Reaction of Cyclohexanone Benzylimines with Ethylidenemalonate Diesters. Diphenyl 2-Ethylidenemalonate: A Highly Electrophilic Synthetic Equivalent of Crotonic Esters

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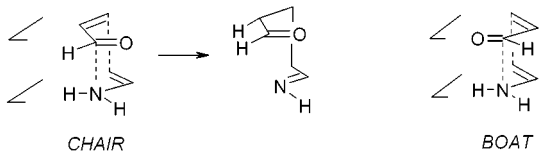
The diastereoselective Michael alkylation of α-substituted and α,α′-disubstituted cyclohexanone benzylimines with ethylidenemalonate diesters was carried out for mechanistic and synthetic purposes. In the first case, an inverse regioselectivity occurred in comparison with what is generally observed since the Michael adducts resulted from alkylation of the non substituted enamine tautomer. With α,α′-disubstituted imines, in all cases, the stereochemistry of the major diastereomer was the one anticipated from a mechanism including a chairlike complex approach with a preferred *exo* position for the *β*-methyl group of the ethylidenemalonic acid diesters. Furthermore, diphenyl 2-ethylidenemalonate **4** was found to be a highly electrophilic synthetic equivalent of crotonic esters.

Introduction

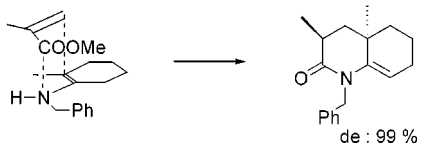
Since the first report concerning the general method of deracemizing Michael alkylation using chiral imines of 2-substituted cyclanones,[1] studies have been undertaken in order to find a valid transition-state model for this important reaction and consequently to rationalize the high stereoselectivity observed. First, a theoretical ab initio SCF−CI MO calculation study of the addition of vinylamine to propenal has shown that the reactive complex has a compact structure (syn approach) with attractive secondary interactions between the C-atom of the carbonyl group and the N-atom, largely outweighing the steric interactions. Within the syn approaches, the energy of the chairlike complex is about 4 kcal/mol lower than the boatlike one. The reaction proceeds with concomitant formation of the C−C bond and H-transfer (Scheme 1).[2]

Later, the proposed chair geometry of the reactive complex was experimentally confirmed by reacting the imine obtained from 2-methylcyclohexanone and benzylamine with α or *β*-substituted electrophilic olefins (methyl methacrylate, methyl crotonate and maleic anhydride).[3] As expected, the observed diastereoselectivity was high in each case (de from 89% to 99%). The major adduct had the stereochemistry predicted by a mechanism involving a chair complex approach of the reactants as shown in Scheme 2 (the example given being with methyl methacrylate, the olefin being arbitrarily shown above the enamine).

Scheme 1



Scheme 2



Furthermore, a study with chiral imines and methyl-substituted acrylic esters has shown that the expected major diastereomer (resulting from the chairlike geometry of the complex) was also produced with a high enantioselectivity[4] and that the favored diastereofacial selectivity was in accordance with a heuristic rule elaborated previously.[2a] The utility of this highly stereoselective reaction with substituted olefins has since been illustrated by synthetic applications in the terpene field.[5] Nevertheless, the examples mentioned above, i.e., with substituted electrophilic olefins, have also shown that

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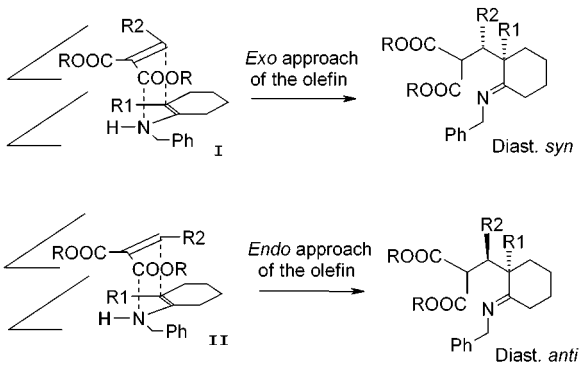
Scheme 3



regioisomers, resulting from an α-alkylation at the less substituted position of the imine, are formed in significant proportions. Likewise, a drastic loss of reactivity was observed with α or *β*-substituted electrophilic olefins in comparison with non substituted ones, thus limiting their synthetic usefulness.

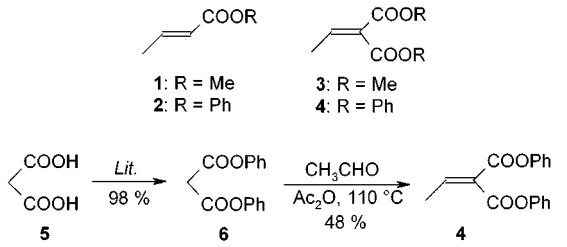
The present study was undertaken for mechanistic and synthetic purposes. First, it was interesting to see if good diastereoselectivity would also be observed when imines are reacted with diesters of ethylidenemalonic acid. Indeed, in such a case the crucial attractive secondary interaction between the C-atom of the carbonyl group and the N-atom of the enamine can take place with either carbonyl of the two ester groups. Thus, two reactive complexes with a chairlike geometry are possible (**I** and **II**), each of them leading to a different diastereomer (syn or anti respectively). In other words, our aim was to determine the tendency of the R_2 group to adopt an exo (complex **I**) or endo (complex **II**) position in the reactive complex (Scheme 3). Moreover, a high reactivity was expected for diesters of ethylidenemalonic acid and if such olefins could lead to diastereoselective Michael reactions, they would constitute interesting synthetic equivalents of crotonic esters.

Recently an example of a stereoselective Michael reaction of a secondary enaminone with a *β*-substituted electrophilic olefin (mixture of *Z* and *E* isomers) containing two different electronwithdrawing groups (an ester and a keto groups) has been described.[6] The present work will contribute to the rationalization of the remarkable stereoselectivity observed in this case.

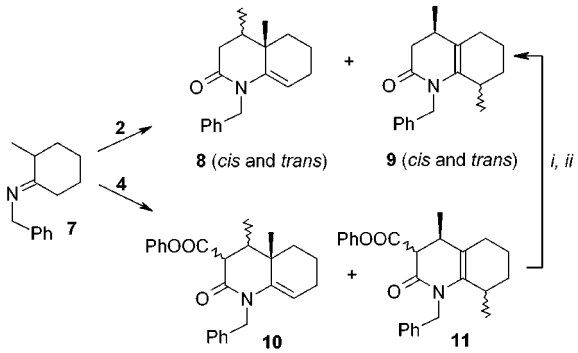
Results and Discussion

Preliminary results have shown that phenyl esters of crotonic or methacrylic acid are much more electrophilic than methyl ones.[4] Thus, we decided to compare the reactivity and the stereoselectivity of the Michael reaction with methyl and phenyl crotonic esters **1** and **2** and their corresponding ethylidenemalonic acid diesters **3** and **4**. The synthesis of diphenyl ethylidenemalonate **4** was achieved in a two-step procedure from malonic acid **5**. Diphenyl malonate **6** was obtained in 98% yield according to a literature procedure.[7] A first attempt to prepare **4** from diphenyl malonate **6** according to the classic Knoevenagel procedure[8] failed. Diphenyl 2-ethylidenemalonate **4** was finally obtained (48% yield) under acidic conditions at high temperature according to a literature procedure dealing with closely related compounds.[9] It is important to note for synthetic purposes that **4**, despite its high electrophilicity, is a stable solid which can withstand flash chromatographic purification on silica gel (Scheme 4).

Scheme 4



Scheme 5[a]



(i) NaOH, MeOH, 70 °C; (ii) 110 °C, toluene

[a] Key: (i) NaOH, MeOH, 70 °C; (ii) 110 °C, toluene.

Table 1. Michael Reaction with Crude Imine 7 (Scheme 5)

entry	olefin	reaction conditions	% overall yield from **7**[a]	regio-selectivity[b] **8**:**9**	diastereo-selectivity for **8** cis/trans[b]
1[c]	1	120 °C, 10 d	89	74:26	98:2
2	2	110 °C, 7 d	59	70:30	97:3
3	4	110 °C, 15 h	55	19:81	84:16

[a] For the mixture of diastereomers cis and trans of **8** and **9** after flash chromatography. [b] Relative % by GC−MS analysis of crude mixtures of regioisomeric lactams **8** and **9**. [c] Reference 3.

In a first set of experiments**,** imine **7** was reacted with phenyl crotonate **2** and with diphenyl ethylidenemalonate **4** leading respectively to regioisomeric bicyclic lactams **8** and **9** or **10** and **11** (Scheme 5 and Table 1).[10] Through decarboxylation, crude lactam esters **10** and **11** were readily converted to the corresponding lactams **8** and **9**. To have a reliable measurement of the regioselectivity, GC−MS analyses were carried out on the crude mixtures of lactams **8** and **9**. Isolation of these mixtures by flash chromatography allowed the determination of the overall yield from imine **7**.

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(10) Imine **7** was also reacted with olefin **3** affording Michael adducts which were converted to regioisomeric lactams **8** and **9**. However, GC−MS analysis of the reaction mixture has shown that other regioisomers have also been formed in this case, thus complicating the interpretation of the results. These regioisomers are certainly due to the different position that can adopt the double bond in structure **9**.

Table 2: Michael Reaction between Crude Imine 13 and Olefins 1, 2, 3, or 4 (Scheme 6)

entry	olefin	reaction conditions	% conversion[a]	% overall yield of **14** from **12**[b]	diastereo-selectivity cis/trans[c]
1	1	110 °C, 11 d	<1		
2	2	rt, 9 d	<1		
3	2	110 °C, 11 d	>99	53	94:6
4	3	rt, 9 d	ca. 12		
5	3	70 °C, 3 d	>99	48	87:13
6	3	110 °C, 15 h	>99		85:15
7	4	rt, 9 d	ca. 90		
8	4	70 °C, 12 h	>99	61	73:27
9	4	110 °C, 2 h 30	>99		75:25

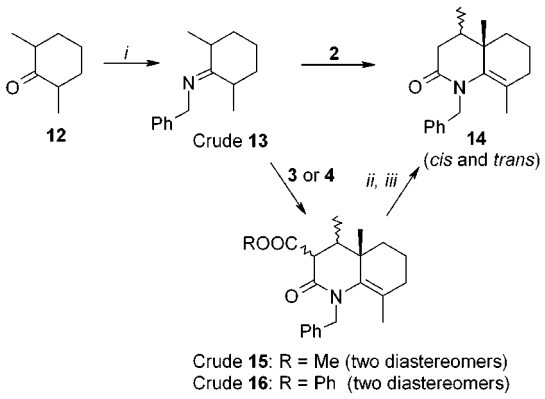
[a] By GC−MS determination. [b] For the mixture of diastereomers cis and trans of **14** after flash chromatography. [c] For the reactions with complete conversion of imine **13**, by GC−MS analysis of crude lactam **14**.

As mentioned above, these results show that substituted olefins lead to an important proportion of regioisomeric adducts (i.e., lactams **9** and **11** in the present instance). For the first time, an adduct resulting from the alkylation of the less substituted secondary enamine tautomer is even the major compound of the reaction (Table 1, entry 3). The regioselectivity of the Michael reaction of α-substituted imines with electrophilic olefins could not be clearly rationalized yet.[11] In our case, (Table 1), we can suggest that steric interaction with the methyl group of the enamine is responsible for the tendency of bulky electrophilic olefins to react with the less substituted enamine form.

The structure determination of the major diastereomer of **8** was made by ^{1}H NMR analysis of the inseparable cis/trans diastereomeric mixture obtained after flash chromatography. The ^{1}H NMR spectrum of the major diastereomer was in accordance with a cis relationship of the two vicinal methyl groups. Indeed, the two H-atoms in the α-position of the carbonyl group display two coupling constants (besides their geminal coupling of 18.4 Hz) of 5.9 and 12.5 Hz, which are characteristic of an axial position for the vicinal tertiary H-atom. In the two examples, the stereoselectivity of the Michael reaction strongly favors the formation of the cis diastereomer. Thus, the stereochemistry of the major diastereomer is the one anticipated from a mechanism including a chairlike complex approach with an exo position for the methyl group of the electrophilic olefin.

To avoid the formation of regioisomeric adducts resulting from alkylation at the less substituted α-position, the symmetrical α,α′-disubstituted imine **13** was used in all other experiments. Thus, imine **13** was reacted with electrophilic olefins **1**, **2**, **3**, and **4** (Table 2) giving either no reaction (with **1**)[12] or cyclized adducts **14**, **15**, and **16**, respectively. As before, the crude lactam esters **15** and **16** were readily converted into lactam **14**.[13] The stereoselectivity of the Michael reaction with electrophilic olefins **2**, **3**, and **4** was determined by GC−MS analysis of crude lactam **14**. In each case, purification of the crude lactam **14** by flash chromatography gave a mixture of inseparable diastereomers, allowing determination of the overall yield from 2,6-dimethyl-cyclohexanone **12** (Scheme 6).

Scheme 6[a]



[a] Key: (i) benzylamine, Et_2O, $TiCl_4$; (ii) NaOH, MeOH, 70 °C; (iii) 110 °C, toluene.

As it has been mentioned above, olefins with a phenyl ester electronwithdrawing group are much more reactive than their methyl ester counterpart (Table 2, entries 1 vs 3 and entries 5 vs 8). Moreover, as expected, the presence of a second ester function greatly enhances the electrophilicity of the olefin (Table 2, entries 1 vs 6 and entries 3 vs 9). *Addition of these two structural factors as in diphenyl 2-ethylidenemalonate **4**, gives a highly reactive synthetic equivalent of methyl crotonate **1*** (Table 2, entries 1 vs 9).

The structure determination of the major diastereomer of **14** was made by ^{1}H NMR analysis of the inseparable cis/trans diastereomeric mixture obtained after flash chromatography. One can note that the cis/trans diastereoselectivities measured on ^{1}H NMR spectra of the purified mixture of diastereomers **14** are quasi-identical with those obtained by GC−MS analysis of the crude compound.[14] In the three instances (Table 2, entries 3, 5, and 8), ^{1}H NMR spectra of the major diastereomer were similar and again in accordance with a cis relationship of the two vicinal methyl groups (the coupling constants of 7.8 and 10.2 Hz for the two H-atoms in the α-position of the carbonyl group are characteristic of an axial position for the vicinal tertiary H-atom). The relative configuration between the vicinal methyl groups was also confirmed by NOEDIFF experiment.

If one considers the results displayed in Table 2, the following deductions can be made:

(1) With trans olefin **2** bearing only one electronwithdrawing group, the usual high diastereoselectivity is observed (entry 3, cf. Table 1, entry 2), resulting from a chairlike approach of the reactants, implying an exo position for the methyl group. The small occurrence of an adduct having the opposite stereochemistry results from the presence of cis olefin **2** and/or from a boat approach of the reactants.

(2) When two identical electron-withdrawing groups are present (olefins **3** and **4**), one can a priori expect that both possible chairlike complexes (Scheme 3) have close energies, i.e., that only a small diastereoselectivity would occur. In fact, one still observes a significant diastereoselectivity (lower than that observed with olefin **2**) in

(11) Comments on regioselectivity have been previously discussed.[4]
(12) Traces of diastereomeric adducts **14** were detected by GC−MS analysis of the reaction mixture after 11 days at 110 °C.
(13) In other experiments, lactams **15** and **16** have been isolated and characterized.
(14) Since GC−MS determinations were done on crude mixtures of diastereomers and since GC−MS measurements are usually more precise than NMR ones, GC−MS values are used for the discussion.

favor of an approach with the methyl group in the exo position (entries 6 and 9, cf Table 1, entry 3). This result can be rationalized, assuming that when the methyl group is in the endo position, some steric interaction with the enamine should occur (Scheme 3, **II**, R_2 = Me). Of course, the observed diastereoselectivity also depends somewhat on the contribution of a boat approach.

(3) The lower diastereoselectivity observed with olefin **4** compared to olefin **3** (entries 9 and 6) can in turn be rationalized if one now admits that some steric interaction should occur between the *exo*-methyl group of the electrophilic olefin and the bulky phenyl group of the ester function not included in the chair.

(4) Slight elevation of the reaction temperature does not affect significatively the stereoselectivity of the Michael reaction (Table 2, entries 5 vs 6 and 8 vs 9).

If we consider the previously reported example mentioned above in the Introduction,[6] the observed stereoselectivity is in accordance with our results since the only stereoisomer which is obtained should result from a chairlike complex approach of the reactants with an exo position for the β-substituent (i.e., the phenyl group). It is worthy to note that in this case, the attractive secondary interaction between the nitrogen atom of the enaminone takes place preferentially with the carbon atom of the carbonyl group of the ketone rather than that of the ester group.

Conclusion

Reaction of imine **7** with diphenyl 2-ethylidenemalonate **4** has shown that Michael alkylation of the less substituted enamine tautomer largely prevails. A study on the regioselectivity of this reaction is in progress in our Laboratory in an attempt to rationalize this result.

Additions of imine **13** with diesters of ethylidenemalonic acid (i.e., olefins **3** and **4**) have shown that the geometry of the major diastereomeric Michael adduct (cis) is the one which arises from a mechanism involving a chairlike complex. In all examples, an exo approach of the β-substituent (methyl group) of the electrophilic olefin is observed. With **3** and **4**, the observed diastereoselectivities are good to moderate (87:13 and 75:25, respectively) but their reactivity is much higher than those observed with crotonic esters. The example of diphenyl 2-ethylidenemalonate **4** is remarkable since it can lead to Michael adducts, using moderate temperatures and short times. Thus **4** constitutes a highly reactive synthetic equivalent of crotonic esters in cases where the problem of regioselectivity does not occur, i.e., when imines are identically substituted in the α and α′ positions (e.g., imine **13**) or when secondary enamino esters or ketones (e.g., ref 6) are used. Its use in reactions other than Michael additions is under investigation in our laboratory.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 200 and 50 MHz. Thin-layer chromatographies (TLC) were performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230−400 mesh) was used for flash chromatography separations. Gas chromatography−mass spectrometry (GC−MS) was performed with a GC apparatus equipped with a 25 m capillary column, at 90 °C for 2 min, then 10 °C/min up to 290 °C. All reactions were performed under an inert atmosphere. All extractions were usually followed by water and saturated NaCl aqueous solution washings, $MgSO_4$ drying, filtration, and evaporation.

Synthesis of Diphenyl 2-Ethylidenemalonate (4). To a mixture of malonic acid **5** (11.0 g, 106 mmol) and phenol (19.95 g, 212 mmol) was slowly added at 0 °C $POCl_3$ (11.5 mL, 123 mmol). The mixture was heated at 115 °C until strong release of HCl ceased (about 1.5 h). The upper layer was poured into 150 mL of water and three extractions with ether followed by the usual workup gave diphenyl malonate **6** (26.6 g, 98%) as a pale brown solid which was pure enough to be used without further purification in the next step. An analytical sample of **6** was obtained by recrystallization from a mixture of ether/pentane: mp 51 °C (ether/pentane) (lit.[15] mp 50 °C (EtOH/H_2O)); EIMS *m*/*z* (rel int) 256 (M^+, 2), 95 (12), 94 (base), 77 (18), 65 (13); IR (Nujol) 1746, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 2H), 7.10−7.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 41.81, 121.5 (4C), 126.5 (2C), 129.7 (4C), 150.5 (2C), 164.9 (2C).

A mixture of diphenyl malonate **6** (5.05 g, 19.7 mmol), acetaldehyde (2.33 mL, 41.3 mmol), and acetic anhydride (2.96 mL, 31.6 mmol) was heated at 110 °C in a bomb for 16 h. After distillation under reduced pressure of the acetic anhydride, a flash chromatography (10% EtOAc/hexanes) of the residue gave diphenyl 2-ethylidenemalonate **4** (2.69 g, 48%) as a colorless oil which crystallized on standing. An analytical sample of **4** was obtained as a white solid by recrystallization from a mixture of ether/pentane: mp 52 °C (ether/pentane); EIMS *m*/*z* (rel int) 282 (M^+, 5), 190 (10), 189 (85), 121 (78), 95 (base), 94 (38), 93 (11), 77 (51), 65 (29), 53 (17), 51 (15); IR (Nujol) 1746, 1730, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18 (d, J = 7.5 Hz, 3H), 7.10−7.50 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 16.19, 121.6 (4C), 126.3 (2C), 128.6, 129.7 (4C), 149.1, 150.6 (2C), 162.4, 163.6. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.36; H, 5.03.

Synthesis of 1-Benzyl-4,4a-dimethyl-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (8) and 1-Benzyl-4,8-dimethyl-3,4,5,6,7,8-hexahydroquinolin-2(1*H*)-one (9). Reaction of imine (7) with phenyl crotonate (2). A mixture of imine **7**[3] (0.37 g, 1.84 mmol) and phenyl crotonate **2**[4] (0.41 g, 2.53 mmol) in the presence of a trace of hydroquinone was heated at 110 °C for 7 d. A GC−MS analysis showed the presence of four isomers with the following retention times in min: 12.090 (regioisomer **9**, 11%), 12.377 (diastereomer of **9**, 19%), 12.654 (diastereomer trans of **8**, 2%), 12.889 (diastereomer cis of **8**, 68%).[16] The reaction mixture was diluted in 20 mL of ether, washed with an aqueous solution of NaOH (10%) then with an aqueous solution of HCl (10%). After extraction with ether and the usual workup, the residue was purified by flash chromatography (15% then 25% and 30% EtOAc/hexanes) affording a mixture of lactams **8** and **9** (0.29 g, 59%) as a colorless oil. During the chromatography, a fraction gave an analytical sample of a mixture 90:10 of diastereomers cis and trans of **8**. **8** (diastereomer cis): EIMS *m*/*z* (rel int) 270 (13), 269 (M^+, 65), 268 (12), 226 (31), 200 (22), 199 (30), 198 (13), 91 (base), 65 (21); IR (film) 1667, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 0.94 (s, 3H), 1.15−2.18 (m, 7H), 2.32 (dd, J_1 = 18.4 Hz, J_2 = 12.5 Hz, 1H), 2.62 (dd, J_1 = 18.4 Hz, J_2 = 5.9 Hz, 1H), 4.57 (d, J = 16.0 Hz, 1H), 4.98 (dd, J_1 = 5.1 Hz, J_2 = 3.1 Hz, 1H), 5.22 (d, J = 16.6 Hz, 1H), 7.15−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.33, 16.19, 17.96, 24.87, 35.55, 35.94, 36.44, 37.75, 47.87, 106.6, 126.5 (2C), 126.8, 128.5 (2C), 138.0, 143.6, 168.8. **8** (diastereomer trans): EIMS *m*/*z* (rel int) 270 (12), 269 (M^+, 71), 268 (12), 226 (45), 200 (22), 199 (36), 198 (13), 91 (base), 65 (18). **9** (minor diastereomer): EIMS *m*/*z* (rel int) 269 (M^+, 45), 255 (11), 254 (52), 178 (17), 92 (12), 91 (base), 65 (14). **9** (major diastereomer): EIMS *m*/*z* (rel int) 269 (M^+, 23), 254 (30), 178 (11), 91 (base), 65 (12).

(15) Junek, H.; Ziegler, E.; Herzog, U.; Kroboth, H. *Synthesis* **1976**, 332−334.

(16) Diastereomers of **9** as well as diastereomers of **8** have an identical mass spectrum pattern with slightly different relative intensities. On the other hand, these spectra are different from those of their respective regioisomers. For further precisions, see ref 4.

Reaction of Imine (7) with Diphenyl 2-Ethylidenemalonate (4). A mixture of imine **7** (0.37 g, 1.84 mmol) and diphenyl 2-ethylidenemalonate **4** (0.68 g, 2.41 mmol) in the presence of a trace of hydroquinone was heated at 110 °C for 15 h. A GC−MS analysis showed the absence of imine **7** and peaks corresponding to decomposition products of compounds **10** and **11**. A 20 mL portion of methanol and 10 mL of an aqueous solution of NaOH (2.5 M) were added, and the reaction mixture was heated at 70 °C for 15 h. After removal of the methanol under reduced pressure, the residue was acidified with an aqueous solution of HCl (10%). Extraction with CH_2Cl_2 followed by the usual workup afforded a residue which was diluted in 15 mL of toluene and heated at 110 °C for 15 h. A GC−MS analysis showed the presence of four isomers with the following retention times in min: 12.082 (**9**, 21%), 12.371 (diastereomer of **9**, 60%), 12.653 (diastereomer trans of **8**, 3%), 12.874 (diastereomer cis of **8**, 16%). After removal of the toluene under reduced pressure, the residue was diluted in 20 mL of ether and washed with an aqueous solution of NaOH (10%). After extraction with ether and the usual workup, the residue was purified by flash chromatography (15% then 25% EtOAc/hexanes) affording a mixture of lactams **8** and **9** (0.27 g, 55%) as a colorless oil. A fraction of this chromatography gave an analytical sample of a mixture ca. 85:15 of respectively diastereomers cis and trans of **9**. The four mass spectra (diastereomers cis and trans of **8** and **9**) were identical with those of the compounds obtained from the reaction of imine **7** with phenyl crotonate **2**. **9** (mixture ca. 85:15 of diastereomers cis and trans): IR (film) 1664 cm^{-1}; ^1H NMR ($CDCl_3$) (major diastereomer) δ 1.00 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 1.28−1.75 (m, 4H), 1.80−2.70 (m, 6H), 4.19 (d, J = 16.0 Hz, 1H), 5.57 (d, J = 16.0 Hz, 1H), 7.10−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 17.34, 18.37, 20.54, 25.68, 28.04, 29.63, 30.54, 40.65, 43.34, 120.8, 126.3 (2C), 126.8, 128.5 (2C), 135.6, 138.6, 171.6.

Synthesis of 1-Benzyl-4,4a,8-trimethyl-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (14). Preparation of *N*-Benzyl-*N*-(2,6-dimethylcyclohexylidene)amine (13).[1717] 2,6-Dimethylcyclohexanone **12** (10.8 mL, 79.0 mmol) and benzylamine (26.0 mL, 238 mmol) were dissolved in 50 mL of anhydrous ether. To the stirred reaction mixture was slowly added $TiCl_4$ (4.40 mL, 39.5 mmol) in solution in 30 mL of anhydrous pentane at 0 °C. The reaction mixture was then stirred vigorously at room temperature for 16 h. The resulting precipitate was removed by filtration and washed with toluene and the solvent evaporated under reduced pressure yielding 17.2 g of crude imine **13**, which was used without further purification in the next step: EIMS m/z (rel int) 215 (M^+, 21), 92 (19), 91 (base), 65 (13), 55 (11); IR (film) 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 0.94 (s, 3H), 1.17−2.10 (m, 6H), 2.51 (m, 1H), 3.15 (m, 1H), 4.63 (s, 2H), 7.18−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.72, 17.38, 17.46, 20.71, 31.41, 33.36, 36.97, 52.97, 126.3, 127.4 (2C), 128.3 (2C), 141.4, 179.5.

Reaction of Imine (13) with Phenyl Crotonate (2). A mixture of crude imine **13** (1.01 g) and phenyl crotonate **2** (0.84 g, 5.19 mmol) in the presence of a trace of hydroquinone was at 110 °C for 11 d. A GC−MS analysis showed the absence of imine **13** and the presence of two isomers with the following retention times in min: 12.495 (diastereomer trans of **14**, 6%), 12.649 (diastereomer cis of **14**, 94%). The reaction mixture was diluted in 40 mL of ether, washed with an aqueous solution of NaOH (10%) then with an aqueous solution of HCl (10%). After extraction with ether and the usual workup, the residue was purified by flash chromatography (15% then 25% and 30% EtOAc/hexanes) affording a mixture of diastereomeric lactams **14** (cis and trans)[18] (0.71 g, 53% overall yield from **12**) as a colorless oil which crystallized on standing. Attempts to recrystallize the major isomer of lactam **14** failed because of its high solubility even in cold pentane and its apparently low melting point. Mixture of diastereomeric lactams **14** (cis and trans), IR (Nujol) 1644 cm^{-1}. Diastereomer cis of **14**: EIMS m/z (rel int) 283 (M^+, 30), 240 (10), 192 (47), 91 (base), 69 (19), 65 (21), 55 (10); ^1H NMR ($CDCl_3$) δ 0.28 (s, 3H), 0.77 (d, J = 7.0 Hz, 3H), 1.10−2.15 (m, 7H), 1.72 (s, 3H), 2.01 (dd, J_1 = 18.4 Hz, J_2 = 10.2 Hz, 1H), 2.57 (dd, J_1 = 18.0 Hz, J_2 = 7.8 Hz, 1H), 4.23 (d, J = 14.1 Hz, 1H), 5.32 (d, J = 14.1 Hz, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.42, 15.89, 19.17, 21.21, 33.44, 37.53, 38.00, 38.16, 38.67, 50.48, 120.6, 127.4, 128.1 (2C), 129.5 (2C), 137.9, 139.5, 171.3. Diastereomer trans of **14**: EIMS m/z (rel int) 283 (M^+, 44), 240 (14), 213 (13), 192 (47), 91 (base), 69 (18), 65 (17). Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.42; H, 9.18; N, 5.08.

Reaction of Imine (13) with Dimethyl 2-Ethylidenemalonate (3). A mixture of crude imine **13** (1.20 g) and dimethyl 2-ethylidenemalonate **3** (1.06 g, 6.71 mmol) in the presence of a trace of hydroquinone was heated at 70 °C for 3 d. A GC−MS analysis showed the absence of imine **13** and peaks corresponding to lactam **15** and its decomposition products. A 20 mL portion of an aqueous solution of HCl (10%) was added, and extraction with CH_2Cl_2 followed by the usual workup afforded a residue which was purified by flash chromatography (15% then 20% EtOAc/hexanes) giving a mixture (ca. 90:10, determined by ^1H NMR) of two diastereomers of lactam **15** (0.94 g, 50% overall yield from **12**) as a pale yellow solid. An analytical sample of the major diastereomer of **15** was obtained by recrystallization from EtOAc/hexanes (10:90) as a white solid: mp 93 °C (EtOAc/hexanes); EIMS m/z (rel int) 341 (M^+, 29), 250 (37), 95 (12), 92 (10), 91 (base), 69 (16), 65 (11); IR (Nujol) 1740, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.34 (s, 3H), 0.85 (d, J = 6.7 Hz, 3H), 1.20−1.45 (m, 2H), 1.55−1.80 (m, 2H), 1.71 (s, 3H), 1.95−2.20 (m, 3H), 3.06 (d, J = 9.4 Hz, 1H), 3.73 (s, 3H), 4.33 (d, J = 14.1 Hz, 1H), 5.18 (d, J = 14.5 Hz, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.51, 16.85, 19.01, 20.99, 33.21, 37.33, 38.55, 42.59, 51.33, 52.58, 55.97, 122.4, 127.5, 128.1 (2C), 129.2 (2C), 137.3, 138.3, 167.0, 171.4. Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.86; H, 8.18; N, 4.18.

The same reaction procedure was repeated on a different scale, i.e., with 0.27 g of crude imine **13** and 0.22 g (1.40 mmol) of dimethyl 2-ethylidenemalonate **3**, affording crude lactam **15** which was dissolved in 15 mL of methanol and 7.5 mL of an aqueous solution of NaOH (2.5 M) and heated at 70 °C for 15 h. After removal of the methanol under reduced pressure, the residue was acidified with an aqueous solution of HCl (10%). Extraction with CH_2Cl_2 followed by the usual workup afforded a residue which was diluted in 6 mL of toluene and heated at 110 °C for 2 h. A GC-MS analysis showed the presence of two diastereomers with the following retention times in min: 12.546 (diastereomer trans of **14**, 13%), 12.702 (diastereomer cis of **14**, 87%). After removal of the toluene under reduced pressure, the residue was directly purified by flash chromatography (25% EtOAc/hexanes) affording a mixture of diastereomeric (cis and trans) lactams **14** (0.17 g, 48% overall yield from **12**) as a colorless oil. All analytical data for the diastereomers cis and trans of **14** were identical with those obtained from reaction of imine **13** with phenyl crotonate **2**.

Reaction of Imine (13) with Diphenyl 2-Ethylidenemalonate (4). A mixture of imine **13** (0.12 g) and diphenyl 2-ethylidenemalonate **4** (0.19 g, 0.67 mmol) in the presence of a trace of hydroquinone was heated at 55 °C for 24 h. A GC-MS analysis showed the absence of imine **13** and peaks corresponding to decomposition products of lactam **16**. The reaction mixture was directly purified by flash chromatography (20% EtOAc/hexanes) giving a mixture (ca. 70:30, determined by ^1H NMR) of two diastereomeric lactams of **16** (0.14 g, 62% overall yield from **12**) as a colorless oil: IR (film) 1767, 1659, 1592 cm^{-1}; major diastereomer of **16**: ^1H NMR ($CDCl_3$) δ 0.40 (s, 3H), 0.75−2.10 (m, 6H), 0.96 (d, J = 7.0 Hz, 3H), 1.68 (s, 3H), 2.16 (dd, J_1 = 9.1 Hz, J_2 = 7.0 Hz, 1H), 3.28 (d, J = 9.4 Hz, 1H), 4.40 (d, J = 14.1 Hz, 1H), 5.13 (d, J = 14.9 Hz, 1H), 7.00−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ complex mixture of isomers.

This reaction was repeated on a different scale, i.e. with 0.31 g of crude imine **13** and 0.49 g (1.74 mmol) of diphenyl

(17) Imine **13** was prepared according to a known procedure: White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213-214.

(18) Diastereomers cis and trans of **14** possess the same R_f on TLC (eluent, 10% EtOAc/hexanes).

2-ethylidenemalonate **4** at 70 °C for 12 h, affording crude lactam **16**. The latter was dissolved in 20 mL of methanol and 11.5 mL of an aqueous solution of NaOH (2.5 M) and heated at 70 °C for 15 h. After removal of the methanol under reduced pressure, the residue was acidified with an aqueous solution of HCl (10%). Extraction with ether followed by the usual workup afforded a residue which was diluted in 10 mL of toluene and heated at 110 °C for 1 h. A GC-MS analysis showed the presence of two diastereomers with the following retention times in min: 12.553 (diastereomer trans of **14**, 27%), 12.710 (diastereomer cis of **14**, 73%). After removal of the toluene under reduced pressure, the residue was diluted in ether and washed with an aqueous solution of NaOH (10%). After extraction with ether and the usual workup, the residue was purified by flash chromatography (15% EtOAc/hexanes) affording a mixture of diastereomeric (cis and trans) lactams of **14** (0.25 g, 61% overall yield from **12**) as a colorless oil. All the analytical data for the diastereomers cis and trans of **14** were identical with those obtained from reaction of imine **13** with phenyl crotonate **2**.

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectra of compounds **4**, **6**, **8** (mixture ca. 90:10 of diastereomers), **9** (mixture ca. 85:15 of diastereomers), crude **13**, **14** (mixture ca. 95:5 of diastereomers), **15** and the ^{1}H spectrum of **16** (mixture ca. 70:30 of diastereomers) as well as the NOEDIFF spectra of compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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