Diastereoselectivity in the Michael-Type Addition of Imines Reacting as Their Secondary Enamine Tautomers

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Michael-type reactions of 2-methyl(benzylimino)cyclohexane (reacting as its secondary enamine tautomer **1**) were performed with methyl methacrylate (**2**), methyl crotonate (**5**), and maleic anhydride (**7**). In each case, the stereochemical relationship of the substituents in the major cyclized adducts **4**, **6**, and **8** obtained with excellent diastereoselectivities was shown to be the one predicted in a previous theoretical calculation which established that the complex of the reactants has a chairlike geometry. The predicted concomitant H-transfer and C–C bond formation in these reactions was also confirmed in the methyl methacrylate case. Besides, these experiments have shown that regioisomers are formed in appreciable amounts when substituted electrophilic olefins are used.

The α-alkylation of carbonyl compounds, using imine derivatives reacting as their secondary enamine tautomers, with electrophilic olefins, has been described[1] (Scheme 1).

The imine method gives essentially additions at the more substituted α-carbon atom,[2,3] contrary to Stork's method which uses tertiary enamines.[4] More recently, this characteristic has been exploited to synthesize compounds bearing an asymmetric quaternary carbon atom center. A general method of deracemizing alkylation has been proposed[3] using imines arising from a chiral nonracemic amine and 2-substituted cyclanones giving, after hydrolysis, functionalized 2,2-disubstituted cyclanones in excellent yield and with high enantioselectivity.

In a previous theoretical *ab initio* SCF-CI MO calculation study[5] of the Michael reaction with secondary enamines (Scheme 1), a model was proposed using vinylamine and propenal: the reactive complex has a compact structure (*syn* approach),[6] stabilized by secondary orbital interaction between the *N*-atom and the *C*-atom of the carbonyl group.[8] Within the *syn* approaches, the energies of the chair complexes were shown to lie at about 4 kcal/mol under the ones of the boat complexes, the chair complex with a *s-cis* conformation for the carbonyl group (*pseudo*-axial) having the lowest energy[11] (Figure 1). It must be also recalled and emphasized that "these complexes cannot change their overall topology once they are formed: they can evolve toward a unique product or dissociate, since complexation is endothermic".[7]

The present work has been undertaken to test experimentally the validity of the model, *i.e.*, to confirm that the reaction proceeds essentially through a compact complex having a chair conformation. If at least two asymmetric carbon atoms are created in the adduct, by introducing substituents at the 2-position of the aminoethylene moiety and on the electrophile, the diastereoisomeric relationship of these substituents will validate (or invalidate) the proposed model of a chair complex approach. This kind of experiment was suggested and its stereochemical implications are predicted in the last paragraph and in the conclusion of ref 5.[12] Moreover, given the fact that *ca.* 4 kcal/mol of energy (*vide supra*) separates the energy of the chair complexes from the ones of the boat complexes (which would give the opposite

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(2) Reference 1d. Hickmott, P. W. *Tetrahedron* **1982**, *38*, 3363–3446 (see p 3411). Hickmott, P. W.; Rae, B. *Tetrahedron Lett.* **1985**, *26*, 2577–2580. Hickmott, P. W.; Jutle, K. K.; Pienar, D. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2399–2402.

(3) (a) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273–274. Reviews: (b) Oare, D. A.; Heathcock, C. H. *Topics Stereochem.* **1991**, *20*, 87–170 (see pp 114–115). (c) Revial, G.; Pfau, M. *Org. Synth.* **1991**, *70*, 35–46. (d) d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymm.* **1992**, *3*, 459–505.

(4) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

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

(6) Although the complex having a loose structure (*anti* approach) has a slightly lower energy (7.81 kcal/mol), it leads reversibly to a high-energy zwitterionic species. In the case of a compact complex, early H-transfer from NH to the developing zwitterion can take place, thus avoiding the formation of a high-energy species.[5,7]

(7) Sevin, A.; Masure, D.; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552–573.

(8) Two other kinds of approaches have been proposed for the reaction, without argumentation: an "aza ene synthesis-like cyclic activated complex" (with the carbonyl group not included in the cycle)[9] and a "Diels–Alder-like transition state" (with the oxygen atom of the carbonyl group included in the cycle).[10]

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

(10) Matsuyama, H.; Ebisawa, Y.; Kobayashi, M.; Kamigata, N. *Heterocycles* **1989**, *29*, 449–452.

(11) In a later theoretical study dealing with substituted vinylamines,[7] the chair complex with the carbonyl group in the *s-trans* conformation (pseudoequatorial) was shown to be the more stable, the carbonyl group thus lying in the less hindered region of the system.

(12) Using this concept, a study has been already accomplished[9] with two examples dealing with (*R*)-2-methyl-α-methyl(benzylimino)cyclohexane. In the first one, crotonyl cyanide was used as the electrophile but the two reaction products (which have the same stereochemistry) could be only isolated in less than 50% combined yield; moreover, they possibly arise from a different mechanism.[3b] In the second example, methyl α-(phenylthio)acrylate was used and a diastereoisomeric mixture of adducts was obtained in 80% yield. However, since the major compound has a diastereoisomeric relationship of the substituents which could arise from a chairlike approach but only if the sulfur atom rather than the carbon atom of the carbonyl group is included in the chair, no unambiguous conclusion can be reached from this experiment.

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Table 1. Cyclic Adducts with Nucleophile 1 (Schemes 2–4)

electrophile	"quaternary" adducts: diastereoselectivity	"quaternary" adducts: major adduct[a]	"quaternary" adducts: diastereoisomer[a]	regioisomeric adducts[a,b]	% global yield of isomeric adducts
methyl methacrylate (**2**)	98.8:1.2	**4**:80	1	19	92.5
methyl crotonate (**5**)	98:2	**6**:72	1.5	26.5	89
maleic anhydride (**7**)[c]	89:11	**9**:63.5	8	28.5	80

[a] Relative % by GC–MS determination of the reaction mixture after flash chromatography. [b] See text. [c] Methyl esterification of the crude acid mixture followed the reaction.

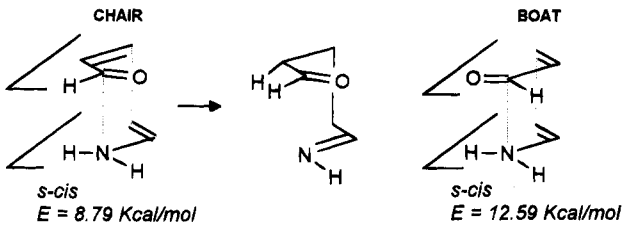
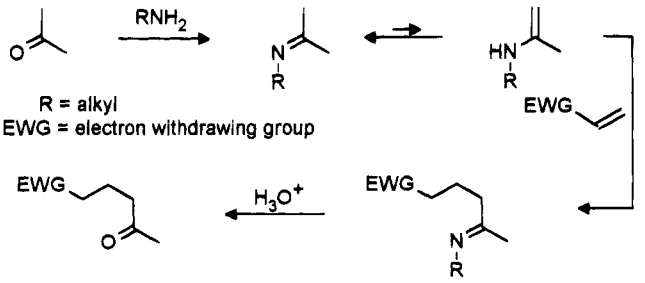
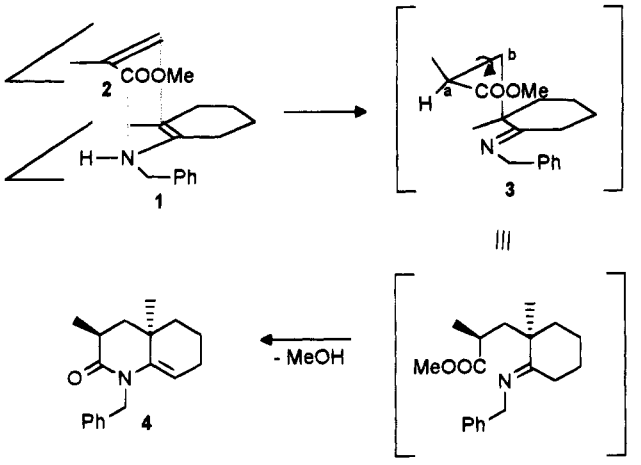


Figure 1.

Scheme 1



Scheme 2

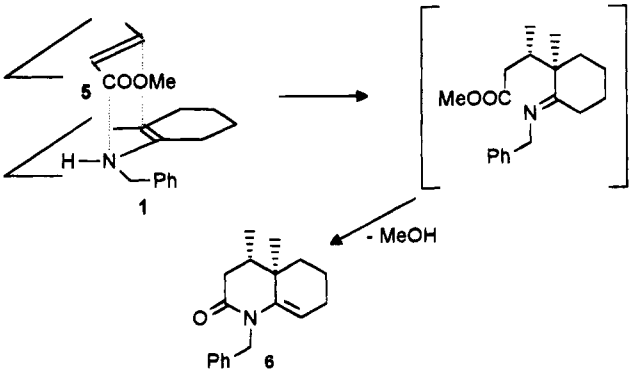


diastereomeric relationship), one can anticipate an excellent diastereoselectivity for the reaction.

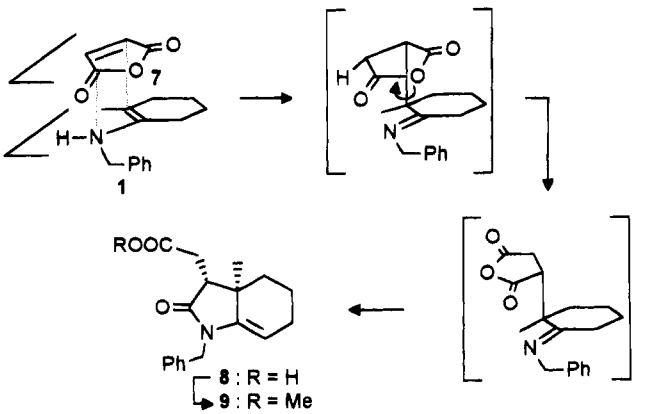
Results and Discussion

The nucleophile used in this study was 2-methyl-(benzylimino)cyclohexane reacting as its secondary enamine tautomer **1**. The olefinic partners were selected in order to cover the three stereochemical possibilities offered by monosubstituted acrylic derivatives: methyl methacrylate (**2**) (Scheme 2), methyl crotonate (*trans*) (**5**) (Scheme 3), and maleic anhydride (*cis*) (**7**) (Scheme 4). Schemes 2–4 show the reaction paths arising from a chair approach, including the anticipated relative configurations of the carbon centers bearing the substituents in the adducts, which, in the reaction conditions used,

Scheme 3



Scheme 4



were spontaneously cyclized, thus allowing an easier method to determine the relationship between the substituents. In each case the reaction mixture was subjected to GC–MS analysis, and Table 1 displays the results.

A first point about regioselectivity must be mentioned. With α-substituted cyclanones, imines, and unsubstituted electrophilic olefins the relatively fast Michael reaction yields essentially the "quaternary" adducts; *i.e.*, the reaction occurs almost exclusively at the most substituted α-carbon atom of the imine.[2,3] The present study shows, however, that the same reaction performed with substituted electrophilic olefins gives in addition to the quaternary adducts the regioisomers arising from reaction at the less substituted α-carbon atom, in 19–28.5 rel % in our examples (Table 1). Besides, the reaction is much slower with esters **2** and **5** which require prolonged heatings at 100–120 °C[13] (with highly electrophilic maleic anhydride, however, the reaction is extremely fast).

In each case of the study, the major adduct was isolated and its structure determined *(vide infra)*, showing that *its stereochemistry was the one anticipated from a mechanism including a chair complex approach* (Schemes 2–4), *thus experimentally confirming the theoretical*

prediction.[5] As also expected the diastereoselectivity is good (with maleic anhydride **7**) to excellent (with esters **2** and **5**) (Table 1).

The experiment with methyl methacrylate (**2**) (Scheme 2) is interesting from a mechanistic point of view for two reasons. First, *the experiment confirms that the proton transfer is very fast during the addition process*;[14] i.e., once the bond is formed, proton transfer is faster than a half-rotation along the a–b bond since diastereoselectivity is observed. Second, the experiment also shows that the proton transfer most probably takes place on the carbon atom rather than on the oxygen atom since in the latter case the enol → ester conversion would equilibrate the carbon center, thus implying a low probability for observing a very high diastereoselectivity, contrary to the experimental result (Table 1).

Stereochemical Assignments for the Major "Quaternary" Cyclic Adducts 4, 6, and 8. The ^{1}H NMR spectrum of lactam **4** displays two coupling constants of 6.5 and 12.8 Hz for the tertiary H-atom (besides its coupling with the methyl group), which is characteristic for an axial position, showing that the two methyl groups are in a *trans* relationship. Additionally, the steric proximity of the angular methyl group and the tertiary H-atom is confirmed by NOE difference experiments.

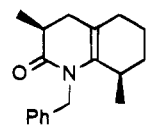
Similarly, for lactam **6**, the two H-atoms in the α-position to the carbonyl group display two coupling constants of 6.0 and 12.6 Hz (besides their geminal coupling of 18.5 Hz) characteristic of an axial position for the vicinal tertiary H atom, showing that the two methyl groups are *cis* to each other.

It was not possible to demonstrate unambiguously the stereochemistry of lactam **8** from the NMR data. In this instance a single-crystal X-ray analysis shows a *cis* relationship between the methyl and the carboxymethyl substituents. Additionally, the X-ray analysis confirmed that the primary adduct cyclized to give a five-membered ring rather than a six-membered one.[15]

Minor "Quaternary" Diastereoisomers and Regioisomers of Cyclic Adducts 4, 6, and 9. In the three experiments leading to cyclic adducts **4**, **6**, and **9**, GC–MS spectra showed that all detected minor compounds have the same molecular mass as that of their corresponding major cyclic adduct.

For the experiments with methyl methacrylate and methyl crotonate, the reaction was monitored by GC–MS. At different stages of the reaction the spectra displayed a constant pattern for the relative quantities of the isomers formed. This observation indicates that no reversibility of the reaction takes place. The experiment with maleic anhydride was so fast that a GC–MS spectra could only be recorded after the end of the reaction.

The GC–MS spectra corresponding to the reaction of 2-methyl(benzylimino)cyclohexane with methyl methacrylate (Scheme 2) display the major cyclic adduct **4** and four isomers of it. Two out of these four minor compounds could be isolated and their NMR spectra recorded. The first one (12%, regioisomer **10**, *vide infra*) displays



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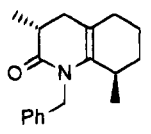

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two coupling constants of 5.8 and 3.5 Hz for the tertiary H-atom in the α-position to the carbonyl group (besides the coupling with the methyl group) characteristic of an equatorial position. The other tertiary H-atom, after methyl irradiation, is a massive signal with a width of 9.0 Hz measured at half-height, showing that it is also in an equatorial position. Thus, the two methyl groups are axial. The second minor regioisomer **11** (6.5%) displays two coupling constants of 15.0 and 5.9 Hz, characteristic of an axial position for the teriary H-atom in α-position to the carbonyl group, while the other tertiary H-atom signal, after methyl irradiation, has a width of 9.0 Hz at half-height; *i.e.*, it is in equatorial position. The implication of these results is that these two minor regioisomers differ only in the configuration of the methyl in α-position to the carbonyl group, which is axial in the first one and equatorial in the second one, the other methyl group being axial in both instances.

Calculations[17] were then performed on these flexible structures to determine which conformation is the most stable for the *cis* as well as for the *trans* regioisomer. The results indicate that in the most stable conformation of the *cis* regioisomer, both methyl groups are axial, thus showing that the first minor compound (12%) corresponds to the *cis* regioisomer **10**. On the other hand, the *trans* regioisomer has an equatorial methyl group in α-position to the carbonyl group while the other methyl is axial, showing in turn that the second minor compound (6.5%) is *trans* regioisomer **11**. Diastereoisomers **10** and **11** display quasi-identical mass spectra.

The structure of the third minor isomeric compound (0.5%) could not be determined; its mass spectrum is different from both "quaternary" adduct **4** and regioisomers **10** and **11**. It is probably a regioisomer with the double bond located in the alternate position. The fourth isomeric minor compound (1.0%) has a mass spectrum which is quasi-identical with that of compound **4** but very different from those of the three regioisomers, showing that it is the diastereoisomer of the major "quaternary" cyclic adduct **4** (Table 1).

In the case of methyl crotonate (Scheme 3), four minor compounds were detected by GC–MS but none could be isolated. However, by analogy with the conclusions reached upon mass spectra examination of the minor compounds observed in the reaction with methyl methacrylate, the following deductions can be made: The first (12%) and second (5%) minor compounds have quasi-identical mass spectra while the third (10%) has a different one. The three mass spectra being different from that of adduct **6** indicates that these three minor compounds are regioisomers. The fourth minor compound (1%) has a mass spectrum quasi-identical with that of the major "quaternary" cyclic adduct **6**, thus showing that it is its diastereoisomer (Table 1).

None of the three minor compounds detected by GC–MS could be isolated in the reaction with maleic anhydride (Scheme 4). Two of them (19% and 9.5%) have quasi-identical mass spectra which are different from

(13) Reference 3d (pp 473–4) claims that esters **2** and **5**, respectively, polymerized and did not react with the imine obtained from 2-methylcyclohexanone and (*S*)-2-methylbenzylamine.

(14) Reference 7, p 570.

(15) In a similar case (addition of (cyclohexylimino)cyclohexane to maleic anhydride), the heteroring of the cyclized adduct was shown unambiguously by chemical and spectrometric means to be the five-membered ring rather than the six-membered one.[16]

(16) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* **1976**, 776–780.

(17) Calculations were done using the discover module of the Biosym software package, running on an IBM RISC 6000 computer.

that of compound **9**, showing that they are regioisomers. The third compound (8%) has a mass spectrum quasi-identical with that of the "quaternary" cyclic adduct **9** (Table 1) and is thus its diastereoisomer.

Conclusion

Unambiguous confirmation of a theoretical prediction concerning the chairlike geometry of the reactive complexes between secondary enamines and α,β-ethylenic carbonyl compounds, as well as the concomitant H-transfer and C−C bond formation in these reactions, was experimentally achieved by using substituted partners, through structural determinations of the major compounds obtained in these Michael-type reactions. As also anticipated, a high degree of diastereoselectivity was observed. These experiments have also shown that regioisomers are produced in appreciable amounts when substituted electrophilic olefins are used.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 300 and 75.5 MHz. Chemical shifts for hydrogen and carbon resonances are reported in ppm (δ) relative to TMS. Thin-layer chromatographies (TLC) were performed with glass plates (0.25 mm) precoated with silica gel, using 30−60% EtOAc/hexanes as eluent. In the general case involving reactions with 2-methyl(benzylimino)cyclohexane, the analyses were done by first depositing a drop of 10% HCl on the starting spot and drying the plate before elution, thus showing the presence or absence of 2-methylcyclohexanone corresponding to the imine. Reaction components where then visualized under UV light, in an iodine chamber and/or dipped in a Dragendorff's solution. Silica gel (200−450 mesh) for flash chromatography was purchased from Merck. Gas chromatography−mass spectrometry (GC−MS) was performed with a Hewlett-Packard 5890 GC apparatus (equipped with a 12 m × 0.20 mm dimethylpolysiloxane capillary column) linked to a Model 5971 EIMS.

All addition reactions were performed under a nitrogen atmosphere in the presence of a few hydroquinone crystals.

2-Methyl(benzylimino)cyclohexane. A solution of 2-methylcyclohexanone (11.2 g, 100 mmol), benzylamine (10.7 g, 100 mmol, 1 equiv), and 50 mL of toluene was heated to reflux in a Dean-Stark water separator under nitrogen. After 24 h the crude reaction mixture was cooled and the solvent was removed with a rotary evaporator. The residue was then distilled under reduced pressure to afford 17.1 g (85% yield) of 2-methyl(benzylimino)cyclohexane as a colorless liquid: bp 85 °C/0.02 mmHg; GC−MS (oven temperature: 100 °C for 2 min then 8 °C/min to 250 °C) t_R = 10.69 min; EIMS *m/z* (rel int) 201 (M^+, 33), 186 (10), 173 (5), 172 (6), 158 (3), 110 (4), 106 (3), 92 (20), 91 (base); IR (thin film) 1640 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 1.0−1.6 [m, 9H, including 1.27 (d, *J* = 7.0 Hz)], 1.7−1.8 (m, 1H), 2.05−2.2 (m, 1H), 2.4−2.5 (m, 1H), 4.48 (s, 2H), 7.0−7.5 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.26, 24.56, 27.31, 28.19, 35.99, 42.18, 53.47, 126.13, 127.31, 128.12, 140.92, 176.33.

Reaction of 2-Methyl(benzylimino)cyclohexane with Methyl Methacrylate (2). To 2-methyl(benzylimino)cyclohexane (1.0 g, 4.97 mmol) was added methyl methacrylate (750 mg, 7.5 mmol, 1.5 equiv). The mixture was then heated at 100 °C for 3 days. After cooling, the reaction mixture was flash chromatographed (30% EtOAc/hexanes), and 1.24 g (92.5% global yield) of the isomeric adducts mixture was obtained after evaporation. This mixture was then analyzed by GC−MS (oven temperature: 150 °C for 2 min, then 8 °C/min to 270 °C). Five signals were observed: 9.98 min (0.5%), 10.10 (6.5%), 10.38 (12%), 10.57 (1.0%), 10.77 (80%). Analytical samples of the three main compounds were obtained by careful flash chromatography separations.

***trans*-1-Benzyl-3,5-dimethyl-2-oxo-1,2,3,4,4a,5,6,7-octahydroquinoline (4)**: GC−MS t_R = 10.77 min; EIMS *m/z* (rel int) 269 (M^+, 69), 241 (18), 240 (23), 226 (27), 200 (19), 199 (88), 198 (25), 171 (16), 92 (9), 91 (base), 65 (19); IR (thin film) 1660, 1635, 1575 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.45 (dd, *J* = 12.8, 13.1 Hz, 1H), 1.35−1.65 (m, 5H), 1.77 (dd, *J* = 6.5, 13.1 Hz, 1H), 1.90−2.15 (m, 2H), 2.73 (ddq, *J* = 6.5, 7.0, 12.8 Hz, 1H), 4.60 (d, *J* = 15.8 Hz, 1H), 4.94 (dd, *J* = 3.0, 5.0 Hz, 1H), 5.21 (d, *J* = 15.8 Hz, 1H), 7.1−7.3 (m, 5H); NOE difference experiments: irradiation of the angular methyl group at 1.12 ppm increased the signal of the tertiary H-atom at 2.73 ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.57, 18.66, 23.14, 24.42, 32.54, 33.67, 37.82, 43.40, 47.65, 105.28, 126.26, 126.46, 128.30, 137.96, 142.55, 172.22.

***cis*-1-Benzyl-3,8-dimethyl-2-oxo-1,2,3,4,5,6,7,8-octahydroquinoline (10)**: GC−MS t_R = 10.38 min; EIMS *m/z* (rel int) 269 (M^+, 44), 227 (10), 226 (6), 179 (5), 178 (39), 92 (9), 91 (base), 65 (9); IR (thin film) 1670, 1660 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 0.82 (d, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.1−1.5 (m, 5H), 1.63 (m, 1H), 1.73−1.86 (m, 1H), 2.17 (m, 1H), 2.29 (m, 1H), 2.63 (ddq, *J* = 3.5, 5.8, 7.2 Hz, 1H), 4.13 (d, *J* = 16.1 Hz, 1H), 5.71 (d, *J* = 16.1 Hz, 1H), 7.0−7.2 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.33, 17.70, 19.64, 27.75, 30.22, 30.30, 33.21, 36.05, 43.31, 113.70, 126.24, 126.71, 128.48, 134.72, 138.61, 174.55.

***trans*-1-Benzyl-3,8-dimethyl-2-oxo-1,2,3,4,5,6,7,8-octahydroquinoline (11)**: GC−MS t_R = 10.10 min; EIMS *m/z* (rel int) 269 (M^+, 49), 227 (12), 226 (6), 179 (6), 178 (44), 92 (9), 91 (base), 65 (9); IR (thin film) 1670, 1660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 1.35−1.75 (m, 4H), 1.89 (dd, *J* = 5.9, 15.6 Hz, 1H), 2.0−2.25 (m, 3H), 2.3−2.4 (m, 1H), 2.48 (ddt, *J* = 5.9, 6.7, 15.0 Hz, 1H), 4.17 (d, *J* = 16.1 Hz, 1H), 5.59 (d, *J* = 16.1 Hz, 1H), 7.1−7.3 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.14, 18.18, 19.97, 27.77, 29.49, 30.35, 34.41, 35.32, 43.59, 116.94, 126.25, 126.56, 128.32, 135.93, 138.62, 174.15.

Undefined regioisomer of adduct 4: GC−MS t_R = 9.98 min; EIMS *m/z* (rel int) 269 (M^+, 44), 241 (13), 240 (11), 226 (13), 199 (14), 198 (14), 178 (57), 91 (base), 69 (12), 65 (10).

***cis*-1-Benzyl-3,5-dimethyl-2-oxo-1,2,3,4,4a,5,6,7-octahydroquinoline (diastereoisomer of adduct 4)**: GC−MS t_R = 10.57 min; EIMS *m/z* (rel int) 269 (M^+, 58), 241 (15), 240 (20), 226 (23), 200 (15), 199 (60), 198 (17), 171 (12), 92 (11), 91 (base), 65 (16).

Reaction of 2-Methyl(benzylimino)cyclohexane with Methyl Crotonate (5). To 2-methyl(benzylimino)cyclohexane (1.0 g, 4.97 mmol) was added methyl crotonate (750 mg, 7.5 mmol, 1.5 equiv). The mixture was then heated at 120 °C for 10 days (91% conversion). After cooling, the reaction mixture was flash chromatographed (30% EtOAc/hexanes), and 950 mg (89% global yield based on converted imine) of the isomeric adducts mixture was obtained after evaporation. This mixture was then analyzed by GC−MS chromatography (oven temperature: 150 °C for 2 min and then 8 °C/min to 270 °C). Five signals were observed: 10.36 (9.5%), 10.47 (12%), 11.00 (5%), 11.50 (1.5%), 11.93 (72%). After several flash chromatographies and a distillation, an analytical sample of compound **6** was isolated as a clear and colorless oil.

***cis*-1-Benzyl-4,4a-dimethyl-2-oxo-1,2,3,4,4a,5,6,7-octahydroquinoline (6)**: bp 100 °C/0.02 mmHg; GC−MS t_R = 11.93 min; EIMS *m/z* (rel int) 269 (M^+, 74), 254 (6), 241 (11), 240 (11), 227 (11), 226 (50), 200 (29), 199 (45), 198 (21), 171 (9), 92 (9), 91 (base), 65 (18). IR (thin film) 1665, 1635, 1575 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 3H), 1.29 (ddd, *J* = 3.1, 12.9, 13.1 Hz, 1H), 1.4−1.66 (m, 2H), 1.71−1.80 (m, 1H), 1.85 (ddt, *J* = 6.0, 6.7, 12.7 Hz, 1H), 1.92−2.12 (m, 2H), 2.33 (dd, *J* = 12.7, 18.5 Hz, 1H), 2.63 (dd, *J* = 6.0, 18.5 Hz, 1H), 4.61 (d, *J* = 15.8 Hz, 1H), 5.00 (dd, *J* = 2.8, 5.3 Hz, 1H), 5.22 (d, *J* = 15.8 Hz, 1H), 7.1−7.3 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.10, 15.95, 17.73, 24.62, 35.30, 35.69, 36.20, 37.51, 47.60, 106.31, 126.31, 126.50, 128.28, 137.79, 143.38, 168.50.

Three undefined regioisomers of adduct 6: GC−MS t_R = 10.36 min; EIMS *m/z* (rel int) 269 (M^+, 46), 241 (6), 240 (7), 226 (21), 213 (4), 198 (13), 179 (9), 178 (76), 150 (5), 92 (9), 91 (base), 69 (20), 65 (12); GC−MS t_R = 10.47 min; EIMS *m/z* (rel int) 269 (M^+, 38), 255 (9), 254 (47), 227 (4), 226 (8),

198 (2), 178 (15), 162 (3), 92 (8), 91 (base), 65 (7). GC-MS t_R = 11.00 min; EIMS *m/z* (rel int) 269 (M^+, 37), 255 (8), 254 (43), 227 (3), 226 (5), 198 (3), 178 (17), 162 (3), 92 (8), 91 (base), 69 (3), 65 (9).

***trans*-1-Benzyl-4,4a-dimethyl-2-oxo-1,2,3,4,4a,5,6,7-octahydroquinoline (diastereoisomer of adduct 6)**: GC–MS t_R = 11.50 min; EIMS *m/z* (rel int) 269 (M^+, 71), 268 (13), 254 (8), 241 (9), 240 (10), 227 (15), 226 (59), 200 (23), 199 (40), 198 (17), 171 (8), 92 (10), 91 (base), 69 (8), 65 (14), 55 (5).

Reaction of 2-Methyl(benzylimino)cyclohexane with Maleic Anhydride (7). To a solution of 2-methyl(benzylimino)cyclohexane (1.07 g, 5.3 mmol) in 3 mL of THF cooled in an ice bath was added a solution of maleic anhydride (0.58 g, 5.9 mmol, 1.1 equiv) in 2 mL of THF. After 10 min the solution was allowed to reach room temperature, and TLC (60% EtOAc/hexanes) showed that the reaction had ended. Five mL of dry methanol, 3 mL of methyl orthoformate, and a few crystals of PTSA were then added, and the mixture was heated to reflux for 1 h. TLC (40% EtOAc/hexanes) showed that esterification was completed. The solution was evaporated and the residue flash chromatographed (30% EtOAc/hexanes) giving 1.33 g (80% global yield) of a mixture of the esterified isomeric adducts which was then analyzed by GC–MS (oven temperature: 170 °C for 2 min and then 8 °C/min to 270 °C). Four signals were observed: 10.92 (8%), 11.31 (63.5%), 11.76 (19%), 11.93 (9.5%). The solution was evaporated, and an analytical sample of lactam–ester **9** was isolated by recrystallization of the residue.

***cis*-1-Benzyl-2-oxo-3a-methyl-2,3,3a,4,5,6-hexahydroindole-3-acetic acid, methyl ester (9)**: mp 111–112 °C (EtOH); GC–MS t_R = 11.31 min (oven temperature: 170 °C for 2 min and then 8 °C/min to 270 °C); EIMS *m/z* (rel int) 313 (M^+, 38), 298 (24), 282 (10), 266 (8), 253 (10), 238 (20), 226 (7), 225 (32), 224 (7), 212 (9), 210 (5), 162 (5), 92 (9), 91 (base), 65 (10), 55 (4); IR (thin film) 1735, 1675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.5–1.85 (m, 4H), 1.95–2.2 (m, 2H), 2.45 (dd, J = 10.1, 17.5 Hz, 1H), 2.85–2.95 (m, 2H), 3.72 (s, 3H), 4.44 (d, J = 15.4 Hz, 1H), 4.77 (d, J = 15.4 Hz, 1H), 4.78 (m, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.00, 20.47, 22.57, 29.45, 33.57, 39.53, 43.40, 50.35, 51.69, 98.80, 127.14, 127.18, 128.40, 136.40, 143.95, 172.76, 174.13.

Two undefined regioisomers of adduct 9: GC–MS t_R = 11.76 min (oven temperature: 170 °C for 2 min and then 8 °C/min to 270 °C); EIMS *m/z* (rel int) 313 (M^+, 32), 298 (4), 282 (7), 259 (20), 254 (9), 253 (27), 238 (11), 226 (3), 225 (6), 224 (4), 212 (3), 211 (4), 198 (14), 162 (7), 92 (9), 91 (base), 65 (8); GC–MS t_R = 11.93 min (oven temperature: 170 °C for 2 min and then 8 °C/min to 270 °C); EIMS *m/z* (rel int) 313 (M^+, 36), 298 (3), 282 (8), 259 (29), 254 (9), 253 (23), 238 (12), 226 (3), 225 (8), 224 (4), 212 (4), 211 (4), 198 (14), 162 (7), 92 (9), 91 (base), 65 (9).

***trans*-1-Benzyl-2-oxo-3a-methyl-2,3,3a,4,5,6-hexahydroindole-3-acetic acid, methyl ester (diastereoisomer of adduct 9)**: GC–MS t_R = 10.92 min (oven temperature: 170 °C for 2 min and then 8 °C/min to 270 °C); EIMS *m/z* (rel int) 313 (M^+, 38), 298 (6), 282 (82), 266 (3), 253 (9), 238 (12), 226 (7), 225 (25), 224 (7), 222 (28), 212 (15), 210 (7), 162 (8), 92 (8), 91 (base), 65 (11), 55 (5).

***cis*-1-Benzyl-2-oxo-3a-methyl-2,3,3a,4,5,6-hexahydroindole-3-acetic Acid (8).** A solution of 2-methyl(benzylimino)-cyclohexane (5.20 g, 25.9 mmol) in 6 mL of THF was cooled in an ice bath, and a solution of maleic anhydride (2.70 g, 27.5 mmol, 1.1 equiv) in 6 mL of THF was slowly added. After 10 min the solution was allowed to reach room temperature and was partially evaporated. Ten mL of ethyl acetate was added, inducing a precipitate which was filtered and dried. A total of 5.25 g of crude major compound **8** was thus obtained. Recrystallization in ethyl acetate yielded 3.97 g (51.5% yield) of lactam–acid **8** which was crystallized by slow evaporation of an ethanolic solution, thus giving monocrystals for X-ray analysis: mp 150–151 °C; GC–MS t_R = 14.93 min (oven temperature: 150 °C for 2 min and then 8 °C/min to 270 °C); EIMS *m/z* (rel int) 299 (M^+, 46), 298 (14), 284 (4), 253 (11), 238 (7), 226 (7), 225 (32), 224 (6), 212 (12), 91 (base), 65 (11); IR (thin film) 1630, 1670, 1705, 1730, 2500–3500 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.64 (s, 3H), 1.1–1.4 (m, 3H), 1.4–1.5 (m, 1H), 1.6–1.85 (m, 2H), 2.27 (dd, J = 5.8, 15.6 Hz, 1H), 2.52 (dd, J = 5.8, 8.3 Hz, 1H), 2.70 (dd, J = 8.3, 15.6 Hz, 1H), 4.08 (d, J = 15.2 Hz, 1H), 4.49 (t, J = 3.6 Hz, 1H), 4.61 (d, J = 15.2 Hz, 1H), 7.0–7.50 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.91, 20.33, 22.59, 30.21, 33.38, 39.94, 43.62, 49.93, 99.94, 127.22, 127.34, 128.46, 135.97, 143.63, 175.21, 176.18.

X-ray Structure Determination of Compound 8 ($C_{18}H_{21}O_3N$, M = 299.4). A suitable crystal was investigated on a Synthex $P2_1$ diffractometer (Mo Kα radiation = 0.710 69 Å, graphite monochromator). Twenty-five reflections in the range $2 < 2\theta < 22°$ were used to refine the unit cell parameters; monoclinic, space group $P2_1/a$, Z = 4, a = 8.854-(7) Å, b = 17.354(10) Å, c = 10.243(8) Å, V = 1566.2 Å^3, d_x = 1.28, d_m = 1.27 g·cm^{-3}, μ = 0.08 mm^{-1}. A total of 3843 reflections up to 2θ = 55° of which 1049 with $I \geq 4\sigma(I)$ were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[18] and refined by a full-matrix least-squares method with SHELX76,[19] minimizing the quantity $\sum w(F_o - F_c)^2$. Non-hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located in a difference Fourier map at observed positions. Convergence was reached at R = 0.059 and R_w = 0.060. The residual electron density in the final difference Fourier map shows no features up to 0.20 e·Å^{-3} and down to −0.28 e·Å^{-3}. Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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Supplementary Material Available: ^1H NMR spectra of 2-methyl(benzylimino)cyclohexane and compounds **4**, **6**, **8**, **9**, **10**, and **11**, X-ray crystal structure of compound **8**, GC–MS spectra of the five isomeric cyclic adducts from the reaction of 2-methyl(benzylimino)cyclohexane with methyl methacrylate (**2**), Scheme 2, and structures of the most stable conformations of *cis* and *trans* regioisomers **10** and **11**, determined by calculations (11 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 masthead page for ordering information.

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