

ENANTIOSELECTIVE ACCESS TO FIVE- AND SIX-MEMBERED NITROGEN-CONTAINING HETEROCYCLES, BASED ON THE ASYMMETRIC MICHAEL ADDITION OF CHIRAL IMINES AND CHIRAL ENAMINO ESTERS

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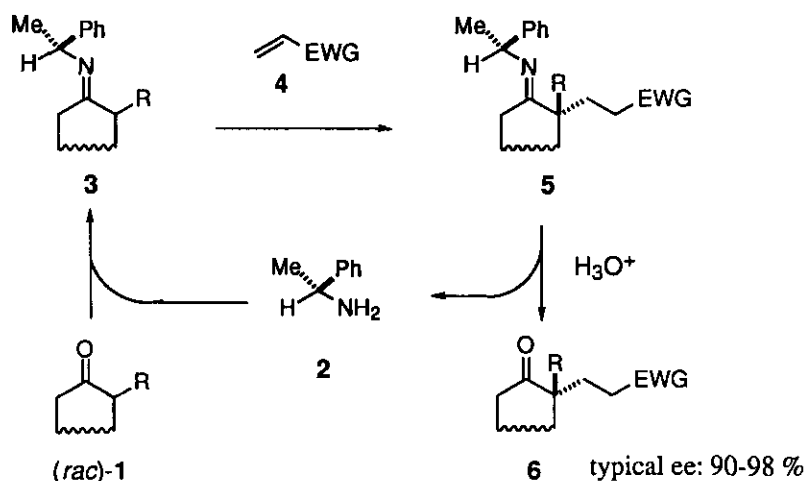
Abstract- The addition reaction of chiral imines, (*ent*-**10**, **48**, **70**) and chiral enamino esters (**52**, **55**, **73**) with maleic anhydride (**32**), citraconic anhydride (**57**), α -chloroacrylonitrile (**29**), and nitroethylene (**74**), has been investigated. These condensations proved to be in general highly regio-, diastereo-, and enantioselective. In most cases the primary adducts underwent an *in situ* *N*-heterocyclization, allowing the enantioselective access to nitrogen-containing, five- and six-membered heterocycles.

INTRODUCTION

In 1985, we disclosed a highly potent methodology for the stereocontrolled elaboration of quaternary carbon centers, based on the conjugate addition of chiral imines to electron-deficient alkenes.¹ Thus, chiral imines (**3**), derived from *racemic* 2-substituted cyclanones (**1**) and optically active 1-phenylethylamine (**2**), reacted, *under neutral conditions*, with Michael acceptors (**4**) to furnish, with a high degree of regio- and stereoselectivity, adducts (**5**). Hydrolysis of these adducts then delivered with an excellent overall yield the 2,2-disubstituted cyclanones (**6**), along with the recovered, unchanged chiral auxiliary (**2**). This "*deracemizing alkylation process*", which tolerates a great variation in the nature of both reagent partners, has been widely applied by ourselves and others to the synthesis of various targets (terpenes, steroids, alkaloids, etc.)² (Scheme 1).

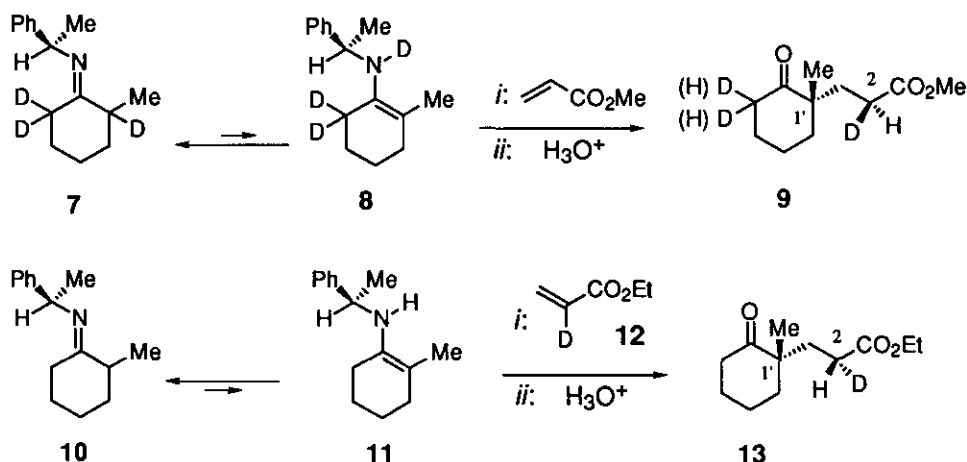
The mechanistic aspects of this Michael reaction have been extensively studied, on the basis of both experimental and theoretical investigations.³ Thus, from the very beginning, we have postulated that the nucleophilic species implicated in this process are, in fact, the more substituted secondary enamines, in tautomeric equilibrium with imines (**3**). Strong evidences in support of a *cyclic transition state*, and of a *concerted proton transfer* from the nitrogen atom of the secondary enamine to the electrophilic alkene were obtained, characteristic of an "*aza-ene-synthesis*". This hypothesis was recently reinforced by the following set of experiments, using deuterium-labelled starting materials.³

Scheme 1



Addition of deuterated imine (7), derived from (*R*)-1-phenylethylamine (2), to methyl acrylate gave, after hydrolytic work-up, adduct (2*S*, 1'*S*)-9, containing a deuterium atom at the α -position to the ester group. The complete control of the configuration at the newly created stereogenic center at C-2 in adduct (9) clearly established that the deuterium atom borne at the nitrogen center of secondary enamine (8) was transferred to the α -vinylic center of methyl acrylate, *more or less concertedly* with the creation of the C-C bond. Conversely, addition of imine (10) (the non-deuterated counterpart of imine (7)) to ethyl 2-deuteroacrylate (12) gave, also in a highly stereoselective manner, deuterated adduct (2*R*, 1'*S*)-13, differing from adduct (9) in its reverse configuration at the C-2 stereocenter. These remarkable, consistent stereochemical outcomes can be interpreted by invoking the corresponding compact, "endo"-approaches of the reactants, of type (16) (*vide infra*, Scheme 4) (Scheme 2).

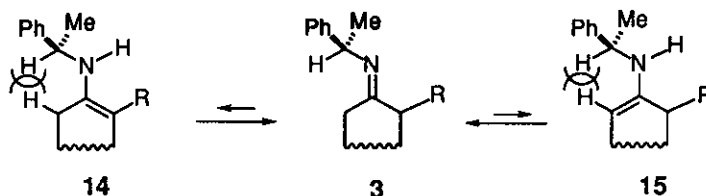
Scheme 2



In general, this Michael addition is *highly regioselective*, the alkylation taking place predominantly, if not exclusively, at the *more* substituted α -side of the imine functionality. This can be readily interpreted by

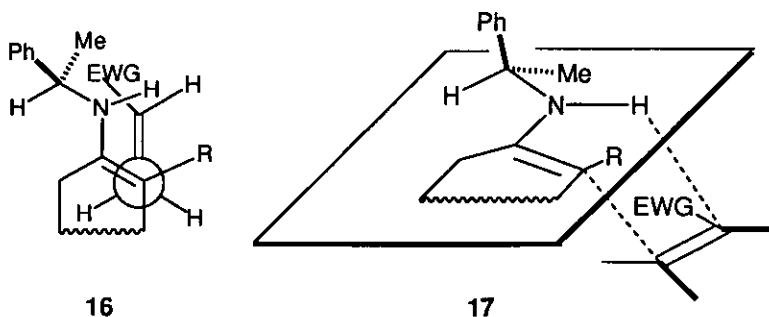
examining the tautomeric equilibrium of chiral imine (**3**) with the two possible secondary enamines (**14**) and (**15**), portrayed in their energetically preferred conformations, minimizing the 1,3-allylic-type strain. In *the more* substituted enamine (**14**), the N-H linkage is *syn* to the enamine double bond, and consequently the above-mentioned internal, concerted proton transfer is allowed. In contrast, in the case of *the less* substituted regioisomer (**15**), this crucial, concerted proton transfer is prevented for obvious geometrical reasons (N-H *anti* to the enamine double bond) (Scheme 3).

Scheme 3



We have proposed that addition of chiral imines to electrophilic alkenes proceeds through a compact approach, that involves the *syn*-arrangement of the two reactant partners (**16**).² In this respect the [4+2]-type "aza-ene-synthesis-like" complex (**17**), that implicates a concerted proton transfer from the nitrogen center of the secondary enamine to the Michael acceptor, appears to be a convenient transition-state model. Accordingly, the alkylation process takes place predominantly, as indicated, on the less hindered π -face of the enamine (*anti* to the bulky phenyl group), the chiral enamine moiety being depicted in its energetically preferred conformation (Scheme 4). Recently, to help rationalize this remarkable stereoselectivity, the two diastereotopic approaches involving a chiral enamino ester and methyl acrylate have been theoretically simulated by using the MOPAC program.⁴ An excellent agreement was obtained between these calculations and the experimental findings.

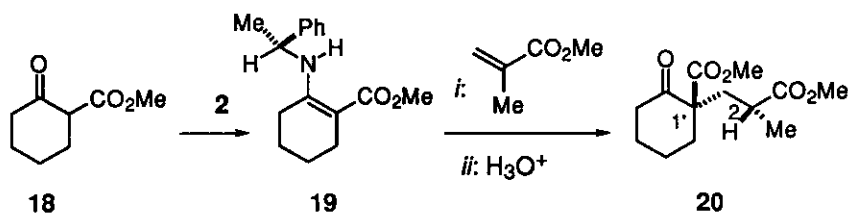
Scheme 4



The reactivity of chiral β -enamino esters toward Michael acceptors has also been investigated. Thus, addition of enamino ester (**19**), prepared by condensing β -keto ester (**18**) with (*R*)-1-phenylethylamine (**2**), to methyl methacrylate gave, after hydrolytic work-up, adduct (2*R*, 1'*R*)-**20**, with a complete control of the two newly created stereogenic centers.⁵ This stereochemical outcome can be rationalized by invoking

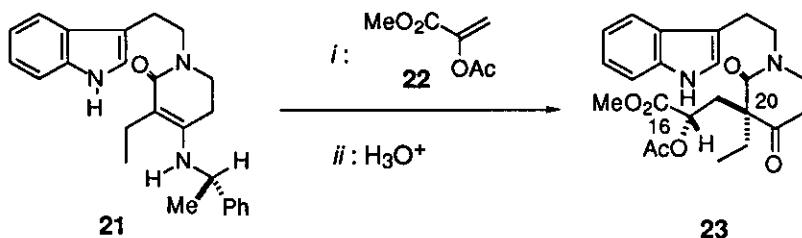
a *syn*, "endo"-approach of type (16) (*vide supra*, Scheme 4), in which the ester group of methyl methacrylate faced the nitrogen atom of the enamino ester partner (Scheme 5).

Scheme 5



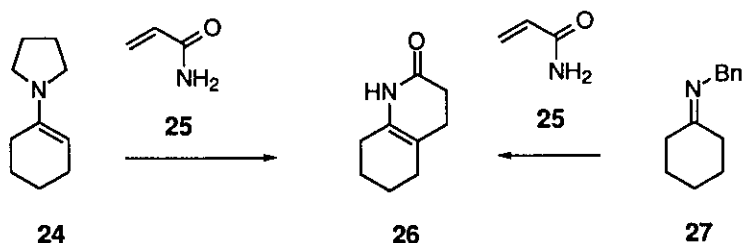
Similarly, we have established that addition of chiral β -enamino lactam (*S*)-21 to methyl 2-acetoxyacrylate (22) furnished, after hydrolytic work-up, adduct (16*S*, 20*R*)-23, as a *single isomer* (Scheme 6).^{5,6} This remarkable stereochemical result can be also interpreted by invoking the *syn*, "endo"-approach of the two reactants.

Scheme 6



In connection with the present Michael addition, we were interested in an "aza-annulation" reaction involving the conjugate addition of enamines, imines, or enamino esters to various electrophilic alkenes. Thus, in 1968, Stork reported that addition of cyclohexanone enamine (24) to acrylamide (25) afforded the hexahydroquinolinone (26).⁷ This reaction has been extended to imines, such as (27), by Ninomiya (Scheme 7).⁸

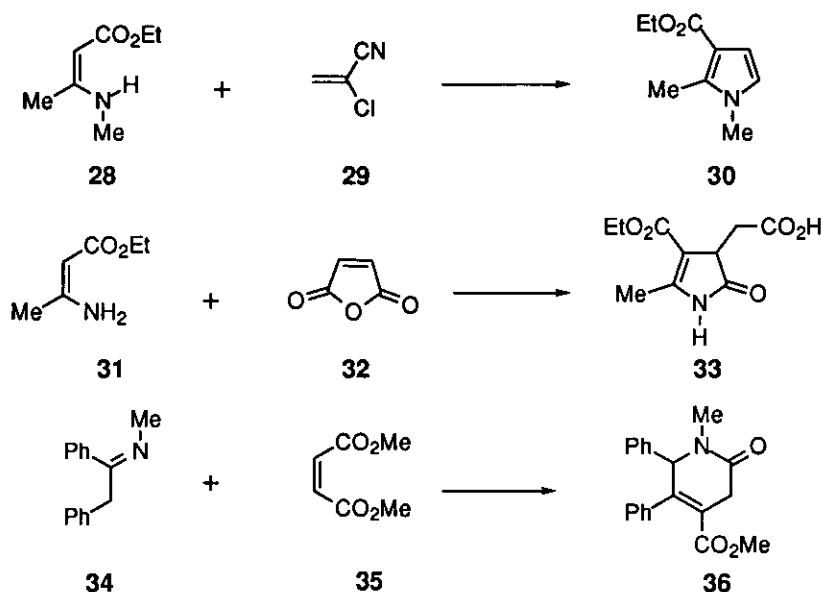
Scheme 7



Several other Michael-type condensations of imines or enamino esters with various electrophilic alkenes, leading to nitrogen-containing heterocycles, were also investigated. For example in 1968, Lawesson⁹

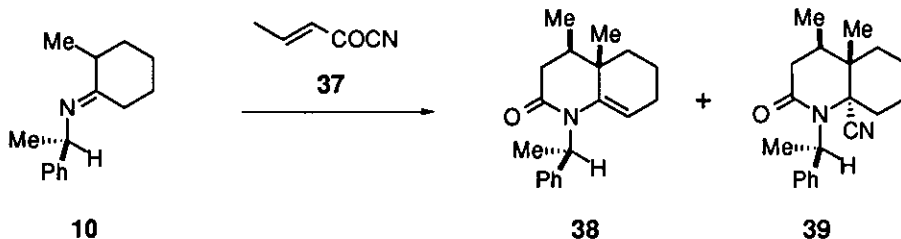
established that addition of enamino ester (**28**) to α -chloroacrylonitrile (**29**) furnished the pyrrole derivative (**30**). In 1970, Bean¹⁰ reported that the condensation of enamino ester (**31**), with maleic anhydride (**32**) delivered the pyrrolinone (**33**) in good yield. In 1974 a Spanish group led by Barluenga¹¹ disclosed that addition of imine (**34**) to dimethyl maleate (**35**) gave efficiently the six-membered heterocycle (**36**) (Scheme 8).

Scheme 8



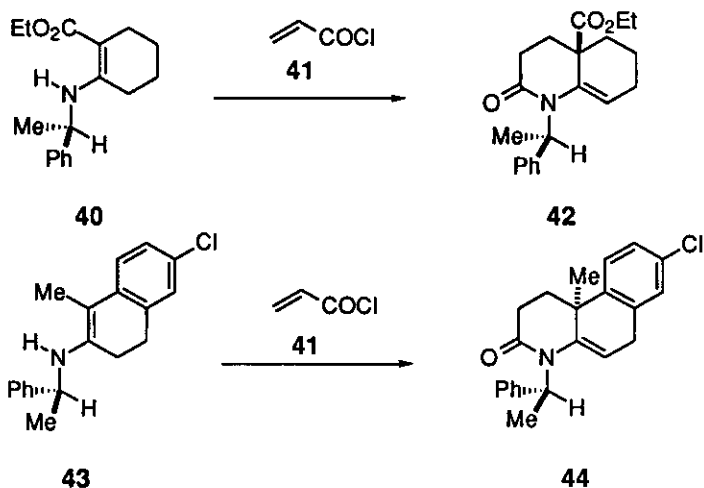
In 1988, we reported an asymmetric version of the previous aza-annulations, based on the addition of chiral imines (**10**) to crotonoyl cyanide (**37**): adducts (**38**) and (**39**) were thus obtained with an excellent stereoselectivity (Scheme 9).¹²

Scheme 9



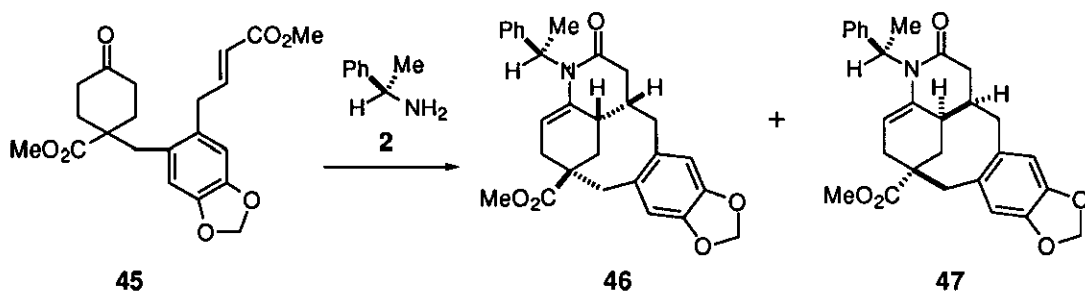
In a similar fashion, condensations of chiral enamino ester (**40**),¹³ or chiral secondary enamine (**43**),¹⁴ with acryloyl chloride (**41**) furnished stereoselectively the expected adducts (**42**) and (**44**), respectively (Scheme 10).

Scheme 10



Recently, we have established that treatment of ketoenone (45) with (*R*)-1-phenylethylamine (2) afforded a 2:1 mixture of isomeric adducts (46) and (47) (Scheme 11).¹⁵

Scheme 11



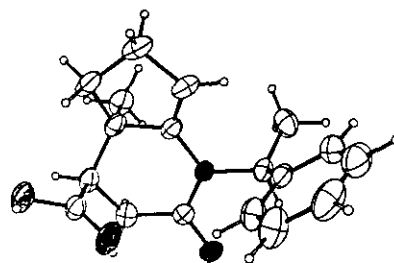
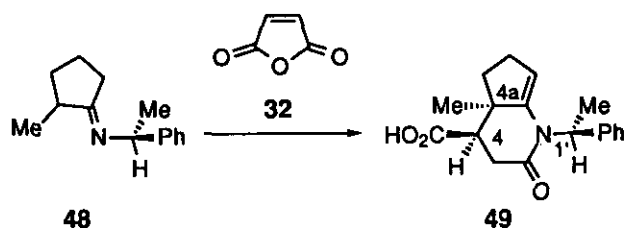
In this paper, we report on the reaction of several chiral imines and enamino esters with maleic anhydride (32), citraconic anhydride (57), α -chloroacrylonitrile (29), and nitroethylene (74). We show that these condensations are in general highly regio- and stereoselective, allowing the enantioselective access to various five- and six-membered nitrogen-containing heterocycles. We show also that the stereochemical findings in these reactions can be readily interpreted, on the basis of the above mechanistic proposals.

RESULTS

Maleic Anhydride as Michael Acceptor

Condensation of imine (48), derived from 2-methylcyclopentanone and (*S*)-1-phenylethylamine (*ent*-2), with maleic anhydride (32) (THF, 1 h at 20 °C) gave almost quantitatively the bicyclic derivative (49), as a *single* isomer. The configuration at the newly created stereogenic centers in this adduct (4*R*, 4*aR*) was unambiguously determined through an X-Ray crystal structure analysis (Scheme 12).

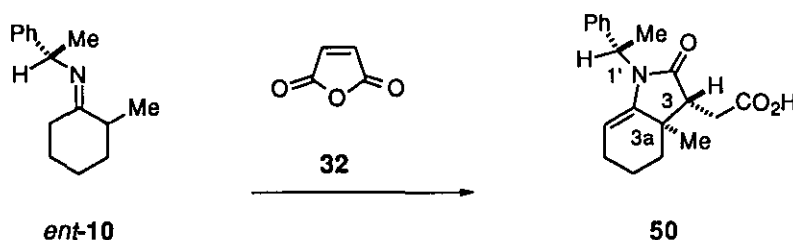
Scheme 12



X-Ray crystal structure of 49

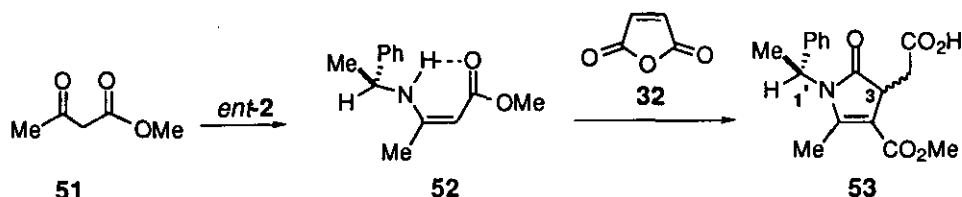
We have previously established that addition of imine (*ent*-10), prepared by condensing 2-methylcyclohexanone with amine (*ent*-2), to (32) (THF, 1 h at 0 °C), afforded in 65 % yield, and with a high degree of stereocontrol, the bicyclic adduct (3*R*, 3*aR*, 1'*S*)-50 (Scheme 13).⁵

Scheme 13



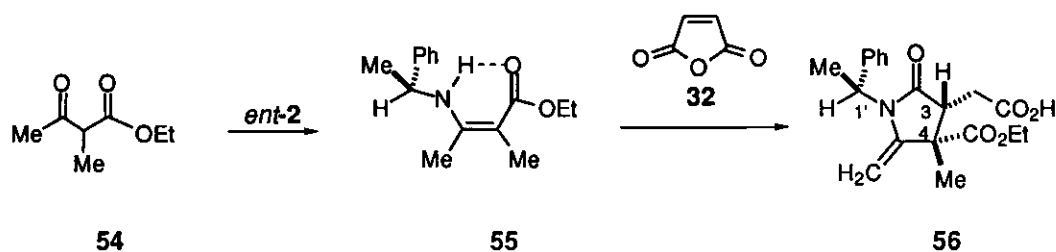
Condensation of enamino ester (52), derived from β -keto ester (51) and *ent*-2, with maleic anhydride (32) (THF, 2 h at 20 °C), gave with a 69 % yield an equimolar mixture of diastereomeric acids (53) (Scheme 14).

Scheme 14



When enamino ester (55), prepared from β -keto ester (54) and *ent*-2, was exposed to anhydride (32) (THF, 12 h at 20 °C), the monocyclic adduct (3*R*, 4*S*, 1'*S*)-56 was obtained as a *single* diastereomer with a 70 % yield. The relative stereochemical relationship between the two newly created stereogenic centers in 56 was established by ¹H NMR spectroscopy, including NOE experiments; their depicted absolute stereochemistry, although not definitely established, rests on the putative mechanism of the present Michael process (*vide infra* : chapter Discussion) (Scheme 15).

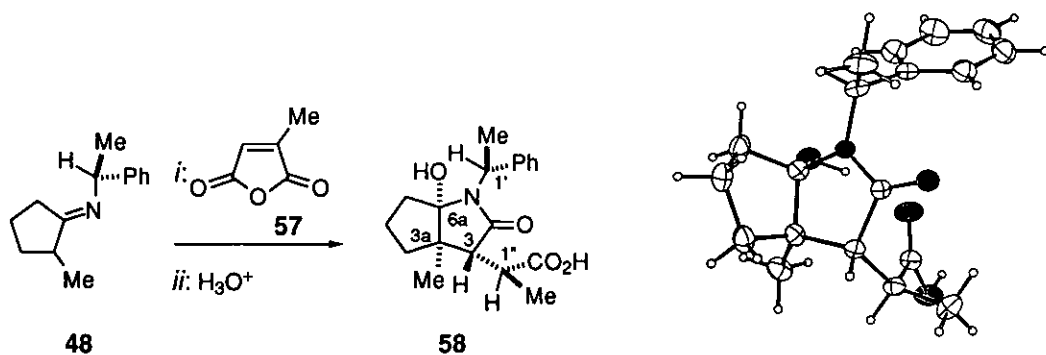
Scheme 15



Citraconic Anhydride as Michael Acceptor

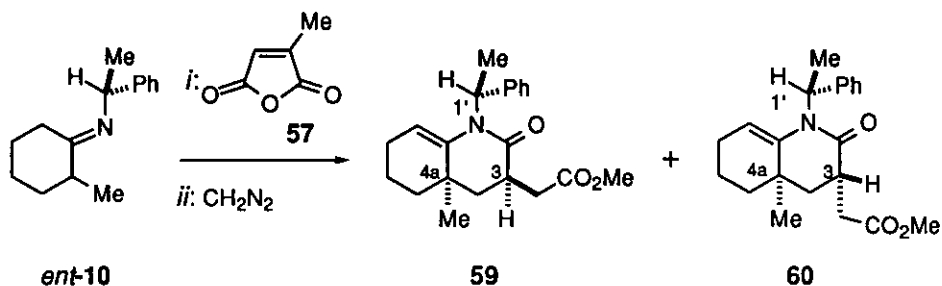
When imine (**48**) was added to citraconic anhydride (**57**) (24 h in THF at reflux, followed by neutral aqueous treatment at 20 °C), the crystalline adduct (3*R*, 3*aR*, 6*aS*, 1'*S*, 1''*S*)-**58** was isolated in 35 % yield, along with unidentified minor side compounds. Configuration at the four newly created, contiguous stereogenic centers in **58** was proved through an X-Ray diffraction analysis (Scheme 16).

Scheme 16

X-Ray crystal structure of **58**

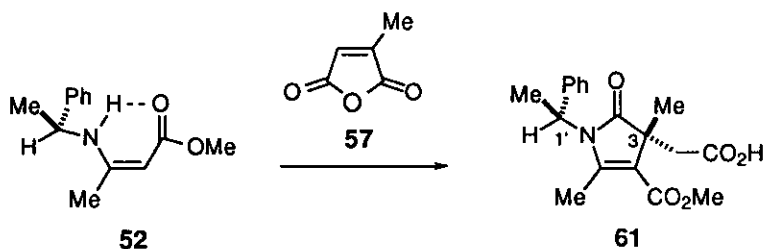
Condensation of imine (*ent*-**10**) with **57** (4 h in THF at reflux) furnished, after esterification of the crude with diazomethane, a mixture of bicyclic adducts (3*R*, 4*aR*, 1'*S*)-**59** and (3*S*, 4*aR*, 1'*S*)-**60**, in the ratio of 4: 1, respectively, with a 65 % combined yield. The relative stereochemistry at the two newly created stereogenic centers in **59** and **60** was established by ¹H NMR spectroscopy, including NOE experiments (Scheme 17).

Scheme 17



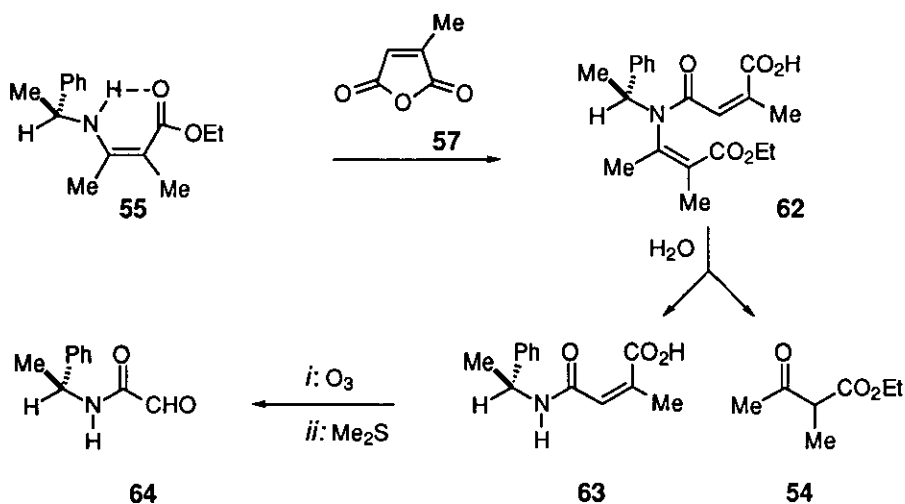
When enamino ester (**52**) was condensed with anhydride (**57**) (12 h in refluxing THF), adduct (*3R,1'S*)-**61** was obtained with a 73 % yield. The depicted stereochemistry at the newly created stereogenic center in **61** rests on the putative mechanism of the present Michael process (*vide infra* : Discussion) (Scheme 18).

Scheme 18



Addition of enamino ester (**55**) to **57** (5 h in refluxing THF) afforded water-sensitive adduct (**62**) (not fully characterized). Hydrolysis, under neutral conditions (10 min at 20 °C), of this crude adduct then furnished acid-amide (**63**) (60 % yield) and keto ester (**54**) (40 % yield). Structure of **63** was proved through its ozonolysis into glyoxamide (**64**) (Scheme 19).

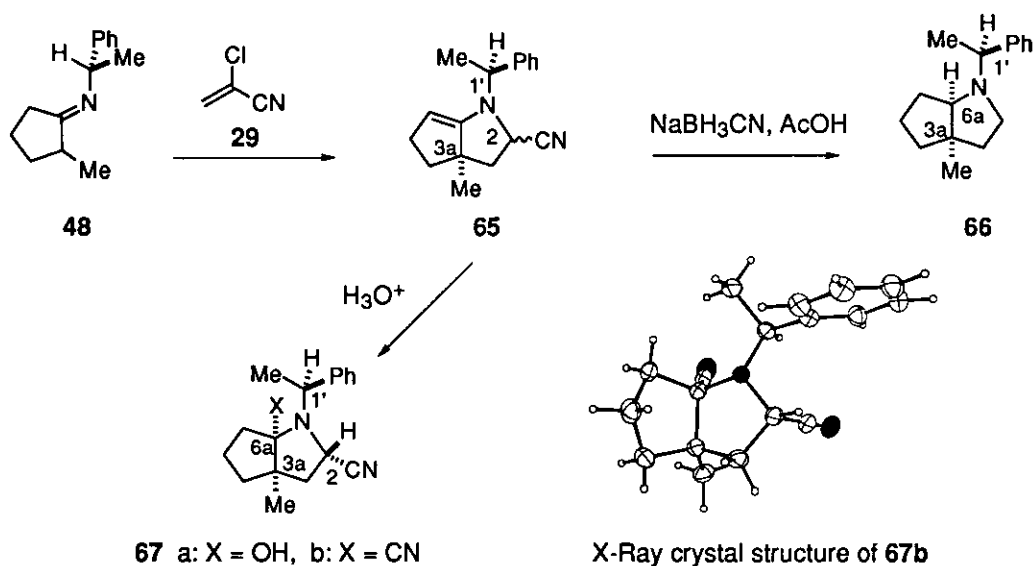
Scheme 19



α -Chloroacrylonitrile as Michael Acceptor

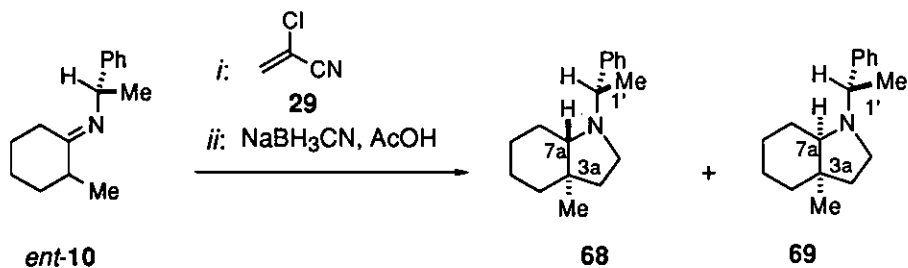
Condensation of imine (**48**) with α -chloroacrylonitrile (**29**) (THF, 2,6-lutidine, 12 h at 20 °C) led to bicyclic adduct (**2S**, **3aR**, **1'S**)-**65** (not fully characterized). Reduction of this crude adduct (NaBH_3CN , MeOH-AcOH, 12 h at 60 °C) gave bicycle (**3aR**, **6aR**, **1'S**)-**66** as a *single* isomer, with a 60 % yield. Hydrolysis of crude **65** (THF, AcOH, H_2O , 12 h at 20 °C) gave carbinolamine (**67a**), along with a substantial amount of crystalline dicyano derivative (**2S**, **3aR**, **6aR**, **1'S**)-**67b**, whose structure was unambiguously established through an X-Ray diffraction analysis (Scheme 20).

Scheme 20



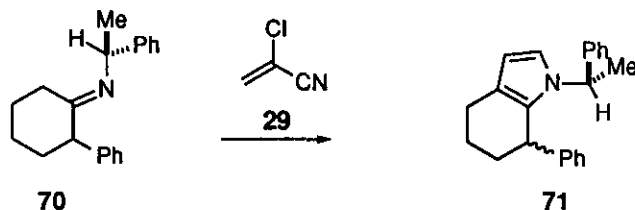
When the same protocol was applied to the six-membered imine (*ent*-**10**), a mixture of the two stereomeric adducts (**3aR**, **7aS**, **1'S**)-**68** and (**3aR**, **7aR**, **1'S**)-**69** was obtained, in the ratio of 1: 6, respectively with a 65 % yield (Scheme 21).

Scheme 21



Addition of chiral imine (**70**), prepared from 2-phenylcyclohexanone and (*ent*-**2**), required somewhat more drastic operating conditions (THF, 2,6-lutidine, 12 h at 50 °C). The annulated pyrrole (**71**) was obtained as a 2.5 :1 mixture of stereomers, with a 70 % yield (Scheme 22).

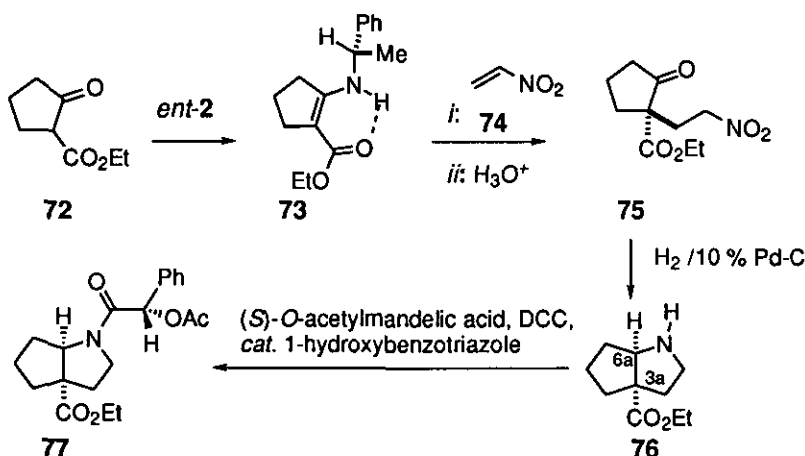
Scheme 22



Nitroethylene as Michael Acceptor

Attempts at condensing imines (**48**) or (*ent*-**10**) with nitroethylene (**74**) gave invariably polymeric materials. In contrast, addition of enamino ester (**73**), prepared from cyclic β -keto ester (**72**) and amine (*ent*-**2**), to **74** (THF, 10 min at -15 °C, then 20 % aqueous AcOH-MeOH, 20 h at -20 °C) furnished in 80 % yield adduct (*S*)-**75** with a 90 % ee. Catalytic reduction of **75** (10 % Pd/C, 3 bars of H₂, EtOH-AcOH, 12 h at 20 °C)¹⁶ gave with a 80 % yield bicyclic compound (3*aS*, 6*aR*)-**76**, whose ee was determined by ¹H NMR spectroscopy at the level of its *O*-acetylmandelamide derivative (**77**) (Scheme 23).

Scheme 23



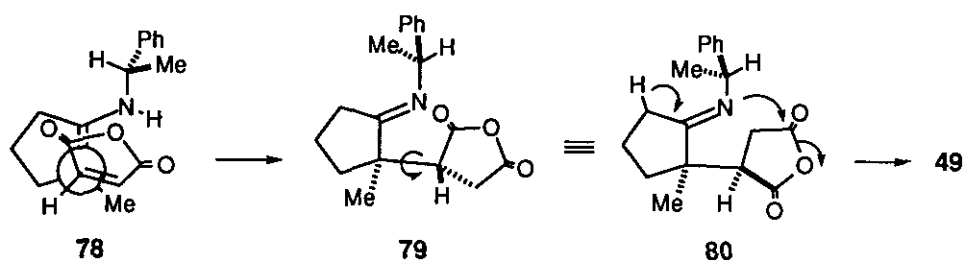
DISCUSSION

The outcomes in the preceding Michael additions can be readily interpreted, on the basis of the mechanistic proposals developed in the introductory part of this paper.

Maleic Anhydride as Michael Acceptor

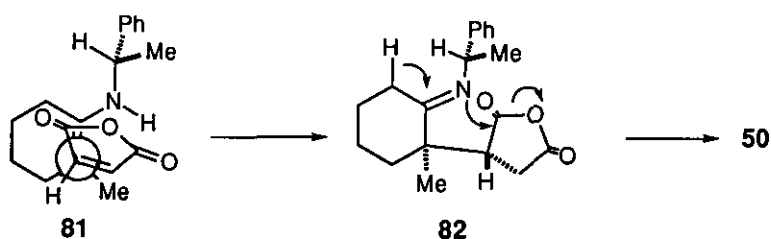
Addition of chiral imine (48) to maleic anhydride (32) can be rationalized by invoking the compact approach (78), with a *syn*-arrangement of the two reactants (more substituted secondary enamine in tautomeric equilibrium with 48, and anhydride (32)). This addition, which took place on the less hindered π -face of the enamine (*anti* to the phenyl ring of the chiral enamine moiety), furnished the primary adduct (79). Six-membered cyclization of 80 (rotamer of 79) then delivered product (49) (Scheme 24).

Scheme 24



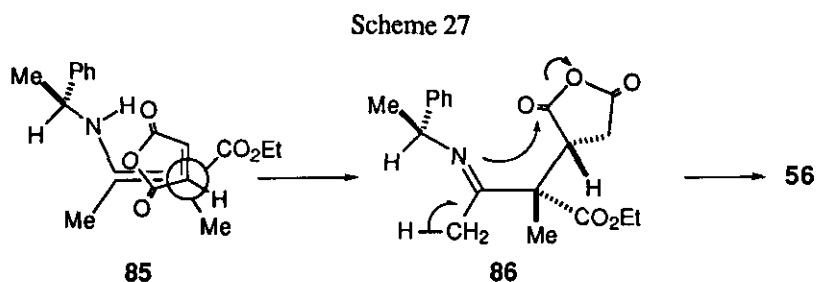
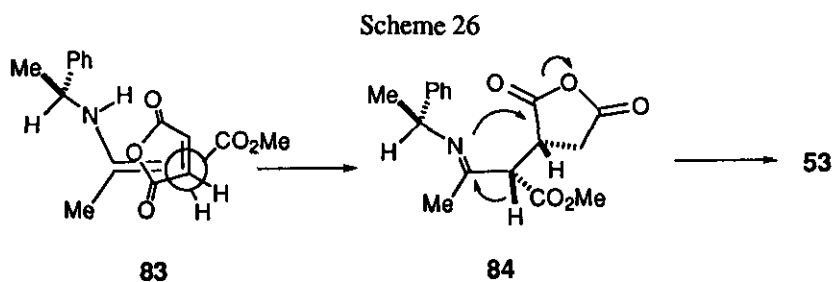
A similar mechanistic pathway can be invoked in the condensation of the six-membered imine (*ent*-10) with 32. *Syn*-approach of the two reactants (81) gave the intermediary adduct (82) which, upon five-membered ring-closure, afforded product (50) (Scheme 25).

Scheme 25



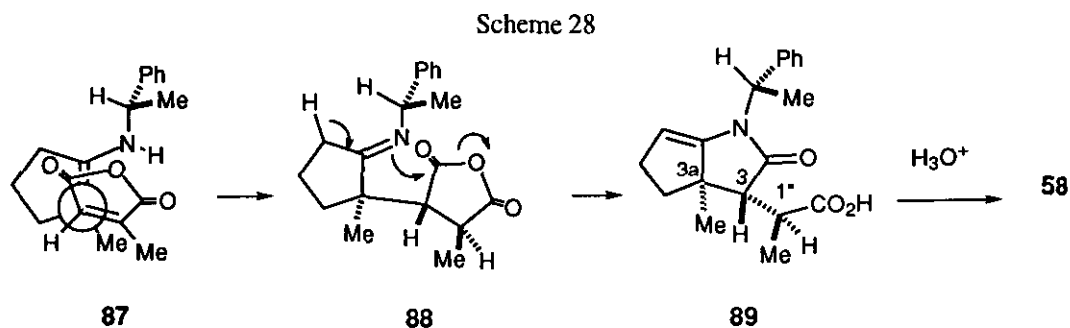
Formation of pyrrolinone (53), in the addition of enamino ester (52) to maleic anhydride, probably involved the *syn*-approach of the reactants (83), leading to the transient adduct (84). Five-membered cyclization of 84 then gave 53. However, in view of the fact that compound (53) is readily epimerizable, through its 2-hydroxypyrrole tautomeric form, no stereocontrol was obtained at the level of the newly created stereogenic center (Scheme 26).

Production of methylene-pyrrolidinone (56), in the condensation of enamino ester (55) with anhydride (32), can be analogously interpreted, by invoking approach 85, and the resulting intermediary adduct (86), precursor of 56. However an excellent stereocontrol at the level of the two newly created stereogenic centers in 56 was presently observed, as the above-mentioned heterocycle tautomerism, probable cause for the epimerization of 53, was now prevented (Scheme 27).



Citraconic Anhydride as Michael Acceptor

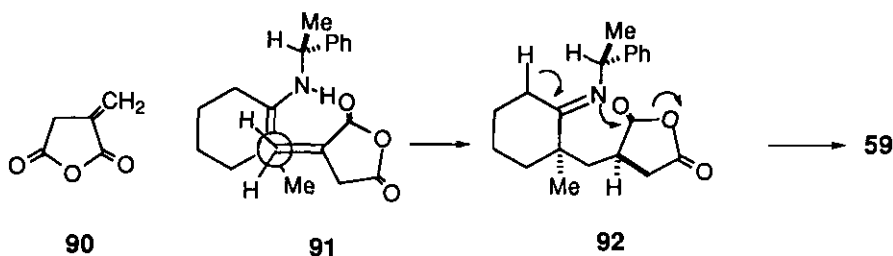
Addition of imine (**48**) to citraconic anhydride (**57**) afforded, after hydrolytic work-up, product (**58**). Formation of this compound implicated the *syn*-approach of the reactants (**87**), the attack taking place at the *less* substituted vinylic site of **57**. Control of the additional stereogenic center in the β -position to the quaternary one in primary adduct (**88**) (future C-1' center in product (**58**)) originated from the transfer of the NH proton of the secondary enamine to the electrophilic alkene, *concerted with the creation of the C-C bond*. Five-membered ring-closure of **88** delivered the bicycle (**89**) whose, upon addition of a molecule of water, gave product (**58**), exhibiting the thermodynamically preferred *cis* ring junction at C_{3a}-C_{6a} centers (Scheme 28).



The electrophile implicated in the condensation of imine (*ent*-**10**) with **57** was clearly not citraconic anhydride itself, but its itaconic anhydride tautomeric form (**90**). This somewhat surprising tautomerization should be attributed to the marked basic character of the imine partner. Formation of the major isomer (**59**) in the present addition probably resulted from the "*endo*"-approach **91** (the conjugate carbonyl group of **90**

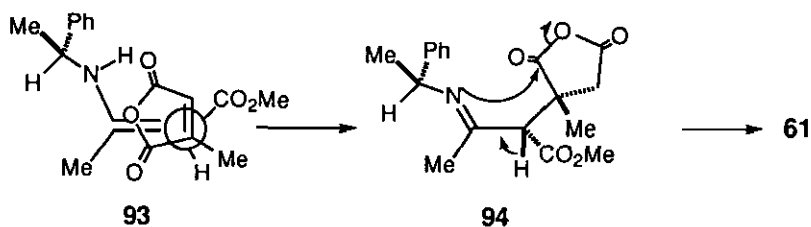
facing the nitrogen atom of the nucleophilic reactant). As above-mentioned, the concerted proton transfer in this process ensured the control of the tertiary stereogenic center in **92** (future C-3 center in **59**). Six-membered cyclization of **92** then furnished product (**59**). Minor isomer (**60**) might result from the "exo"-approach of the two reactants (Scheme 29).

Scheme 29



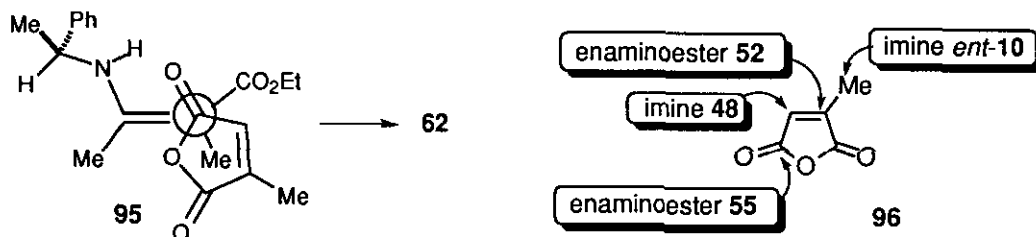
Addition of enamino ester (**52**) to anhydride (**57**) probably involved approach **93**, the attack taking place at *the more* substituted vinylic site of **57**. Five-membered ring-closure of resulting adduct (**94**) then gave product (**61**) (Scheme 30).

Scheme 30



Condensation of enamino ester (**55**) with citraconic anhydride (**57**) took place on *the less* hindered carbonyl group of the latter molecule (approach **95**, leading to product (**62**)). Thus, quite remarkably, *each of the four previous experiments discriminated a specific electrophilic site in citraconic anhydride* (**96**); in this respect this compound can be regarded as an "electrophilic chameleon" (Scheme 31).

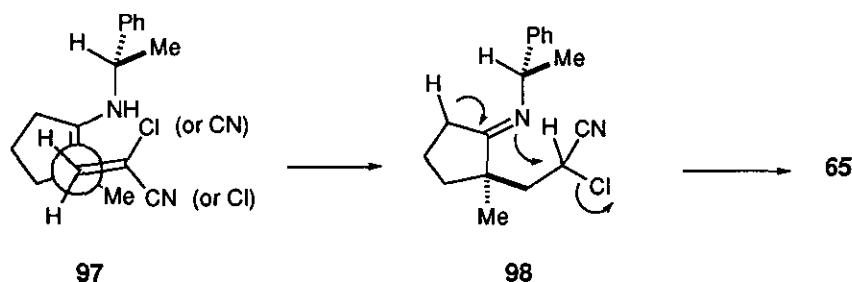
Scheme 31



α -Chloroacrylonitrile as Michael Acceptor

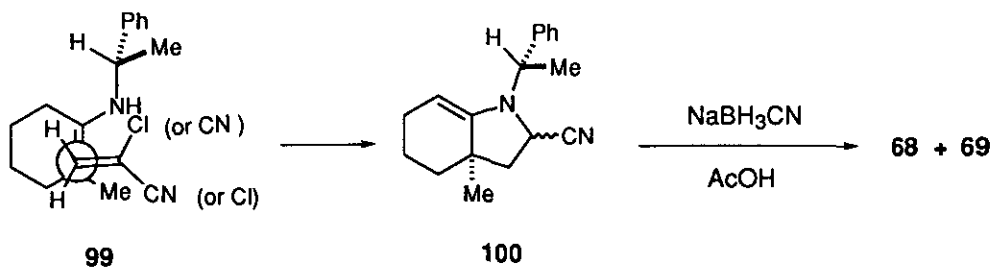
No definitive assignment can be made, regarding the (*endo/lexo*)-orientation of the electrophilic partner (**29**) in approach **97**, involved in addition $48 + 29 \rightarrow 65$. Indeed, we should keep in mind that the stereochemistry at the readily epimerizable C-2 center in fully characterized dicyano compound (**67b**), deriving from **65**, corresponds in fact to the thermodynamically preferred, *exo*-arrangement of the C-2 cyano substituent, and consequently does not necessarily reflect the orientation of electrophile (**29**) in approach (**97**). *N*-Heterocyclization of primary adduct (**98**) then furnished **65**. Treatment of **65** with NaBH_3CN achieved two goals: reductive removal of the cyano group, and reduction of the enamine double bond, affording the energetically favored *cis* ring junction in resulting product (**66**). Hydrolysis of **65** gave a mixture of **67a** and **67b**. Formation of dicyano derivative (**67b**) is quite intriguing: it necessarily involved the intermolecular migration of a cyano group (note that a related migration of a cyano group was implicated in the formation of adduct (**39**), (*vide infra* : Scheme 9) (Scheme 32).

Scheme 32



A close mechanistic pathway can be proposed in the condensation of imine (*ent*-**10**) with **29** ($99 \rightarrow 100$). However, NaBH_3CN -reduction of primary adduct (**100**) (not fully characterized) was less stereoselective than in the case of compound (**65**): a substantial amount of derivative (**68**), having the *trans* ring junction, was actually formed, in addition to the *cis* isomer (**69**) (Scheme 33).

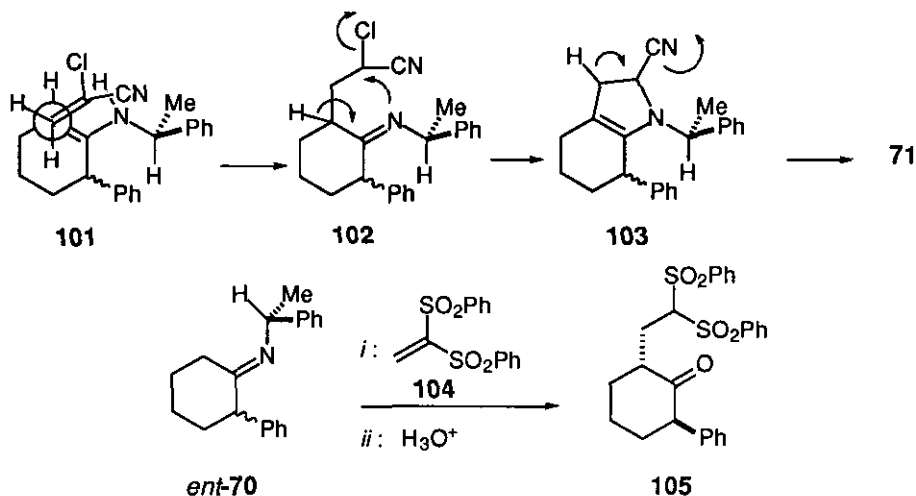
Scheme 33



Formation of the annulated pyrrole (**71**) in the addition of imine (**70**) to α -chloroacrylonitrile probably involved approach **101**, and the intermediates (**102**) and (**103**). It is worthy to note that, in sharp contrast with the previous Michael condensations, this addition now took place at the *less* substituted α -side of

imine (**70**). A similar "abnormal" regiochemical behavior was reported in the condensation of imine (*ent*-**70**) with electrophilic alkene (**104**) (Scheme 34).¹⁷

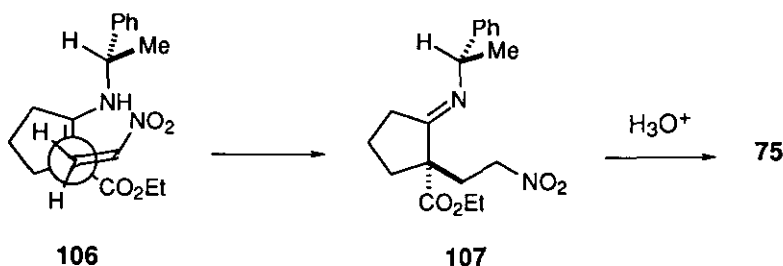
Scheme 34



Nitroethylene as Michael Acceptor

The extensive polymerization of the starting materials in the attempted addition of imines (**48**) or (*ent*-**10**) to nitroethylene (**74**) should be attributed to the pronounced basic character of the latter nucleophiles. Condensation of the less basic enamino ester (**73**) to **74** corroborates this proposal: the expected Michael adduct (**75**) was now obtained with a good yield. Formation of **75** can be rationalized by invoking the *syn*-approach **106** of the reactants, leading to adduct (**107**), whose hydrolytic cleavage gave **75** (Scheme 35).

Scheme 35



CONCLUSION

The Michael-type alkylation of chiral imines and chiral enamino esters, derived from 1-phenylethylamine, constitutes one of the most efficient methods for the stereocontrolled elaboration of quaternary carbon centers. Through this work, we have shown that one or two additional stereogenic centers can be also created at the α - or β -position to the quaternary one, by using maleic anhydride, citraconic anhydride, or

α -chloroacrylonitrile as Michael acceptors. These reactions were in general highly regio-, enantio-, and diastereoselective, reflecting an *aza-ene-synthesis-like*, cyclic transition state. The primary Michael adducts thus formed underwent an *in situ* *N*-heterocyclization, leading to nitrogen-containing five- or six-membered heterocycles. Addition of chiral enamino esters to nitroethylene constitutes also a promising methodology for the construction of such heterocycles.

EXPERIMENTAL SECTION

General Methods. Melting points were recorded on a capillary tube melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^1H NMR spectra and ^{13}C NMR spectra were recorded in CDCl_3 , unless otherwise stated. Recognition of methyl, methylene, methine and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Optical rotations were measured at 589 nm in a 1 dm-cell at specified temperature. MS were recorded by electron impact at 70 eV. Analytical thin-layer chromatography was performed on Merck silica gel 60F₂₅₄ glass precoated plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230-400 mesh ASTM). Ether and tetrahydrofuran (THF) were distilled from Na-benzophenone ketyl. Methanol was dried over magnesium and distilled. Benzene and CH_2Cl_2 were distilled from calcium hydride, under a nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Organic layers were dried over anhydrous MgSO_4 . Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were obtained from the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France. *X-Ray crystallographic intensity data* of **49**, **58** and **67b** were measured using graphite-monochromated $\text{Cu K}\alpha$ radiation, and the $(\theta-2\theta)$ scan technique up to given θ . The structure was solved by direct methods using SHELXS86¹⁸, and refined by full matrix least-squares with SHELX93¹⁹, minimizing the function $\sum w(\text{Fo}^2 - \text{IFcl}^2)^2$. The coordinates of the hydrogen atoms, located in difference Fourier maps, were introduced in theoretical position ($d(\text{C-H}) = 1.00 \text{ \AA}$) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at given R and R_w .

(1'S, 4R, 4aR)-1-(1-Phenylethyl-2-oxo-4a-methyl-1,3,4,4a,5,6-hexahydro[1]pyrindin-4-yl)carboxylic acid (49). To a solution of **48** (201 mg, 1.0 mmol) in THF (5 mL) was added at 0 °C a solution of maleic anhydride (**32**) (118 mg, 1.2 mmol) in THF (5 mL). The mixture was kept 1 h at 20 °C. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexane 1:2), giving **49** (284 mg, 95%); mp 168-170 °C (AcOEt); IR: 3446, 1727, 1595 cm^{-1} ; $[\alpha]_D^{20} -17.8^\circ$ (c 6.2, MeOH); ^1H NMR (200 MHz, CDCl_3) δ : 9.30 (br s, 1H), 7.51-7.20 (m, 5H), 6.25 (q, $J = 7.1$ Hz, 1H), 4.46 (dd, $J = 2.6, 1.9$ Hz, 1H), 2.85-2.67 (m, 3H), 2.33-1.67 (m, 4H), 1.61 (d, $J = 7.1$ Hz, 3H), 1.25 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ : 178.2 (C), 168.3 (C), 140.9 (C), 140.7 (C), 128.2 (2 CH), 127.4 (CH), 126.2 (2 CH), 108.4 (CH), 50.1 (CH), 46.7 (CH), 46.1 (C), 34.0 (CH_2), 32.5 (CH_2), 28.1 (CH_2), 23.9 (CH_3), 15.1 (CH_3); Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3$: C, 72.22; H, 7.07; N, 4.67. Found: C, 72.32; H, 7.10; N, 4.60. X-Ray crystallographic analysis: Crystal data: $\text{C}_{18}\text{H}_{21}\text{NO}_3$

$M_w = 299.37$, colorless crystal of 0.35 x 0.35 x 0.45 mm, orthorhombic, space group $P 2_1 2_1 2_1$, $Z = 4$, $a = 8.160$ (2), $b = 11.972$ (3), $c = 16.650$ (2) Å, $V = 1626$ (1) Å³, $d_{\text{calc}} = 1.28$ g cm⁻³, $F(000) = 640$, λ (Cu K α) = 1.5418 Å, $\mu = 0.63$ mm⁻¹; $\theta = 68.9^\circ$. Of the 6326 collected reflexions ($-9 \leq h \leq 9$, $-14 \leq k \leq 14$, $0 \leq l \leq 19$), 2954 were unique ($R_{\text{int}} = 0.043$) of which 2680 were considered as observed having $I \geq 2 \sigma(I)$. Cell parameters were refined from 25 well centered reflexions with $12.2 \leq \theta \leq 26.5^\circ$. Convergence was reached at $R = 0.055$ and $wR_2 = 0.161$, goodness of fit 1.06. The residual electron density in the final difference map was located between -0.21 and 0.21 e Å⁻³. O18. Two molecules are linked through a strong hydrogen bond O21-H...O18 (2.640 Å).

(1'S, 3R)-1-(1-Phenylethyl-2-oxo-5-methyl-4-carbomethoxy-4-pyrrolin-3-yl)acetic acid and (1'S, 3S)-1-(1-Phenylethyl-2-oxo-5-methyl-4-carbomethoxy-4-pyrrolin-3-yl)acetic acid (53). To a solution of **52** (219 mg, 1.0 mmol) in THF (5 mL) was added at 0 °C a solution of maleic anhydride (**32**) (122 mg, 1.3 mmol) in THF (5 mL). The mixture was kept 2 h at 20 °C. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexane 1:2), giving **53** (218 mg, 69 %); mp 137-139 °C (AcOEt); IR: 3600-3100, 1731, 1666, 1613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 13.0 (br s, 1H), 7.35-7.25 (m, 5H), 5.64 (q, $J = 7.1$ Hz, 1H), 3.70 (s, 3H), 3.52 and 3.46 (m, 1H), 3.24-3.10 (m, 2H), 2.17 and 2.16 (s, 3H), 1.75 and 1.74 (d, $J = 7.1$ Hz, 3H).

(1'S, 3R, 4S)-1-(1-Phenylethyl-2-oxo-4-carbomethoxy-4-methyl-5-methylenepyrrolidin-3-yl) acetic acid (56). To a solution of enamino ester (**55**) (500 mg, 2.02 mmol) in THF (10 mL) was added at 0 °C a solution of maleic anhydride (**32**) (294 mg, 3.0 mmol) in THF (10 mL). The mixture was kept 12 h at 20 °C. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexane 1:1.5), giving **56** (490 mg, 70 %); amorphous solid; IR: 3600-3100, 1740, 1722, 1643 cm⁻¹; (α)_D²⁰ - 7.5° (c 18.3, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 9.8 (br s, 1H), 7.35-7.26 (m, 5H), 5.66 (q, $J = 7.2$ Hz, 1H), 4.24 (d, $J = 3.0$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 4.10 (d, $J = 3.0$ Hz, 1H), 3.13 (dd, $J = 5.5$ Hz, $J = 5.6$ Hz, 1H), 2.96 (dd, $J = 16.7$ Hz, $J = 5.6$ Hz, 1H), 2.39 (dd, $J = 16.7$ Hz, $J = 5.5$ Hz, 1H), 1.70 (d, $J = 7.2$ Hz, 3H), 1.50 (s, 3H), 1.21 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 175.3 (C), 174.9 (C), 171.2 (C), 146.5 (C), 139.1 (CH₂), 128.6 (2 CH), 127.3 (CH), 126.4 (2 CH), 89.5 (C), 61.7 (CH₂), 51.5 (C), 49.8 (CH), 46.8 (CH), 31.4 (CH₂), 20.6 (CH₃), 14.2 (CH₃), 14.0 (CH₃).

(1'S, 2S, 3R, 3aR, 6aS)-2-(1'-Phenylethyl-2-oxo-3a-methyl-6a-hydroxyhexahydro-cyclopenta-(b)pyrrol-3-yl)propanoic acid (58). To a solution of **48** (402 mg, 2.0 mmol) in THF (10 mL) was added at 0 °C a solution of citraconic anhydride (**57**) (336 mg, 3.0 mmol) in THF (10 mL). The mixture was kept 24 h in THF at reflux. The solvent was removed under reduced pressure, and water (5 mL) was added to the residual oil. The mixture was extracted with ether (3 x 25 mL), and the combined organic layers were washed with brine, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 1:1) giving **58** (231 mg, 35 %); mp 169-171 °C (AcOEt); IR: 3460, 3400-3100, 1721, 1658 cm⁻¹; [α]_D²⁰ -37.1° (c 2.1, MeOH); ¹H NMR (200 MHz, CDCl₃) δ 12.0 (br s, 1H), 7.35-7.15 (m, 2H), 7.05-6.90 (m, 3H), 4.65 (q, $J = 7.1$ Hz, 1H), 4.30 (br s,

1H), 2.60-2.40 (m, 1H), 2.15 (d, $J = 5.5$ Hz, 1H), 1.80-1.30 (m, 6H), 1.45 (d, $J = 7.1$ Hz, 3H), 1.15 (d, $J = 7.0$ Hz, 3H), 0.75 (s, 3H); Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.22. Found: C, 68.59; H, 7.71; N, 4.19; X-Ray crystallographic analysis: Crystal data : $C_{19}H_{25}NO_4$ $M_w = 331.41$, colorless crystal of 0.10 x 0.35 x 0.45 mm, orthorhombic, space group $P 2_1 2_1 2_1$, $Z = 4$, $a = 8.200$ (3), $b = 11.580$ (4), $c = 18.115$ (8) Å, $V = 1720$ (1) Å³, $d_{calc} = 1.28$ g cm⁻³, $F(000) = 712$, λ (Cu K α) = 1.5418 Å, $\mu = 0.72$ mm⁻¹; $\theta = 67.8^\circ$. Of the 7192 collected reflexions ($-9 \leq h \leq 9$, $-13 \leq k \leq 13$, $0 \leq l \leq 21$), 3113 were unique ($R_{int} = 0.041$) of which 2964 were considered as observed having $I \geq 2 \sigma(I)$. Cell parameters were refined from 25 well centered reflexions with $13.6 \leq \theta \leq 17.1^\circ$. Convergence was reached at $R = 0.038$ and $wR_2 = 0.101$, goodness of fit 1.05. The residual electron density in the final difference map was located between -0.17 and 0.19 e Å³. The cyclopentane ring is disordered with two positions for the carbon atom C5 (relative occupation factor 0.90, 010). An intramolecular hydrogen bond links the hydroxy group at C6a to the carbonyl oxygen of the carboxylic acid (O23... O20: 2.805 Å). Two molecules are linked through a strong hydrogen bond O21-H...O17 (-X, -1/2 + Y, 1/2 -Z) (2.660 Å).

(1'S, 3R, 4aR)-2-(1'-Phenylethyl-2-oxo-4a-methyl-hexahydro-(1H)-quinolin-3-yl)-acetic acid methyl ester (59). To a solution of *ent*-10 (430 mg, 2.0 mmol) in THF (5 mL) was added at 0 °C a solution of citraconic anhydride (57) (336 mg, 3.0 mmol) in THF (5 mL). The mixture was kept 4 h in THF at reflux. The crude adducts were next esterified with diazomethane giving after chromatography over silica gel (hexane: ethyl acetate 1:1) compounds (59) and (60), in the ratio 4:1, respectively, with 65 % combined yield. Only the isomer (59) is described; amorphous solid; IR: 1742, 1669, 1640 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ : 7.32-7.18 (m, 5H), 6.18 (q, $J = 7.1$ Hz, 1H), 4.85 (dd, $J = 5.5$, $J = 2.8$ Hz, 1H), 3.70 (s, 3H), 2.97 (m, 1H), 2.83 (dd, $J = 6.0$, $J = 4.0$ Hz, 2H), 2.10-1.40 (m, 8H), 1.59 (d, $J = 7.1$ Hz, 3H), 1.17 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ : 172.6 (C), 170.4 (C), 142.4 (C), 139.3 (C), 128.3 (2 CH), 126.2 (CH), 125.7 (2 CH), 109.7 (CH), 51.6 (CH), 51.4 (CH₃), 40.6 (CH₂), 38.3 (CH₂), 36.9 (CH₂), 36.1 (CH), 33.2 (C), 24.8 (CH₂), 23.0 (CH₃), 17.9 (CH₂), 15.4 (CH₃).

(1'S, 3R)-1-[1-Phenylethyl-2-oxo-3,5-dimethyl-4-carbomethoxy-4-pyrrolin-3-yl]acetic acid (61). To a solution of 52 (438 mg, 2.0 mmol) in THF (5 mL) was added at 0 °C a solution of citraconic anhydride (57) (336 mg, 3.0 mmol) in THF (5 mL). The mixture was kept 12 h in THF at reflux. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexane 1:2), giving 61 (482 mg, 73 %); amorphous solid; IR: 3600-3100, 1730-1680, 1622 cm⁻¹; $[\alpha]_D^{20} - 55.2^\circ$ (c 12.3, EtOH); ¹H NMR (200 MHz, CDCl₃) δ 10.0 (br s, 1H), 7.40-7.15 (m, 5H), 5.70 (q, $J = 7.0$ Hz, 1H), 3.70 (s, 3H), 3.20 (d, $J = 18.0$ Hz, 1H), 2.95 (d, $J = 18.0$ Hz, 1H), 2.15 (s, 3H), 1.60 (d, $J = 7.0$ Hz, 3H), 1.40 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ 181.9 (C), 175.7 (C), 164.5 (C), 155.5 (C), 140.1 (C), 128.6 (2 CH), 126.7 (CH), 126.1 (2 CH), 110.9 (CH), 51.5 (CH₃), 49.0 (CH), 46.5 (CH₂), 40.1 (C), 20.9 (CH₃), 15.0 (CH₃), 13.8 (CH₃).

(Z)(S)-N-(1-Phenylethyl)-2-methylmaleamic acid (63): To a solution of 55 (500 mg, 2.02 mmol) in THF (5 mL) was added at 0 °C a solution of citraconic anhydride (57) (336 mg, 3.0 mmol) in THF (5 mL). The mixture was kept 5 h in THF at reflux. The solvent was removed under reduced

pressure, and water (5 mL) was added to the residual oil. The mixture was extracted with ether (3 x 25 mL), and the combined organic layers were washed with brine, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 1:1), giving **63** (283 mg, 60 %); mp 143-147 °C (AcOEt); IR: 3460, 3400-3100, 1721, 1658 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.4 (br s, 1H), 7.3-7.20 (m, 5H), 6.60 (br s, 1H), 6.28 (q, *J* = 1.5 Hz, 1H); 5.16 (q, *J* = 7.1 Hz, 1H), 2.12 (d, *J* = 1.5 Hz, 3H), 1.58 (d, *J* = 7.1 Hz, 3H); Anal. Calcd for C₁₃H₁₅NO₃: C, 66.91; H, 6.49; N, 6.00. Found: C, 66.69; H, 6.53; N, 5.96.

General procedure for the condensation of imines (48) and (*ent*-10) with 2-chloroacrylonitrile (29). To a solution of imine (5.0 mmol) and 2,6-lutidine (555 mg, 5.2 mmol) in hexane (6 mL) was added at 0 °C, 2-chloroacrylonitrile (437 mg, 5.0 mmol). After being stirred for two days at 20 °C, the mixture was diluted with dry ether and filtered over a plug of Celite. The filtrate was concentrated over reduce pressure to leave a yellow oil which was taken-up into anhydrous methanol (10 mL). A crystal of Bromocresol Green was added, and sodium cyanoborohydride (1.26 g, 20 mmol) was next added portionwise. Acetic acid was then added dropwise, until the blue solution turned yellow. The resulting mixture was then heated at 60 °C for 8 h. After cooling, the reaction mixture was poured into aqueous saturated sodium bicarbonate, and extracted with ether. The organic phases were dried, and concentrated under reduced pressure to give a yellow oil, which was chromatographed over alumina, leading to the pure amines.

[1'S-[3aα(*R*), 6aα]]-3a-Methyl-1-(1-phenylethyl)octahydrocyclopenta[*b*]pyrrole (66): Colorless oil; ¹H NMR (200 MHz, CDCl₃) δ: 7.45-7.20 (m, 5H), 3.50 (q, *J* = 6.8 Hz, 1H), 2.68-2.50 (m, 2H), 2.35 (m, 1H), 1.90-1.20 (m, 8H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.08 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ: 145.6 (C), 128.0 (2 CH), 127.3 (2 CH), 126.4 (CH), 74.5 (CH), 64.5 (CH), 52.2 (CH₂), 49.6 (C), 41.2 (CH₂), 39.1 (CH₂), 34.6 (CH₂), 28.1 (CH₃), 25.3 (CH₂), 23.9 (CH₃); [α]_D²⁰ = -45.5° (*c* = 3.0, EtOH); Anal. Calcd for C₁₆H₂₃N: C, 83.79; H, 10.10; N, 6.10. Found: C, 83.64; H, 10.08; N, 6.09.

[1'S-[2b(*S*), 3aα, 6aα]]-3a-Methyl-1-(1-phenylethyl)octahydrocyclopenta[*b*]pyrrole-2, 6a-dicarbonitrile (67b): mp 145 °C; X-Ray crystallographic analysis: Crystal data : C₁₈H₂₁N₃ M_w = 279.39, colorless crystal of 0.20 x 0.40 x 0.40 mm, monoclinic, space group P 2₁, Z = 2, a = 7.443 (3), b = 11.406 (3), c = 9.356 (2) Å, β = 100.06(2)°, V = 782.1 (4) Å³, d_{calc} = 1.19 g cm⁻³, F(000) = 300, λ (Cu Kα) = 1.5418 Å, μ = 0.52 mm⁻¹; θ = 67.9°. Of the 3140 collected reflexions (-17 ≤ h ≤ 17, -27 ≤ k ≤ 27, 0 ≤ l ≤ 11), 2818 were unique (R_{int} = 0.037) of which 2785 were considered as observed having I ≥ 2 σ(I). Cell parameters were refined from 25 well centered reflexions with 13.9 ≤ θ ≤ 20.3°. Convergence was reached at R = 0.044 and wR₂ = 0.115, goodness of fit 1.06. The residual electron density in the final difference map was located between -0.14 and 0.15 e Å³.

[1'S-[3aα(*R*), 7aα]]-3a-Methyl-1-(1-phenylethyl)-3a,4,5,6,7,7a-hexahydroindole (69): Colorless oil; ¹H NMR (200 MHz, C₆D₆) δ: 7.28 (d, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 3.74 (q, *J* = 6.8 Hz, 1H), 2.80 (ddd, *J* = 9.6, *J* = 9.6, *J* = 4.9 Hz, 1H), 2.75 (ddd, *J* =

9.6, $J = 9.6$, $J = 5.6$ Hz, 1H), 1.60-1.50 (m, 3H), 1.42 (m, 2H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.40-1.27 (m, 3H), 1.25-1.00 (m, 2H), 1.03 (s, 3H), 1.00-0.93 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ : 144.0 (C), 127.9 (2 CH), 127.7 (2 CH), 126.4 (CH), 63.8 (CH), 57.7 (CH), 45.5 (CH₂), 39.9 (C), 35.4 (CH₂), 35.0 (CH₂), 27.3 (2 CH₃), 23.3 (CH₂), 22.3 (CH₂), 22.3 (CH₂).

7-Phenyl-1-(1-phenylethyl)-4,5,6,7-tetrahydroindole (71). To a solution of imine (70) (0.70 g, 2.5 mmol) and 2,6-lutidine (0.28 g, 2.6 mmol) in THF (4 mL), was added at 0 °C, 2-chloroacrylonitrile (0.40 g, 4.6 mmol). After being stirred for 12 h at 50 °C, the mixture was diluted with ether and filtered over a plug of Celite. The filtrate was concentrated, and the oily residue chromatographed over alumina (hexane, AcOEt: 1: 7) to give 0.53 g (70 %) of pyrrole (71) as a mixture of stereomers; colorless oil; IR (neat, cm^{-1}) 1600, 1492; ^1H NMR (200 MHz, CDCl_3), *major isomer* δ : 7.30-7.23 (m, 4H), 7.10-7.00 (m, 4H), 6.86 (dd, $J = 8.0$, $J = 1.8$ Hz, 2H), 6.82 (d, $J = 2.8$ Hz, 1H), 6.10 (d, $J = 2.8$ Hz, 1H), 4.68 (q, $J = 7.1$ Hz, 1H), 3.71 (dd, $J = 4.7$, $J = 4.5$ Hz, 1H), 2.70-2.45 (m, 2H), 2.20-1.50 (m, 4H), 1.51 (d, $J = 7.1$ Hz, 3H), *minor isomer* δ : 7.30-7.23 (m, 4H), 7.10-7.00 (m, 4H), 6.86 (dd, $J = 8.0$, $J = 1.8$ Hz, 2H), 6.52 (d, $J = 2.9$ Hz, 1H), 6.02 (d, $J = 2.9$ Hz, 1H), 4.92 (q, $J = 7.1$ Hz, 1H), 4.14 (dd, $J = 5.8$, $J = 5.5$ Hz, 1H), 2.70-2.45 (m, 2H), 2.20-1.50 (m, 4H), 1.63 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (50 MHz, CDCl_3), only the *major isomer* is described δ : 148.0 (C), 147.3 (C), 128.4 (2 CH), 128.1 (2 CH), 127.8 (2 CH), 126.7 (CH), 126.5 (C), 126.0 (C), 125.3 (2 CH), 119.7 (C), 116.3 (CH), 105.9 (CH), 54.0 (CH), 38.5 (CH), 33.7 (CH₂), 23.3 (CH₃), 21.9 (CH₂), 19.4 (CH₂).

(S)-Ethyl-2-oxo-1-nitroethylcyclopentanecarboxylate (75). To a solution of enamino ester (73) (1.56 g, 6.0 mmol), in THF (20 mL) cooled at -15 °C, was added dropwise nitroethylene (0.48 g, 6.6 mmol). The reaction mixture was stirred 10 min, diluted with anhydrous methanol (15 mL), cooled at -20 °C and treated by a 20 % aqueous acetic acid solution (15 mL). The mixture was kept at -20 °C for 24 h. 2 N HCl was then added, followed by solid NaCl, and the resulting mixture was thoroughly extracted with ether. The combined organic phases were washed with brine, dried, and concentrated under reduced pressure to give an oil which was chromatographed over silica gel (ethyl acetate: hexane 1: 4) to give pure adduct (75) as a pale yellow oil (1.11 g, 81 %); bp 100 °C (0.1 Torr); $[\alpha]_{\text{D}}^{20} +17.2^\circ$ (c 2.6, EtOH); IR: 1751, 1732, 1554 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ : 4.69 (ddd, $J = 6.45$, $J = 8.75$, $J = 14.2$, 1H), 4.51 (ddd, $J = 5.93$, $J = 8.43$, $J = 14.2$, 1H), 4.19 (q, $J = 7.0$ Hz, 2H), 2.58-2.28 (m, 5H), 2.11-1.85 (m, 3H), 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ : 213.8 (C), 170.6 (C), 71.5 (CH₂), 61.9 (CH₂), 57.6 (C), 37.7 (CH₂), 34.4 (CH₂), 30.3 (CH₂), 19.7 (CH₂), 14.0 (CH₃); Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_5$: C, 52.41; H, 6.60; N, 6.11. Found: C, 52.31; H, 6.71; N, 6.09.

(3a*S*, 6a α)-Ethyl-2,3,3a,6a-tetrahydro-3a-cyclopenta[*b*]pyrrole carboxylate (76). A solution of nitro ester (75) (0.50 g, 2.18 mmol) in ethanol (2 mL) was subjected to hydrogenation at 3 bars, in presence of 10 % Pd/C (0.10 g). After 12 h at 20 °C, the reaction mixture was filtered and concentrated under reduced pressure. The residue was distilled to give pure amine (76) as a colorless oil (0.31 g, 78 %); bp 50 °C (0.1 Torr); $[\alpha]_{\text{D}}^{20} - 9.5^\circ$ (c 7.9, EtOH); IR: 3272, 1725 cm^{-1} ; ^1H NMR (200 MHz, C_6D_6) δ : 3.93 (q, $J = 7.1$ Hz, 2H), 3.84 (dd, $J = 6.9$, $J = 3.2$ Hz, 1H), 2.74 (t, $J = 6.4$ Hz, 2H), 2.56 (br s, 1H), 2.28 (dd, $J = 12.3$, $J = 5.9$ Hz, 1H), 2.22-2.12 (m, 1H), 1.82-1.31 (m, 6H), 0.96 (t, $J =$

7.1 Hz, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ : 176.1 (C), 69.1 (CH), 60.2 (CH_2), 59.2 (C), 47.0 (CH_2), 38.3 (CH_2), 37.2 (CH_2), 33.6 (CH_2), 25.2 (CH_2), 13.9 (CH_3); MS, m/z 183 (M^+ , 4), 155 (33), 154 (16), 138 (16), 126(25), 110 (56), 82 (57), 49 (59), 43 (100).

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