Heterocycles in Asymmetric Synthesis. Part 1. Construction of the Chiral Building Blocks for Enantioselective Alkaloid Synthesis *via* an Asymmetric Intramolecular Michael Reaction

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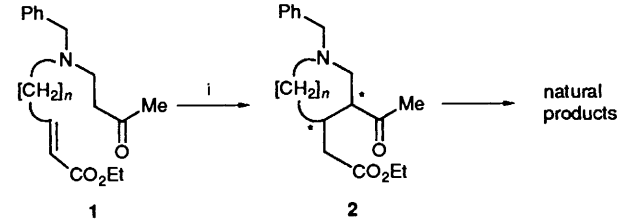
The asymmetric intramolecular Michael reaction of acyclic compounds ethyl (*E*)-4-[benzyl-(3-oxobutyl)amino]but-2-enoate **9**, and ethyl (*E*)-5-[benzyl-(3-oxobutyl)amino]pent-2-enoate **10** was investigated under a variety of conditions, and the pyrrolidine ethyl (4-acetyl-1-benzylpyrrolidin-3-yl)acetate **11** and piperidine ethyl (3-acetyl-1-benzylpiperidin-4-yl)acetate **12**, versatile chiral building blocks for alkaloid synthesis, were obtained in moderate to excellent optical yield. Cyclization of the aforementioned but- and pent-2-enoate using (*R*)-1-phenylethylamine in THF in the presence of molecular sieves 5 Å gave the (+)-pyrrolidine derivative (+)-**11** and the (−)-piperidine derivative (−)-**12** in 60 and 90% ee, respectively. When (*S*)-1-phenylethylamine was used, pyrrolidine (−)-**11** and piperidine derivatives (+)-**12** were obtained in similar optical yields, respectively. The ee of (−)- and (+)-piperidine derivatives increased up to 98% upon recrystallization of their hydrobromide salts.

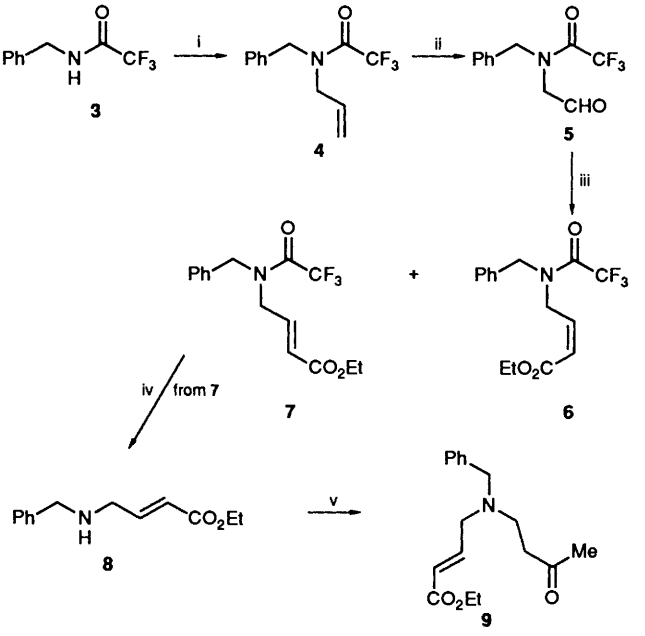
The intramolecular Michael reaction is a powerful method for the stereocontrolled construction of cyclic systems from acyclic precursors.[1] Asymmetric modifications of this procedure are a subject of current interest in the field of synthetic organic chemistry. Although a number of highly enantioselective 'intermolecular' Michael reactions have been reported,[2] there are few practical examples of an 'intramolecular' version[3] capable of providing both enantiomers in a highly enantioselective manner from a single starting material. In an effort to effect an intramolecular Michael cyclization of an acyclic compound, Stork and Saccomano have shown that a chiral ester can work as a 'built-in auxiliary' and provide an optically active carbocycle.[4] Their work has prompted us to investigate an asymmetric 'intramolecular' Michael reaction using a chiral enamine. An enamine approach to Michael coupling is among the potential methods for induction of chirality by the allylic strain (nonchelate-controlled mode)[5] of chiral enamines. The advantage of asymmetric induction by 'transient enamine' catalysis includes the direct formation of chiral products, since troublesome procedures to remove the chiral auxiliary at a later stage are thereby unnecessary. This type of induction of chirality has recently attracted considerable attention from a synthetic point of view.[6] We have designed the acyclic compound **1** as a substrate for intramolecular cyclization and have demonstrated[7] that (a) cyclization could be controlled to give the desirable *trans* arrangement of the ring substituents at the site of cyclization, (b) the cyclic products **2**, especially the piperidine derivatives, are obtained with high enantioselectivity, and (c) this reaction could provide an important method for the construction of complex, natural products, such as *Rauwolfia* alkaloids (Scheme 1). Herein we present a full account of the experimental details of the asymmetric, intramolecular Michael reaction induced by the 1,3-allylic strain of chiral enamines.



Scheme 1 *Reagent:* i, chiral base

Results and Discussion

The synthesis of the model systems **9** (≡ **I**; $n = 1$) and **10** (≡ **I**; $n = 2$) possessing a ketone carbonyl and an α,β-unsaturated ester group is outlined in Scheme 2. Condensation of *N*-benzyltrifluoroacetamide **3** with allyl bromide in the presence of pulverized potassium hydroxide and 18-crown-6[8] gave the amide **4** in 84% yield. Ozonolysis (to the aldehyde **5**, 78% yield) of **4** was followed by a Wittig reaction with ethyl (triphenylphosphoranylidene)acetate in CH_2Cl_2 to afford a 1:4 mixture of the unsaturated esters **6** and **7** (95% combined yield from **5**), which were easily separated by flash column chromatography.



Scheme 2 *Reagents and conditions:* i, allyl bromide, KOH, 18-crown-6; ii, O_3, CH_2Cl_2, then Me_2S; iii, $Ph_3P{=}CHCO_2Et$; iv, 5% K_2CO_3; v, methyl vinyl ketone

Table 1 Intramolecular Michael reaction of compound **9**

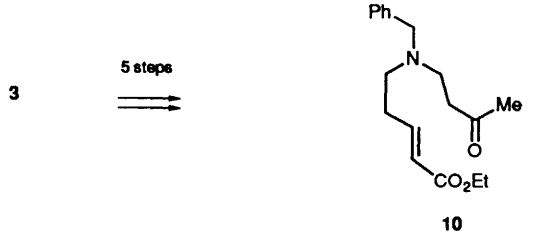
Run	Base[a]	Product	Temperature	Solvent	Time (days)	ee (%)[c]	Yield (%)
1	L-Proline	(+)-**11**	room	DMF	7	34	45
2	(*R*)-1-Phenylethylamine	(+)-**11**	room	THF	4	48	89
3	(*R*)-1-Phenylethylamine	(+)-**11**	5 °C	THF[b]	13	61	96
4	(*S*)-1-Phenylethylamine	(−)-**11**	5 °C	THF[b]	10	62	84

[a] 1 mol equiv. of a chiral base was used. [b] In the presence of molecular sieves 5 Å. [c] Determined from the ^{1}H NMR spectrum in the presence of europium trisheptafluorobutyrylcamphorate Eu(hfc)$_3$ in $CDCl_3$, and from the optical rotation.

Table 2 Intramolecular Michael reaction of compound **10**

Run	Base[a]	Product	Temperature	Solvent	Time (days)	ee (%)[c]	Yield (%)
1	L-Proline	(−)-**12**	room	DMF	40		60
2	(+)-2,5-Dimethylpyrrolidine		room	THF	40		
3	(*R*)-1-Phenylethylamine	(−)-**12**	room	THF	19	83	76
4	(*R*)-1-Phenylethylamine	(−)-**12**	5 °C	THF[b]	21	90	82
5	(*S*)-1-Phenylethylamine	(+)-**12**	5 °C	THF[b]	21	90	77
6	(*R*)-1-Phenylethylamine	(−)-**12**	5 °C	MeOH	4	53	62
7	(*R*)-1-Phenylethylamine	(−)-**12** and **13**	5 °C	CH_2Cl_2	24		54[d]

[a] 1 mol equiv. of a chiral base was used. [b] In the presence of molecular sieves 5 Å. [c] Determined from the ^{1}H NMR spectrum of the (+)-MTPA ester of the corresponding alcohols (−)-**18** and (+)-**18**. [d] The yield of a mixture of (−)-**12** and **13** is given.



10

Hydrolysis of *E*-ester **7** with 5% aq. potassium carbonate gave the secondary amine **8** in 62% yield. This was condensed with methyl vinyl ketone in dry CH_2Cl_2 to furnish the key intermediate **9** in 98% yield. The substrate **10** has previously been synthesized[9] similarly in 5 steps from amide **3**.

To demonstrate the feasibility of the intramolecular asymmetric Michael reaction as an efficient entry to the optically active *trans*-substituted piperidine and pyrrolidine systems, the cyclization of the *E*-esters **9** and **10** by using chiral bases was then examined.

In our first experiments we used 1 mol equiv. of a chiral base. Treatment of the acyclic compound **9** with L-proline in *N*,*N*-dimethylformamide (DMF) at room temperature for 7 days gave the pyrrolidine derivative (+)-**11** (≡**2**; n = 1) in only 34% enantiomeric excess (ee). Use of (*R*)-1-phenylethylamine* as a chiral base increased the ee up to 48%. The ee was further increased up to 60% when this cyclization was carried out at 5 °C in tetrahydrofuran (THF) in the presence of molecular sieves 5 Å. No reaction occurred at 0 °C. The results are summarized in Table 1. We next examined the cyclization of *E*-ester **10**. The results are summarized in Table 2. Best results were obtained by the treatment with (*R*)-1-phenylethylamine in THF in the presence of molecular sieves 5 Å at 5 °C (Run 4 in Table 2). Use of (*S*)-1-phenylethylamine† afforded the piperidine derivative (+)-**12** (≡**2**; n = 2), the enantiomer of (−)-**12**, with a similar ee (Scheme 3). Use of (*R*,*R*)-2,5-dimethylpyrrolidine as a chiral secondary amine did not lead to cyclization. To obtain an asymmetrically catalysed, intramolecular reaction, the cyclization of compound **10** was examined with 30% mol equiv. of (*R*)-1-phenylethylamine under reaction conditions identical with those of Run 4 in Table 2. However, the reaction rate was very slow and the TLC indicated that a large quantity of the starting material remained unchanged even after 3 weeks. Several characteristic features were noted. (1) In general, a high ee was obtained at lower temperatures. (2) A modest solvent effect on the product distribution was observed, and the concomitant formation of the *cis*-product **13** (≡**2**; n = 2)‡ was observed on changing the solvent from THF to CH_2Cl_2. Use of a protic solvent (MeOH) decreased the ee of the cyclic product. (3) To obtain cyclized products effectively, 1 mol equiv. of the chiral base must be used.

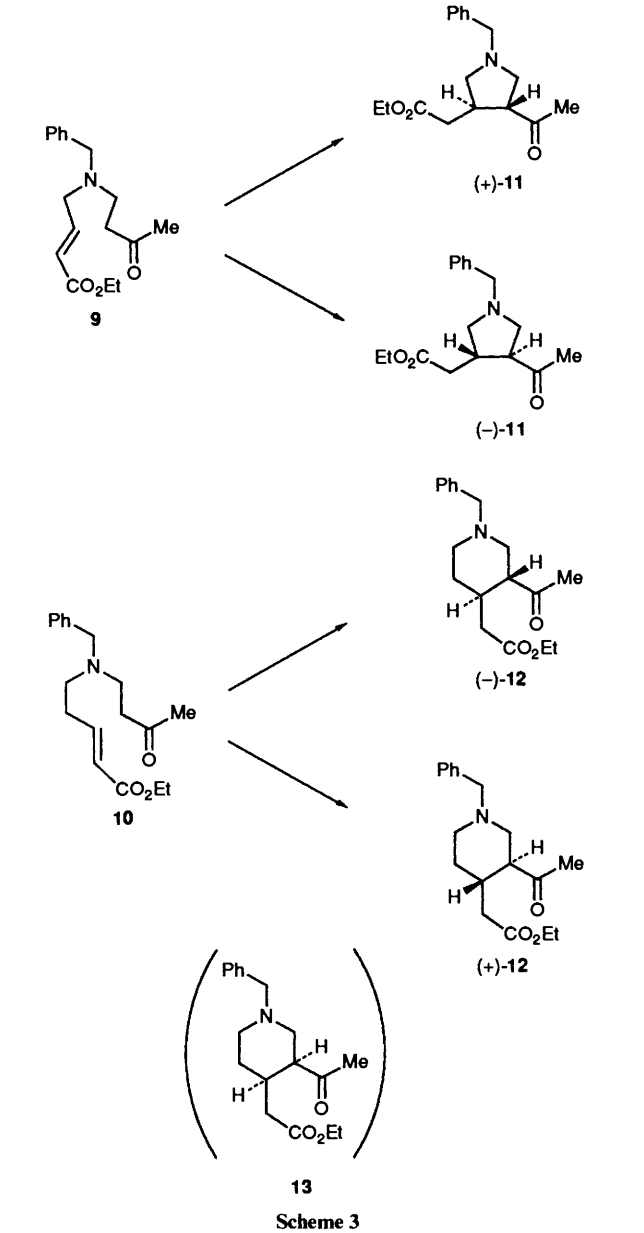
The enantiomeric excess of cycloadducts (+)-**11** and (−)-**11** was determined by integration of signals due to their acetyl methyls in the ^{1}H NMR spectra in the presence of Eu(hfc)$_3$ (1.1 mol equiv.) in $CDCl_3$. The absolute configuration of the cyclized products (+)-**11** and (−)-**11** was determined by chemical correlation of (−)-**11** to the pyrrolidine derivative **15** derived from α-allokainic acid as shown in Scheme 4. Wittig reaction of (−)-**11** with methyltriphenylphosphonium iodide in the presence of butyllithium, followed by catalytic hydrogenation over $Pd(OH)_2$, afforded the secondary amine **15** in 33% overall yield. The synthetic product **15** was identical with an authentic sample obtained from α-allokainic acid through sequential oxidative decarboxylation,[11] esterification, and catalytic hydrogenation. Thus, the absolute configuration of (+)-**11** or (−)-**11** was (3*R*,4*R*) or (3*S*,4*S*), respectively.

The optical purity of the cycloadducts (−)-**12** and (+)-**12** was determined as follows (Scheme 5). Treatment of (−)-**12** and (+)-**12** with methyl chloroformate, followed by reduction with sodium borohydride, afforded the alcohols (−)-**18** and (+)-**18**, respectively, which were treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MTPACl][12] in pyridine to give the corresponding MTPA esters **19** and **20**, respectively. The integration of signals due to the methoxy in the ^{1}H NMR spectra allowed us to estimate the % ee as described in Table 2. The absolute configuration of these cyclized products,

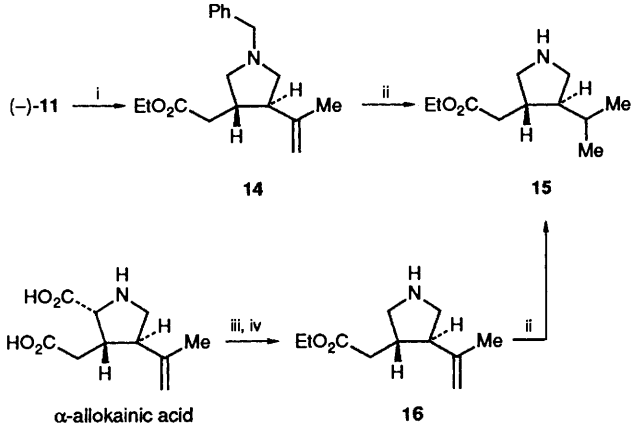
* Commercially available amine, $[\alpha]_D^{20}$ +39° (neat) (ee >99%), was used.

† Commercially available amine, $[\alpha]_D^{20}$ −39° (neat) (ee >99%), was used.

‡ The absolute configuration of compound **13** was determined by its chemical correlation to the enantiomer of the lactone (−)-**29**.[10]

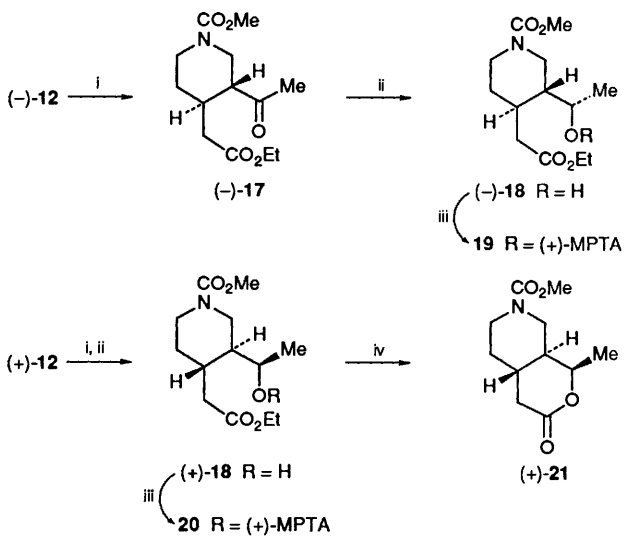


Scheme 3



Scheme 4 *Reagents and conditions:* i, $Ph_3PMe^+ I^-$, BuLi, THF; ii, H_2, $Pd(OH)_2$, EtOH; iii, $NaIO_4$, CH_2Cl_2–water, then $NaBH_3CN$; iv, *p*-TsOH, EtOH

(−)-**12** and (+)-**12**, was determined by chemical correlation of (+)-**12** with the lactone (+)-**21**. Lactonization of the alcohol

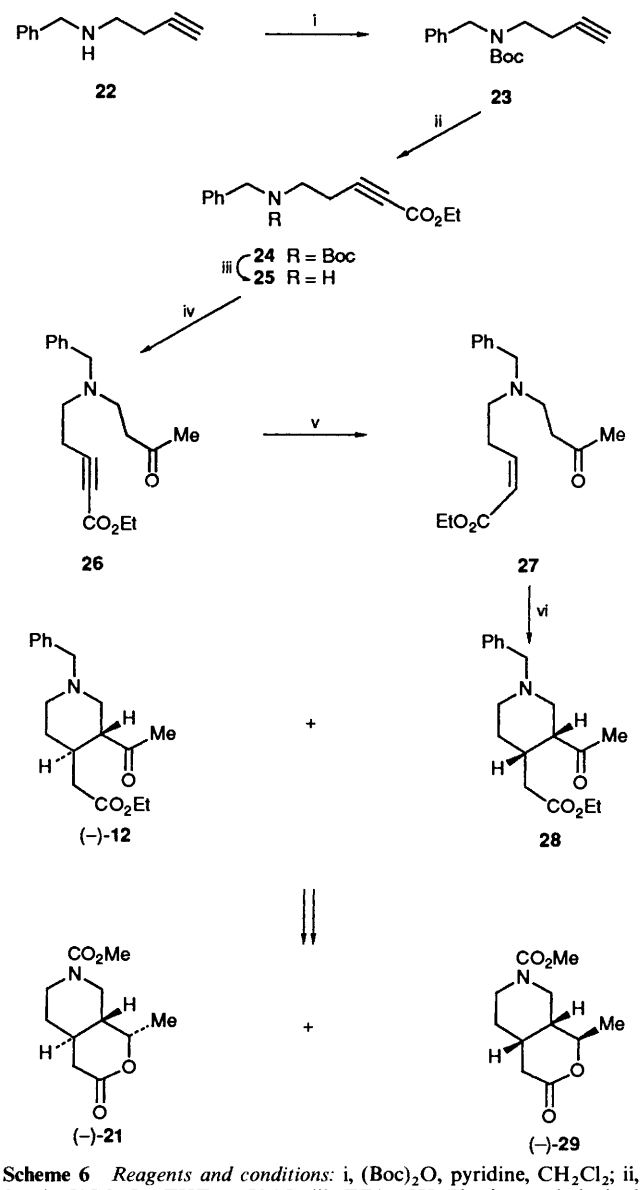


Scheme 5 *Reagents and conditions:* i, $ClCO_2Me$, benzene, reflux; ii, $NaBH_4$, −10 °C; iii, (+)-MTPACl, pyridine; iv, *p*-TsOH, benzene, 60 °C

(+)-**18** derived stereoselectively from (+)-**12** gave (+)-**21** in 95% yield. This compound, (+)-**21**, was identified by spectral comparison with an authentic sample[10] which was elaborated from diethyl L-tartrate *via* an intramolecular hetero-Diels–Alder reaction. Thus, the absolute configuration of (−)-**12** or (+)-**12** was determined to be (3*R*,4*R*) or (3*S*,4*S*), respectively.

In order to determine the effect of the double-bond geometry in the acyclic compound **10** on the stereochemical outcome of the intramolecular Michael reaction, cyclization of the *Z*-isomer **27** was examined. The substrate **27** was synthesized from the secondary amine **22** as shown in Scheme 6. Protection of amine **22**, which was readily obtained from benzylamine by alkylation with but-3-ynyl toluene-*p*-sulfonate, with di-*t*-butyl dicarbonate in pyridine followed by homologation with ethyl chloroformate in the presence of BuLi, gave the ester **24** in 69% yield. Removal of the Boc group in compound **24**, followed by treatment of the resulting secondary amine **25** with methyl vinyl ketone, afforded the ketone **26**. Catalytic hydrogenation of alkynyl ketone **26** over a Lindlar catalyst under hydrogen atmosphere gave the desired compound **27** in 96% yield. Cyclization of *Z*-ester **27** was carried out under the same conditions as those of Run 4 in Table 2 to give a mixture of *cis*- and *trans*-substituted piperidine derivatives **28** and (−)-**12**) in the ratio 2:1 in 45% combined yield, which could be fractionated only poorly by column chromatography on silica gel. The stereochemistry of *cis*-product **28** was determined by its chemical correlation to the lactone (−)-**29** by the same procedure as that for the lactone (+)-**21**. Attempted cyclization of alkynyl ester **26** resulted in recovery of the starting material.

The enantio-differentiations observed throughout this work are consistent with the transition-state topologies depicted in Scheme 7. Initially, reaction of the acyclic compound **10** and (*R*)-1-phenylethylamine gave the enamine in which *E*-isomer **A** should be the major product. Cyclization of the *E*-enamine **A** might proceed through the six-membered cyclic transition state. This transient conformation forces the chiral centre to take the conformation in which the amino hydrogen is situated parallel to the enamino olefin proton to minimize the 1,3-allylic strain and the hydrogen on the chiral centre is also situated parallel to the crotyl methyl. The unsaturated ester should then approach the reaction site (enamino β-carbon) preferentially from the less hindered methyl side (the *re*-face), since the phenyl group blocks the attack from its *si*-face. Cyclization of the minor *Z*-enamine might afford the *cis*-substituted piperidine **13** *via* transition state **B**, and this was isomerized on work-up to the *trans*-piperidine

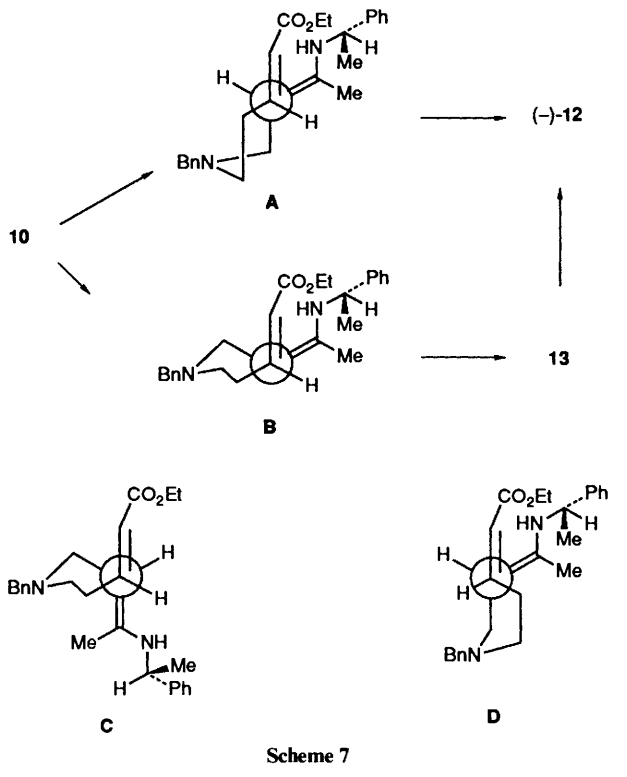


Scheme 6 *Reagents and conditions:* i, $(Boc)_2O$, pyridine, CH_2Cl_2; ii, BuLi, $ClCO_2Et$, THF, −78 °C; iii, TFA, CH_2Cl_2; iv, methyl vinyl ketone, CH_2Cl_2; v, H_2, Lindlar catalyst (5% $Pd/CaCO_3/PbO$); vi, (*R*)-1-phenylethylamine, THF, molecular sieves 5 Å, 5 °C

(−)-**12**. The observed enantio-differentiating selectivity has also been rationalized in terms of presumed distortions in frontier orbital topologies.[13]

The poor enantioselectivity observed for the formation of compound **12** in MeOH can be explained by assuming the *anti*-relationship **C** which is kinetically more preferable than the *gauche* relationship **A** because of better solvation of the donor and acceptor heteroatoms. Cyclization of the *Z*-olefin **27** to **28** may also be explained by the postulated transition state **D**. The tendency to lower enantioselectivity for compound **11** in comparison with that for **12** can be rationalized by assuming that the contribution of the free-energy change in enantio-differentiation would be reduced for the transition state leading to the cyclization into a five-membered ring as compared with that for the six-membered one, because the reaction period for completion of the pyrrolidine was much shorter than that for the piperidine at 5 °C (2 weeks for the pyrrolidine as against 3 weeks for the piperidine).

Thus, the intramolecular asymmetric Michael reaction of acyclic compounds in which an α-ketonic carbanion donor, as its transient enamine with an optically active amine, links to an



Scheme 7

α,β-unsaturated ester moiety has been exploited for the design of versatile chiral building blocks for the synthesis of natural products. Cycloadducts obtained should serve as useful intermediates in the synthesis of *Rauwolfia* alkaloids and α-allokainic acid. Significantly, the basic strategy employed here may be readily modified to accommodate the synthesis of related alkaloids. Application of this work to the synthesis of natural products are reported in the following paper.

Experimental

Optical rotations were measured with a JASCO DIP-140 polarimeter. IR spectra were recorded on a JASCO A-102 grating spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. NMR spectra were taken on a JEOL GX-270 spectrometer for solutions in deuteriochloroform. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane, and *J*-values are given in Hz. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a JEOL JMS D-200 spectrometer. M.p.s were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed by the micro analytical laboratory of this University. All reactions were carried out in flame-dried flasks under argon except in those cases where water was present. Reagents and solvents were dried and distilled before use. Column chromatography was performed with 270–400 mesh silica gel (Merck-9385). Ether refers to diethyl ether.

N-Allyl-N-benzyltrifluoroacetamide **4**.—Allyl bromide (0.7 g, 5.79 mmol) was added to a mixture of *N*-benzyltrifluoroacetamide **3** (1 g, 4.93 mmol), pulverized KOH (85%; 0.4 g, 6.06 mmol), 18-crown-6 (130 mg, 0.49 mmol), and THF (10 cm^3) at 0 °C. After being stirred for 12 h at room temperature, the reaction mixture was poured into ice–water (10 cm^3) and extracted with ether. The separated organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 20 g; elution with benzene) to give

compound **4** (1.0 g, 4.12 mmol) as an oil (Found: M^+, 243.0876. $C_{12}H_{12}F_3NO$ requires M, 243.0870); ν_{max}(neat)/cm^{-1} 1690 (CO); δ_H 3.92 (2 H, d, *J* 10, NC*H*$_2$CH=), 4.62 (2 H, s, NCH$_2$Ar), 4.86–5.40 (2 H, m, CH$_2$C*H*=), 5.40–6.16 (1 H, m, CH$_2$CH=C*H*$_2$) and 7.00–7.60 (5 H, m, ArH).

N-*Benzyl*-N-(*formylmethyl*)*trifluoroacetamide* **5**.—Ozone was bubbled into a solution of compound **4** (1.42 g, 5.84 mmol) in CH_2Cl_2 (30 cm^3) cooled at −78 °C for 1.2 h. After passage of argon for 10 min, Me_2S (0.76 g, 12.3 mmol) was added, and the solution was warmed up to room temperature during 30 min. The mixture was then concentrated under reduced pressure and the resulting residue was subjected to column chromatography [silica gel, 30 g; elution with benzene–CH_2Cl_2 (1 : 1)] to give the *aldehyde* **5** (1.11 g, 4.53 mmol) as an oil (Found: M^+, 245.0620. $C_{11}H_{10}F_3NO_2$ requires M, 245.066 29); ν_{max}(neat)/cm^{-1} 1740 (CO) and 1690 (NCO); δ_H 4.12 (2 H, distorted d, *J* 10, NC*H*$_2$CHO), 4.62 (2 H, br s, NCH$_2$Ar), 7.00–7.50 (5 H, m, ArH) and 9.68 (1 H, s, CHO).

Wittig Reaction of the Aldehyde **5**.—Ethyl (triphenylphosphoranylidene)acetate (1.91 g, 5.47 mmol) was added to a stirred solution of the aldehyde **5** (1.34 g, 5.47 mmol) in CH_2Cl_2 (30 cm^3) in one portion at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was concentrated to leave a syrup, which was subjected to column chromatography [silica gel, 120 g; elution with hexane–EtOAc (19 : 1)] to give, in order of elution, ethyl (*Z*)-4-(*N*-benzyltrifluoroacetamido)but-2-enoate **6** (0.32 g, 1.02 mmol) (Found: C, 57.2; H, 5.1; N, 4.3. Calc. for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44%) and the *E*-ester **7** (1.32 g, 4.19 mmol) (Found: C, 57.4; H, 5.1; N, 4.6%) as viscous oils.

For compound **6**: ν_{max}(neat)/cm^{-1} 1710sh (CO) and 1690 (NCO); δ_H 1.27 (3 H, t, *J* 7.1, OCH$_2$*Me*), 4.10 and 4.17 (2 H, q, *J* 7.1, OC*H*$_2$Me), 4.57 (2 H, dd, *J* 6.0 and 2.0, NC*H*$_2$CH=), 4.61–4.69 (2 H, br s, NCH$_2$Ar), 5.81 and 5.89 (1 H, dt, *J* 11.5 and 2.0, CH=C*H*CO), 6.03 and 6.06 (1 H, dt, *J* 11.5 and 5.9, C*H*=CHCO) and 7.20–7.41 (5 H, m, ArH); *m*/*z* 316 (M^+ + 1).

For compound **7**: ν_{max}(neat)/cm^{-1} 1720 (CO) and 1690 (NCO); δ_H 1.29 and 1.32 (3 H, t, *J* 7.0, OCH$_2$*Me*), 4.03–4.12 (2 H, m, NC*H*$_2$CH=), 4.20 and 4.23 (2 H, q, *J* 7.0, OC*H*$_2$Me), 4.64 (2 H, br s, NCH$_2$Ar), 5.81 and 5.93 (1 H, dt, *J* 15.9 and 1.7, CH=C*H*CO), 6.74 and 6.80 (1 H, dt, *J* 15.9 and 5.6, C*H*=CHCO) and 7.16–7.53 (5 H, m, ArH); *m*/*z* 315 (M^+).

Ethyl (E)-4-(*Benzylamino*)*but*-2-*enoate* **8**.—Aq. K_2CO_3 (5%; 10 cm^3) was added to a solution of compound **7** (1.32 g, 4.19 mmol) in EtOH (20 cm^3) and the reaction mixture was stirred for 5 h at room temperature, then concentrated under reduced pressure below room temperature and extracted with CH_2Cl_2. The extract was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 45 g; elution with CH_2Cl_2) to give the *secondary amine* **8** (567 mg, 2.59 mmol) as an oil (Found: M^+, 219.1236. $C_{13}H_{17}NO_2$ requires M, 219.1258); ν_{max}(neat)/cm^{-1} 1720 (CO); δ_H 1.30 (3 H, t, *J* 7.0, OCH$_2$*Me*), 3.46 (2 H, dd, *J* 5.0 and 2.0, NC*H*$_2$CH=), 3.85 (2 H, s, NCH$_2$Ar), 4.23 (2 H, q, *J* 7.0, OC*H*$_2$Me), 5.96–6.23 (1 H, dt, *J* 16.5 and 2.0, CH=C*H*CO), 7.06 (1 H, dt, *J* 16.5 and 5, C*H*=CHCO) and 7.26–7.60 (5 H, br s, ArH).

Ethyl (E)-4-[*Benzyl*-(3-*oxobutyl*)*amino*]*but*-2-*enoate* **9**.—Methyl vinyl ketone (218.0 mg, 3.11 mmol) was added dropwise to a stirred solution of the amine **8** (567 mg, 2.59 mmol) in CH_2Cl_2 (15 cm^3) at room temperature. After being stirred for 20 h, the mixture was concentrated under reduced pressure to give compound **9** (734.9 mg, 2.54 mmol) as a yellow oil (Found: M^+, 289.1635. Calc. for $C_{17}H_{23}NO_3$: M, 289.167 66). The compound **9** obtained here was unstable for purification using column chromatography on silica gel, and was used for the next reaction without further purification. It showed ν_{max}(neat)/cm^{-1} 1720sh (ester CO) and 1710 (ketone CO); δ_H 1.30 (3 H, t, *J* 7.0, OCH$_2$*Me*), 2.10 (3 H, s, COMe), 2.60 (2 H, t, *J* 7.0), 2.79 (2 H, t, *J* 7.0), 3.20 (2 H, dd, *J* 6.2 and 1.8, NC*H*$_2$CH=), 3.58 (2 H, s, NCH$_2$Ar), 4.20 (2 H, q, *J* 7.0, OC*H*$_2$Me), 5.99 (1 H, dt, *J* 15.8 and 1.8, CH=C*H*CO), 6.95 (1 H, dt, *J* 15.8 and 6, C*H*=CHCO) and 7.24–7.34 (5 H, m, ArH).

Asymmetric Intramolecular Michael Reaction of the Acyclic Compound **9**.—*Using* L-*Proline*. L-Proline (57.6 mg, 0.5 mmol) was added to a solution of compound **9** (144.6 mg, 0.5 mmol) in DMF (15 cm^3) and the mixture was stirred at room temperature. After disappearance of the starting material as shown by TLC (*ca.* 1 week), the reaction mixture was concentrated under reduced pressure below 25 °C. The resulting residue was dissolved in benzene (25 cm^3) and the organic phase was washed with water (5 cm^3), dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel 7.5 g; elution with CH_2Cl_2) to give ethyl (3*R*,4*R*)-(4-acetyl-1-benzylpyrrolidin-3-yl)acetate (+)-**11** (65 mg, 0.22 mmol) as an oil (Found: C, 70.3; H, 7.9; N, 4.6. Calc. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84%); $[\alpha]_D^{26}$ +1.3° (*c* 0.90, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester) and 1710 (CO); δ_H 1.23 (3 H, t, *J* 7.3, OCH$_2$*Me*), 2.17 (3 H, s, COMe), 2.32–2.40 (1 H, m), 2.43–2.50 (2 H, m), 2.55–2.63 (1 H, m), 2.74–2.92 (4 H, m), 3.58 (2 H, dd, *J* 7.8 and 12.8, NCH$_2$Ar), 4.09 (2 H, q, *J* 7.3, OC*H*$_2$Me) and 7.2–7.3 (5 H, m, ArH); *m*/*z* 289 (M^+).

Using (R)-1-*phenylethylamine*. (*R*)-1-Phenylethylamine (123.6 mg, 1.02 mmol) was added to a stirred solution of compound **9** (294.7 mg, 1.02 mmol) in THF (15 cm^3) at 0 °C. Molecular sieves 5 Å (120 mg) was added and the mixture was stirred at ~5 °C. After disappearance of the starting material on TLC (*ca.* 2 weeks), the molecular sieves were filtered off through Celite. The filtrate was concentrated under reduced pressure to give the residue, which was subjected to column chromatography (silica gel, 20 g; elution with CH_2Cl_2) to give compound (+)-**11** (281.3 mg, 0.97 mmol) as an oil; $[\alpha]_D^{26}$ +7.1° (*c* 0.93, $CHCl_3$).

Using (S)-1-*phenylethylamine*. As described for (+)-**11**, the acyclic compound **9** (114.3 mg, 0.396 mmol) was transformed into ethyl (3*S*,4*S*)-(4-acetyl-1-benzylpyrrolidin-3-yl)acetate (−)-**11** (96.1 mg, 0.333 mmol); $[\alpha]_D^{25}$ −5.5° (*c* 0.85, $CHCl_3$), as an oil by treatment with (*S*)-1-phenylethylamine (48.9 mg, 0.404 mmol) as a chiral base.

Asymmetric Michael Reaction of the Acyclic Compound **10**.—*Using* L-*Proline*. L-Proline (104 mg, 0.903 mmol) was added to a solution of compound **10** (273.5 mg, 0.903 mmol) in DMF (10 cm^3) at room temperature. After disappearance of the starting material as shown by TLC, the reaction mixture was concentrated under reduced pressure below 20 °C. The resulting residue was dissolved in benzene (30 cm^3) and the mixture was washed with water (5 cm^3), dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 15 g; elution with CH_2Cl_2) to give ethyl (3*R*,4*R*)-(3-acetyl-1-benzylpiperidin-4-yl)acetate (−)-**12** (164.9 mg, 0.544 mmol) as an oil (Found: C, 71.1; H, 8.35; N, 4.6. Calc. for $C_{18}H_{25}NO_5$: C, 71.25; H, 8.31; N, 4.62%); $[\alpha]_D^{26}$ −2.0° (*c* 0.95, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1710 (ketone CO); δ_H 1.24 (3 H, t, *J* 7.1, CO$_2$CH$_2$*Me*), 1.3–1.5 (1 H, m, 5-H^{ax}), 1.7–1.9 (2 H, m), 1.91–2.05 (2 H, m), 2.06–2.23 (1 H, m), 2.13 (3 H, s, COMe), 2.31 (1 H, dd, *J* 18.5 and 8.2, C*H*HCO$_2$Et), 2.64 (1 H, dt, *J* 10.3 and 4.1, 2-H^{ax}), 2.8–2.9 (1 H, m, 6-H^{eq}), 2.95 (1 H, dq, *J* 11.0 and 2.7, 2-H^{eq}), 3.50 (2 H, s, ArCH$_2$), 4.10 (2 H, q, *J* 7.1, OC*H*$_2$Me) and 7.2–7.4 (5 H, m, ArH); *m*/*z* 303 (M^+).

Using (R)-1-*phenylethylamine*. (*R*)-1-Phenylethylamine (123.6 mg, 1.02 mmol) was added to a solution of compound **10** (309.1 mg, 1.02 mmol) in THF (15 cm^3) at 0 °C. Molecular sieves 5 Å (300 mg) were added and the mixture was stirred at 5 °C. After disappearance of the starting material on TLC inspection (*ca.* 2 weeks), molecular sieves 5 Å were filtered off through Celite. The filtrate was concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 20 g; elution with CH_2Cl_2) to give the piperidine derivative (−)-**12** (253.5 mg, 0.84 mmol) as a pale yellow oil, and the recovered (*R*)-1-phenylethylamine (99.4 mg, 0.82 mmol), that could be recycled, from elution with CH_2Cl_2–MeOH (10:1). The hydrobromide of compound (−)-**12** was recrystallized from ethanol–ether to afford crystals (m.p. 160–164 °C); $[\alpha]_D^{26}$ −30.7° (*c* 0.99, $CHCl_3$).

Using (S)-1-*phenylethylamine*. As described for (−)-**12**, the acyclic compound **10** (884.8 mg, 2.92 mmol) was transformed into ethyl (3*S*,4*S*)-(3-acetyl-1-benzylpiperidin-4-yl)acetate (+)-**12** (682 mg, 2.25 mmol) as an oil, using (*S*)-1-phenylethylamine (354 mg, 2.92 mmol) as a chiral base. The hydrobromide of compound (+)-**12** was recrystallized from ethanol–ether to afford crystals (m.p. 167–170 °C); $[\alpha]_D^{26}$ +30.3° (*c* 1.06, $CHCl_3$).

Ethyl (3R,4R)-(1-*Benzyl*-4-*isopropenylpyrrolidin*-3-*yl*)-*acetate* **14**.—Butyllithium (0.212 cm^3, 10% w/v in hexane) was added to a solution of methyl triphenylphosphonium iodide (134 mg, 0.332 mmol) in THF (3 cm^3) at 0 °C. After this mixture had been stirred for 30 min at room temperature, a solution of (−)-**11** (47.9 mg, 0.1657 mmol) in THF (3 cm^3) was added to the ylide at 0 °C. After being stirred for 1.5 h at room temperature, the reaction mixture was poured into ice-water (5 cm^3) and extracted with ether. The organic phase was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 5 g; elution with CH_2Cl_2) to give *compound* **14** (40 mg, 0.139 mmol) as an oil (Found: M^+, 287.1873. $C_{18}H_{25}NO_2$ requires M, 287.1884); $[\alpha]_D^{26}$ −17.1° (*c* 0.6, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1734 (CO); δ_H 1.22 (3 H, t, *J* 7.1, OCH_2Me), 1.72 (3 H, s, =CMe), 2.3–2.5 (6 H, m), 2.73 (1 H, dd, *J* 10.6 and 11.7), 2.85 (1 H, dd, *J* 6.4 and 8.5), 3.59 (2 H, s, $ArCH_2$), 4.07 (2 H, q, *J* 7.1, OCH_2Me), 4.71 (2 H, d, *J* 7.3, $C{=}CH_2$) and 7.2–7.4 (5 H, m, ArH).

Ethyl (3S,4S)-(4-*Isopropylpyrrolidin*-3-*yl*)*acetate* **15**.—A solution of compound **14** (64 mg, 0.223 mmol) in EtOH (3 cm^3) was catalytically hydrogenated over palladium(II) hydroxide (5 mg) under hydrogen at room temperature for 22 h. The catalyst was removed through Celite and the filtrate was concentrated under reduced pressure. The resulting residue was subjected to column chromatography [silica gel, 3 g; elution with CH_2Cl_2–MeOH (9:1)] to give compound **15** (17.7 mg, 0.09 mmol) as an oil; $[\alpha]_D^{26}$ −26.4° (*c* 0.28, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (CO); δ_H 0.90 (3 H, d, *J* 6.6, CHMe*Me*), 0.96 (3 H, d, *J* 6.6, CH*Me*Me), 1.27 (3 H, t, *J* 7.1, OCH_2Me), 1.5–1.8 (2 H, m), 2.2–2.4 (2 H, m), 2.50 (1 H, dd, *J* 3.9 and 14.7), 2.6–2.8 (2 H, m), 3.0–3.3 (3 H, m) and 4.13 (2 H, q, *J* 7.1, OCH_2Me), The IR (neat) and ^1H NMR spectra of this sample were identical with those of an authentic sample derived from α-allokainic acid.

Ethyl (3S,4R)-(4-*Isopropenylpyrrolidin*-3-*yl*)*acetate* **16**.—A solution of sodium periodate (95.5 mg, 0.446 mmol) in water (1 cm^3) was added to a mixture of α-allokainic acid (34.4 mg, 0.149 mmol), water (1 cm^3) and CH_2Cl_2 (1 cm^3). After the mixture had been stirred for 30 min, the aq. layer was separated and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), and concentrated under reduced pressure to give an oil, which was dissolved in methanol (5 cm^3) containing HCl gas. Sodium cyanoborohydride (8.6 mg, 0.137 mmol) was added to this stirred solution in one portion and the solution was then stirred for 2 h. The mixture was concentrated under reduced pressure to give an oil, which was dissolved in ethanol (5 cm^3). Toluene-*p*-sulfonic acid (PTSA) (4 mg, 0.021 mmol) was added and the mixture was heated under reflux for 14 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was treated with saturated aq. $NaHCO_3$ (3 cm^3) and extracted with benzene. The organic phase was dried (K_2CO_3), and concentrated under reduced pressure to give the residue, which was subjected to column chromatography (silica gel, 30 g; elution with CH_2Cl_2) to afford *compound* **16** (15 mg, 0.076 mol) as a yellow oil (Found: M^+, 197.1397. $C_{11}H_{19}NO_2$ requires M, 197.1415); $[\alpha]_D^{26}$ +106.7° (*c* 0.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1732 (CO); δ_H 1.26 (3 H, t, *J* 7.1, CH_2Me), 1.73 [3 H, s, $C(=CH_2)Me$], 2.2–2.4 (4 H, m), 2.50 (1 H, dd, *J* 4.2 and 14.7, $CHHCO_2$), 2.65 (1 H, dd, *J* 7.3 and 11.0), 2.83 (1 H, dd, *J* 8.1 and 11.0), 3.13 (1 H, dd, *J* 7.3 and 11.0), 3.33 (1 H, dd, *J* 6.6 and 11.0), 4.12 (2 H, q, *J* 7.1, OCH_2Me) and 4.80 (2 H, d, *J* 1.5, $C{=}CH_2$).

Catalytic Hydrogenation of Compound **16**.—A solution of compound **16** (2.7 mg, 0.014 mmol) in EtOH (1 cm^3) was catalytically hydrogenated over palladium(II) hydroxide (1 mg) under hydrogen at room temperature for 12 h. The catalyst was removed through Celite and the filtrate was concentrated under reduced pressure. The resulting residue was subjected to column chromatography [silica gel 3 g; elution with CH_2Cl_2–MeOH (9:1)] to give compound **15** (2.6 mg, 0.013 mmol) as an oil; $[\alpha]_D^{26}$ −30.0° (*c* 0.1, $CHCl_3$).

Ethyl (3R,4R)-(3-*Acetyl*-1-*methoxycarbonylpiperidin*-4-*yl*)-*acetate* (−)-**17**.—A mixture of compound (−)-**12** (567.2 mg, 1.87 mmol), methyl chloroformate (212.8 mg, 2.25 mmol), and benzene (20 cm^3) was heated at 50 °C for 11 h. The solvent was removed under reduced pressure to give the residue, which was subjected to column chromatography [silica gel, 20 g; elution with benzene–CH_2Cl_2 (1:1)] to give diester (−)-**17** (481.9 mg, 1.78 mmol) as a pale yellow oil (Found: C, 57.4; H, 7.8; N, 5.0. Calc. for $C_{13}H_{21}NO_5$: 57.55; H, 7.80; N, 5.16%); $[\alpha]_D^{27}$ −53.1° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (CO); δ_H 1.25 (3 H, t, *J* 7.1, OCH_2Me), 1.13–1.36 (1 H, m, 5-H^{ax}), 1.81 (1 H, dq, *J* 13.4 and 2.9, 5-H^{eq}), 2.1–2.4 (1 H, m), 2.15 (1 H, dd, *J* 15.6 and 9.2, $CHHCO$), 2.25 (3 H, s, COMe), 2.32 (1 H, dd, *J* 15.6 and 4.2, $CHHCO$), 2.57 (1 H, dt, *J* 10.4 and 3.4, 3-H), 2.61–2.90 (2 H, m, 2- and 6-H^{ax}), 3.73 (3 H, s, NCO_2Me), 4.13 (2 H, q, *J* 7.1, OCH_2Me) and 4.1–4.4 (2 H, br, 2- and 6-H^{eq}); *m*/*z* 272 ($M^+ + 1$).

Ethyl (3S,4S)-(3-*Acetyl*-1-*methoxycarbonylpiperidin*-4-*yl*)-*acetate* (+)-**17**.—As described for the carbamate (−)-**17**, compound (+)-**12** (600.9 mg) was transformed into (+)-**17** (488.8 mg), $[\alpha]_D^{26}$ +51.7° (*c* 1.2, $CHCl_3$). The IR (neat) and ^1H NMR spectra of this sample were identical with those of its enantiomer (−)-**17**.

Ethyl (3R,4R,1′S)-[3-(1′-*Hydroxyethyl*)-1-*methoxycarbonyl*-*piperidin*-4-*yl*]*acetate* (−)-**18**.—Sodium borohydride (96.1 mg, 2.54 mmol) was added to a solution of compound (−)-**17** (68.7 mg, 0.254 mmol) in EtOH (2 cm^3) at −15 °C. After being stirred at the same temperature for 2 h, the mixture was evaporated under reduced pressure at 0 °C. The resulting residue was partitioned between CH_2Cl_2 (10 cm^3) and water (5 cm^3), and the separated aq. layer was then extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue [silica gel, 2 g; elution with benzene–CH_2Cl_2 (1:1)] afforded the alcohol (−)-**18** (49.1 mg, 0.18 mmol) as an oil (Found: C, 56.8; H, 8.5; N, 4.95. Calc. for

$C_{13}H_{23}NO_5$: C, 57.12; H, 8.48; N, 5.13%); $[\alpha]_D^{26}$ −18.1° (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.25 [3 H, d, *J* 6.3, CH(OH)*Me*], 1.27 (3 H, t, *J* 7.1, OCH_2Me), 1.1–1.4 (2 H, ddd, *J* 13.3, 3.9 and 3.5, 3-H), 2.05–2.20 (1 H, m, 4-H), 2.28 (1 H, dd, *J* 16.4 and 5.7, C*H*HCO), 2.54 (1 H, dd, *J* 16.4 and 7.0, CH*H*CO), 2.8–3.1 (3 H, br, 2- and 6-H^{ax} and OH), 3.69 (3 H, s, NCO_2Me), 3.8–4.0 [3 H, m, 2- and 6-H^{eq} and C*H*(OH)Me] and 4.16 (2 H, q, *J* 7.1, OCH_2Me); *m*/*z* 273 (M^+).

Ethyl (3S,4S,1′R)-[3-(1′-*Hydroxyethyl*)-1-*methoxycarbonylpiperidin*-4-*yl*]*acetate* (+)-**18**.—As described for the alcohol (−)-**18**, (+)-**17** (234.7 mg) was transformed into the alcohol (+)-**18** (166.9 mg); $[\alpha]_D^{26}$ +18.2° (*c* 1.1, $CHCl_3$). The IR (neat) and ^{1}H NMR spectra of this sample were identical with those of (−)-**18**.

Reaction of the Alcohol (−)-**18** *with* (+)-α-*Methoxy*-α-(*trifluoromethyl*)*phenylacetyl Chloride*.—(+)-MTPACl (22.4 mg, 0.089 mmol) was added to a solution of the alcohol (−)-**18** (20.1 mg, 0.074 mmol) in pyridine (0.5 cm^3) at room temperature. After being stirred for 2 h, the solution was evaporated under reduced pressure. The resulting residue was partitioned between benzene (5 cm^3) and water (5 cm^3). The benzene layer was then washed successively with 5% HCl, brine, and saturated aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure to give the *MTPA ester* **19** (29.6 mg, 0.061 mmol) as a yellow oil (Found: M^+, 489.1973. $C_{23}H_{30}F_3NO_7$ requires M, 489.1972); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.25 (3 H, t, *J* 7.1, OCH_2Me), 1.13–1.36 (1 H, m, 5-H^{ax}), 1.40 (3 H, d, *J* 6.4, CH*Me*), 1.38–1.55 (1 H, m, 5-H^{eq}), 1.55–1.80 (3 H, m), 2.11 (1 H, dd, *J* 15.1 and 8.5, C*H*HCO), 2.55 (1 H, dd, *J* 15.1 and 3.7, CH*H*CO), 2.55–2.80 (1 H, m), 3.56 (3 H, br q, *J* 1.2, OMe), 3.67 (3 H, s, NCO_2Me), 3.90–4.30 (2 H, br, 2- and 6-H^{eq}), 4.05 (2 H, q, *J* 7.1, OCH_2Me), 5.40–5.53 (1 H, m, C*H*Me) and 7.3–7.6 (5 H, m, ArH).

Reaction of the Alcohol (+)-**18** *with* (+)-α-*Methoxy*-α-(*trifluoromethyl*)*phenylacetyl Chloride* **20**.—As described for the MTPA ester **19**, compound (+)-**18** (10.7 mg) was transformed into the MTPA ester **20** (13.6 mg) (Found: M^+, 489.1933); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.26 (3 H, t, *J* 7.1, OCH_2Me), 1.33 (3 H, d, *J* 6.6, CH*Me*), 1.15–1.38 (1 H, m, 5-H^{ax}), 1.38–1.55 (1 H, m, 5-H^{eq}), 1.60–1.95 (3 H, m), 2.14 (1 H, dd, *J* 15.1 and 9.0, C*H*HCO), 2.58 (1 H, dd, *J* 15.1 and 3.9, CH*H*CO), 2.64–2.82 (1 H, m), 3.52 (3 H, br q, *J* 1.2, OMe), 3.67 (3 H, s, NCO_2Me), 3.92–4.30 (2 H, br, 2- and 6-H^{eq}), 4.13 (2 H, q, *J* 7.1, OCH_2Me), 5.32–5.50 (1 H, m, C*H*Me) and 7.3–7.6 (5 H, m, ArH).

Methyl (1R,4aS,8aS)-3a,4,4a,5,6,7,8,8a-*Octahydro*-1-*methyl*-3-*oxo*-1H-*pyrano*[3,4-c]*pyridine*-7-*carboxylate* (+)-**21**.[10]—A catalytic amount of PTSA monohydrate (49.3 mg, 0.259 mmol) was added to a solution of the alcohol (+)-**18** (707.8 mg, 2.59 mmol) in benzene (30 cm^3) and the mixture was heated under reflux for 10 h. The reaction mixture was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give a residue, which was subjected to column chromatography [silica gel, 10 g; elution with benzene–CH_2Cl_2 (1:1)] to give the lactone (+)-**21** (555.2 mg, 2.45 mmol) as crystals (Found: C, 57.7; H, 7.4; N, 5.8. Calc. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16%); m.p. 76–80 °C (from Et_2O); $[\alpha]_D^{26}$ +56.9° (*c* 1.0, MeOH); ν_{max}(neat)/cm^{-1} 1725 (lactone CO) and 1690 (carbamate CO); δ_H 1.13–1.37 (1 H, m, 5-H^{ax}), 1.30 [3 H, d, *J* 6.8, CH(OH)*Me*], 1.76–2.05 (3 H, m), 2.11 (1 H, dd, *J* 17.8 and 11.3, CH*H*CO_2Et), 2.50 (1 H, br t, *J* 13.2, 6-H^{ax}), 2.73 (1 H, dd, *J* 17.8 and 4.9, C*H*HCO_2Et), 2.70–2.85 (1 H, m, 8-H^{ax}), 3.71 (3 H, s, NCO_2Me), 4.03–4.40 (2 H, br, 6- and 8-H^{eq}) and 4.70 (1 H, m, CMe*H*CO); *m*/*z* 227 (M^+). These spectral data were identical with those of an authentic sample.

N-Benzylbut-3-*ynamine* **22**.—Benzylamine (3.84 g, 35.81 mmol) and sodium iodide (0.11 g, 0.752 mmol) were added to a solution of but-3-ynyl toluene-*p*-sulfonate (4.02 g, 17.91 mmol) in dimethyl sulfoxide (25 cm^3). After being stirred for 35 h at room temperature, the reaction mixture was poured into 2% aq. NaOH (40 cm^3) and extracted with ether (70 cm^3 × 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 160 g; elution with $CHCl_3$) to give the *secondary amine* **22** (2.52 g, 15.85 mmol) as an oil (Found: M^+, 159.103. $C_{11}H_{13}N$ requires M, 159.1047); ν_{max}(neat)/cm^{-1} 3310 (NH); δ_H 1.65 (1 H, br s, NH), 1.95 (1 H, t, *J* 3.0, C≡CH), 2.2–2.5 (2 H, m), 2.6–2.9 (2 H, m), 3.80 (2 H, s, $ArCH_2$) and 7.25 (5 H, s, ArH).

t-*Butyl* N-*Benzyl*-N-(*but*-3-*ynyl*)*carbamate* **23**.—Di-*t*-butyl dicarbonate (22.37 g, 0.103 mol) was added to a solution of the amine **22** (16.32 g, 0.103 mol) and pyridine (8.11 g, 0.103 mol) in ether (100 cm^3) at 0 °C. After being stirred for 4 h, the reaction mixture was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 200 g; elution with benzene) to give the carbamate **23** (23.43 g, 90.46 mmol) as an oil (Found: C, 74.3; H, 8.1; N, 5.35. Calc. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40%); ν_{max}(neat)/cm^{-1} 1696 (CO); δ_H 1.46 (9 H, s, Bu^{t}O), 1.91 (1 H, t, *J* 3.0, C≡CH), 2.1–2.6 (2 H, m, CH_2C≡), 3.33 (2 H, t, *J* 7.0, NCH_2CH_2), 4.50 (2 H, s, $ArCH_2N$) and 7.25 (5 H, s, ArH); *m*/*z* 260 (M^+ + 1).

Ethyl 5-[N-*Benzyl*-N-(t-*butoxycarbonyl*)*amino*]*pent*-2-*ynoate* **24**.—BuLi (10% w/v in hexane; 20.4 cm^3) was added to a solution of compound **23** (7.50 g, 28.96 mmol) in THF (45 cm^3) at −78 °C. After the mixture had been stirred for 0.5 h, ethyl chloroformate was added and the mixture was stirred for 15 h at −78 °C. The reaction mixture was quenched by the addition of saturated aq. NH_4Cl (20 cm^3) and extracted with ether (30 cm^3 × 5). The combined organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel 200 g; elution with benzene) to give compound **24** (7.52 g, 22.72 mmol) as an oil (Found: C, 68.9; H, 7.55; N, 4.3. Calc. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23%); ν_{max}(neat)/cm^{-1} 1701 (CO); δ_H 1.29 (3 H, t, *J* 7.0, OCH_2Me), 1.46 (9 H, s, Bu^{t}O), 2.50 (2 H, t, *J* 7.0, CH_2C≡CCO), 3.39 (2 H, t, *J* 7.0, NCH_2CH_2), 4.19 (2 H, q, *J* 7.0, OCH_2Me), 4.50 (2 H, s, $ArCH_2N$) and 7.26 (5 H, br s, ArH); *m*/*z* 332 (M^+ + 1).

Ethyl 5-(*Benzylamino*)*pent*-2-*ynoate* **25**.—Trifluoroacetic acid (TFA) (5.92 g, 51.9 mmol) was added to a solution of compound **24** (3.17 g, 9.57 mmol) in CH_2Cl_2 (12 cm^3) at 0 °C. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure to give an oil, which was dissolved in saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 100 g; elution with CH_2Cl_2) to give compound **25** (1.62 g, 7.0 mmol) as a pale yellow oil (Found: C, 72.8; H, 7.3; N, 6.15. Calc. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06%); ν_{max}(neat)/cm^{-1} 1710 (CO); δ_H 1.26 (3 H, t, *J* 7.0, OCH_2Me), 1.55 (1 H, br s, NH), 2.3–3.0 (4 H, m, NCH_2CH_2), 3.80 (2 H, s, $ArCH_2N$), 4.20 (2 H, q, *J* 7.0, OCH_2Me) and 7.50 (5 H, br s, ArH); *m*/*z* 231 (M^+).

Ethyl 5-[*Benzyl*-(3-*oxobutyl*)*amino*]*pent*-2-*ynoate* **26**.—Methyl vinyl ketone (224 mg, 3.20 mmol) was added to a solution of compound **25** (617 mg, 2.67 mmol) in CH_2Cl_2 (20 cm^3) at 0 °C. The reaction mixture was stirred for 24 h at room

temperature and was then concentrated under reduced pressure to give compound **26**, which was unstable for purification using column chromatography on silica gel, and was used for the next reaction without further purification (Found: C, 71.5; H, 7.5; N, 4.9. Calc. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65%); ν_{max}(neat)/cm^{-1} 1710 (CO); δ_H 1.30 (3 H, t, *J* 7.1, OCH_2Me), 2.12 (3 H, s, COMe), 2.45 (2 H, t, *J* 7.1), 2.60 (2 H, t, *J* 7.1), 2.73 (2 H, t, *J* 6.8), 2.82 (2 H, t, *J* 6.8), 3.61 (2 H, s, $ArCH_2N$), 4.21 (2 H, q, *J* 7.1, OCH_2Me) and 7.2–7.4 (5 H, m, ArH); *m*/*z* 301 (M^+).

Ethyl (Z)-5-[*Benzyl*-(3-*oxobutyl*)*amino*]*pent*-2-*enoate* **27**.—A solution of the ynoate **26** (942.5 mg, 3.13 mmol) in ethyl acetate (15 cm^3) was hydrogenated over Lindlar catalyst (20 mg) under hydrogen at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated to give the *enoate* **27** (908.2 mg, 2.99 mmol) as an oil (Found: M^+, 303.1847. $C_{18}H_{25}NO_3$ requires M, 303.1833). Compound **27** was used for the next reaction without further purification, and showed ν_{max}(neat)/cm^{-1} 1700 (ester CO), 1690 (ketone CO) and 1650; δ_H 1.27 (3 H, t, *J* 7.1, OCH_2Me), 2.07 (3 H, s, COMe), 2.50–2.60 (4 H, m), 2.7–2.9 (4 H, m), 3.58 (2 H, s, $ArCH_2N$), 4.15 (2 H, q, *J* 7.1, OCH_2Me), 5.79 (1 H, dt, *J* 11.5 and 1.5, CH=C*H*CO), 6.22 (1 H, dt, *J* 11.5 and 7.3, C*H*=CHCO) and 7.2–7.4 (5 H, m, ArH); *m*/*z* 303 (M^+).

Asymmetric Intramolecular Michael Reaction of Compound **27**.—Cyclization of *Z*-ester **27** (908.2 mg) was carried out according to the same procedure as that of Run 4 in Table 2 to afford a mixture of the cyclized products **28** and (−)-**12** (409.6 mg), which was separated from the chiral base. This mixture was used for the next reaction without further fractionation.

Methyl (1R,4aS,8aR)-3,4,4a,5,6,7,8,8a-*Octahydro*-1-*methyl*-3-*oxo*-1H-*pyrano*[3,4-c]*pyridine*-7-*carboxylate* (−)-**29**.[10]—As described for the lactone (+)-**21**, a mixture of piperidine derivatives **28** and (−)-**12** (201.5 mg) was transformed into a mixture of the lactones (−)-**29** (49.7 mg) and (−)-**21** (24.8 mg) in 3 steps; the product mixture was fractionated by silica gel column chromatography. For (−)-**29** (Found: C, 58.0; H, 7.6; N, 6.1. Calc. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16%); $[\alpha]_D^{26}$ −3.3° (*c* 0.7, MeOH); ν_{max}(neat)/cm^{-1} 1725 (ester CO) and 1690 (carbamate CO); δ_H 1.46 (3 H, d, *J* 6.4, CH*Me*), 1.55–1.74 (2 H, m, 5-H_2), 1.75–1.90 (1 H, m, 8a-H), 2.12–2.28 (1 H, m, 4a-H), 2.44 (1 H, dd, *J* 17.6 and 3.9, C*H*HCO), 2.67 (1 H, dd, *J* 17.6 and 6.6, CH*H*CO), 2.88–3.04 (1 H, m, 6-H^{ax}), 3.13 (1 H, dd, *J* 13.9 and 5.0, 8-H^{ax}), 3.70 (3 H, s, NCO_2Me), 3.86–4.20 (2 H, br, 6- and 8-H^{eq}) and 4.40–4.53 (1 H, m, C*H*Me); *m*/*z* 227 (M^+). These spectral data of the lactone (−)-**29** were identical with those of an authentic sample.

Methyl (1S,4aR,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-1-*methyl*-3-*oxo*-1H-*pyrano*[3,4-c]*pyridine*-7-*carboxylate* (+)-**29**.—As described for the lactone (+)-**21**, a mixture of the piperidine derivatives **13** and (−)-**12** (41.6 mg, 0.137 mmol) was transformed into a mixture of the lactones (+)-**29** (4.9 mg, 0.022 mmol) and (−)-**21** (6.5 mg, 0.029 mmol) in 3 steps; the products were separated by column chromatography on silica gel. Compound (+)-**29** (Found: C, 58.0; H, 7.5; N, 6.1%); m.p. 81–83 °C (from Et_2O); $[\alpha]_D^{27}$ +16.3° (*c* 0.245, MeOH). The IR (neat) and ^{1}H NMR spectra of this sample were identical with those of its enantiomer (−)-**29**.

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