Stereochemical Aspects in the Asymmetric Michael Addition of Chiral Imines to Substituted Electrophilic Alkenes

Christian Cavé, Didier Desmaële, and Jean d'Angelo*

Laboratoire de Chimie Organique associé au CNRS, Université Paris-Sud, Centre d'Etudes Pharmaceutiques, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France

Claude Riche and Angèle Chiaroni

Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

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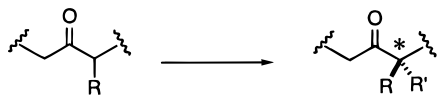
The Michael-type addition of chiral imines, derived from *racemic* α-substituted cyclanones and optically active 1-phenylethylamine, to electrophilic alkenes, in neutral conditions, constitutes one of the most efficient methods for the stereocontrolled construction of quaternary carbon centers. In order to create an additional stereogenic center at the α- or *β*-position to the quaternary one, the behavior of a variety of α- and *β*-substituted alkenyl acceptors was examined. In general, these additions are *highly regioselective*, the alkylation taking place predominantly, if not exclusively, at the more substituted α-side of the imine function; however, in some cases (electrophilic alkenes **28** and **49**), significant amounts (10−15%) of regioisomeric adducts were obtained. With the exception of methyl propiolate **52**, a remarkable *control of the absolute configuration* of the adducts were always observed with these Michael acceptors. According to the general rule we have previously proposed, the alkylation process takes place preferentially on the less hindered *π*-face of the more substituted secondary enamine, in tautomeric equilibrium with the starting imine. An excellent *diastereocontrol* was always obtained by using the present α- and *β*-substituted alkenes. These stereochemical outcomes can be interpreted by invoking that the reaction proceeds through a compact approach of the reactants, the hydrogen atom at the nitrogen center of the enamine being transferred to the α-vinylic carbon atom of the acceptor, concertedly with the creation of the C−C bond. In this respect the "*endo-approach*" **58**, in which the electron-withdrawing group of the acceptor faced to the nitrogen atom of the enamine (case of acceptors **10**, methyl methacrylate, **24**, **28**, **43**, **47**, and **49**) largely prevails over the "*exo-approach*" **59** (case of acceptor **38**). This predominant "*endo*-preference" can be reasonably interpreted in terms of a cooperative effect between steric and stereoelectronic factors.

Introduction

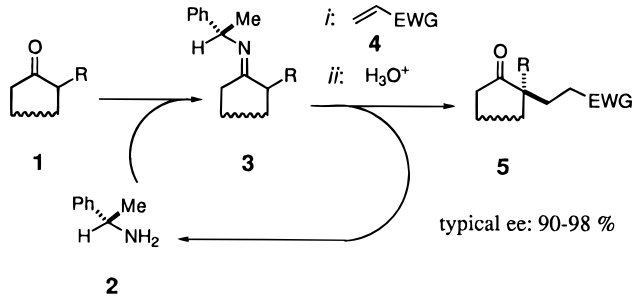
Owing to the presence, as a key structural feature, of quaternary carbon centers in many important naturally occurring products (terpenes, steroids, alkaloids, etc.), the enantioselective elaboration of such pivotal entities constitutes a major, fascinating area of the asymmetric synthesis.[1] Conceptionally, one of the simplest methods for the stereocontrolled construction of quaternary carbon centers is the alkylation, in a suitable chiral environment, of α-disubstituted ketones (or their equivalents) (eq 1). Although highly attractive, this methodology however requires that the regio- and stereoselectivity of the alkylation process should be controlled simultaneously.



(1)

A decade ago, we proposed a particularly efficient and simple solution to this challenging problem (at least in the case of cyclic ketones), based on the Michael-type alkylation of chiral imines.[2] Thus, we have shown that imines **3**, derived from *racemic* α−substituted cyclanones

Scheme 1



1 and optically active 1-phenylethylamine **2** add, *under neutral conditions*, to electrophilic alkenes **4** to furnish, after acidic hydrolytic workup, α-disubstituted cyclanones **5**, in good yields and with a high degree of regio- and stereoselectivity, along with the recovered unchanged chiral auxiliary (Scheme 1).

This reaction, which tolerates a great variation in the nature of both reagent partners, has been successfully applied by ourselves and others to the enantioselective synthesis of various natural compounds.[2] The mechanistic aspects of this Michael addition have also been extensively investigated, from both experimental and theoretical viewpoints.[2] It has thus been proposed that the nucleophilic partners in the reaction are the more substituted secondary enamines, in tautomeric equilibrium with imines **3**, a view strengthened by the fact that addition of deuterated imine **6** to methyl acrylate led

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) Review: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(2) Reviews: (a) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459−505. (b) d'Angelo, J.; Cavé, C.; Desmaële, D.; Dumas, F. *Trends in Organic Synthesis;* Pandalai, S. G., Ed.; Trivandrum: India, 1993; Vol. 4, pp 555−615.

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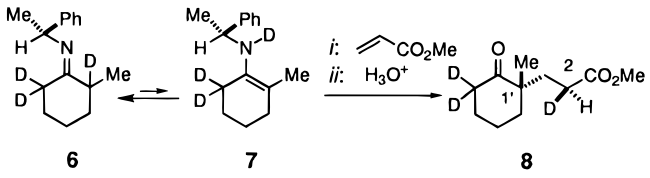
Scheme 2



6 **7** **8**

cleanly to adduct **8**, which contains a deuterium atom at the α-position to the ester group.[3] On the other hand, the complete control of the stereogenic center at C-2 position in adduct **8** supports the hypothesis that the deuteron borne by the nitrogen atom in the secondary enamine **7** was transferred to the α-vinylic center of methyl acrylate *concertedly* with the creation of the C−C bond (Scheme 2).

Of peculiar interest from both synthetic and mechanistic viewpoints, was the creation of an additional stereogenic center at the α- or *β*-position to the quaternary one, by using adequately substituted electrophilic alkenes. In this paper, we report the stereochemical results obtained by using a variety of α- and *β*-substituted alkenyl acceptors, and of methyl propiolate as electrophilic alkyne. Excellent stereoselectivities were generally observed in such additions. These stereochemical outcomes can be rationalized by evoking that the reaction proceeds through an "aza-ene-synthesis-like" transition state, the geometry of which is governed by steric and stereoelectronic factors.

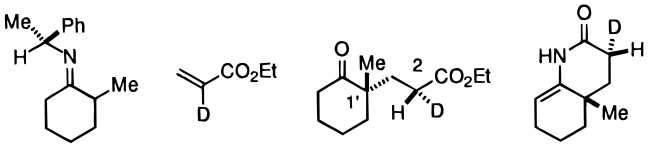
Results and Discussion

Chiral imine **9**, prepared by condensing *racemic* 2-methylcyclohexanone with (*R*)-1-phenylethylamine, or its enantiomer, were used as nucleophilic reagents in all experiments. Chiral enamino ester **14** and enamino lactam **35** were also employed in some cases. Considering the significant propensity of the adducts to equilibrate (through a retro-Michael-type fragmentation),[4] only the experiments performed under relatively mild operating conditions were taken into account in the present investigation.

α-Substituted Alkenyl Acceptors. Addition of imine **9** to ethyl 2-deuteroacrylate (**10**) (neat, 48 h at 20 °C, and then 20% aqueous AcOH, 2 h at 20 °C) furnished in 75% yield keto ester (2*R*,1′*S*)-**11**.[3] The depicted relative configuration of the two stereogenic centers in adduct **11** was determined at the level of the bicyclic lactam derivative **12**, obtained by addition of NH_3 to **11** (MeOH, 3 days at 20 ° C, then *p*-TsOH, heated 3 h to reflux in benzene). A strong NOE (10%) was actually observed between the angular methyl group and the hydrogen atom in the α-position to the lactam function in the ^{1}H NMR spectrum of **12** (Chart 1).

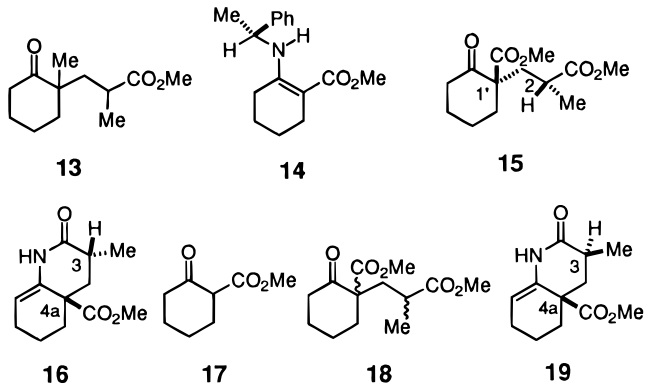
Condensation of imine **9** with methyl methacrylate produced adduct **13** in very low yield (1%).[5] In contrast, $MgBr_2$-catalyzed addition of chiral enamino ester (*R*)-**14** to this electrophile (7 days at 20 °C and then 10% aqueous AcOH, 24 h at 20 °C) gave with a 72% yield adduct (2*R*,1′*R*)-**15**.[6] This adduct was found to be homogeneous by ^{1}H NMR spectroscopy [after adding $Eu(hfc)_3$ as chiral shift reagent]. The relative configuration of the two stereogenic centers in **15** was determined through its cyclization, by addition of ammonia (NH_3 in MeOH, 5 days at 20 °C, then *p*-TsOH heated to reflux in toluene), to bicyclic lactam (3*R*,4a*R*)-**16**. The *trans* relationship between the two substituents at C-3 and C-4a in **16** was determined as follows. Addition of keto ester **17** to methyl methacrylate (Triton B, THF, 12 h at 20 °C) furnished **18** (as an equimolar mixture of racemic diastereomers), which was cyclized by addition of ammonia, followed by treatment with *p*-TsOH heated to reflux in toluene, to a 1:1 mixture of racemic lactams **16** and **19** (an experiment which, incidentally, established that **16** and **19** did not interconvert in such operating conditions). Lactams **16** and **19** were easily separated by flash chromatography over silica gel (Chart 2). Structure of lactam (±)-**16** was unequivocally established by an X-ray diffraction analysis (Figure 1).[7]

Chart 1



9 **10** **11** **12**

Chart 2



13 **14** **15**

16 **17** **18** **19**

Determination of the absolute configuration of the quaternary carbon center in **15** was established by chemical correlation, starting from keto ester (*R*)-**20**, of known configuration. This was first protected as ketal derivative **21**. Sequential deprotonation of **21** (LDA, THF, −78 °C) and methylation (MeI, −78 °C, 3 h) produced a mixture of diasteromers **22** and **23**, which were easily separated by flash chromatography, in the ratio of 4.5:1. Acidic hydrolysis of the minor isomer **23** finally led to the corresponding keto ester which proved to be identical in all respects, including the optical rotation, with **15** (Chart 3).

(3) Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 9705−9708.

(4) (a) Huffman, J. W.; Rowe, C. D.; Matthews, F. J. *J. Org. Chem.* **1982**, *47*, 1438−1445. (b) Desmaële, D.; d'Angelo, J.; Bois, C. *Tetrahedron: Asymmetry* **1990**, *1*, 759−762.

(5) When, in our hands, all attempts at condensing methyl methacrylate or methyl crotonate with imine **9**, under thermal conditions, furnished essentially polymeric materials (see Experimental Section), the authors claimed that, somewhat paradoxically, the Michael adducts were formed in good yields and with excellent stereoselectivities, by using highly forcing conditions (*30 days at 120* °C for methyl crotonate).[12] In any case, considering such very drastic operating conditions, there is no certainty that the so-called adducts were formed under kinetic control,[4] and therefore the reported stereochemistries do not necessarily reflect the geometrical arrangement of the reactants in the corresponding transition states.

(6) Cavé, C.; Daley, V.; d'Angelo, J.; Guingant, A. *Tetrahedron: Asymmetry* **1995**, *6*, 79−82.

(7) In our original paper, structures **16** and **19** have been permuted by inadvertence.[6]

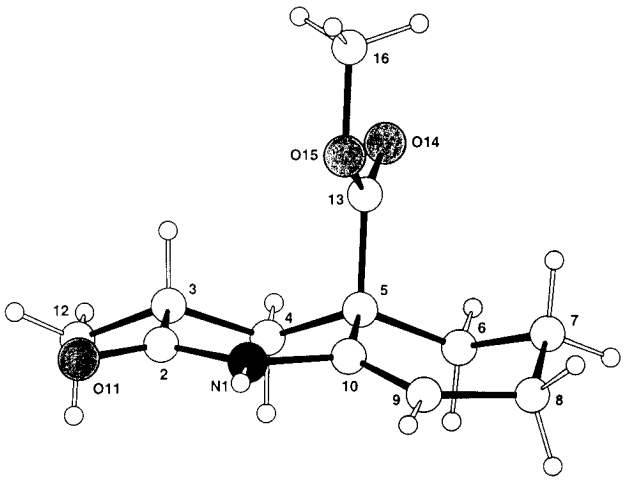
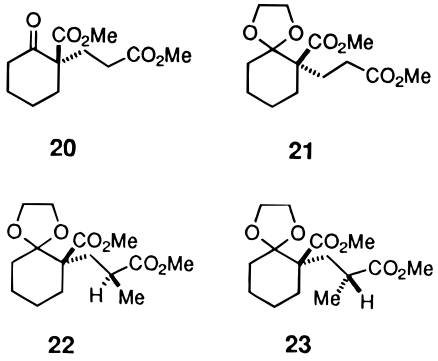


Figure 1. X-ray crystal structure of lactam (±)-**16**.

Chart 3



Addition of imine *ent*-**9** to α-methylene-γ-butyrolactone **24** (3 days at 40 °C in THF, and then 10% aqueous AcOH, 2 h at 20 °C) furnished adduct (2*R*,1′*R*)-**25** with a 54% yield. The relative configuration of the two stereogenic centers in **25** was established by chemical correlation. For this purpose **25** was first cyclized to lactam **26** by addition of ammonia (NH_3 in MeOH, 72 h at 20 °C). Dehydration of **26** (heated 12 h to reflux in benzene, in the presence of a catalytic amount of *p*-TsOH) then gave (3*R*,4a*R*)-**27** (70% overall yield). The depicted relative stereochemistry in **27** was assigned by ^{1}H NMR spectroscopy, a strong NOE (11%) was indeed observed between the angular methyl and the H atom at C-3. An enantiomeric excess of 97% (after correction of the enantiomeric purity of the starting chiral amine) in adduct **25** was measured by ^{1}H NMR spectroscopy [after adding Eu(hfc)$_3$ as chiral shift reagent]. The portrayed absolute configuration in **25**, although not definitively established, rests on a heuristic rule we have proposed *(vide infra*, Figure 3), predicting that the alkylation takes place predominantly on the less hindered π-face of imine *ent*-**9**, *anti* to the phenyl group (Chart 4).

Condensation of imine *ent*-**9** with methyl 2-acetoxyacrylate (**28**) (neat, 90 min at 20 °C, then 20% aqueous AcOH, 1 h at 20 °C) furnished adduct (2*S*,1′*R*)-**29** (60% yield), accompanied by 10% of regioisomer **30** (mixture of not fully characterized stereomers).[3] The relative configuration of the two stereogenic centers in **29** was determined by converting this compound by addition of ammonia (NH_3 in MeOH, 4 days at 20 °C, 72% yield) to bicyclic lactam **31** (concomitant cleavage of the acetoxy group by ammonia took place during this reaction). Dehydration of **31** then afforded **32** (*p*-TsOH, heated 2 h to reflux in benzene, 90% yield). A strong NOE was observed between the angular methyl group and H_3 in the ^{1}H NMR spectrum of **32**, ascertaining the *cis* relationship between these two substituents. The *R* configuration at the quaternary carbon in **29** was determined as follows.This keto ester was protected as ketal **33.** The acetoxy group in **33** was then cleaved by reduction (SmI_2/HMPA/THF/MeOH) giving, after acidic hydrolytic workup, the known, enantiopure keto ester (*R*)-**34** (Chart 5).

Chart 4

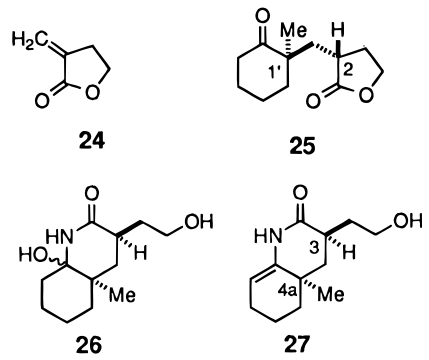
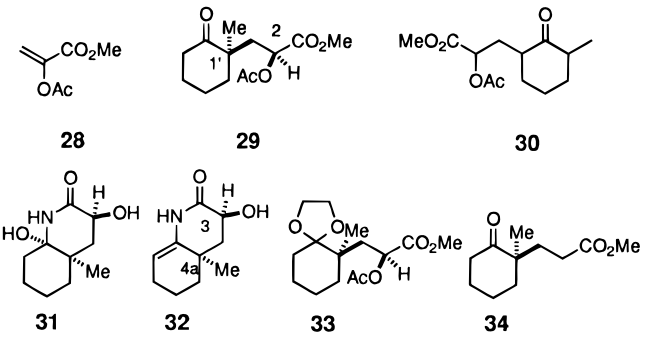


Chart 5



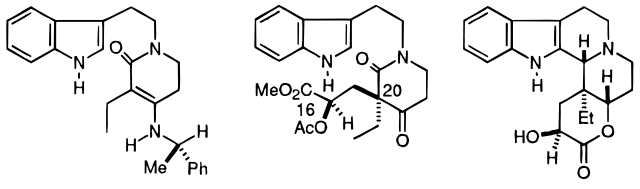
Addition of enamino lactam (*S*)-**35** to electrophilic alkene **28** (THF, 24 h at 20 °C, and then 20% aqueous AcOH, 12 h at 20 °C) afforded with a 55 % yield adduct (16*S*,20*R*)-**36**,[8] as a single isomer. The relative configuration of the two stereogenic centers in **36** was established by ^{1}H NMR spectroscopy including NOE experiments at the level of the pentacyclic lactone derivative **37** [i: LiAl(O*t*-Bu)$_3$,THF, 20 °C; ii: separation of epimers; iii: Amberlyst R15, heated 24 h to reflux in benzene; iv: $POCl_3$, heated 12 h to reflux in MeCN, and then 1 atm of H_2, Pd−C, AcOEt, 12 h at 20 °C] (Chart 6).

Addition of imine **9** to methyl α-(phenylthio)acrylate (**38**) (THF, 24 h at 20 °C, and then 20% aqueous AcOH, 2 h at 20 °C) produced adduct (2*S*,1′*S*)-**39** with a 80% yield.[9] The relative configuration of the two stereogenic centers in **39** was established as follows. Treatment of adduct **39** with aqueous ammonia led to bicyclic lactam **40** which was converted (DBU) to the thermodynamically more stable epimer **41**; thus the PhS group is *axial* in compound **40** and *equatorial* in isomer **41**. Further data in support of these stereochemical assignments were obtained from the ^{1}H NMR spectra of these diastereomers (thus a 18% NOE was observed between the angular methyl group and H-3 in **41**). The *S* configuration (90% ee) at the quaternary carbon center in **39** was unam-

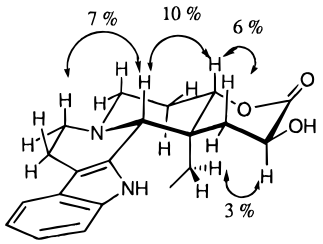
(8) Mekouar, K.; Ambroise, L.; Desmaële, D.; d'Angelo, J. *Synlett* **1995**, Special Issue May, 529−532.

(9) d'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1988**, *29*, 2667−2670.

Chart 6

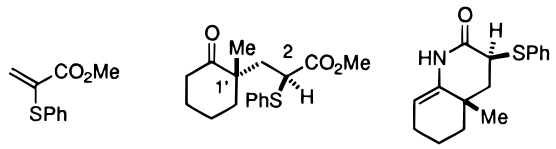


35 **36** **37**

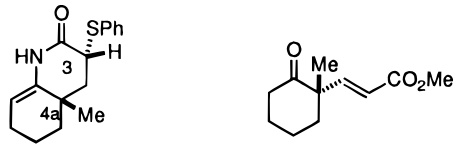


Observed NOE for H-H interaction in **37**

Chart 7

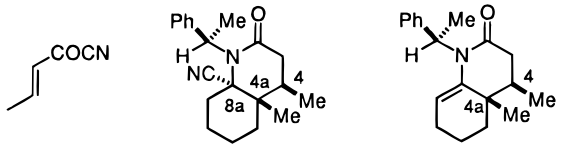


38 **39** **40**



41 **42**

Chart 8



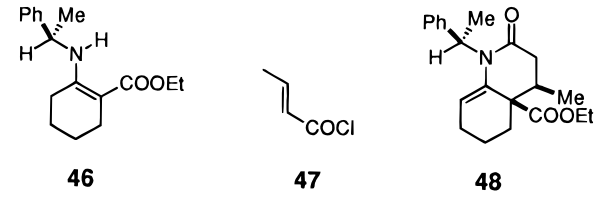
43 **44** **45**

biguousy determined by converting this compound to the known keto ester *ent*-**34**, through the intermediate **42** (i: *m*-chloroperbenzoic acid, and then heat; ii: H_2/PtO_2) (Chart 7).

***β*-Substituted Alkenyl Acceptors.** No definite compound was obtained in the condensation of imine **9** with methyl crotonate.[5] In contrast, this imine reacted smoothly with the very reactive crotonyl cyanide **43** (cyclohexane, 24 h at 5 °C), giving with a 50% combined yield a mixture of bicyclic lactams (4*R*,4a*S*,8a*R*)-**44** and (4*R*,4a*R*)-**45**.[9] The *cis* relationship between the methyl groups at C-4 and C-4a in adducts **44** and **45** was unequivocally assigned from their ^{1}H NMR spectra; indeed analysis of the H_3-H_4 coupling constants established that, in both cases, the methyl group at C-4 is *equatorial*. Moreover, the absolute configurations of the three newly created stereogenic centers in **44** were ascertained by an X-ray diffraction analysis of this compound (Chart 8).

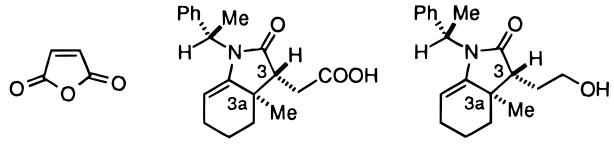
Interestingly, Stille recently reported that addition of enamino ester (*R*)-**46** to crotonyl chloride **47** (refluxing

Chart 9



46 **47** **48**

Chart 10



49 **50** **51**

THF) afforded bicyclic lactam **48** with an excellent stereoselectivity (Chart 9).[10]

Addition of imine *ent*-**9** to maleic anhydride **49** (THF, 1 h at 0 °C) furnished with a 65% yield adduct (3*R*,3a*R*)-**50**, accompanied by ca. 15% of regioisomers (as a mixture of diastereomers), resulting from the alkylation at the less substituted α-side of imine *ent*-**9**.[11] These regioisomers (not fully characterized) were separated from **50** by flash chromatography over silica gel. The portrayed relative configuration of the stereogenic centers at C-3 and C-3a in acid **50** was established through its convertion to alcohol **51** (i: $NaHCO_3$, then drying of the sodium salt; ii: ClCOCOCl; iii: $NaBH_4$ in THF). The *cis* relationship of the angular methyl and the appendage at C-3 in **51** was assigned through the analysis of the ^{1}H and ^{13}C NMR resonances, including 1D and 2D experiments, phase sensitive DFQ COSY, DFQ NOESY, and ^{1}H−^{13}C direct and long range correlations (HMQC and HMBC). The depicted absolute configuration in **50** rests on the heuristic rule we have proposed (*vide infra*, Figure 3) (Chart 10).

Methyl Propiolate as Alkynyl Acceptor. The Michael-type condensation of chiral imines with electrophilic alkynes would be also of peculiar value, since it potentially provides the direct access of highly functionalized adducts, such as **42**. Thus addition of imine **9** to methyl propiolate **52** (heated 14 h to reflux in THF, and then 20% aqueous AcOH, 2 h at 20 °C) gave with a 70% yield adducts (*S*)-(*E*)-**42** and (*S*)-(*Z*)-**53**, in the respective ratio of 13:1, accompanied by ca. 4% of regioisomers, resulting from the alkylation at the less substituted α-side of imine **9**. However an important decrease in the enantioselectivity was observed with this acceptor, compared to previous electrophilic alkenes; thus, the enantiomeric purity of known keto ester *ent*-**34**, obtained by catalytical hydrogenation of the present adduct (*S*)-(*E*)-**42** (1 atm of H_2, Pd−C), was only 43% (Chart 11).

Discussion

We have proposed that the addition of chiral imines to electrophilic alkenes proceeds through a compact complex, that involves as nucleophilic partners the secondary enamines, in tautomeric equilibrium with the starting imines.[2] This view was recently reinforced by

(10) Barta, N. S.; Brode, A.; Stille, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6201−6206.

(11) For the Michael-type reaction of 2-methyl(benzylimino)cyclohexane with maleic anhydride, see: Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143−1147.

Chart 11

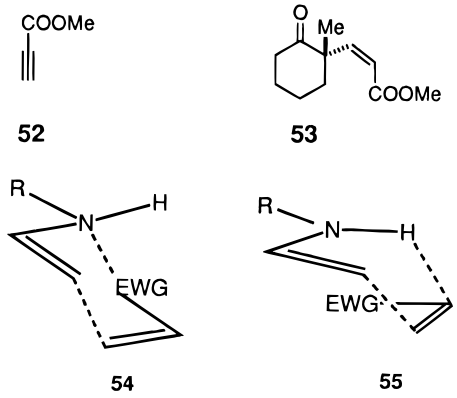
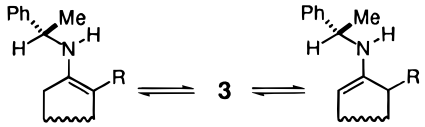


Figure 2.

Scheme 3



the observation that, in conversion **6** → **8** (*vide supra*), the deuterium atom in the α-position to the imine group of **6** was transferred to the α-vinylic center of the electrophilic alkene *concertedly with the creation of the C−C bond*.[3] The [3 + 3]-type structure **54**, stabilized by bonding orbital interaction between the N-atom of the enamine and the electron-withdrawing group of the electrophile, has been proposed as reactive complex.[12] Although supported by theoretical calculations, this interpretation, however, offers no satisfactory explanation for the above-mentioned crucial, concerted proton transfer. In this respect, the alternative [4 + 2]-type "aza-ene-synthesis-like" complex **55**, which implicates the hydrogen atom at the enamine nitrogen center, appears to be a more realistic model (Figure 2).

In general the addition of chiral imines derived from 2-substituted cyclanones to electrophilic alkenes 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 **56** and **57**, portrayed in their energetically preferred conformations, minimizing the main steric interactions.[2] In *the more* substituted enamine **56,** the N−H bond is *syn* to the enamine double bond and consequently the internal, concerted proton transfer is allowed. In contrast, in the case of *the less* substituted regioisomer **57**, the crucial, concerted proton transfer is prevented for obvious geometrical reasons. It should be also noted that, incidentally, the more reactive enamine **56** appears to be also the energetically preferred one, since it is stabilized by the additional hyperconjugative interaction of the R group (Scheme 3).

With the exception of methyl propiolate **52**, all electrophilic partners mentioned in this work led to a high control of the absolute configuration of the Michael adducts. To help rationalize this remarkable *enantioselectivity*, the two diastereotopic approaches involving a

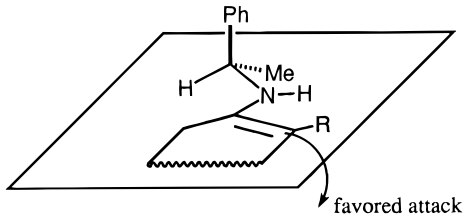
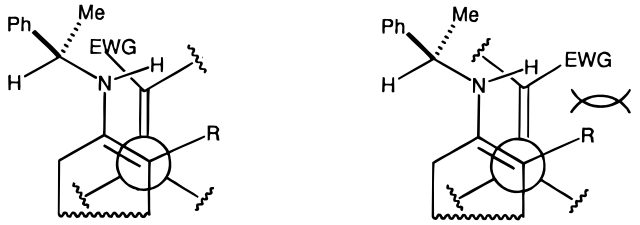


Figure 3.



58: "*endo*-approach" **59:** "*exo*-approach"

Figure 4.

chiral enamino ester and methyl acrylate have been theoretically simulated by using the MOPAC program.[2] An excellent agreement was obtained between these calculations and the experimental findings. In this regard, a practical, general rule has been developed, enabling the prediction of the predominant facial selectivity. According to this rule, the alkylation process takes place preferentially on the less hindered π-face of the enamine (*anti* to the bulky phenyl group), depicted in its energetically preferred conformation (Figure 3).

An excellent *diastereocontrol* was always obtained by using the present α- and β-substituted alkenes as Michael acceptors. In this respect, the "*endo*-approach" **58**, in which the electron-withdrawing-group of the acceptor faced the nitrogen atom of the enamine partner (case of acceptors **10**, methyl methacrylate, **24**, **28**, **43**, **47**, and **49**) largely prevails over the "*exo*-approach" **59** (case of acceptor **38**)**.** This "*endo*-preference" has been tentatively rationalized, invoking that the *endo*-approach is stabilized by attractive orbital interaction between the nitrogen center of the enamine and the electron-withdrawing-group of the Michael acceptor.[12,13] *However, this interpretation ignored all steric interactions which are necessarily engendered in such compact approaches.* Thus, it is manifest that a destabilizing steric interaction between the R substituent of the enamine and the electron-withdrawing-group of the acceptor is specifically developed in the *exo*-approach **59**, a factor which should be imperatively taken into account in the present investigation (Figure 4).

On this basis, the predominant *endo*-preference reported here can be reasonably interpreted in terms of a cooperative effet between steric and stereoelectronic factors; the *endo*-approach is, however, disfavored when the electrophilic alkene is substituted in the α-position by a bulky group (case of acceptor **38**). Finally it should be pointed out that the largely predominant formation of (*E*)-adduct **42** [13:1 over the (*Z*)-isomer **53**], observed in the addition of imine **9** to methyl propiolate **52**, provides an additional support to the above-mentioned internal, concerted proton transfer.

(12) Jabin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795−1812.

(13) Sevin, A.; Tortajada, J.; Pfau, M. *J. Org. Chem.* **1986**, *51*, 2671−2675.

Concluding Remarks

The Michael-type addition of chiral imines, derived from racemic α-substituted cyclanones and optically active 1-phenylethylamine, to electrophilic alkenes in neutral conditions constitutes one of the most efficient methods for the stereocontrolled construction of quaternary carbon centers. Through this work we have shown that an additional stereogenic center could be created at the α- or *β*-position to the quaternary one, by using a variety of α- and *β*-substituted alkenyl acceptors. The regioselectivity of such addition reactions is generally excellent; however, in some cases (acceptors **28** and **49**), significant amounts (10−15%) of regioisomeric adducts, resulting from the alkylation at the less substituted α-side of starting imines, were observed. Very high levels of enantio- and diastereoselectivity were always obtained. These stereochemical outcomes can be interpreted by invoking that the reaction involves an "aza-ene-synthesis-like" cyclic transition state, the geometry of which is controlled by steric and stereoelectronic factors. Application of the present powerful methodology to the asymmetric synthesis of various targets is currently under investigation in our laboratory.

Experimental Section

General Methods. Melting points were recorded on a Kofler bench. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^{1}H 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. Mass spectra were recorded by electron impact at 70 eV. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230−400 mesh ASTM). Diethyl 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 (±)-**16** were measured using graphite-monochromated Cu Kα radiation, and the ($\theta-2\theta$) scan technique up to given $\theta = 60°$. The structure was solved by direct methods using SHELXS86[14] and refined by full matrix least-squares with SHELX76,[15] minimizing the function $\sum w(F_o - |F_c|)^2$. The hydrogen atoms, located in difference Fourier maps, were introduced in theoretical position (d(C−H) = 1.00 Å) 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 (with $R_w = \{Sw(F_o - |F_c|)^2 / \sum wF_o^2\}^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.001F_o^2]$).[16]

Attempted Addition of Imine 9 to Methyl Methacrylate.[12] A mixture of distilled imine **9**[2] (3 g, 14 mmol), freshly distilled methyl methacrylate (2.1 g, 21 mmol), and hydroquinone (10 mg) was heated at 85 °C under nitrogen for 7 days. The yellow, sticky jelly obtained was taken up in methanol (8 mL). A 10% aqueous acetic acid solution (10 mL) was added, and the mixture was stirred for 2 h at 20 °C. Insoluble white polymeric material (650 mg), identified as poly(methyl methacrylate) by ^{1}H NMR, was removed by filtration. The filtrate was concentrated, and the residue was taken up in diethyl ether, washed with 1 N hydrochloric acid and brine, and dried. Careful chromatography of the crude over silica gel (hexane: ethyl acetate 4:1) afforded adduct **13**[12] (30 mg, 1%) and acetophenone (90 mg, 5%, a compound which probably originates from the hydrolysis of the imine formed by 1,3-prototropic rearrangement of starting imine **9**). No definite compound was isolated when the above experiment was repeated, by using prolonged reaction times (24 days at 85 °C).[12]

Attempted Addition of Imine 9 to Methyl Crotonate.[12] A mixture of distilled imine **9** (1.07 g, 5 mmol), freshly distilled methyl crotonate (0.75 g, 7.5 mmol), and hydroquinone (5 mg) was heated at 120 °C under nitrogen for 6 days. A dark brown gum was obtained. Workup conditions were as described for the addition of imine **9** to methyl methacrylate. Chromatography over silica gel furnished ca. 50 mg of a complex mixture of compounds (by TLC and ^{1}H NMR).

[*R*-(*R,*R**)]-α-Methyl-1-(methoxycarbonyl)-2-oxocyclohexanepropanoic Acid Methyl Ester (15).** A solution of enamino ester **14**[6] (4 g, 15.44 mmol) in diethyl ether (20 mL) and methyl methacrylate (0.5 mL, 4.7 mmol) were added to a solution of $MgBr_2$ (16.46 mmol) in diethyl ether (60 mL). The mixture was stirred at 20 °C for 7 days. During this period, portions of methyl methacrylate (0.5 mL, 4.7 mmol) were added to this mixture each 12 h. A 10% aqueous acetic acid (20 mL) was then added, and the resulting mixture was stirred for 24 h. The solvents were removed under reduced pressure, and 1 N HCl (5 mL) was added to the residual oil. The mixture was extracted with ether (3 × 25 mL), and the collected organic phases were washed with brine, dried, and concentrated in vacuum. Chromatography over silica gel (hexane:ethyl acetate 4:1) afforded pure keto ester **15** as a colorless oil (2.85 g, 72%). IR (neat, cm^{-1}) 1740, 1715; $[\alpha]^{20}_D$ +56 (*c* 1.7, CCl_4); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 3.70 (s, 3H), 3.60 (s, 3H), 2.50−1.30 (m, 11H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 207.2 (C), 176.7 (C), 172.5 (C), 59.9 (C), 52.3 (CH_3), 51.5 (CH_3), 40.7 (CH_2), 37.8 (CH_2), 35.5 (CH_2), 35.2 (CH), 27.1 (CH_2), 22.2 (CH_2), 19.9 (CH_3). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.71; H, 7.94.

(3*R-trans*)-3-Methyl-4a-(methoxycarbonyl)-3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (16). A stream of ammonia was bubbled through an ice-cooled solution of keto ester **15** (100 mg, 0.39 mmol), in anhydrous methanol (30 mL). After standing 12 h at 20 °C, ammonia was again bubbled through the mixture. This operation was repeated each 12 h, until no more starting material was detected by TLC. After 2 days, the solution was evaporated, and the residue was dissolved in benzene (40 mL), *p*-toluenesulfonic acid (10 mg, 0.06 mmol) was added, and the mixture was refluxed 3 h with azeotropic removal of water. The solution was cooled to 20 °C and concentrated. Chromatography over silica gel (ethyl acetate: hexane 4:1) afforded lactam **16** (62 mg, 72%) as a a solid: mp 149−151 °C (diethyl ether); IR ($CHCl_3$, cm^{-1}) 1730, 1662; $[\alpha]^{20}_D$ +21.4 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 8.00 (broad s, 1H), 5.03 (t, *J* = 3.5 Hz, 1H), 3.65 (s, 3H), 2.34−2.24 (m, 3H), 2.18−1.93 (m, 2H), 1.77−1.63 (m, 1H), 1.50−1.27 (m, 3H), 1.15 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 175.0 (C), 172.9 (C), 133.8 (C), 106.3 (CH), 52.5 (CH_3), 45.9 (C), 39.1 (CH_2), 33.9 (CH), 33.7 (CH_2), 23.2 (CH_2), 19.0 (CH_2), 16.1 (CH_3).

α-Methyl-1-(methoxycarbonyl)-2-oxocyclohexanepropanoic Acid Methyl Ester (18). To a mixture of 1-(methoxycarbonyl)-2-oxocyclohexane (**17**) (4 g, 25.64 mmol) and Triton B (1.04 g, 2.5 mmol) in THF (40 mL) was added methyl methacrylate (5 mL, 4.68 mmol) at 0 °C. The mixture was refluxed for 12 h. After cooling, the solvent was removed under reduced pressure and diethyl ether (15 mL) was added. The organic phase was washed with brine, dried, and concentrated. Distillation of the residue afforded **18** as an equimolar mixture of racemic diastereomers (4.54 g, 69%): bp 130−140 °C (0.03 Torr); IR ($CHCl_3$, cm^{-1}) 1740, 1715; ^{1}H NMR (200 MHz, $CDCl_3$)

(14) Scheldrick, G. SHELSX86. Program for crystal structure determination: University of Göttingen: Germany, 1985.

(15) Scheldrick, G. SHELSX76. Program for crystal structure determination: University of Cambridge: United Kingdom, 1976.

(16) The authors have deposited atomic coordinates for (±)-**16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

δ 3.6 (s, 3H), 3.5 (s, 3H), 2.5−1.2 (m, 11H), 1.10 (2 d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.6 (C), 207.4 (C), 177.1 (C), 176.9 (C), 172.2 (C), 172.0 (C), 60.4 (C), 60.0 (C), 52.5 (CH_3), 52.4 (CH_3), 51.7 (CH_3), 51.6 (CH_3), 41.1 (CH_2), 41.0 (CH_2) 38.3 (CH_2), 38.0 (CH_2), 36.6 (CH_2), 35.8 (CH_2), 35.7 (CH), 35.4 (CH), 27.8 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 20.1 (CH_3), 19.8 (CH_3). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.89; H, 7.93.

(*trans*)-3-Methyl-4a-(methoxycarbonyl)-3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (16) and (*cis*)-3-Methyl-4a-(methoxycarbonyl)-3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (19). The procedure, starting from keto ester **18** (1.0 g, 3.9 mmol), was as described for the addition of ammonia to keto ester **15**. Chromatography over silica gel (ethyl acetate:hexane 4:1), followed by recrystallization in diethyl ether, afforded (±)-lactam **16** (300 mg, 34%) and (±)-lactam **19** (320 mg, 37%). **(**±**)-16**: mp 170−172 °C. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 60.92; H, 7.86. Found: C, 60.89; H, 7.93; the IR, ^{1}H and ^{13}C NMR specta were identical with those of (+)-**16**. Slow evaporation of a solution of **(**±**)-16** in diethyl ether gave small monocrystals, suitable for an X-ray crystallographic analysis: $C_{12}H_{17}NO_3$, M_w = 223.28, crystal of 0.07 × 0.08 × 0.23 mm, triclinic, space group *P*-1, Z = 2, a = 7.824(8), b = 8.644(12), c = 12.093(13) Å, α = 75.13(4), β = 117.49(4), γ = 125.73(4)°, V = 589(1) Å^3, d_{calc} = 1.26 g cm^{-3}, F(000) = 240, λ (Cu Kα) = 1.5418 Å, μ = 0.70 mm^{-1} . Of the 2118 collected reflexions ($-8 \le h \le 8$, $-13 \le k \le 12$, $-9 \le k \le 16$), 1726 were unique (R_{int} = 0021) and 847 were considered as observed having $I \ge 2\sigma(I)$. Cell parameters were refined from 23 well-centered reflexions with 7.5 ≤ 32.8°. Convergence was reached at R = 0.0054 and R_W = 061. The residual electron density in the final difference map was located between −0.23 and 0.20 eÅ^3. In the crystal two molecules of **16** form a centrosymmetric dimer linked by two hydrogen bonds: N1···O11′···N1′ (N1···O11′: 2.894(5) Å, H1···O11′: 2.41 Å, N1−H···O11: 163°, symmetry: $-x$,1 − y,$-z$). The eight atoms N1, C2, C3, C5, C7, C8, C9, C10 are approximately planar (maximum deviations: −0.14, 0.11 Å), C4 and C6 are, respectively, at −0.69 and −0.55 Å of this plane (Figure 1). **(**±**)-19**; mp 150−155 °C; IR ($CHCl_3$, cm^{-1}) 1729, 1657; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (broad s, 1H), 5.08 (t, J = 3.7 Hz, 1H), 3.71 (s, 3H), 2.64 (ddq, J = 1.8, 7.1, 7.8 Hz, 1H), 2.30 (m, 2H), 2.23 (dd, J =1.8, 14.0 Hz, 1H), 2.15−2.10 (m, 1H), 1.91 (dd, J = 7.1, 14.0 Hz, 1H), 1.74−1.71 (m, 1H), 1.50−1.22 (m, 3H), 1.15 (d, J = 7.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.4 (C), 172.9 (C), 133.7 (C), 107.4 (CH), 52.5 (CH_3), 44.0 (C), 37.7 (CH_2), 35.2 (CH_2), 34.2 (CH), 23.5 (CH_2), 19.2 (CH_2), 18.0 (CH_3).

(*R*)-(6-Carbomethoxy-1,4-dioxaspiro[4.5]decan-6-yl)-propanoic Acid Methyl Ester (21). To a solution of TMSOTf (22 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) were successively added 1,2-bis(trimethylsilyloxy)ethane (2 mL, 5.4 mmol) and ketone **20** (1.3 g, 5.4 mmol) at −78 °C. The mixture was stirred for 3 h at −78 °C, quenched by addition of dry pyridine (0.2 mL), poured into a saturated $NaHCO_3$ aqueous solution (15 mL), and extracted with diethyl ether (3 × 15 mL). The organic layers were dried and concentrated. Chromatography over silica gel (cyclohexane:ethyl acetate 2:1) afforded pure ketal **21** as a oil (1.45 g, 94%); IR (neat, cm^{-1}) 1737; [α]$^{20}_D$ +9.3 (*c* 3.0, CCl_4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (m, 4H), 3.57 (s, 3H), 3.53 (s, 3H), 2.30−1.20 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9 (C), 173.7 (C), 110.6 (C), 64.7 (CH_2), 64.4 (CH_2), 53.9 (C), 51.7 (CH_3), 51.5 (CH_3), 31.9 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 20.8 (CH_2). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.72; H, 7.74. Found: C, 58.61; H, 7.81.

[*S*-(*R,*S**)]-(6-Carbomethoxy-1,4-dioxaspiro[4.5]decan-6-yl)-α-methylpropanoic acid methyl ester (22) and [*R*-(*R**,*R**)]-(6-Carbomethoxy-1,4-dioxaspiro[4.5]decan-6-yl)-α-methylpropanoic acid methyl ester (23).** Ketal **21** (200 mg, 0.7 mmol) was added to a solution of lithium diisopropylamide (107 mg, 1 mmol) in THF (2 mL) at −78 °C. The mixture was stirred at −78 °C for 2 h. Methyl iodide (0.07 mL, 1.12 mmol) was added and the mixture was stirred for 3 h at −78 °C. The solvent was removed under reduced pressure, and water was added (2 mL). The mixture was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuum. The crude mixture (180 mg, 86%) was analyzed by GC on a BP column of 5.5 m × 0.22 mm, at 180 °C; retention times: **22**: 4620 s (81.7%), **23**: 4674 s (18.3%). Chromatography over silica gel (cyclohexane:ethyl acetate 2:1) afforded pure ketals **22** and **23** as colorless oils. **22**; IR (neat, cm^{-1}) 1737; [α]$^{20}_D$ +27.7 (*c* 1.4, CCl_4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (m, 4H), 3.70 (s, 3H), 3.66 (s, 3H), 2.40−1.20 (m, 11H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.5 (C), 174.8 (C), 111.1 (C), 65.1 (CH_2), 64.9 (CH_2), 54.7 (C), 52.0 (CH_3), 51.9 (CH_3), 36.7 (CH), 34.7 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 23.2 (CH_2), 20.7 (CH_2), 19.6 (CH_3). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.01; H, 8.11. **23**; IR (neat, cm^{-1}) 1737; [α]$^{20}_D$ −1.0 (*c* 5.8, CCl_4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.90 (m, 4H), 3.66 (s, 3H), 3.63 (s, 3H), 2.60−1.30 (m, 11H), 1.15 (d, J = 6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.0 (C), 174.5 (C), 110.7 (C), 64.8 (CH_2), 64.3 (CH_2), 53.8 (C), 51.6 (CH_3), 51.5 (CH_3), 35.6 (CH), 35.5 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 23.0 (CH_2), 21.1 (CH_2), 19.8 (CH_3). Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.79; H, 7.98.

[*R*-(*R,*R**)]-3-[(2-Oxo-1-methylcyclohexyl)methyl]-2(5*H*)-3,4-dihydrofuranone (25)**. α-Methylene-γ-butyrolactone **24** (325 mg, 3.3 mmol) and hydroquinone (10 mg) were added to a solution of imine *ent*-**9** (2.15 g, 10 mmol) in THF (3 mL) at 20 °C, and the mixture was heated at 40 °C for 72 h. During this period, two other portions of **24** (125 mg, 1.3 mmol) were added each 24 h. The mixture was cooled to 20 °C and diluted with THF (20 mL). A 20% aqueous acetic acid solution was then added (10 mL), and the resulting mixture was stirred for 3 h. The solvents were removed under reduced pressure, and 1 N HCl (5 mL) was added to the residual oil. The mixture was extracted with diethyl ether (5 × 25 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuum. Chromatography over silica gel (hexane:ethyl acetate 2:1), followed by distillation, afforded pure ketolactone **25** (433 mg, 54%): bp 120−130 °C (0.05 Torr); [α]$^{20}_D$ +31.0 (*c* 7.6, EtOH); IR (neat, cm^{-1}) ν: 1771, 1706; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (ddd, J = 1.7, 8.8, 9.0 Hz, 1H), 4.09 (ddd, J = 6.2, 9.0, 10.9 Hz, 1H), 2.50−2.44 (m, 3H), 2.40−2.34 (m, 1H), 2.25 (dddd, J = 1.7, 8.7, 11.5, 14.4 Hz, 1H), 1.98 (m, 1H), 1.90−1.60 (m, 6H), 1.48 (dd, J = 8.7, 14.4 Hz, 1H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δSPCLN 214.4 (C), 179.1 (C), 65.9 (CH_2), 47.9 (C), 39.1 (CH_2), 38.3 (2 CH_2), 35.8 (CH), 31.1 (CH_2), 26.8 (CH_2), 23.0 (CH_3), 20.5 (CH_2); MS, *m*/*z*: 210 (M$^{\bullet+}$, 10), 166 (15), 125 (35), 112 (55), 99 (30), 97 (30), 86 (100). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.53.

(3*R*-*trans*)-3,4,4a,5,6,7-Hexahydro-4a-methyl-3-(hydroxyethyl)-2(1*H*)-quinolinone (27). The procedure, starting from lactone **25** (150 mg, 0.71 mmol), was as described for the addition of ammonia to keto ester **15**. Chromatography over silica gel (ethyl acetate) afforded lactam **27** (110 mg, 80%), as a colorless oil. Because this product readily decomposed in $CDCl_3$, NMR spectra were recorded in C_6D_6. IR (neat, cm^{-1}) 3400, 1679, 1652; ^{1}H NMR (400 MHz, C_6D_6) δ 9.75 (s, 1H), 5.0 (t, J = 3.5 Hz, 1H), 4.69 (broad s, 1H), 3.85 (m, 1H), 3.71 (dt, J = 3.7, 10.1 Hz, 1H), 2.54 (m, 1H), 2.12 (m, 1H), 1.85 (m, 2H), 1.48−1.35 (m, 3H), 1.30 (dt, J = 13.0, 3.3 Hz, 1H), 1.22 (dd, J = 6.1, 13.0 Hz, 1H), 1.10 (dd, J = 3.3, 13.4 Hz, 1H), 1.03 (d, J = 13.4 Hz, 1H), 0.86 (s, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 173.9 (C), 139.5 (C), 103.9 (CH), 61.3 (CH_2), 41.8 (CH_2), 37.3 (CH), 36.7 (CH_2), 35.2 (CH_2), 31.5 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 18.1 (CH_2).

[*S*-(*R,*S**)]-α-(Acetyloxy)-1-methyl-2-oxocyclohexanepropanoic acid methyl ester (29).** A mixture of imine **9** (4.0 g, 18.6 mmol), freshly distilled 2-acetoxyacrylate **28** (2.94 g, 20.4 mmol), and hydroquinone (10 mg) was stirred at 20 °C for 90 min. THF (20 mL) and a 20% aqueous acetic acid solution (10 mL) were added. The mixture was stirred for 2 h at 20 °C. The solvent was removed under reduced pressure, and 1 N HCl (5 mL) was added to the residual oil. The mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuum. Chromatography over silica gel (cyclohexane:ethyl acetate 9:1), followed by distillation, afforded pure keto ester **29** (2.55 g, 53%); bp 100−110 °C (0.02 Torr); [α]$^{20}_D$ = −11.0 (*c* 7.5, EtOH); IR (neat, cm^{-1}) 1748, 1708; ^{1}H NMR (200 MHz,

$CDCl_3$) δ 4.97 (dd, J = 3.2, 9.0, Hz, 1H), 3.69 (s, 3H), 2.50−2.30 (m, 2H), 2.20 (dd, J = 3.2, 15.0 Hz, 1H), 2.07 (s, 3H), 1.92 (dd, J = 9.0, 15.0, Hz, 1H), 1.90−1.60 (m, 6H), 1,13 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 213.9 (C), 170.7 (C), 169.9 (C), 69.6 (CH), 52.2 (CH_3), 47.4 (C), 39.1 (CH_2), 38.2 (CH_2), 37.9 (CH_2), 27.0 (CH_2), 22.2 (CH_3), 20.7 (CH_2), 20.4 (CH_3); MS, m/z: 256 ($M^{\bullet+}$, 0.5), 214 (8), 183 (7), 164 (3), 155 (14), 137 (12), 125 (17), 112 (100).

[3*R*-(3*β*, 4a*α*, 8a*α*)]-3,8a-Dihydroxy-4a-methyl-octahydro-2(1*H*)-quinolinone (31). A stream of ammonia was bubbled through an ice-cooled solution of keto ester **29** (1 g, 3.9 mmol), in anhydrous methanol (30 mL). After standing 12 h at 20 °C, ammonia was again bubbled through the mixture. The process was repeated each 12 h, until no more starting material was detected by TLC. After 3 days the solvent was evaporated. Crude lactam-alcohol was chromatographed over silica gel (ethyl acetate:methanol 9:1) to give **31** (0.57 g, 73%) as an amorphous solid: IR (neat, cm^{-1}) 3400, 1660; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (broad s, 1H), 6.10 (broad s, 1H), 4.40 (t, J = 8.6 Hz, 1H), 4.1 (s, 1H), 2.15−1.90 (m, 3H), 1.70−1.25 (m, 7H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 178.6 (C), 106.7 (C), 75.5 (CH), 44.4 (C), 42.7 (CH_2), 35.3 (CH_2), 32.4 (CH_2), 23.0 (CH_3), 21.3 (CH_2), 18.7 (CH_2); MS, m/z: 199 ($M^{\bullet+}$, 2), 181 (4), 155 (100), 137 (25), 125 (14), 112 (16), 111 (16), 95 (18), 75 (55). Anal. Calcd for $C_{12}H_{18}O_3$: C, 60.30; H, 8.54; N, 7.03. Found: C, 60.09; H, 8.69; N, 6.94.

(3*R*-*trans*)-3-Hydroxy-3,4,4a,5,6,7-hexahydro-4a-methyl-2(1*H*)-quinolinone (32). A solution of quinolinone **31** (0.25 g, 1.25 mmol) and *p*-toluenesulfonic acid (10 mg, 0.06 mmol) in anhydrous benzene (20 mL) was refluxed 4 h with azeotropic removal of water. The solution was cooled to 20 °C, and concentrated in vacuum. Chromatography over silica gel (ethyl acetate) afforded lactam **27** (110 mg, 48%) as an amorphous solid: IR (neat, cm^{-1}) 3400, 1679, 1652; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (broad s, 1H), 4.80 (t, J = 3.7 Hz, 1H), 4.35 (dd, J = 6.3, 12.1 Hz, 1H), 3.40 (s, 1H), 2.20−2.00 (m, 2H), 1.80−1.20 (m, 6H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 172.3 (C), 138.7 (C), 105.2 (CH), 65.3 (CH), 41.8 (C), 36.7 (CH_2), 32.4 (CH_2), 23.7 (CH_3), 23.2 (CH_2), 17.2 (CH_2); MS, m/z: 181 ($M^{\bullet+}$, 1), 155 (100), 137 (25), 125 (20), 112 (22), 111 (22), 95 (20), 75 (52).

[*S*-(*E*)]-1-Methyl-2-oxocyclohexane-2-propenoic Acid Methyl Ester (42) (from imine 9 and methyl propiolate 52). Methyl propiolate **52** (0.45 g, 5.4 mmol) was added to a solution of imine **9** (1 g, 4.65 mmol) in THF (5 mL), at 20 °C. The mixture was refluxed for 14 h. The solution was cooled to 20 °C and diluted with THF (20 mL). A 10% aqueous acetic acid solution was added (10 mL), and the resulting mixture was stirred for 3 h. The solvents were removed under reduced pressure, and 1 N HCl (5 mL) was added to the residual oil. The mixture was extracted with diethyl ether (3 × 25 mL), and the combined organic layers were washed with brine, dried, and concentrated in vacuum. Chromatography over silica gel (hexane:ethyl acetate 4:1) followed by distillation, afforded ketone **42** as a colorless oil (635 mg, 69%): bp 105−110 °C (0.02 Torr); $[\alpha]^{20}_D$ −61.9 (*c* 20.1, MeOH); IR (neat, cm^{-1}) 1712, 1649; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.12 (d, J = 16.1 Hz, 1H), 5.75 (d, J = 16.1 Hz, 1H), 3.72 (s, 3H), 2.40−2.30 (m, 2H), 2.10−1.50 (m, 6 H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 211.2 (C), 166.6 (C), 151.8 (CH), 120.7 (CH), 51.6 (CH), 51.40 (C), 39.5 (CH_2), 39.3 (CH_2), 27.3 (CH), 23.2 (CH_2), 21.6 (CH_3). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.11; H, 8.01. Compound (*E*)-**42** was accompanied by *ca* 7% of not fully characterized (*Z*)-isomer **53** [^{1}H NMR: δ 6.27 (d, J = 11.0 Hz, 1H), 5.89 (d, J = 11.0 Hz, 1H)] which was separated by flash chromatography.

[3*R*-(1*S),3α,3aα]-1-(1-Phenylethyl)-2-oxo-3a-methyl-2,3,3a,4,5,6-hexahydroindole Acetic Acid (50).** To a solution of *ent*-**9** (500 mg, 2.32 mmol) in THF (5 mL) was added at 0 °C a solution of maleic anhydride **49** (0.25 g, 2.52 mmol) in THF (1 mL). The mixture was kept 1 h at 0 °C. The solvent was removed under vacuum, and the residue was chromatographed over silica gel (ethyl acetate: hexane 1:1.5), giving **50** (472 mg, 65%): mp 163−165 °C (EtOH); $[\alpha]^{20}_D$ +16.4 (*c* 5.3, MeOH); IR (neat, cm^{-1}) 3427, 1737, 1715; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.5 (broad s, 1H), 7.32−7.20 (m, 5H), 5.56 (q, J = 7.0 Hz, 1H), 4.59 (t, J = 3.6 Hz, 1H), 2.88−2.81 (m, 2H), 2.48−2.40 (m, 1H), 2.10−1.50 (m, 9 H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 176.1 (C), 175.4 (C), 141.8 (C), 140.1 (C), 128.5 (2 CH), 127.2 (CH), 126.4 (2 CH), 103.1 (CH), 50.2 (CH), 49.1 (CH), 40.6 (C), 33.4 (CH_2), 30.4 (CH_2), 23.1 (CH_2), 20.2 (CH_3), 17.8 (CH_2), 15.2 (CH_3). Anal. Calcd for $C_{19}H_{23}NO_3 \cdot 1H_2O$: C, 70.81; H, 7.45; N, 4.35. Found: C, 70.62; H, 7.49; N, 4.35.

[3*R*-(1*S), 3α,3aα]-1-(1-Phenylethyl)-2-oxo-3-(2-hydroxyethyl)-3a-methyl-2,3,3a,4,5,6-hexahydroindole (51).** An aqueous solution of 1 N NaOH (1 mL, 1 mmol) was added to lactam-acid **50** (100 mg, 0.32 mmol). The mixture was kept 30 min at 20 °C, and the water was removed under vacuum (50 °C, 0.1 Torr). The anhydrous sodium salt obtained was suspended in THF (2 mL), and a solution of oxalyl chloride (0.165 mg, 1.3 mmol) in THF (1 mL) was added dropwise over a period of 30 min at 20 °C. The mixture was concentrated in vacuum, and the residue was taken up in THF (1 mL). Sodium borohydride (0.039 g, 1.13 mmol) was added at once to the suspension at 10 °C, and the mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with water (3 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried, and the solvent was removed under reduced pressure. The residue was chromatographed over silica gel (ethyl acetate: hexane 1:1), affording lactam-alcohol **51** (84 mg, 88%): amorphous solid; $[\alpha]^{20}_D$ +10.2 (*c* 5.75, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36−7.20 (m, 5H), 5.58 (q, J = 7.2 Hz, 1H), 4.70 (br d, 1H, exchangeable with D_2O), 4.55 (t, J = 4.5 Hz, 1H), 3.90 (m, 1H), 3.69 (ddd, J = 3.0, 10.4, 11.0 Hz, 1H), 2.39 (dd, J = 3.3, 10.4 Hz, 1H), 2.1−1.66 (m, 7H), 1.63 (d, J = 7.2 Hz, 3H), 1.48 (m, 1 H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 177.1 (C), 142.5 (C), 140.4 (C), 128.5 (2 CH), 127.1 (CH), 126.3 (2 CH), 102.0 (CH), 62.6 (CH_2), 55.0 (CH), 48.7 (CH), 40.7 (C), 33.3 (CH_2), 27.6 (CH_2), 23.2 (CH_2), 20.4 (CH_3), 17.8 (CH_2), 15.2 (CH_3).

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Supporting Information Available: Copies of ^{1}H NMR spectra (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current mastehead page for ordering information.

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