), 2.60—3.16 (2 H, m, CH_2CO_2Et), 3.56 (1 H, dd, *J* 12.0 and 4.0 Hz, HC*H*N), 3.68—4.24 (3 H, m), 4.28—4.64 (1 H, m), 4.84—5.12 (1 H, m, HC*H*OAc), 5.16—5.40 (1 H, m, C*H*OAc), and 7.17—7.44 (5 H, m, ArH) (Found: M^+, 332.1140. $C_{17}H_{18}NO_6$ requires *M*, 332.1135). From the later fractions, the *lactone* (**28**) (294 mg, 38%) was obtained as needles after recrystallisation from benzene, m.p. 187.5—188.5 °C (Found: C, 62.55; H, 5.05; N, 4.95. $C_{15}H_{15}NO_5$ requires C, 62.3; H, 5.25; N, 4.85%); $[\alpha]_D^{26}$ −131.7° (*c* 0.35, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 790, 1 740, and 1 620 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.98 (3 H, s, OCOMe), 2.84 (2 H, br s, CH_2CO_2), 3.69 (1 H, d, *J* 14.0 Hz, 7a-H), 3.89 (1 H, dd, *J* 14.0 and 4.0 Hz, 7b-H), 4.85 (1 H, d, *J* 6.0 Hz, 1-H), 4.90—5.08 (1 H, m, 3-H), 5.20 (1 H, d, *J* 4.0 Hz, 5-H), and 7.20—7.32 (5 H, m, ArH); *m/z* 289 (M^+).

(+)-(1S,5R,8S)-*Ethyl* 8-*Acetoxy*-3-*oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**26**).—A mixture of the lactone (**22**) (22 mg, 0.102 mmol), acetic anhydride (0.25 ml), and pyridine (0.25 ml) was stirred at room temperature for 12 h. After evaporation of the excess of reagents, the residue was chromatographed using hexane–ethyl acetate (7:3, v/v) as eluant to afford the *acetate* (**26**) (16 mg, 61%) as leaflets after recrystallisation from ethanol–hexane, m.p. 137—139 °C (Found: C, 50.9; H, 5.95; N, 5.4. $C_{11}H_{15}NO_6$ requires C, 51.35; H, 5.9; N, 5.45%); $[\alpha]_D^{24}$ +47.6° (*c* 0.96, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 795, 1 745, and 1 695 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.5 Hz, OCH_2Me), 2.10 (3 H, s, OCOMe), 2.81 (1 H, dd, *J* 18.5 and 6.3 Hz, −*H*CHCO−), 2.93 (1 H, d, *J* 18.5 Hz, C*H*CO), 3.67 (1 H, dd, *J* 13.1 and 3.9 Hz, −HC*H*N), 3.75 (1 H, d, *J* 13.1 Hz, *H*CHN), 4.15 (2 H, q, *J* 7.5 Hz, OCH_2Me), 4.64 (1 H, dd, *J* 6.3 and 4.4 Hz, NCH), 4.87 (1 H, d, *J* 4.4 Hz, CHOCO), and 5.34 (1 H, d, *J* 3.9 Hz, C*H*OAc); *m/z* 257 (M^+).

(+)-(2S,3S,4S)-*Ethyl* 3,4-*Diacetoxy*-2-*ethoxycarbonylmethylpyrrolidine*-1-*carboxylate* (**27**).—According to the procedure for (**26**), the ester (**23**) (32 mg, 0.123 mmol) was converted into the *acetate* (**27**) (26 mg, 61%) as an oil after column chromatography using hexane–ethyl acetate (7:3, v/v) as eluant (Found: C, 51.8; H, 6.7; N, 3.95. $C_{15}H_{23}NO_8$ requires C, 52.15; H, 6.7; N, 4.05%); $[\alpha]_D^{26}$ +39.3° (*c* 0.48, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 740 and 1 695 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.27 (6 H, t, *J* 7.5 Hz, OCH_2Me × 2), 2.08 and 2.11 (3 H each, s, OCOMe), 2.62 (1 H, dd, *J* 15.5 and 10.0 Hz, *H*CHCO$_2$Et), 2.96 (1 H, m, HC*H*CO$_2$Et), 3.52 (1 H, d, *J* 12.5 Hz, HC*H*N), 3.85 (1 H, dd, *J* 12.5 and 4.0 Hz, *H*CHN), 4.16 (4 H, q, *J* 7.5 Hz, OCH_2Me × 2), 5.10 (1 H, d, *J* 4.0 Hz, C*H*OAc), and 5.17 (1 H, s, C*H*OAc); *m/z* 300 (M^+ − OEt).

(1S,5R,8S)-*Ethyl* 8-(*Imidazol*-1-*ylthiocarbonyloxy*)-3-*oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**31**).—To a stirred solution of the lactone (**22**) (44 mg, 0.205 mmol) in anhydrous 1,2-dichloroethane (1 ml) was added a solution of thiocarbonyldi-imidazole (81 mg, 0.410 mmol) in anhydrous 1,2-dichloroethane (1 ml). The resulting solution was heated at 70 °C for 2 h after which the solvent was evaporated off to give the residue which was chromatographed using hexane–ethyl acetate (2:3, v/v) as eluant to afford the ester (**31**) (60 mg, 90%) as a pale yellow oil; $\nu_{max.}$($CHCl_3$) 1 800 and 1 700 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.6 Hz, OCH_2Me), 2.90 (2 H, d, *J* 4.0 Hz, CH_2CO_2), 3.81—4.44 (4 H, m), 4.72 (1 H, m, CHN), 5.14 (1 H, d, *J* 5.0 Hz, CHOCO), 5.97 (1 H, d, *J* 3.6 Hz, CHOCS), and 7.04, 7.54, and 8.24 (1 H each, br s, ArH). The material thus obtained was used immediately for the next reaction.

(−)-(1S,5R)-*Ethyl* 3-*Oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**32**).[11a]—To a stirred solution of 97% tributyltin hydride (469 mg, 1.56 mmol) in anhydrous toluene (68 ml) was added dropwise a solution of the imidazolide (**31**) (332 mg, 1.02 mmol) in anhydrous toluene (17 ml) under reflux for 0.5 h. The mixture was then further heated under reflux for 0.5 h, after which the solvent was evaporated off to give the residue which was chromatographed using hexane–ethyl acetate (1:1, v/v) as eluant to afford the *lactone* (**32**) (172 mg, 85%) as an oil, $[\alpha]_D^{24}$ −146.7° (*c* 1.61, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 790 and 1 700 cm^{-1}; δ_H (100 MHz; $CDCl_3$; at 80 °C*) 1.25 (3 H, t, *J* 7.6 Hz, OCH_2Me), 1.80—2.44 (2 H, m, 8-H), 2.77 (2 H, d, *J* 4.0 Hz, 4-H), 3.38 (1 H, ddd, *J* 12.0, 10.0, and 7.2 Hz, 7-H), 3.77 (1 H, ddd, *J* 12.0, 8.0, and 5.6 Hz, 1-H), and 5.00 (1 H, m, 5-H); δ_C (25 MHz; [$^2H_5$]-pyridine; at 80 °C) 14.736 (q), 30.705 (t), 36.341 (t), 44.619 (t), 58.534 (d), 61.352 (t), 83.603 (d), 175.305 (s) (Found: M^+, 199.0849. $C_9H_{13}NO_4$ requires *M*, 199.0799).

The (+)-*Geissman Lactone* (**10**).—A solution of the lactone (**32**) (148 mg, 0.744 mmol) and barium hydroxide octahydrate (740 mg, 2.35 mmol) in water (5 ml) was heated under reflux for 16 h. To the mixture was passed through gaseous carbon dioxide at room temperature for 1.5 h, the resulting mixture was filtered, and the filtrate was concentrated to give a solid which was taken up with 1M-hydrogen chloride (1 ml). The solution was heated at 80—90 °C for 1 h after which the solvent was evaporated off to give a crystalline solid which was recrystallised from ethanol to afford the Geissman lactone (**10**) (48 mg, 40%) as needles, m.p. 185—186.5 °C (lit.,[11b] m.p. 185—186 °C); $[\alpha]_D^{25}$ +48.8° (*c* 0.20, MeOH) {lit.,[11b] $[\alpha]_D$ +48.5° (*c* 1.5, MeOH)}.

(+)-(4S)-2,2-*Diethyl*-4-(2-*phthalimido*)*ethyl*-1,3-*dioxolane* (**35**).—According to the general procedure for (**14**), the alcohol (**34**)[21] (1.74 g, 10.0 mmol) was converted into the *phthalimide* (**35**) (3.0 g, 100%) as a pale yellow oil after column chromatography using hexane–ethyl acetate (4:1, v/v) as eluant, $[\alpha]_D^{28}$ +11.8° (*c* 1.45, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 770 and 1 710 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.82 (6 H, t, *J* 8.0 Hz, CH_2Me × 2), 1.26—2.20 (6 H, m), 3.36—4.40 (5 H, m,), and 7.54—7.95 (4 H, m, ArH) (Found: M^+, 200.0700. $C_{12}H_{10}NO_2$ requires *M*, 200.0710).

(+)-(4S)-*Ethyl* 4-*Aminoethyl*-2,2-*diethyl*-1,3-*dioxolane*-4-*carboxylate* (**36**).—According to the procedure for (**15**), the phthalimide (**35**) (3.00 g, 10.5 mmol) was converted into the *carbamate* (**36**) (2.35 g, 91%) as an oil after column chromatography using hexane–ethyl acetate (7:3, v/v) as eluant (Found: C, 58.7; H, 9.7; N, 5.75. $C_{12}H_{23}NO_4$ requires C, 58.75; H, 9.45; H, 5.7%); $[\alpha]_D^{26}$ +1.85° (*c* 1.26, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 and 1 710 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.89 (6 H, t, *J* 8.0 Hz, CH_2Me × 2), 1.23 (3 H, t, *J* 8.0 Hz, OCH_2Me), 4.09 (2 H, q, *J* 8.0 Hz, OCH_2Me), and 5.00 (1 H, br s, NH).

* At ambient temperature, the signals in the spectra are duplicated or not clear presumably due to amide isomerism.

(+)-(3S)-*Ethyl* 1-*Amino*-3,4-*dihydroxybutanecarboxylate* (**37**).—A solution of the carbamate (**36**) (1.21 g, 4.94 mmol) in 6M-hydrogen chloride (6 ml) and THF (6 ml) was stirred at room temperature for 15 min. After evaporation of the solvent, residual water was removed by azeotropic distillation with benzene. The residue was taken up in chloroform and the solution dried ($MgSO_4$) and evaporated to afford the crude *diol* (**37**) (0.96 g, 100%) as a crystalline solid which was used directly for the next reaction. An analytical sample of (**37**), obtained by recrystallisation from chloroform, formed needles, m.p. 72—73 °C (Found: C, 47.05; H, 8.9; N, 7.9. $C_7H_{15}NO_4$ requires C, 47.45; H, 8.55; N, 7.9%); $[\alpha]_D^{28}$ +1.15° (*c* 0.60, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 and 1 700 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 8.0 Hz, OCH_2Me), 4.08 (2 H, q, *J* 8.0 Hz, OCH_2Me), and 5.32 (1 H, br s, NH).

(+)-(3S)-*Ethyl* 1-*Amino*-3-*hydroxy*-4-(2,2,3,3-*tetramethyl*-(*propylsiloxy*)*butane*-N-*carboxylate* (**38**).—A solution of the diol (**37**) (380 mg, 2.15 mmol), dimethyl-t-butylsilyl chloride (421 mg, 2.79 mmol), imidazole (219 mg, 3.22 mmol), and a catalytic amount of 4-dimethylaminopyridine in anhydrous methylene dichloride (8 ml) was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was chromatographed using hexane–ethyl acetate (3:2, v/v) as eluant to afford the *silyl ether* (**38**) (593 mg, 95%) as an oil (Found: C, 53.95; H, 10.05; N, 4.95. $C_{13}H_{29}NO_4Si$ requires C, 53.55; H, 10.05; N, 4.8%); $[\alpha]_D^{29}$ +2.70° (*c* 1.85, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 and 1 710 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.90 (9 H, s, CMe_3), 1.22 (3 H, t, *J* 7.6 Hz, OCH_2Me), 1.47—1.76 (2 H, m), 2.77 (1 H, br s, OH, D_2O disappeared), 4.07 (2 H, q, *J* 7.6 Hz, OCH_2Me), and 5.14 (1 H, br s, NH); *m/z* 234 ($M^+ - C_4H_9$).

(−)-(3S)-*Ethyl* 1-*Amino*-3-*methoxymethoxy*-4-(2,2,3,3-*tetramethylpropylsiloxy*)*butane*-N-*carboxylate* (**39**).—To a stirred solution of the silyl ether (**38**) (800 mg, 2.75 mmol) in anhydrous methylene dichloride (15 ml) was added di-isopropylethylamine (660 mg, 4.95 mmol) and chloromethyl methyl ether (350 mg, 4.40 mmol) at 0 °C. The mixture was stirred at room temperature for 24 h after which it was diluted with water and the aqueous layer separated and extracted with methylene dichloride. The combined organic phases were washed with saturated brine and the residue upon work-up was the crude *methoxymethoxy derivative* (**39**) (955 mg, 100%) as a pale yellow oil which was used directly for the next reaction. An analytical sample of (**39**) was obtained by column chromatography using hexane–ethyl acetate (7:3, v/v) as an oil (Found: C, 53.55; H, 10.4; N, 4.1. $C_{15}H_{33}NO_5Si$ requires C, 53.7; H, 9.9; N, 4.2%); $[\alpha]_D^{27}$ −50.0° (*c* 0.61, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 and 1 700 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.89 (9 H, s, CMe_3), 1.23 (3 H, t, *J* 7.6 Hz, OCH_2Me), 3.37 (3 H, s, OMe), 4.09 (2 H, q, *J* 7.6 Hz, OCH_2Me), 4.68 (2 H, dd, *J* 10.4 and 6.4 Hz, OCH_2OSi), and 5.07 (1 H, br s, >NH); *m/z* 304 (M^+ − OMe).

(+)-(3S)-*Ethyl* 1-*Amino*-3-*hydroxy*-4-*methoxymethoxybutane*-N-*carboxylate* (**40**).—To a stirred solution of the ether (**39**) (699 mg, 2.09 mmol) in anhydrous THF (15 ml) was added dropwise tetrabutylammonium fluoride (1.0M solution of THF; 2.3 ml, 2.3 mmol) at room temperature. The mixture was stirred for 10 min after which the solvent evaporated off to give a residue which was chromatographed using hexane–ethyl acetate (1:4, v/v) as eluant to afford the *alcohol* (**40**) (467 mg, 100%) as an oil (Found: C, 48.6; H, 8.7; N, 6.05. $C_9H_{19}NO_5$ requires C, 48.85; H, 8.65; N, 6.35%); $[\alpha]_D^{30}$ +12.0° (*c* 0.75, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450 and 1 710 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.6 Hz, OCH_2Me), 3.49 (3 H, s, OMe), 4.17 (2 H, q, *J* 7.6 Hz, OCH_2Me), 4.28 (2 H, s, OCH_2O), and 5.10 (1 H, br s, NH); *m/z* 190 (M^+ − OMe).

Swern Oxidation of (**40**).—According to the general procedure for (**17**), the alcohol (**40**) (97 mg, 0.439 mmol) was converted into the *hemiacetal* (**41**) (97 mg, 100%) as an oil after column chromatography using hexane–ethyl acetate (1:4, v/v) as eluant; $\nu_{max.}$($CHCl_3$) 3 400 and 1 690 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.6 Hz, OCH_2Me), 4.67 (2 H, s, OCH_2O), and 5.38 (1 H, m, NC*H*OH) (Found: M^+, 219.1127. $C_9H_{17}NO_5$ requires *M*, 219.1107).

Sequential Horner-Emmons and Michael Reaction of (**41**).—(a) *Using sodium hydride.* According to procedure (a) for (**19**), the hemiacetal (**41**) (0.8 g, 3.65 mmol) was treated at room temperature for 3 h. After the work-up and column chromatography using hexane–ethyl acetate (7:3, v/v) as eluant, the *ester* (**42**) (0.84 g, 79%), a mixture of two diastereoisomers was obtained as a pale yellow oil (Found: C, 53.7; H, 7.95; N, 4.8. $C_{13}H_{23}NO_6$ requires C, 53.95; H, 8.0; N, 4.85%); $\nu_{max.}$($CHCl_3$) 1 730 and 1 690 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 1.26 (6 H, t, *J* 7.6 Hz, OCH_2Me × 2), 3.36 (3 H, s, OMe), 4.13 (4 H, q, *J* 7.6 Hz, OCH_2Me × 2), and 4.53—4.77 (2 H, m, OCH_2O); *m/z* 244 (M^+ − OEt).

(b) *Using potassium hydride.* The reaction mixture, containing a catalytic amount of 18-crown-6, was stirred at room temperature for 95 min. The hemiacetal (**41**) (136 mg, 0.621 mmol) was converted into the ester (**42**) (134 mg, 75%).

(+)-(1S,5R)-*Ethyl* 3-*Oxo*-2-*oxa*-6-*azabicyclo*[3.3.0]*octane*-6-*carboxylate* (**43**) and (−)-(2R,3S)-*Diethyl* 3-*Hydroxy*-2-*methylpyrrolidine*-1,2-*dicarboxylate* (**44**).—(a) According to the general procedure for (**22**) and (**23**), the ester (**42**) (800 mg, 2.77 mmol), prepared by the method (a) using sodium hydride, was converted, after column chromatography using chloroform as an eluant, into the *lactone* (**43**) (196 mg, 36%), the enantiomer of (**32**), as an oil, $[\alpha]_D^{29}$ +144.1° (*c* 0.517, $CHCl_3$) (Found: M^+, 199.0858. $C_9H_{13}NO_4$ requires *M*, 199.0845), and the *hydroxy ester* (**44**) (344 mg, 51%) (Found: C, 53.95; H, 8.2; N, 5.4. $C_{11}H_{19}NO_5$ requires C, 53.85; H, 7.8; N, 5.7%); $[\alpha]_D^{24}$ −44.0° (*c* 1.28, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 400, 1 720, and 1 690 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.6 Hz, OCH_2Me × 2), 2.60—3.24 (2 H, m, one of these D_2O disappeared), and 3.84—4.44 (6 H, m,); δ_C (25 MHz; [$^2H_5$]pyridine; at 80 °C*) 14.207 (q), 14.853 (q), 32.173 (t), 38.102 (t), 45.089 (t), 60.413 (t), 60.941 (t), 63.935 (d), 73.914 (d), 155.465 (s), and 171.200 (s); *m/z* 227 (M^+ − H_2O).

(b) The ester (**42**) (133 mg, 0.46 mmol), prepared by method (b) using potassium hydride, was converted into the lactone (**43**) (33 mg, 36%) and the hydroxy ester (**44**) (57 mg, 51%).

(−)-(2R,3S)-*Diethyl* 3-*Acetoxy*-2-*methylpyrrolidine*-1,2-*dicarboxylate* (**45**).—A mixture of the hydroxy ester (**44**) (9 mg, 0.0367 mmol), pyridine (0.5 ml), and acetic anhydride (0.5 ml) in the presence of a catalytic amount of 4-dimethylaminopyridine was stirred at room temperature. After removal of the excess of reagents, the residue was chromatographed using hexane–ethyl acetate (7:3, v/v) as an eluant to afford the *acetate* (**45**) (7 mg, 66%) as an oil, $[\alpha]_D^{31}$ −1.99° (*c* 3.23, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 735 and 1 690 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.6 Hz, OCH_2Me), 1.26 (3 H, t, *J* 7.6 Hz, OCH_2Me), 2.04 (3 H, s, OCOMe), 4.12 (5 H, m), and 5.12 (1 H, m, C*H*OAc) (Found: M^+ − OEt, 242.1007. $C_{11}H_{16}NO_5$ requires *M* − OEt, 242.1027).

The Horner-Emmons Reaction of (**41**): *Method A.*—To a suspension of potassium hydride (60 mg, 1.49 mmol) in anhydrous DME (4 ml) was added triethylphosphonoacetate

* At ambient temperature, the signals in the spectra are duplicated or not clear presumably due to amide isomerism.

(260 mg, 1.17 mmol) at 0 °C and the resulting mixture was stirred for 25 min. A solution of the hemiacetal (**41**) (111 mg, 0.507 mmol) in anhydrous DME (2 ml) was then added to the mixture at 0 °C, and the mixture was further stirred at the same temperature for 45 min. After being quenched with saturated aqueous ammonium chloride, the mixture was extracted with methylene dichloride and the extract was washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (3:2, v/v) to afford the *unsatured ester* (**46**) (134 mg, 92%), a mixture of two isomers, as a pale yellow oil; $\nu_{max.}$($CHCl_3$) 3 450 and 1 710 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.23 and 1.28 (3 H each, t, *J* 7.6 Hz, OCH_2Me), 3.35 (0.6 H, s, OMe), 3.37 (2.4 H, s, OMe), 4.08 (5 H, m), 4.69 (2 H, br s, OCH_2O), 4.92 (1 H, br s, NH), 5.72—6.26 (1.2 H, m, olefinic H), and 6.78 (0.8 H, dd, *J* 16.0 and 6.0 Hz, olefinic H) (Found: M^+, 289.1547. $C_{13}H_{23}NO_6$ requires *M*, 289.1525).

The Wittig Reaction of (**41**): *Method B.*—A solution of the hemiacetal (**41**) (477 mg, 2.18 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (805 mg, 2.40 mmol) in acetonitrile (10 ml) was heated under reflux for 1 week. After evaporation of the solvent, the residue was chromatographed using hexane–ethyl acetate (3:2, v/v) as eluant to afford the unsaturated ester (**46**) (566 mg, 90%), a 3:1 mixture of the *E* and *Z* isomers, as a yellow oil.

Intramolecular Michael Reaction followed by Cleavage of the MOMO *Ether* (**46**).—(i) To a stirred suspension of sodium hydride (60% in oil; 15 mg, 0.362 mmol) in anhydrous DME (2 ml) was added dropwise at 0 °C a solution of the unsaturated ester (**46**) (95 mg, 0.329 mmol), prepared by the Method B, in anhydrous DME (1 ml). After being stirred at 0 °C for 45 min, the mixture was quenched with saturated aqueous ammonium chloride and the solvent was evaporated off to give a residue which was extracted with methylene dichloride. The organic phase was washed with saturated brine and the residue upon work-up was the ester (**42**) (85 mg, 89%) which was used for the next reaction without further purification. According to the general procedure for (**22**) and (**23**) the crude ester (**42**) (78 mg, 0.27 mmol) was converted into the lactone (**43**) (17 mg, 32%) and the hydroxy ester (**44**) (40 mg, 61%); $[\alpha]_D^{27}$ −45.0° (*c* 0.46, $CHCl_3$).

(ii) To a stirred suspension of potassium hydride (15 mg, 0.369 mmol) in anhydrous THF (3 ml) in the presence of a catalytic amount of 18-crown-6 was added a solution of (**46**) (97 mg, 0.336 mmol), prepared by the Method B, in anhydrous THF (1 ml) at 0 °C. The mixture was stirred at 0 °C for 16 min and gave upon work-up, the ester (**42**) (83 mg, 86%); this was converted into (**43**) (18 mg, 32%) and (**44**) (48 mg, 68%).

(iii) To a stirred suspension of potassium hydride (19 mg, 0.476 mmol) in anhydrous DME (3 ml) in the presence of a catalytic amount of 18-crown-6 was added a solution of (**46**) (125 mg, 0.433 mmol), prepared by the Method A, in anhydrous DME (1 ml) at 0 °C. The mixture was stirred at 0 °C for 34 min and then worked up to give the ester (**42**) (114 mg, 91%); this was converted into (**43**) (11 mg, 15%) and (**44**) (70 mg, 75%).

Horner-Emmons Reaction of (**41**).—To a stirred suspension of potassium hydride (132 mg, 3.28 mmol) in anhydrous THF (25 ml) was added hexamethyldisilazane (551 mg, 3.44 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 0.5 h after which it was cooled to −78 °C, and trimethyl phosphonoacetate (596 mg, 3.28 mmol) and 18-crown-6 (1.3 g, 4.92 mmol) added successively. A solution of the hemiacetal (**41**) (359 mg, 1.64 mmol) in anhydrous THF (4 ml) was then added at −78 °C and stirring was continued for 0.5 h. After being stirred at −10 °C for 0.5 h and at 0—10 °C for 1.5 h, the mixture was quenched with saturated aqueous ammonium chloride. Solvent was then evaporated off to give a residue which was extracted with chloroform. The organic phase was washed with saturated brine, and the residue upon work-up was chromatographed using hexane–ethyl acetate (7:3, v/v) as eluant to afford the *unsaturated ester* (**48**) (321 mg, 71%, 88% based on the consumed starting material), a mixture of the *Z* and *E* isomers, as an oil; $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.5 Hz, OCH_2Me), 1.82 (2 H, m, CH_2), 3.34 (2 H, s, OCH_2OMe), 3.36 (1 H, s, OCH_2OMe), 3.70 (2 H, s, CO_2Me), 3.72 (1 H, s, CO_2Me), 4.10 (2 H, q, *J* 7.5 Hz, OCH_2Me), 4.58 (0.67 H, s, OCH_2OMe), 4.59 (1.33 H, s, OCH_2OMe), 5.20 (2 H, m), 5.77—6.26 (1.67 H, m, olefinic H), and 6.78 (0.33 H, dd, *J* 16.0 and 5.5 Hz, olefinic H) (Found: M^+ − OEt, 230.1035. $C_{10}H_{16}NO_5$ requires *M* − OEt, 230.1029). From the fractions using hexane–ethyl acetate (3:2, v/v), the starting hemiacetal (**41**) (68 mg) was obtained.

(−)-(3S)-*Ethyl 5-Amino-1-(Z)-methoxycarbonyl-3-methoxymethoxy-5-pent-1-enecarboxylate* (**49**).—To a stirred suspension of potassium hydride (11 mg, 0.271 mmol) in anhydrous DME (1 ml) was added methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (78 mg, 0.271 mmol) at 0 °C and the mixture was stirred for 25 min. It was then cooled to −78 °C, when a solution of the hemiacetal (**41**) (49.5 mg, 0.122 mmol) in anhydrous DME (0.2 ml) was added dropwise and stirred for 50 min; stirring was continued for 50 min at −10 °C and then at 0—10 °C for 1.5 h. The mixture was then quenched with saturated aqueous ammonium chloride, and the solvent was evaporated off to give the residue which was extracted with methylene dichloride. The organic phase was washed with saturated brine and the residue upon work-up was chromatographed using hexane–ethyl acetate (4:1, v/v) as eluant to afford the *Z-unsaturated ester* (**49**) (18.6 mg, 30%, 55% based on the consumed starting material) as an oil; $[\alpha]_D^{29}$ −38.9° (*c* 1.54, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 715 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 8.0 Hz, OCH_2Me), 3.35 (5 H, br s), 3.71 (3 H, s, CO_2Me), 4.08 (2 H, q, *J* 8.0 Hz, OCH_2Me), 4.57 (2 H, s, OCH_2OMe), 4.88—5.48 (2 H, m), 5.80 (1 H, d, *J* 12.0 Hz, olefinic H), and 6.15 (1 H, dd, *J* 12.0 and 7.0 Hz, olefinic H) (Found: M^+ − OEt, 230.1035. $C_{10}H_{16}NO_5$ requires *M* − OEt, 230.1029). From the fractions using hexane–ethyl acetate (3:2, v/v), the starting hemiacetal (**41**) (22.7 mg) was obtained.

Sequential Intramolecular Michael Reaction and Cleavage of the MOMO Ether.—(a) *The reaction of* (**48**). To a suspension of potassium hydride (50 mg, 1.25 mmol) in anhydrous DME (9 ml) at 0 °C was added a solution of the unsaturated ester (**48**) (313 mg, 1.14 mmol), a 1:2 mixture of the *E* and *Z* isomers in anhydrous DME (0.4 ml), and a catalytic amount of 18-crown-6. After the mixture had been stirred at 0 °C for 21 min, the ester (**50**) (297 mg, 95%) was obtained as an oil. The latter was converted, by the general procedure, into the lactone (**43**) (24 mg, 11%); $[\alpha]_D^{27}$ +145.2° (*c* 0.656, $CHCl_3$), and the *hydroxy ester* (**51**) (215 mg, 86%) as an oil (Found: C, 51.75; H, 7.4; N, 6.0. $C_{10}H_{17}NO_5$ requires C, 51.95; H, 7.40; N, 6.05%); $[\alpha]_D^{25}$ −40.2° (*c* 0.892, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 450, 1 720, and 1 690 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.6 Hz, OCH_2Me), 2.62—3.25 (2 H, m, one of these D_2O disappeared), 3.73 (3 H, s, OMe), and 4.13 (2 H, q, *J* 7.6 Hz, OCH_2Me); *m/z* 231 (M^+).

(b) *The reaction of* (**49**). According to the procedure for (**48**), the *Z*-unsaturated ester (**49**) (69 mg, 0.251 mmol) was converted into the ester (**50**) (58 mg, 84%), by the reaction at 0 °C for 9 min. Then, the ester (**50**) (52 mg, 0.189 mmol) was transformed into (**43**) (0.6 mg, 1.4%) and (**51**) (24 mg, 55%); $[\alpha]_D^{28}$ −40.4° (*c* 1.16, $CHCl_3$).

The Mesylation of (**44**) *and* (**51**).—(a) To a stirred solution of the hydroxy ester (**44**) (155 mg, 0.63 mmol) in anhydrous methylene dichloride (5 ml) was successively added dropwise

triethylamine (189 mg, 1.89 mmol), methanesulphonyl chloride (104 mg, 0.95 mmol), and a catalytic amount of 4-dimethylaminopyridine at 0 °C. The mixture was stirred at room temperature for 20 min, after which it was diluted with water and the organic layer separated. The aqueous layer was then extracted with methylene dichloride and the combined organic phases were washed with saturated brine. The residue upon work-up was chromatographed using hexane–ethyl acetate (7:3, v/v) as eluant to afford the *methanesulphonate* (**52**) (213 mg, 100%); $[\alpha]_D^{27}$ −4.30° (*c* 0.66, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 720 and 1 685 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.19 (6 H, t, *J* 7.0 Hz, $OCH_2Me \times 2$), 3.07 (3 H, s, OSO_2Me), 4.06 (4 H, q, *J* 7.0 Hz, $OCH_2Me \times 2$), and 5.02 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz) (Found: M^+, 323.1022. $C_{12}H_{21}NO_7S$ requires *M*, 323.1037).

(b) According to procedure (a), the methyl ester (**51**) (150 mg, 0.649 mmol) was converted into the *methanesulphonate* (**53**) (202 mg, 100%); $[\alpha]_D^{31}$ −0.624° (*c* 2.64, $CHCl_3$); $\nu_{max.}(CHCl_3)$ 1 735 and 1 695 cm^{-1}; δ_H (60 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.5 Hz, OCH_2Me), 3.11 (3 H, s, OSO_2Me), 3.69 (3 H, s, CO_2Me), 4.14 (2 H, q, *J* 7.5 Hz, OCH_2Me), and 5.09 (1 H, m) (Found: M^+, 309.0853. $C_{11}H_{19}NO_7S$ requires *M*, 309.0826).

The Lactonisation of (**52**) *and* (**53**).—(*a*) A solution of the methanesulphonate (**52**) (170 mg, 0.53 mmol) and lithium hydroxide monohydrate (44 mg, 1.1 mmol) in a mixture of dioxane (4 ml) and water (1 ml) was stirred at room temperature for 3 h. After evaporation of the solvent, water (5 ml) was added and the mixture was washed with methylene dichloride. The resulting aqueous phase was acidified with 10% hydrogen chloride and extracted with ethyl acetate. The extract was washed with saturated brine and the residue upon work-up afforded the carboxylic acid (**54**) which was used for the next reaction without further purification.

To a solution of the crude acid in acetonitrile (5 ml) was added potassium carbonate (110 mg, 0.79 mmol) and a catalytic amount of 18-crown-6; the resulting mixture was stirred at room temperature for 40 h. After removal of the solvent, water was added and the mixture was extracted with methylene dichloride. The extract was washed with saturated brine and the residue upon work-up was chromatographed using chloroform as an eluant to afford the lactone (**32**) (90 mg, 86%); $[\alpha]_D^{27}$ −144.9° (*c* 0.64, $CHCl_3$).

(*b*) The methyl ester (**53**) (200 mg, 0.647 mmol) was similarly converted into the lactone (**32**) (105 mg, 82%), $[\alpha]_D^{27}$ − 144.6 ° (*c* 3.30, $CHCl_3$).

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References

1 Preliminary communications of a part of this work have appeared; K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, *Heterocycles*, 1985, **23**, 1629; 1986, **24**, 641.
2 For a review of the Michael reaction, see E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React. (N.Y.)*, 1959, **10**, 179.
3 (*a*) R. V. Stevens, 'The Total Synthesis of Natural Products,' ed. J. ApSimon, John Wiley and Sons, Inc., 1977, **3**, 439, and references therein; (*b*) G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, 1963, **85**, 2872; (*c*) T. Kametani, H. Nemoto, T. Kobari, K. Shishido, and K. Fukumoto, *Chem. Ind. (London)*, 1972, 538; (*d*) S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, 1976, 57.
4 An example for 1,6-asymmetric induction, see T. Wakabayashi, Y. Kato, and K. Watanabe, *Chem. Lett.*, 1976, 1283; T. Wakabayashi and M. Saito, *Tetrahedron Lett.*, 1977, 93.
5 For a 1,2-asymmetric induction, see (*a*) M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, *J. Am. Chem. Soc.*, 1985, **107**, 1797; (*b*) *Tetrahedron Lett.*, 1985, **26**, 4133; (*c*) M. Hirama, T. Shigemoto, and S. Ito, *ibid.*, 1985, **26**, 4137.
6 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
7 B. A. Sobin and F. W. Tanner, Jr., *J. Am. Chem. Soc.*, 1954, **76**, 4053.
8 S. M. Colegate, P. R. Dorling, and C. R. Huxtable, *Aust. J. Chem.*, 1979, **32**, 2257.
9 For reviews of pyrrolizidine alkaloids, see (*a*) H. C. S. Wood and R. Wrigglesworth, 'Rodd's Chemistry of Carbon Compounds,' 2nd edn., ed. S. Coffey, Elsevier, Amsterdam, 1977, **IVB**, 7; (*b*) D. J. Robins, *Adv. Heterocycl. Chem.*, 1979, **24**, 247; (*c*) T. Furuya and M. Hikichi, *J. Synth. Org. Chem. Jpn.*, 1977, **35**, 653.
10 T. A. Geissman and A. C. Waiss, Jr., *J. Org. Chem.*, 1962, **27**, 139.
11 For recent syntheses; (±)-retronecine, (*a*) K. Narasaka, T. Sakakura, T. Uchimaru, and D. G. Vuong, *J. Am. Chem. Soc.*, 1984, **106**, 2954; (+)-retronecine, (*b*) H. Ruegner and M. Benn, *Heterocycles*, 1983, **20**, 1331; (*c*) J. G. Buchanan, G. Singh, and R. H. Wightman, *J. Chem. Soc., Chem. Commun.*, 1984, 1299; (*d*) A. R. Chamberlin and J. Y. L. Chung, *J. Org. Chem.*, 1985, **50**, 4425; (+)- and (−)-retronecine, (*e*) Y. Nishimura, S. Kondo, and H. Umezawa, *J. Org. Chem.*, 1985, **50**, 5210.
12 K. Fuji, S. Nakano, and E. Fujita, *Synthesis*, 1975, 276.
13 O. Mitsunobu, M. Wada, and T. Sano, *J. Am. Chem. Soc.*, 1972, **94**, 679.
14 H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 1926, 2348.
15 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651; A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
16 K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, 1979, **44**, 1661.
17 C. A. Brown, *J. Org. Chem.*, 1974, **39**, 1324; P. Eaton and P. G. Jode, *Synthesis*, 1983, 976.
18 (*a*) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, 1979, **101**, 259, and references therein; (*b*) ref. 5 (*c*).
19 J. R. Rasmussen, C. J. Slinger, R. J. Kordish, and D. D. N. Evans, *J. Org. Chem.*, 1981, **46**, 4843.
20 S. Hanessian, A. Ugolini, D. Dubé, and A. Glamyan, *Can. J. Chem.*, 1984, **62**, 2146.
21 S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe, and Y. Ito, *J. Org. Chem.*, 1984, **49**, 2834.
22 H. Nagaoka and Y. Kishi, *Tetrahedron*, 1981, **37**, 3873.
23 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405.

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