Enantioselective Michael Reactions of Chiral Secondary Enaminoesters with 2-Substituted Nitroethylenes. Syntheses of *trans,trans*-2,4-Disubstituted Pyrrolidine-3-carboxylates

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The Michael reaction of chiral 3-substituted secondary enaminoesters with 2-substituted nitroethylenes leads to (*Z*)-adducts, with good to excellent diastereoselectivity. The nitro group of these adducts was catalytically reduced to give, after cyclization and chiral amine elimination, pyrrolines or pyrrolidines after further reduction. In particular, the syntheses of ethyl (2*R*,3*S*,4*S*)-2,4-dimethylpyrrolidine-3-carboxylate and ethyl (2*R*,3*R*,4*S*)-2-(4-methoxyphenyl)-4-(3,4-(methylenedioxy)phenyl)pyrrolidine-3-carboxylate are described.

The Michael-type addition of imines reacting via their secondary enamines tautomers was first described 30 years ago.[1] Theoretical studies[2b,c] have shown that in the general case of a secondary enamine and an electrophilic olefin bearing a carbonyl as the electron-withdrawing group, a compact *syn* approach of the reactants leads to chairlike and boatlike complexes in which the *N*-atom of the secondary enamine and the *C*-atom of the carbonyl group (*endo* position) are included. If an imine derived from a 2-substituted cyclanone is reacted with a substituted electrophilic olefin, and as the chair complex lies at about 4 kcal/mol below the boat one (which would lead to an adduct with the opposite stereochemical relationship of the substituents), the implication is that a high diastereoselectivity should be observed for the reaction and also that the relationship of the substituents could be anticipated (Figure 1). These predictions have been confirmed experimentally.[2d,3]

When a chiral nonracemic amine is used with a racemic 2-substituted carbonyl compound, the secondary

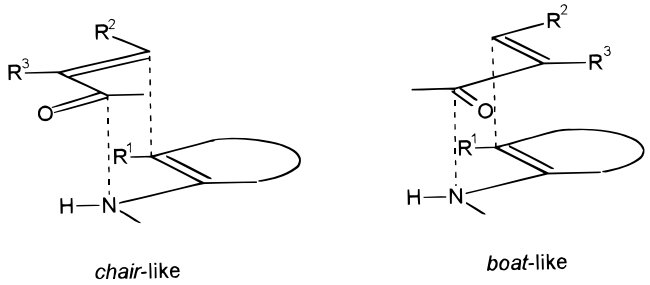

Figure 1. Diastereoselectivity in the syn approach of the reactants.

enamine undergoes enantioselective Michael reactions, allowing the preparation of a variety of building blocks bearing a quaternary stereogenic center, and many synthetic applications have been reported.[2]

Almost 50 years ago, Grob and Camenisch reported that secondary enaminoester **1** reacted with 1-nitropropene to give pyrrole **6** in 70% yield.[4] In a second article, a mechanism was suggested for this reaction in which the *E* isomer **3** of the *Z* adduct **2** is in equilibrium with its *aci*-nitro tautomer **4** which is cyclized to the hydrated nitroso compound **5**, affording pyrrole **6** through water and hyponitrous acid eliminations[5,6] (Scheme 1).

Grob and Schad had also shown that the *N*-benzyl analogue of uncyclized *Z* intermediate **2** could actually be isolated when the reaction was performed in acetonitrile[5] rather than in ethanol. One can suppose that in this case the formation of a stabilizing intramolecular hydrogen bond is allowed, impeding tautomerization to the imine form which can lead to the *E* isomer **3** and pyrrole **6**. In view of this very interesting observation it occurred to us that an enantioselective reaction could be possible for enaminoesters of type **1**, derived from a chiral amine, leading to adducts of type **2** which involve a

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(1) Pfau, M.; Ribière, C. *J. Chem. Soc. Chem. Commun.* **1970**, 66−67. Pfau, M.; Ribière, C. *Bull Soc. Chim. Fr.* **1971**, 2584−2590.

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(3) That the expected relationship was in fact the reverse one in an example reported (Cavé, C.; Daley, V.; d'Angelo, J. *Tetrahedron: Asymmetry* **1995**, *6*, 79−82) led the authors to claim that the carbonyl group is in *exo* rather than in *endo* position (the *boat* complex possibility was not invoked). However, in a later article (Cavé, C.; Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 4361−4368) the authors explained that in the original paper the relevant structures "have been permuted by inadvertence," thus implicitly confirming the generality of the theoretical prediction.[2b]

(4) Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49−58.

(5) Grob, C. A.; Schad, H. P. *Helv. Chim. Acta* **1955**, *38*, 1121−1127.

(6) Recently, the reaction displayed in Scheme 1 was extended to the reaction of cyclohexanones imines with 2-substituted nitroethylenes, affording tetrahydroindoles: Lim. S.; Jabin, I.; Revial, G. *Tetrahedron Lett.* **1999**, *40*, 4177−4180.

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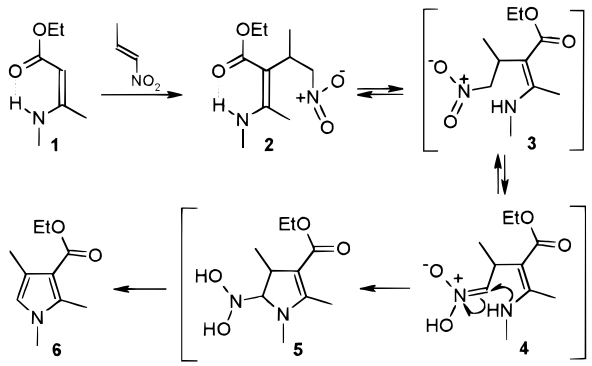
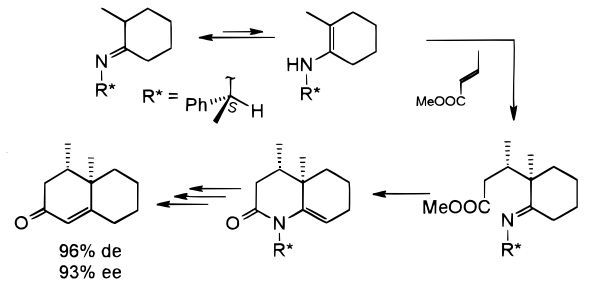
Scheme 1



Scheme 2



tertiary stereogenic center. These adducts in turn could be used in particular for the syntheses of pyrrolines and pyrrolidines. In fact it had already been shown that when a chiral secondary enamine (derived from 2-methylcyclohexanone) reacts with β- (or α-)substituted acrylates, a controlled tertiary stereogenic center is created along the usual quaternary one[2e] (Scheme 2). The reaction proceeds with an excellent diastereoselectivity in accordance again with the theoretical predictions[2b] (vide supra) and with a high enantioselectivity,[2c,f] which in turn is in accordance with the heuristic rule[2b] allowing the prediction of the favored diastereofacial selectivity, i.e., the absolute configuration of the adduct.

Results and Discussion

Chiral Adducts from the Michael Reaction. Experiments with various substituents on both the enaminoester and the nitroolefin were performed under mild conditions to limit the cyclization of the adducts. The first and the last example were chosen for synthetic applications (vide infra) (Scheme 3, Table 1).

Only noncyclized adducts were detected by ^{1}H NMR of the crude mixtures in all examples, with the exception of the reactions of enaminoester **17** with nitroolefins **8** and **11** in which the adducts **18** and **20** are significantly cyclized to afford pyrroles **19** and **21**, respectively. In these cases where a long reaction time was required, we tried to accelerate the reaction by using a Lewis acid catalyst; thus, in one example dealing with enaminoester **17** and nitroolefin **14**, the reaction performed in the presence of $MgCl_2$ was indeed accelerated, but under these conditions a mixture of nitroenaminoester **22** and pyrrole **23** was obtained; moreover, the diastereoselectivity was lowered. Pyrrole **23** was isolated and characterized in this case.

After purification by recrystallization and/or flash chromatography (FC), the structures of adducts **9**, **12**, **15**, **22**, and **26** were determined by ^{1}H and ^{13}C NMR spectrography.

Adduct **20** was inseparable by FC, and in these conditions the proportion of the corresponding cyclized compound **21** increased. In the other example of pyrrole formation, FC purification of adduct **18** was therefore not attempted. In this case, the reaction of enaminoester **17** with nitroolefin **8** was also carried out without solvent, and the reaction time was much reduced. More interestingly, less pyrrole **19** was formed, and the unpurified mixture was used directly for the next step (vide infra).

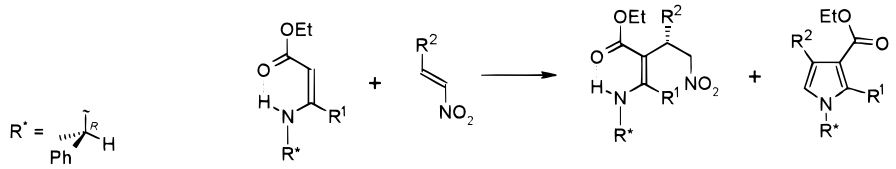
The structures of compounds **18** and **20** (as well as those of the corresponding pyrroles **19** and **21**) were determined by NMR, using in each case the mixture of the two reaction products.

The diastereoselectivities were determined by ^{1}H NMR of the crude reaction mixtures and are good to excellent (93:7 to >99:1) when the nitroolefin bears an alkyl substituent. The diastereoselectivity was much reduced (83:17 to 90:10) when the substituent is an aryl group. Moreover, separation of the major diastereoisomer could not be achieved in any instance.

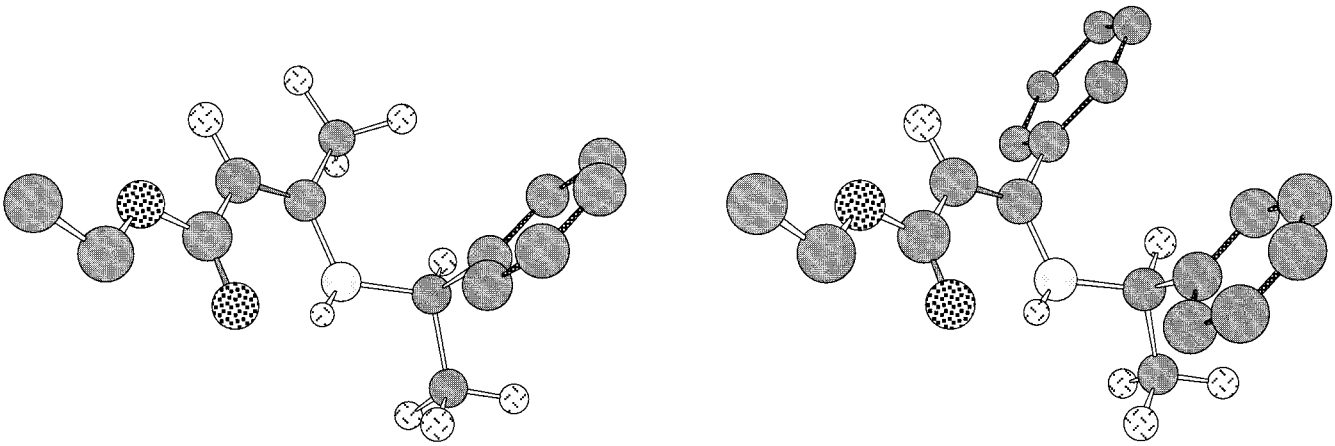
Molecular modeling[7] of enaminoesters **7** and **17** (Figure 2) shows that their two diastereotopic faces are subject to very different steric hindrance as is the case with the usual chiral secondary enamines of 2-substituted cyclohexanone imines,[2b] although in the present instance the phenyl substituent (R^1) in compound **17** is very different in size by comparison with the corresponding methylene group in an 1-amino-2-substituted cyclohexene.

The absolute configuration of adduct **9** was determined by single-crystal X-ray diffraction and those of the other

Scheme 3



$R^1 = R^2 =$ Me	**7**	**8**	**9**	**10**
R^1 = Me; R^2 = Et	**7**	**11**	**12**	**13**
R^1 = Me; R^2 = Ph	**7**	**14**	**15**	**16**
R^1 = Ph; R^2 = Me	**17**	**8**	**18**	**19**
R^1 = Ph; R^2 = Et	**17**	**11**	**20**	**21**
$R^1 = R^2$ = Ph	**17**	**14**	**22**	**23**
R^1 = 4-MeO-Ph; R^2 = 3,4-methylenedioxy-Ph; R*: config. *S*	**24**	**25**	**26** ($C\text{-}R^2$, above plane)	**27**



7 **17**

Figure 2. Modeling of the *R* enantiomers of enaminoesters **7** and **17**.

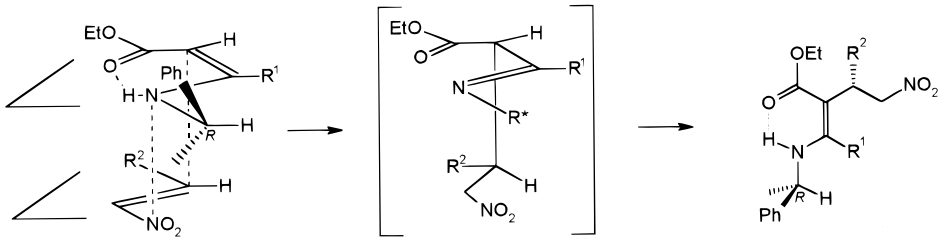


Figure 3. Rule for predicting the absolute configuration of Michael adducts.

Table 1. Chiral Adducts from Michael Reactions of Enaminoesters with Nitroolefins[a]

enamino-ester	nitroolefin (1 equiv)	conditions (MeCN, rt)	product, %	yield, %	diastereo-selectivity
7	**8**	1.2 M, 3 h	**9** >99 **10** <1	95[b]	>99:1
	11	2.5 M, 24 h	**12** >99 **13** <1	87[c]	>99:1
	14	6.5 M, 3 d	**15** >99 **16** <1	80[c]	85:15
17	**8**	2.5 M, 6 d	**18** 70 **19** 30	—[d]	94:6
		no solvent, 23 h	**18** 91 **19** 9	—[d,e]	93:7
	11	2.5 M, 6 d	**20** 70[f] **21** 30	—[g]	96:4
	14	7 M, 6 d	**22** >99 **23** <1	95[c]	90:10
24	**25**	1 M, 18 d[h]	**26** >99 **27** <1	93[c]	83:17

[a] See Scheme 3 for structures and see text for notes *e* and *f*. [b] Washed crystalline compound. [c] FC purification. [d] Not purified. [e] Used directly for the next step. [f] **20/21**: 75:25 before FC. [g] Inseparable mixture of **20** and **21**. [h] Time required for total solubilization of compound **25**.

adducts are assumed by analogy (Scheme 3). The absolute configurations are as predicted[2b] (vide supra) (Figure 3; see also Figure 2).

The results above show that the replacement of a carbonyl by a nitro group in the electrophilic olefin does not alter the mechanism of the Michael reaction, i.e., that the *syn* approach leading to a chairlike complex is still prevalent, meaning that attractive MO interactions arising from frontier orbitals should operate between the *N*-atoms of the amino and nitro groups as they usually do between the *N*-atom of the amino group and the *C*-atom of a carbonyl group.[2b]

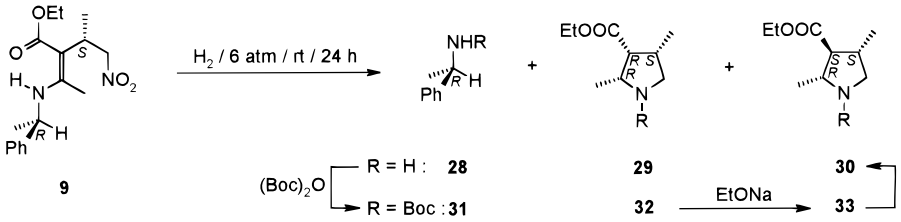
Although all the adducts which are obtained involve a stabilizing H-bond (in ^{1}H NMR, the NH hydrogen atom is typically shifted downfield at ca. 10 ppm) which restricts the isomerization of the double bond, cyclized compounds are nonetheless produced in the reaction of enaminoester **17** with nitroolefin **8** or **11** (Table 1). In these cases, the R^1 substituent is a phenyl group, and one can suppose that for the corresponding *Z* adducts **18** and **20**, there is more crowding than in adducts **9**, **12**, and **15** where R^1 is a methyl group, allowing a slight displacement of the $Z \rightleftharpoons E$ equilibrium to the right, with increased formation of pyrroles **19** and **21** compared to **10**, **13**, and **16**. When enaminoester **17** is reacted with nitroolefin **14**, and enaminoester **24** with nitroolefin **25**, however, pyrrole formation is not observed. In this instance it is possible that in the *E* form of the corresponding adducts **22** and **26**, the bulky aryl substituent in the α-position of the *aci*-nitro group (analogous to structure **4** in Scheme 1) lowers the efficiency of attack of this group by the enamino nitrogen atom.

In one example we have confirmed that stirring adduct **9** at room temperature in a protic solvent (ethanol) suppresses the hydrogen bonding, since it leads to the corresponding Grob's type product, i.e., pyrrole **10**. We have also cyclized the adduct **26** to pyrrole **27**.

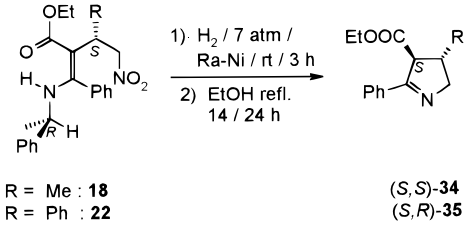
Cyclization of the Reduced Adducts Leading to Chiral Pyrrolidines. Synthesis of Pyrrolidine (*R,S,S*)-

(7) Optimized molecular structures were generated using the combination of CS Chemdraw Pro 5.0 (1998) and CS Chem3D Pro 5.0 (1999), Cambridge Soft (Cambridge, MA). The resulting MM2 geometries were refined with the semiempirical molecular orbital PM3 algorithm available in CS Mopac Pro.

Scheme 4



Scheme 5



30. From 2,4-dialkylpyrrolidine-3-carboxylates, Ohki et al. have prepared a number of racemic 1,2,4-trisubstituted 3-(diphenylmethylidene)pyrrolidinium salts showing anticholinergic activities.[8] In particular they synthesized iodides of a *cis*-2,4-dimethylpyrrolidinium derivative. The Michael adducts of ethyl acetoacetate with 1-nitropropene were reduced (H_2,160 atm; Ra-Ni; 90 °C, 8 h) to afford a mixture of *cis-cis* and *trans-trans* 3-(ethoxycarbonyl)-2,4-dimethylpyrrolidine (the racemic equivalents of compounds **29** and **30**, respectively, Scheme 4) following cyclization and subsequent reduction of the imine double bond thus formed (57% global yield from ethyl acetoacetate). These adducts then yielded the racemic targets.

Our goal was to arbitrarily obtain chiral intermediate (*R*,*S*,*S*)-**30** [and/or (*R*,*R*,*S*)-**29**] starting from adduct **9** (Scheme 3, Table 1). The reduction of nitro compound **9** occurred smoothly at room temperature after 24 h under only 6 atm pressure of hydrogen with Ra-Ni catalysis, leading directly to chiral pyrrolidines (*R*,*R*,*S*)-**29** and (*R*,*S*,*S*)-**30** (Scheme 4). Substituting the H-atom of amine **28** and pyrrolidines **29** and **30** by the Boc group allowed the separation of compound **31** from pyrrolidines **32** and **33**, by FC. Basic epimerization of the pyrrolidine mixture then led to the thermodynamically more stable *trans-trans* compound **33** in 61% yield from adduct **9** (58% global yield from ethyl acetoacetate). Pyrrolidine **33** was deprotected (75% yield) to give the pure target compound (*R*,*S*,*S*)-**30** (ee > 98%).

Synthesis of Pyrrolines (*S*,*S*)-34, (*S*,*R*)-35, and Pyrrolidine (*R*,*R*,*S*)-39. Winn et al. for their part have prepared a number of racemic *N*-substituted 2,4-diarylpyrrolidine-3-carboxylic acids which represent a novel class of endothelin receptor antagonists.[9,10]

The pyrroline (racemic equivalent of compound **36**, Scheme 6) obtained by Michael reaction of ethyl (4-methoxybenzoyl)acetate with 2-(3,4-(methylenedioxy)-phenyl)nitroethylene followed by hydrogenation over Ra-Ni, was reduced with sodium cyanoborohydride to afford three pyrrolidine isomers, the *trans-trans* (racemic equivalent of compound **39**, Scheme 6), the *cis-trans*, and the *cis-cis* (equiv **40**). The *cis-cis* isomer was separated and through basic treatment gave the *trans-trans* compound (12% yield from ethyl (4-methoxybenzoyl)acetate) which was then *N*-substituted. Resolution of the most efficient compound A127722 (*N*-substituted with CH_2NBu_2) led to the active enantiomer corresponding to (*R*,*R*,*S*)-**39**.[9]

As the *trans-trans* pyrrolidine derivative can lead to a variety of interesting compounds, in particular to compound A127722, we decided to attempt the synthesis of pyrrolidine (*R*,*R*,*S*)-**39** (Scheme 6). Before using adduct **26** involving two bulky aryl substituents, we first tried the reduction−cyclization reaction with the two adducts **18** and **22** bearing, respectively, phenyl/methyl and phenyl/phenyl substituents (Scheme 5). Thus the unpurified mixture of adducts **18** (93:7) and pyrrole **19** (**18**/**19**, 91:9) (Scheme 3, Table 1) was catalytically reduced under similar conditions to those used for adduct **9** (Scheme 4). In this case, ^{1}H NMR of the filtered and evaporated reaction mixture showed that compound **18** had totally reacted but that the cyclization was not complete. It was thus necessary to heat an ethanolic solution of the mixture at reflux for 14 h to end the cyclization leading to compound (*S*,*S*)-**34** and its diastereomer (*R*,*S*)-**34** (85:15) in 48% global yield from enaminoester **17** and both with 86% ee. In these conditions, the amount of pyrrole **19** increased slightly and it was also isolated and characterized. When adducts **22** (90:10) were treated under similar conditions (a 24 h ethanol reflux was necessary in this case to complete the cyclization), compound (*S*,*R*)-**35** and its diastereomer (*R*,*R*)-**35** (89:11) were obtained in 76% global yield from adduct **22**, both with 80% ee. In the two experiments, no trace of dihydrogenated products corresponding to compounds **34** and **35** were observed, in contrast with the example (Scheme 4) where the cyclized compounds bear methyl/methyl substituents.

The projected synthesis of pyrrolidine (*R*,*R*,*S*)-**39** was achieved, starting from adduct **26** (Scheme 3, Table 1). Thus, the inseparable mixture of diastereomers **26** (83:17) when treated identically to adduct **22**, gave (*R*,*S*)-**36** and its diastereomer (*S*,*S*)-**38** (94:6) in 84% global yield (Scheme 6).

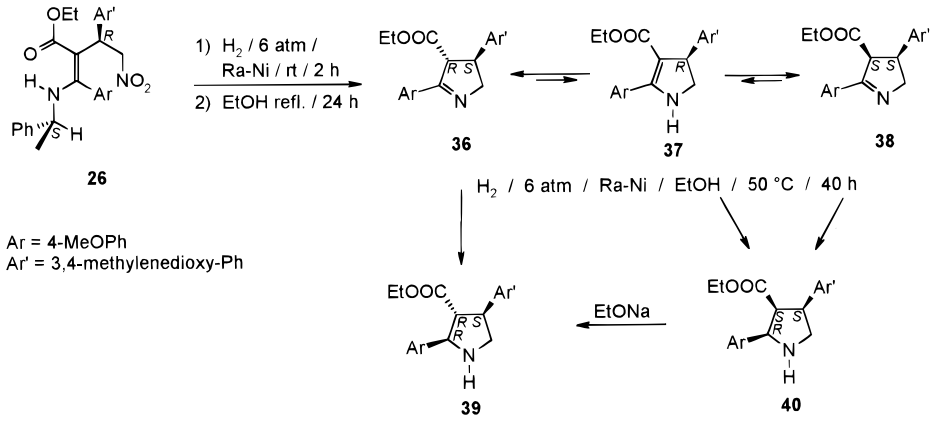
Reduction of the double bond in compound **36** was achieved with H_2 over Ra-Ni (50 °C for 40 h) rather than by cyanoborohydride reduction as performed by Winn et al., yielding a mixture of pyrrolidines (*R*,*R*,*S*)-**39** and its diastereoisomer (*R*,*S*,*S*)-**40** (86:14) and only a trace of a *cis*−*trans* isomer. If the formation of compound (*R*,*R*,*S*)-**39** can be readily accounted for from imine **36**, that of compound (*R*,*S*,*S*)-**40** occurs most probably from the *cis* pyrroline **38** and from the enamine tautomer **37**, even if it is present in undetectable proportion, assuming that

(8) Ohki, S.; Nagasaka, T.; Matsuda, H.; Ozawa, N.; Hamaguchi, F. *Chem Pharm. Bull.* **1986**, *34*, 3606−3613.

(9) Winn, M.; von Geldern, T. W.; Opgenorth, T. J.; Jae, H.-S.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A.; Bal, R.; Sorensen, B. K.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.; Hernandez, L.; Marsh, K. C. *J. Med. Chem.* **1996**, *39*, 1039−1048.

(10) Tasker, A. S.; Sorensen, B. K.; Jae, H.-S.; Winn, M.; von Geldern, T. W.; Dixon, D. B.; Chiou, W. J.; Dayton, B. D.; Calzadila, S.; Hernandez, L.; Marsh, K. C.; Wu-Wong, J. R.; Opgenorth, T. J. *J. Med. Chem.* **1997**, *40*, 322−330.

Scheme 6



its hydrogenation is faster than that of its imines counterparts **36** and **38**. Basic treatment afforded then the target *trans*-*trans* pyrrolidine (*R*,*R*,*S*)-**39** (ee 66%) in 67% yield from pyrrolines **36** and **38**. An optically pure sample of the compound was obtained by *N*-Boc protection, subsequent ester saponification, and recrystallization of the salt derived from (*S*)-2-phenylethylamine followed by deprotection and reesterification.

Experimental Section

General. TLC was performed with glass plates (0.25 mm) precoated with silica gel, and flash chromatography (FC) was carried out with silica gel (200−450 mesh), using EtOAc/hexanes as eluents (proportions given). GC-MS was performed with a HP 5890 GC apparatus (equipped with a 12 m × 0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5971 EIMS. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded respectively at 300 and 75.5 MHz. Anhydrous solvents were freshly distilled under argon, CH_2Cl_2 over $CaCl_2$, ether and THF over Na/benzophenone. Commercial (*R*)- and (*S*)-1-phenylethylamine, ee = 96% and 99%, respectively, were used without further purification. Unless otherwise indicated, organic phases were washed with a saturated NaCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. All Michael reactions were performed under a nitrogen atmosphere in the presence of a few hydroquinone crystals.

Ethyl 3-[(1*R*)-(1-Phenylethyl)amino]but-2-enoate (7). A 2 mL (15.5 mmol) amount of (*R*)-1-phenylethylamine were slowly added at room temperature under nitrogen to 2 mL (15.7 mmol) of ethyl acetoacetate and stirred for 2 h. Toluene was then added and, after the usual workup, 3.50 g (97 % yield) of known oily **7** was obtained: $[\alpha]^{20}_D$ −618 (*c* 1.44, EtOH); EIMS, IR, ^{1}H and ^{13}C NMR in agreement with lit.[11]

Ethyl 3-Phenyl-3-[(1*R*)-(1-phenylethyl)amino]prop-2-enoate (17). A solution of 4.2 mL (24.3 mmol) of ethyl benzoyl acetate, 4.3 mL (34.7 mmol) of (*R*)-1-phenylethylamine, and 2 mL of acetic acid in 25 mL of ethanol was heated at reflux under nitrogen for 4 h. After cooling, the usual workup followed by FC (30:70) afforded 5.2 g (73% yield) of known **17**: $[\alpha]^{20}_D$ −335 (*c* 1.43, EtOH); EIMS, IR, ^{1}H and ^{13}C NMR in agreement with lit.[11]

Ethyl 3-(4-Methoxyphenyl)-3-[(1*S*)-(1-phenylethyl)amino]prop-2-enoate (24). Ethyl 3-(4-methoxyphenyl)-3-oxopropanoate was prepared according to lit.,[12] in 93% yield: bp 120 °C/0.2 Torr; EIMS *m*/*z* (rel int) 222 (M^+, 14), 135 (base); IR (film) 1740, 1675, 1600 cm^{-1}; ^{1}H NMR in agreement with lit.;[12] ^{13}C NMR δ 13.91, 45.60, 55.34, 61.17, 113.72 (2C), 128.94, 130.70 (2C), 163.82, 167.58, 190.84. A solution of 3.40 g (15.3 mmol) of the ketoester, 4 mL (31 mmol) of (*S*)-1-phenylethylamine, and 20 mL of a 10% solution of AcOH in ethanol, was heated at reflux for 24 h. The cooled mixture was then concentrated under reduced pressure and diluted with EtOAc. The usual workup followed by FC (20:80) afforded 3.99 g (80% yield) of **24**: EIMS *m*/*z* (rel int) 325 (M^+, 47), 252 (34), 237 (77), 134 (46), 105 (base); IR (film) 1730, 1645, 1610 cm^{-1}; ^{1}H NMR δ 1.32 (t, *J* = 7.1 Hz, 3H), 1.49 (d, *J* = 6.6 Hz, 3H), 3.83 (s, 3H), 4.15−4.24 (m, 2H), 4.51 (dq, *J* = 9.2, 6.6 Hz, 1H), 4.65 (s, H) 6.81−6.87 (m, 2H), 7.11−7.33 (m, 7H), 8.93 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR δ 14.62, 24.65, 53.90, 55.27, 58.74, 86.53, 113.56 (2C), 125.66 (2C), 126.84, 128.51 (2C), 128.73, 129.16 (2C), 144.92, 160.29, 164.24, 170.45.

(*E*)-1-Nitropropene (8). Intermediate 2-hydroxy-1-nitropropane was obtained in 72% yield by a method describing the preparation of analogous compounds:[13] bp 90 °C/125 Torr; EIMS *m*/*z* (rel int) 104 (M^+ − 1, 1), 90 (27), 62 (70), 59 (base); IR (film) 3400 cm^{-1}; ^{1}H NMR in agreement with lit.;[14] ^{13}C NMR δ 19.76, 64.91, 81.50. Dehydration of the nitro alcohol was achieved according to lit.[15] but in the presence of a few hydroquinone crystals allowing the formation of **8** in 79% yield rather than 30%:[15] EIMS *m*/*z* (rel int) 87 (M^+, base); IR and ^{1}H NMR in agreement with lit.;[15] ^{13}C NMR δ 13.74, 138.12, 140.35.

(*E*)-1-Nitrobutene (11). The 2-hydroxy-1-nitrobutane intermediate was obtained as above[13] in 76.5% yield: bp 100−103 °C/120 Torr; EIMS *m*/*z* (rel int) 90 (M^+ − 29, 81), 72 (30), 62 (base), 55 (95); IR (film) 3400 cm^{-1}, ^{1}H NMR δ 1.00 (t, *J* = 7.0 Hz, 3H), 1.54 (dq, *J* = 7.0, 7.0 Hz, 2H), 2.98 (br s, 1H), 4.14−4.28 (m, 1H), 4.30−4.46 (m, 2H); ^{13}C NMR δ 9.40, 26.75, 69.87, 80.31. Dehydration was achieved as above,[15] giving **11** in 88% yield: bp 60−63 °C/15 Torr; EIMS *m*/*z* (rel int) 101 (M^+, 1), 86 (13), 55 (33), 39 (base); IR and ^{1}H NMR in agreement with lit.;[16] ^{13}C NMR δ 11.63, 21.74, 139.02, 143.91.

2-(3,4-(Methylenedioxy)phenyl)-1-nitroethene (25). This compound was prepared according to lit.,[17] in 72% yield: mp 166 °C (CH_3NO_2−$CHCl_3$) [lit.:[17] 160.5−161 °C (EtOH−PhH)]; EIMS *m*/*z* (rel int) 193 (M^+, base), 146 (91); IR (Nujol) 1630, 1600 cm^{-1}; ^{1}H NMR δ 6.07 (s, 2H), 6.88 (d, *J* = 8.1 Hz, 1H) 7.00 (d, *J* = 1.8 Hz, 1H), 7.09 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.48 (d, *J* = 13.6 Hz, 1H), 7.93 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR δ 102.08, 107.02, 109.09, 124.22, 126.63, 135.42, 139.10, 148.79, 151.40.

Ethyl 2-[(1*S*)-1-(Nitromethyl)ethyl]-3-[(1*R*)-(1-phenylethyl)amino]but-2-enoate (9). A solution of 1.74 g (20 mmol) of **8** in 7 mL of CH_3CN was added dropwise to a solution of 4.0 g (17.2 mmol) of **7** in 7 mL of CH_3CN, in an ice bath. The

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latter was removed and the mixture kept at room temperature for 3 h. After solvent evaporation at room temperature under reduced pressure, the crystalline **9** was washed with ether−hexane (5:95) (5.22 g, 95% yield). An analytical sample was obtained by recrystallization: mp 88−89 °C (ether−hexane); $[\alpha]^{20}_D$ −485 (*c* 0.97, EtOH); calcd for $C_{17}H_{24}N_2O_4$, C 63.73, H 7.55, N 8.74; found C 63.6, H 7.60, N 8.86; IR ($CDCl_3$) 1635, 1590, 1545 cm^{-1}; ^1H NMR δ 1.21 (d, J = 7.0 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.87 (s, 3H), 3.36−3.49 (m, 1H), 4.22 (dq, J = 11.0, 7.0 Hz, 2H), 4.50 (dd, J = 11.4, 7.0 Hz, 1H), 4.64 (dq, J = 7.0, 6.6 Hz, 1H), 4.73 (dd, J = 11.4, 8.0 Hz, 1H), 7.20−7.37 (m, 5H), 10.07 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 14.55, 15.72, 17.93, 25.16, 32.60, 53.56, 58.86, 80.80, 91.99, 125.46 (2C), 127.09, 128.84 (2C), 145.23, 161.07, 170.24. A monocrystal of compound **9** was used for an X-ray structure determination (see the end of the Experimental Section).

Cyclization of Adduct 9 into Ethyl 2,4-Dimethyl-1-[(1*R*)-1-phenylethyl]-1*H*-pyrrole-3-carboxylate (10). A solution of 1.50 g (4.69 mmol) of **9** in 40 mL of ethanol was allowed to stand at room temperature for 24 h. After evaporation, a FC (10:90) of the residue afforded 0.370 g (29% yield) of **10** and 0.570 g of starting **9**. Pyrrole **10** was recrystallized in EtOAc−hexane: mp 105 °C; $[\alpha]^{20}_D$ 23.9 (*c* 8.86, $CHCl_3$); calcd for $C_{17}H_{21}NO_2$, C 75.25, H 7.80, N 5.16; found C 75.3, H 7.82, N 5.05; EIMS *m*/*z* (rel int) 271 (M^+, 45), 105 (base); IR ($CDCl_3$) 1690 cm^{-1}; ^1H NMR δ 1.33 (t, J = 7.0 Hz, 3H), 1.76 (d, J = 7.0 Hz, 3H), 2.25 (d, J = 1.1 Hz, 3H), 2.41 (s, 3H), 4.26 (q, J = 7.0 Hz, 2H), 5.29 (q, J = 7.0 Hz, 1H), 6.47 (br s, 1H), 6.99−7.05 (m, 2H), 7.19−7.33 (m, 3H). ^{13}C NMR δ 11.49, 12.95, 14.52, 21.99, 54.59, 59.01, 111.46, 115.79, 120.33, 125.78 (2C), 127.40, 128.74 (2C), 136.27, 142.48, 166.46.

Ethyl 2-[(1*S*)-1-(Nitromethyl)propyl]-3-[(1*R*)-(1-phenylethyl)amino]but-2-enoate (12). A solution of 1.30 g (12.9 mmol) of **11** and 2.98 g (12.8 mmol) of **7** in 5 mL of CH_3CN was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure at room temperature, a FC (10:90) of the residue afforded 3.74 g (87.5% yield) of solid adduct **12**: mp 78−80 °C (ether−hexane, 5:95); $[\alpha]^{20}_D$ −510 (*c* 3.03, EtOH); calcd for $C_{18}H_{26}N_2O_4$, C 64.65, H 7.84, N 8.37; found C 64.7, H 7.84, N 8.22; IR ($CDCl_3$) 1630, 1590, 1545 cm^{-1}; ^1H NMR δ 0.77 (t, J = 7.3 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H), 1.50 (d, J = 6.6 Hz, 3H), 1.46−1.55 (m, 1H), 1.72−1.80 (m, 1H), 1.84 (s, 3H), 3.11−3.27 (m, 1H), 4.15−4.27 (m, 2H), 4.49 (dd, J = 11.8, 6.6 Hz, 1H), 4.60−4.72 (m, 1H), 4.78 (dd, J = 11.8, 8.8 Hz, 1H), 7.18−7.36 (m, 5H), 10.17 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 11.88, 14.38, 15.99, 24.59, 24.98, 39.40, 53.38, 58.68, 79.90, 89.62, 125.19 (2C), 126.88, 128.66 (2C), 145.22, 162.27, 170.02.

Ethyl 2-[(1*S*)-2-Nitro-1-phenylethyl]-3-[(1*R*)-(1-phenylethyl)amino]but-2-enoate (15). A solution of 1.10 g (7.38 mmol) of **14** and 1.68 g (7.21 mmol) of **7** in 1.1 mL of CH_3CN was stirred at room temperature for 3 days. The solvent was removed under reduced pressure, and ^1H NMR of the crude residue showed the presence of **15** and its diastereomer (85:15, NHPhCHC*H*$_3$ at 1.51 and 1.52 ppm, respectively). A FC (10:90) of the residue afforded 2.20 g (80% yield) of an inseparable oily mixture of these diastereomers: IR (film) 1740, 1645, 1600, 1555 cm^{-1}; ^1H NMR δ 1.10 (t, J = 7.0 Hz, 3H), 1.51 + 1.52 (each, d, J = 7.0 Hz) (3H), 1.95 (s, 3H), 3.95−4.20 (m, 2H), 4.60−4.75 (m, 2H), 4.95−5.15 (m, 2H), 7.00−7.40 (m, 10H), 10.20 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 14.20, 16.04, 25.11, 41.22, 53.65, 58.93, 78.91, 91.85, 125.43 (2C), 126.25, 126.76 (2C), 127.17, 128.22 (2C), 128.94 (2C), 141.45, 145.17, 162.06, 169.92.

Ethyl 2-[(1*S*)-1-(Nitromethyl)ethyl]-3-phenyl-3-[(1*S*)-1-(phenylethyl)amino]prop-2-enoate (18) and Pyrrole 19 Mixture. A 0.219 g (2.52 mmol) amount of **8** and 0.670 g (2.27 mmol) of **17** were stirred without solvent at room temperature for 23 h. The ^1H NMR spectrum of the crude reaction mixture showed the presence of adduct **18** and its diastereomer (93:7, C*H*HNO_2 at 4.69 and 4.61 ppm, respectively) as well as pyrrole **19** (vide infra, 91:9, CHC*H*$_3$/OCH$_2$C*H*$_3$ at 1.07 and 0.99 ppm, respectively). This mixture was used directly for the synthesis of **34**. **Compounds 18**: ^1H NMR δ 1.07 (d, J = 7.0 Hz, 3H), 1.37 (t, J = 7.0 Hz, 3H), 1.39 (d, J = 6.6 Hz, 3H), 2.67−2.80 (m, 1H), 3.93−4.06 (m, 1H), 4.20−4.35 (m, 3H), 4.61 + 4.69 (each, dd, J = 11.0, 8.5 Hz) (1H), 6.58−7.50 (m, 10H), 9.85 (d, J = 8.8 Hz, 1H); ^{13}C NMR δ 14.52, 18.14, 24.63, 33.90, 54.16, 59.18, 80.43, 93.24, 125.65−128.73 (9C), 130.63, 134.66, 144.99, 163.85, 170.30.

Table 2. Reaction of 17 with 14 in Presence of $MgCl_2$

time	conversion %	**22**:**23**	diastereoselectivity
4 h	91	69:31	66:34
44 h	100	67:33	66:34
10 d	100	59:41	54:46

The same reaction was also carried out in CH_3CN (2.5 M solution) at room temperature for 6 d, followed by solvent evaporation. In this case, the ^1H NMR spectrum of the reaction mixture showed adduct **18** and its diastereomer (94:6) as well as pyrrole **19** (70:30).

Ethyl 2-[(1*S*)-1-(Nitromethyl)propyl]-3-phenyl-3-[(1*R*)-(1-phenylethyl)amino]prop-2-enoate (20) and Ethyl 4-Ethyl-2-phenyl-1-[(1*R*)-1-phenylethyl]-1*H*-pyrrole-3-carboxylate (21) Mixture. A 273 mg (2.70 mmol) amount of **11** and 737 mg (2.50 mmol) of **17** in 1.0 mL of CH_3CN were stirred at room temperature for 6 days. The ^1H NMR spectrum of the crude residue showed the presence of adduct **20** and its diastereomer (96:4, CHCH$_2$C*H*$_3$ at 0.67 and 0.73 ppm, respectively) as well as pyrrole **21** (**20**/**21**, 75:25, CHCH$_2$C*H*$_3$/OCH$_2$C*H*$_3$ at 0.67 + 0.73 and 0.98 ppm, respectively). After FC (10:90), 794 mg of an inseparable oily mixture of **20** and **21** (70:30) was obtained. **Compounds 20**: ^1H NMR δ 0.67 + 0.73 (each, t, J = 7.3 Hz) (3H), 1.35 (t, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.31−1.45 (m, 1H), 1.60−1.70 (m, 1H), 2.47−2.59 (m, 1H), 3.93−4.08 (m, 1H), 4.28 (q, J = 7.0 Hz, 2H), 4.30−4.38 (m, 1H), 4.61 + 4.69 (each, dd, J = 11.0, 8.5 Hz)(1H), 6.90−7.50 (m, 10H), 9.98 (d, J = 9.2 Hz, 1H); ^{13}C NMR δ 12.10, 14.41, 24.89, 24.96, 40.48, 54.00, 59.01, 79.70, 91.46, 125.49−130.47 (10C), 134.37, 145.00, 164.44, 170.18. **Compound 21**: EIMS *m*/*z* (rel int) 347 (M^+, 66), 302 (6), 244 (12), 243 (66), 198 (16), 197 (19), 196 (25), 105 (base); ^1H NMR δ 0.98 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H), 1.71 (d, J = 7.0 Hz, 3H), 2.75−2.85 (m, 2H), 4.02 (q, J = 7.0 Hz, 2H), 5.10 (q, J = 7.0 Hz, 1H), 6.54 (br s, 1H), 6.95−7.38 (m, 10H); ^{13}C NMR δ 13.88, 14.60, 20.19, 21.74, 54.54, 58.89, 111.71, 115.34, 126.00 (2C), 127.32, 127.76 (2C), 128.16, 128.51 (2C), 128.66, 130.61 (2C), 132.97, 139.19, 142.47, 165.45.

Ethyl 2-[(1*S*)-2-Nitro-1-phenylethyl]-3-phenyl-3-[(1*R*)-(1-phenylethyl)amino]prop-2-enoate (22). A 2.20 g (14.8 mmol) amount of **14** and 4.20 g (14.2 mmol) of **17** in 2.0 mL of CH_3CN were stirred at room temperature for 6 days. After FC (10:90) of the crude residue of the reaction, 5.90 g (94% yield) of oily adduct **22** and its diastereomer (90:10, one aromatic *H* at 6.63−6.67 and 6.73−6.76 ppm, respectively) were obtained: $[\alpha]^{20}_D$ −325 (*c* 0.84, EtOH); EIMS (direct intro) *m*/*z* (rel int) 444 (M^+, 4), 384 (5), 149 (35), 105 (62), 44 (base); IR (film) 1740, 1645, 1550 cm^{-1}; ^1H NMR δ 1.22 (t, J = 7.0 Hz, 3H), 1.47 (d, J = 6.6 Hz, 3H), 4.05−4.15 (m, 2H), 4.16−4.28 (m, 2H), 4.95 (dd, J = 11.7, 7.0 Hz, 1H), 5.09 (dd, J = 11.7, 8.4 Hz, 1H), 6.63−6.67 + 6.73−6.76 (m, 1H), 7.00−7.60 (m, 14H), 10.04 + 10.14 (m, 1H); ^{13}C NMR δ 14.14, 24.59, 42.63, 54.22, 59.16, 78.88, 92.35, 125.21−129.05 (15C), 134.08, 141.07, 144.77, 164.51, 170.03. HRMS *m*/*z* calcd for $C_{27}H_{28}N_2O_4$ 444.2049, found 444.2047.

Reaction in the Presence of $MgCl_2$. A 253 mg (1.70 mmol) amount of **14,** 500 mg (1.70 mmol) of **17**, and 16 mg (0.170 mmol) of $MgCl_2$ in 0.25 mL of acetonitrile were stirred at room temperature. Samples were analyzed by ^1H NMR at different reaction times. Proportions **22**:**23** and diastereoselectivities were respectively determined using OCH$_2$C*H*$_3$ at 1.22 and 0.82 ppm, and one aromatic *H* at 6.63−6.67 and 6.73−6.76 ppm (Table 2). After 10 days, filtration of the catalyst and evaporation of the solvent was followed by a FC (10:90) of the residue, affording 282 mg (42% yield) of **23**.

Ethyl 2,4-diphenyl-1-[(1*S*)-1-phenylethyl]-1*H*-pyrrole-3-carboxylate (23): EIMS *m*/*z* (rel int) 395 (M^+, 90), 291 (base), 246 (43), 105 (84); IR (film) 1710, 1700 cm^{-1}; ^1H NMR

δ 0.82 (t, J = 7.0 Hz, 3H), 1.74 (d, J = 7.0 Hz, 3H), 3.95 (q, J = 7.0 Hz, 2H), 5.18 (q, J = 7.0 Hz, 1H), 6.8−7.5 (m, 16H); ^{13}C NMR δ 13.52, 21.78, 54.82, 59.26, 111.87, 117.39, 125.97 (2C), 126.20, 126.31, 126.99, 127.07 (2C), 127.44 (2C), 128.24, 128.39 (2C), 129.24 (2C), 130.61 (2C), 132.21, 135.36, 139.04, 141.95, 165.08.

Ethyl 2-[(1*R*)-1-(3,4-(Methylenedioxy)phenyl)-2-nitroethyl]-3-(4-methoxyphenyl)-3-[(1*S*)-(1-phenylethyl)amino]prop-2-enoate (26). A 4.63 g (24.0 mmol) of **25**, 7.81 g (24.0 mmol) of **24**, and 24 mL of CH_3CN were stirred at room temperature for 18 days; a FC (20:80) of the crude residue of the reaction afforded 11.6 g (93.5%) of oily adduct **26** and its inseparable diastereomer (83:17, OCH_2O at 5.87 and 5.90 ppm respectively): IR (film) 3220, 1745, 1640, 1610 cm^{-1}; ^{1}H NMR δ 1.23 (t, J = 7.0 Hz, 3H), 1.39 (d, J = 7.0 Hz, 3H), 3.59 (s, 3H), 4.00−4.26 (m, 4H), 4.82 (dd, J = 11.7, 7.3 Hz, 1H), 5.00 (dd, J = 11.7, 8.5 Hz, 1H), 5.87 + 5.90 (each, s) (2H), 6.40−7.40 (m, 12H), 9.98 + 10.02 (each, d, J = 8.8 Hz) (1H); ^{13}C NMR δ 14.35, 24.62, 42.73, 54.29, 55.21, 59.27, 79.29, 92.71, 100.85, 107.91, 107.96, 113.71, 114.01, 120.15, 125.65 (2C), 126.43, 126.63, 128.49 (2C), 129.07, 129.12, 135.15, 144.88, 145.85, 147.40, 159.91, 164.71, 170.10.

Cyclization of Adduct 26 into Ethyl 2-(4-methoxyphenyl)-4-(3,4-(methylenedioxy)phenyl)-1-[(1*S*)-1-phenylethyl]-1*H*-pyrrole-3-carboxylate (27). A solution of 5.98 g (11.5 mmol) of **26** in 60 mL of EtOH was heated at reflux for 24 h. After evaporation of the mixture at reduced pressure, a FC (30:70) of the residue afforded 2.73 g (51% yield) of **27** which was recrystallized: mp 112 °C (AcOEt/hexane); $[\alpha]^{20}_D$ −34.5 (c 6.42, $CHCl_3$); calcd for $C_{29}H_{27}NO_5$, C 74.18, H 5.80, N 2.98; found C 74.1, H 5.78, N 2.94; EIMS m/z (rel int) 469 (M^+, 58), 364 (base), 105 (54); IR ($CHCl_3$) 1710, 1695, 1610 cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7.0 Hz, 3H), 1.73 (d, J = 7.0 Hz, 3H), 3.82 (s, 3H), 3.98 (q, J = 7.0 Hz, 2H), 5.18 (q, J = 7.0 Hz, 1H), 5.93 (s, 2H), 6.72−7.30 (m, 13H); ^{13}C NMR δ 13.79, 21.86, 54.74, 55.25, 59.32, 100.79, 107.66, 110.06, 111.88, 113.40 (2C), 117.11, 122.17, 124.34, 126.09 (2C), 127.50, 128.61 (2C), 129.57, 131.89 (2C), 138.88, 142.14, 146.13, 146.98, 159.62, 165.20 (one quaternary C not found).

Ethyl (2*R*,3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-2,4-dimethylpyrrolidine-3-carboxylate (33). A 5.00 g amount of ethanol washed Ra−Ni was added to a solution of 1.51 g (4.72 mmol) of **9** in 35 mL of ethanol. The mixture was stirred at room temperature under hydrogen (6 atm) for 24 h. The catalyst was then filtered on Celite and the filtrate concentrated under reduced pressure. A GC-MS analysis showed the presence of **28** as well as two compounds (ca. 2:1, each M^+ = 171) with t_R 4.08 and 4.16 min, respectively, corresponding to **30** (cf EIMS, next experiment) and **29** (identical mass spectrum pattern with slightly different relative intensities, typical for a diastereomer[2d,e]). The oily residue was diluted in 5 mL of CH_2Cl_2 and 1.5 g (6.87 mmol) of di-*tert*-butyl dicarbonate was added. After stirring the mixture for 4 h, the solvent was evaporated; a FC (AcOEt/CH_2Cl_2, 5:95) afforded a mixture of diastereomers which was diluted in 10 mL of a 0.1 M NaOEt ethanol solution and heated at reflux for 1.5 h. The epimerization was followed by GC-MS (100 °C for 1 min, then 18 °C/min up to 280 °C) until complete disappearance of the minor signal (t_R 5.49 min) in favor of the major signal (t_R 5.29 min). Extraction with CH_2Cl_2 was followed by the usual workup giving a residue which was purified by FC (10:90), affording 0.78 g of **33** (61% yield). An analytical sample was obtained by molecular distillation (70−75 °C/15 Torr): $[\alpha]^{20}_D$ −38 (c 6.41, EtOH); EIMS m/z (rel int) 214 (M^+ − 57, 33), 170 (60), 142 (40), 57 (base); IR (film) 1735, 1690 cm^{-1}; ^{1}H NMR (C_6D_5-CD_3, 90 °C) δ 0.87 (d, J = 6.3 Hz, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.33 (d, J = 6.3 Hz, 3H), 1.41 (s, 9H), 2.07 (dd, J = 10.3, 8.1 Hz, 1H), 2.09−2.27 (m, 1H), 2.70 (dd, J = 10.3, 10.7 Hz, 1H), 3.77 (dd, J = 10.7, 7.0, 1H), 3.96 (q, J = 7.0 Hz, 2H), 3.98−4.08 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.28, 16.12, 20.43 + 21.14, 28.51 (3C), 36.41, 53.00 + 53.23, 56.92, 59.45 + 59.94, 60.82, 79.40, 154.13, 172.76; HRMS (CI, NH_3) calcd for $C_{14}H_{24}O_4N$ (M^++1) m/z 272.1862, found m/z 272.1860.

Ethyl (2*R*,3*S*,4*S*)-2,4-Dimethylpyrrolidine-3-carboxylate (30). A mixture of 397 mg (1.47 mmol) of **33**, 0.4 mL of dioxane, and 1.0 mL of 4 N HCl was stirred at room temperature for 1 h. After ether extraction followed by the usual workup, a molecular distillation (60 °C/15 Torr) afforded 189 mg of **30** (75% yield): $[\alpha]^{20}_D$ −31 (c 4.90, EtOH); EIMS m/z (rel int) 171 (M^+, 7), 142 (67), 57 (base); IR (film) 1725 cm^{-1}; ^{1}H NMR δ 1.10 (d, J = 7.0 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.97 (dd, J = 8.5, 8.5 Hz, 1H), 2.17 (s, 1H), 2.39−2.54 (m, 1H), 2.63 (dd, J = 11.0, 7.0 Hz, 1H), 3.18 (dd, J = 11.0, 8.1 Hz, 1H), 3.35 (dq, J = 8.5, 6.3 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H); ^{13}C NMR δ 14.33, 18.89, 20.72, 40.24, 53.96, 59.36, 60.45, 60.51, 174.45; HRMS (CI, NH_3) calcd for $C_9H_{18}O_2N$ (M^+ + 1) m/z 172.1338, found m/z 172.1333.

Ethyl (3*S*,4*S*)-3-Methyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-4-carboxylate (34) and Ethyl 4-Methyl-2-phenyl-1-[(1*R*)-1-phenylethyl]-1*H*-pyrrole-3-carboxylate (19) Mixture. A 2.4 g amount of ethanol washed Ra−Ni was added to a solution of the mixture of **18** and **19** (91:9) (vide supra) in 10 mL of ethanol. After stirring at room temperature under hydrogen (7 atm) for 3 h, the catalyst was filtered on Celite and the filtrate diluted in 20 mL of ethanol was heated at reflux for 14 h. The cooled solution was evaporated under reduced pressure and a FC (20:80) of the residue afforded 134 mg of **19** and 252 mg (48% global yield from **17**) of **34** and its diastereomer (85:15, GC-MS, t_R 3.72 and 4.00 min, respectively). **Compounds 34**: EIMS m/z (rel int) 231 (M^+, 14), 157 (30), 117 (base) (**diastereomer**: identical spectrum pattern, typical for a diastereomer[2d,e]); IR (film) 1730 cm^{-1}; ^{1}H NMR δ 1.11−1.22 (m, 6H), 2.70−2.88 (m, 1H), 3.66−3.80 (m, 2H), 4.04−4.20 (m, 2H), 4.33 (ddd, J = 16.2, 7.4, 2.2 Hz, 1H), 7.35−7.45 (m, 3H), 7.78−7.87 (m, 2H); ^{13}C NMR δ 14.02, 20.24, 38.45, 61.11, 61.71, 68.44, 128.06 (2C), 128.48 (2C), 130.62, 133.64, 168.86, 171.82. **Compound 19**: EIMS m/z (rel int) 333 (M^+, 93), 229 (98), 105 (base); IR (film) 1700 cm^{-1}; ^{1}H NMR δ 0.99 (t, J = 7.0 Hz, 3H), 1.69 (d, J = 7.0 Hz, 3H), 2.31 (d, J = 1.1 Hz, 3H), 4.03 (q, J = 7.0 Hz, 2H), 5.10 (q, J = 7.0 Hz, 1H), 6.52 (d, J = 1.1 Hz, 1H), 6.96−7.45 (m, 10H); ^{13}C NMR δ 12.48, 13.87, 21.62, 54.37, 58.82, 112.32, 116.61, 121.23, 125.97 (2C), 127.30, 127.72 (2C), 128.00, 128.46 (2C), 130.56 (2C), 132.83, 138.98, 142.27, 165.45.

Ethyl (3*R*,4*S*)-3,5-Diphenyl-3,4-dihydro-2*H*-pyrrole-4-carboxylate (35). The same procedure as performed above for obtaining **34** was used with 7.0 g of Ra−Ni, 3.00 g (6.75 mmol) of **22**, and 40 mL of ethanol. The filtered solution was then heated at reflux for 24 h. After cooling and evaporation, a FC (20:80) of the residue afforded 1.51 g (76% yield) of **35** and its diastereomer (89:11, GC-MS, t_R 10.48 and 10.79 min, respectively): EIMS m/z (rel int) 293 (M^+, 8), 220 (36), 117 (base) (**diastereomer**: identical spectrum pattern, typical for a diastereomer[2d,e]); IR (film) 1725 cm^{-1}; ^{1}H NMR δ 1.15 (t, J = 7.0 Hz, 3H), 3.88 (ddd, J = 8.1, 4.4, 4.4 Hz, 1H), 4.10 (dq, J = 11.0, 7.0 Hz, 1H), 4.15 (dq, J = 11.0, 7.0 Hz, 1H), 4.25 (ddd, J = 16.9, 4.4, 1.1 Hz, 1H), 4.26 (ddd, J = 4.4, 2.2, 1.1 Hz, 1H), 4.65 (ddd, J = 16.9, 8.1, 2.2 Hz, 1H), 7.10−7.50 (m, 8H), 7.86−7.92 (m, 2H); ^{13}C NMR δ 13.90, 49.08, 61.23, 62.59, 68.91, 126.91 (2C), 127.04, 127.86 (2C), 128.24 (2C), 128.83 (2C), 130.66. 133.20, 143.35, 168.60, 171.32.

Ethyl (3*S*,4*R*)-5-(4-Methoxyphenyl)-3-(3,4-(methylenedioxy)phenyl)-3,4-dihydro-2*H*-pyrrole-4-carboxylate (36). The same procedure as performed above for obtaining **34** was used with 8.0 g of Ra−Ni, 4.43 g (8.55 mmol) of **26** and its diastereomer (83:17), and 60 mL of ethanol, under hydrogen (6 atm) for 2 h. The filtrate was heated at reflux for 24 h. After evaporation of the cooled solution, a FC (20:80) of the residue afforded 2.64 g (84% yield) of **36** and its diastereomer **38** (94:6, 2 aromatic *H* at 8.06 and 8.20 ppm, respectively; GC-MS, no separation): EIMS m/z (rel int) 367 (M^+, 20), 294 (21), 147 (base); IR (film) 1725 cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.82 (t, J = 7.0 Hz, 3H), 3.25 (s, 3H), 3.77 (ddd, J = 8.1, 4.6, 4.6, 1H), 3.83 (dq, J = 11.0, 7.0 Hz, 1H), 3.90 (dq, J = 11.0, 7.0 Hz, 1H), 4.15 (ddd, J = 16.5, 4.6, 1.0 Hz, 1H), 4.21 (br d, J = 4.6 Hz, 1H), 4.59 (ddd, J = 16.5, 8.1, 1.8 Hz, 1H), 5.34 (s, 2H), 6.43 (dd, J = 8.1, 1.8 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 1.8 Hz, 1H), 6.72 (br d, J = 9.0 Hz, 2H), 8.06 + 8.20 (each, br d, J = 9.0 Hz) (2H); ^{13}C NMR ($CDCl_3$) δ 14.07, 49.09, 55.33,

61.31, 62.87, 68.92, 101.02, 106.91, 108.39, 113.85 (2C), 119.82, 126.03, 129.66 (2C), 137.56, 146.49, 148.07, 161.68, 167.91, 171.50.

Ethyl (2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-4-(3,4-(methylenedioxy)phenyl)pyrrolidine-3-carboxylate (39). A 11.0 g amount of ethanol washed Ra−Ni was added to a solution of 2.49 g (6.80 mmol) of **36** in 60 mL of ethanol, and the mixture was heated at 50 °C under hydrogen (6 atm) for 40 h. The cooled solution was filtered on Celite and concentrated. A ^{1}H NMR spectrum of a sample showed a mixture of **39** and **40** (86:14, OCH_2CH_3 at 1.10 and 0.82 ppm, respectively). A 68 mg (1.0 mmol) amount of NaOEt in 25 mL of ethanol was added to the residue which was heated at reflux for 1 h. The solvent was then evaporated, and a FC (80:20) of the residue afforded 1.70 g (68% yield) of **39**: $[\alpha]^{20}_D$ 35.5 (*c* 11.52, EtOH). A 66% ee value for **39** is given by the diastereomeric ratio (83:17) of (*S*,*R*)-**26** and (*S*,*S*)-**26** determined by ^{1}H NMR. This value is further estimated by LISR ^{1}H NMR determinations with Eu(hfc)$_3$, following the chemical shift of the methyl group of the ester function in **39** (ee = 70%).

Enantiopure **39** was obtained by the following procedure: to a solution of 1.0 g (2.71 mmol) of **39** in 3 mL of CH_2Cl_2 was added 0.70 g (3.20 mmol) of di-*t*-butyl dicarbonate. After stirring the mixture at room temperature for 4 h followed by evaporation of the solvent, a FC (30:70) yielded 1.20 g of the *N*-Boc protected compound which was saponified with 6 mL of a 2 M aqueous KOH solution diluted in 5 mL of ethanol, at room temperature for 2 h. The mixture was then acidified with HCl to pH = 1, and the resulting carboxylic acid derivative was extracted with AcOEt. After the usual workup, the compound was dissolved in 4 mL of AcOEt, and 0.326 g (2.70 mmol) of (*S*)-1-phenylethylamine was added to yield the corresponding salt which crystallized. Four recrystallizations in THF−ether afforded the pure salt which was deprotected and esterified through dissolution in 30 mL of a saturated solution of dry HCl in ethanol and heating at 60 °C overnight. After evaporation, a FC (80:20) of the residue afforded 0.550 g (55% yield) of **39**: $[\alpha]^{20}_D$ 57.7 (*c* 7.68, EtOH); EIMS *m*/*z* (rel int) 369 (M^+, 2), 148 (base); IR (film) 3335, 1725, 1610 cm^{-1}; ^{1}H NMR in agreement with lit.;[10,18] ^{13}C NMR δ 14.19, 50.58, 54.53, 55.20, 60.56, 61.34, 66.68, 100.90, 107.49, 108.17, 113.87 (2C), 120.39, 127.77 (2C), 134.16, 136.37, 146.28, 147.86, 158.97, 173.66. HRMS calcd for $C_{21}H_{23}NO_5$ *m*/*z* 369.1576, found *m*/*z* 369.1576.

X-ray Structure Determination of Compound 9. $C_{17}H_{24}N_2O_4$, M = 320.38. A suitable crystal of size 0.30 mm × 0.35 mm × 0.42 mm was investigated on a Syntex $P2_1$ diffractometer (Mo Kα radiation, λ = 0.71069 Å, graphite monochromator). Cell dimensions were determined by a least-squares fit to the setting angles of 20 reflections with $6.17 \leq 2\theta \leq 11.43°$, orthorhombic, space group $P2_12_12_1$, Z = 8, a = 7.565(4), b = 17.59(2), c = 27.12(3) Å, V = 3609(6) Å^3, d_x = 1.18 g.cm^{-3}, μ = 0.084 mm^{-1}. 8338 reflections were measured up to 2θ = 55° of which 1941 with $I > 2\sigma(I)$ were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[19] and refined by full matrix least-squares with SHELXL93.[20] Non hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located. Convergence was reached at R = 0.11. The poor quality of the crystal has not allowed a best refinement. The residual electron density in the final difference Fourier map does not show any features up to 0.22 e. Å^{-3} and down to −0.15 e. Å^{-3}. The asymmetric unit consists of two independent molecules.

Lists of the fractional atomic coordinates, thermal parameters, and bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supporting Information.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **9**, **10**, **12**, **15**, **18**, **19**, **22**, **24**, **26**, **27**, **30**, **33**, **34**, **35**, **36**, **39**, as well as X-ray structure of compound **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) We thank Dr. Martin Winn (Abbott Laboratories) for a copy of the ^{1}H NMR spectrum of compound **43**.

(19) Sheldrick, G. M. SHELXS86. Program for solution of crystal structures. University of Göttingen. Germany (1985).

(20) Sheldrick, G. M. SHELXL93. Program for refining crystal structures. University of Göttingen. Germany (1993).