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Diastereoselectivity and Enantioselectivity in the Addition of Chiral Imines of 2-Methylcyclohexanone to Crotonic and Methacrylic Acid Esters

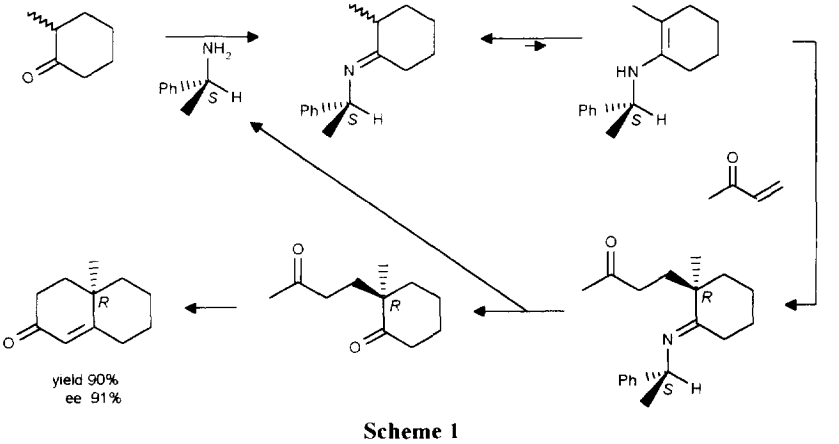
Ivan Jabin,[a] Gilbert Revial,[a] Alain Tomas,[b] Pascale Lemoine,[b] and Michel Pfau*[a]

[a]Laboratoire de Chimie Organique associé au CNRS (URA 476), ESPCI, 10 rue Vauquelin, F 75231 Paris Cedex 05

[b]Laboratoire de Physique, Université de Paris V, 4 avenue de l'Observatoire, F 75270 Paris Cedex 06

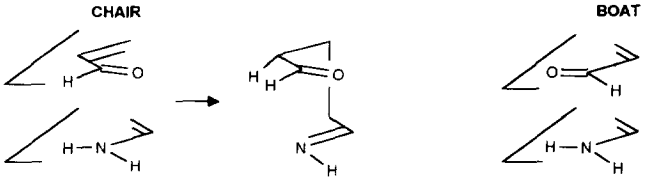
Abstract Additions of the chiral imine (reacting as its secondary enamine tautomer) obtained from (*S*)-1-phenylethylamine and 2-methylcyclohexanone were performed with the phenyl ester of crotonic and methacrylic acid as well as with their methyl ester. In each example, the stereochemical relationship of the substituents in the major adduct was shown to be the one predicted in a previous theoretical calculation which established that the reactants complex has a chairlike geometry. In all the examples, the diastereoselectivity is superior to 98 %. The enantioselectivity of the reactions is excellent as is usually the case with unsubstituted electrophilic olefins, the example with phenyl methacrylate being particularly remarkable (*de* and *ee* >99 %). In each case the favored diastereofacial selectivity is again in accordance with the rule elaborated previously. Relevant facts about the influence of the substituents upon the reactivity, the proportion of regioisomers, the stereoselectivity, and the enantioselectivity of the reaction are given.

A general method of "deracemizing alkylation" has been reported, using ketimines obtained from a chiral non racemic amine and racemic 2-substituted cyclanones[1] or 2,2-disubstituted linear ketones.[2] These imines react as their secondary enamines tautomers (at their most substituted α-carbon atom) with electrophilic olefins, yielding after hydrolysis, chiral non racemic functionalized ketones bearing an asymmetric quaternary carbon centre in the 2-position (example, Scheme 1)



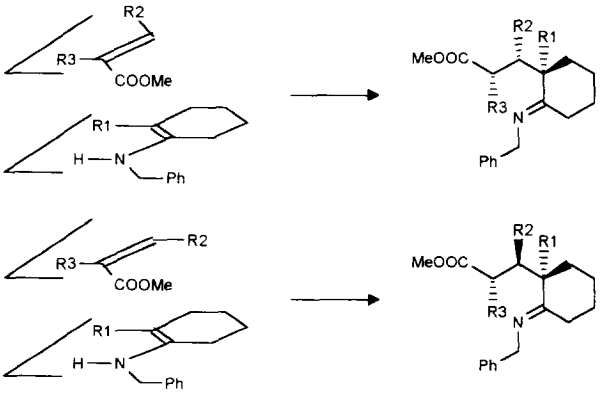
Scheme 1

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, outweighing largely the steric interactions. Within the *syn* approaches, the energy of the chairlike complex lies at about 4 kcal/mol under the boatlike one[3]. The reaction proceeds with concomitant formation of the *C*-*C* bond and *H*-transfer[4] (Scheme 2).



Scheme 2

The geometry of this reactive complex has enabled the prediction[3a] of the major adducts' stereochemistry which would arise from 2-substituted secondary enamines and substituted electrophilic olefins, *i.e.* adducts having two (or three) asymmetric centres. On these major adducts **B**, the R_3 and the R_1 substituents are in *syn* relationship whereas with a R_2 substituent the relationship with R_1 can be either *syn* or *anti*, depending on the *trans* or *cis* relationship of R_2 with respect to the electron withdrawing group in the electrophilic olefin (Scheme 3; **A**: olefin arbitrarily shown above the enamine; **B**: relative configurations). These predictions were experimentally confirmed recently by reacting the imine obtained from 2-methylcyclohexanone and benzylamine with methyl methacrylate, methyl crotonate and maleic anhydride.[4] In each case, the major adduct has a stereochemistry which is the one anticipated from a mechanism including a chair complex approach of the reactants as shown in Scheme 3. Also as expected, the diastereoselectivity is high. Experiments with substituted electrophilic olefins have also shown that in this case, regioisomers are formed in significant proportions.



Scheme 3

High enantioselectivities are generally observed when imines obtained from chiral 1-phenylethylamine are reacted with unsubstituted electrophilic olefins[1,2] (Scheme 1). A theoretical study has shown that the absolute configuration of the newly created stereogenic centre results from the reactions of low energy conformers of olefin-enamine complexes, some of them leading to one configuration, the others to the opposite one. The favored absolute configuration in turn depends on the complexes, the formations of which are kinetically favored.[3b] However, by considering the olefin attack on an enamine having a rigid geometry, a heuristic rule has been proposed,[3a] enabling the prediction of the favored diastereofacial selectivity (in accordance with all known examples[1]), according to the absolute configuration of the chiral auxiliary which induces the formation of two half-spaces of different bulkiness on the enamine sides (example with *S* absolute configuration, Fig. 1).

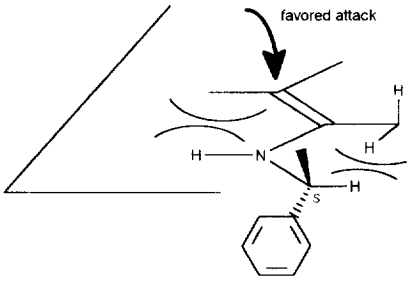
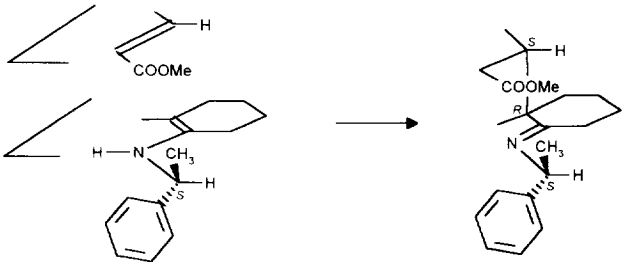


Fig. 1. Rule for the Favored Diastereofacial Selectivity.

The present study was undertaken to see if high enantioselectivities would also be observed when chiral imines are reacted with methyl-substituted acrylic esters, *i.e.* to check in such a case if the anticipated major diastereoisomer would also be produced with a high enantioselectivity[5] (example with methyl crotonate, Scheme 4). If so, interesting synthetic applications of the reaction could be envisioned, particularly in the terpene field.

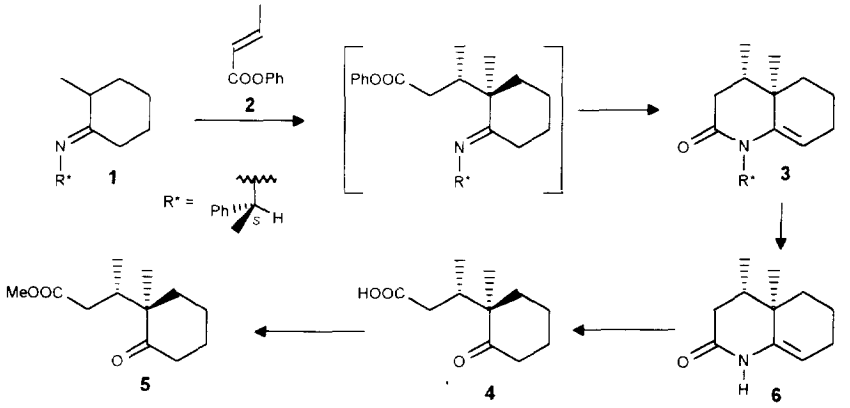


Scheme 4

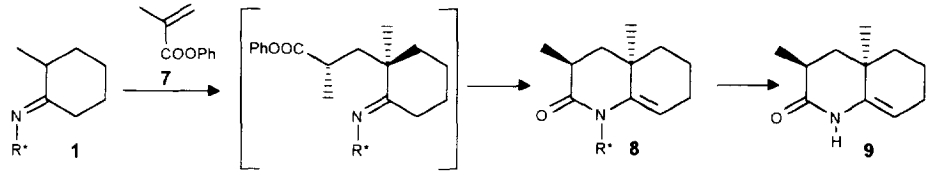
RESULTS AND DISCUSSION

Imine **1**, obtained from 2-methylcyclohexanone and (*S*)-(−)-1-phenylethylamine was used in all experiments dealing on one hand with the phenyl ester of crotonic and methacrylic acid and on the other hand with their methyl ester.

Under the reaction conditions used (Table) the adducts with the phenyl esters (Schemes 5,6) were cyclized, though with the methyl esters they were only partially cyclized (Scheme 7) or not cyclized (Scheme 8). In the four instances, *the structures of the major adducts show that their stereochemistry is the one anticipated from a mechanism including a chairlike complex approach, as was already observed with the achiral* N-*benzyl analog of imine* **1**[4], *again in accordance with the theoretical prediction*[3a]. The enantioselectivity of the four reactions is in each case in favor of the formation of the diastereoisomer having the anticipated absolute configuration (example, Scheme 4), also in accordance with the rule elaborated previously[3a] (Fig. 1). Both the diastereoselectivity and the enantioselectivity of the reactions are very high.



Scheme 5



Scheme 6

Structure determinations of the major adducts.

The absolute configuration of adduct **3** was determined by correlation with the known lactone **12** and octalone **14**. Thus, cleavage of the chiral moiety of lactam **3** afforded lactam **6** which was then hydrolyzed and

esterified to give keto-ester **5** (Scheme 5). On the other hand, the mixture of imino-ester **11** and lactam **3** (and isomers) was hydrolyzed to keto-acid **4** which was cyclized to lactone **12**. The latter was purified by recrystallization and transformed into octalone **14** as well as back into pure keto-ester **5** (Scheme 7). The structure of adduct **8** (Scheme 6) was determined by a single-crystal X-ray analysis (Fig. 2), while that of adduct **16** was determined by correlation with lactam **9** (derived from **8**) which was also obtained after hydrolysis of lactam **16** to keto-ester **17**, followed by lactamization with ammonia (Scheme 8).

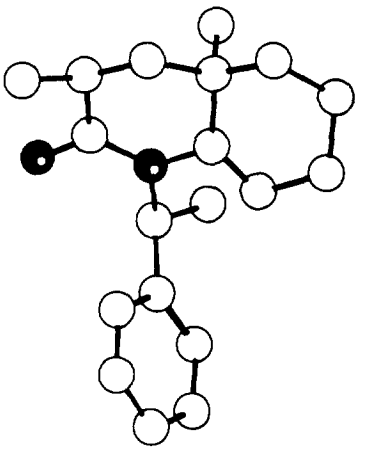
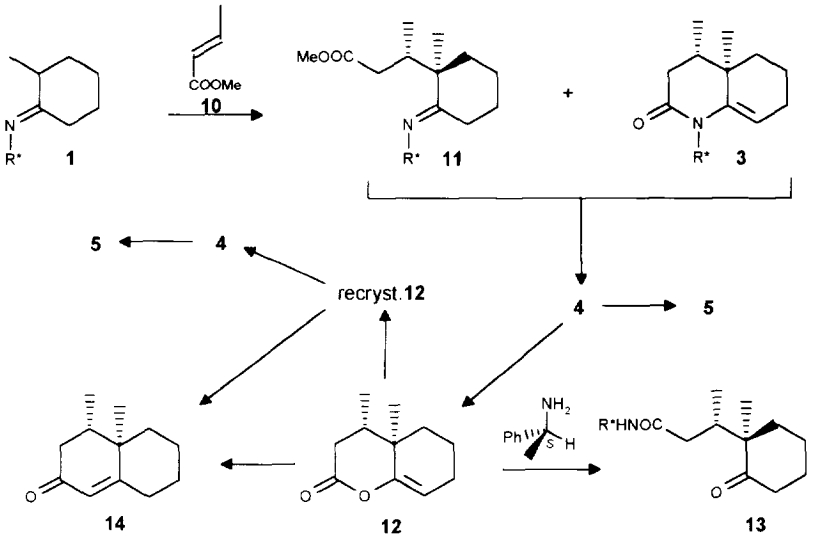


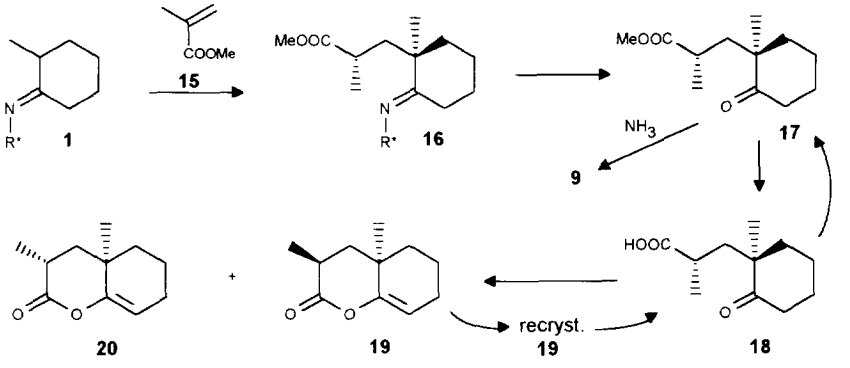
Fig. 2. X-ray Structure Determination of Lactam 8

NMR spectra in turn are compatible with the displayed structures. Thus, ^{1}H NMR spectra of lactams **3** and **6** as well as lactone **12** show that the two H-atoms in the α-position of the carbonyl group, display two coupling constants (besides their geminal couplings) of 6.4/12.4, 5.5/12.5, and 6.0/12.6 Hz respectively, which are characteristic of an axial position for the vicinal tertiary H-atom, showing that the two methyl groups are in a *cis* relationship. Similarly, spectra of lactams **8** and **9** show that the tertiary H-atom displays two coupling constants of 7.0 and 13.0 Hz, showing that the two methyl groups are in a *trans* relationship.

Pure keto-ester **17** as well as the corresponding keto-acid **18** and lactone **19** were needed for characterisation purposes. Keto-acid **18** could not be obtained in pure form by hydrolysis of lactam **9** since in the conditions needed for the reaction (10% HCl, 70 °C, 3 days) epimerization took place, leading to a 50 : 50 mixture of **18** and its diastereoisomer. Therefore, the mixture of keto-ester **17** and its isomers was hydrolyzed to keto-acid **18**, followed by cyclization with acetic anhydride to lactone **19** which was purified by recrystallization before being hydrolyzed back to pure keto-acid **18**.



Scheme 7



Scheme 8

In the mild conditions (10% HCl, 20 °C, 2 h) required for this hydrolysis, no epimerization was observed. Esterification then led to pure keto-ester **17** (Scheme 8). The above acetic anhydride treatment somewhat epimerized *trans* lactone **19**, enabling the isolation of an analytical sample of *cis* lactone **20** (prolonged heating of **18** in acetic anhydride induced an increase in the proportion of **20**, showing unambiguously that **19** was indeed corresponding to **18**). Contrary to the case of lactams **8** and **9**, ^{1}H NMR spectra of lactones **19** and **20** don't permit one to establish the relative stereochemistry of the methyl groups. On the other hand, MS spectra of both diastereoisomers are quasi-identical (*vide infra*).

Regio-, Diastereo-, and enantioselectivities determinations.

In all experiments the reaction products were analyzed by gas chromatography-mass spectrometry (GC-MS). As has been already reported previously[4], this technique permits to differenciate the regioisomers ("tertiary adducts") from the diastereoisomers of the major adducts ("quaternary" adducts) according to their MS patterns which are quasi-identical in each category, thus enabling the determination of the isomers ratio in the corresponding GC chromatograms. In the present instance, with the creation of two stereogenic centres, three diastereoisomers of the major compound are possible but one of them should be formed in a non detectable proportion, taking into account the high diastereoselectivity and enantioselectivity of the reactions, leaving thus only two possible diastereoisomers corresponding to these modes of selectivity. For the reaction with phenyl crotonate, GC-MS spectra are reproduced (Fig. 4), enabling one at first glance to differentiate the regioisomers from the two diastereoisomers. In this case, cleavage of the chiral moiety (Scheme 5) enabled a further discrimination to be made between the two diastereoisomers in Fig. 4. Indeed, in the new GC-MS spectra of the corresponding compounds devoid of the chiral moiety, a *single* diastereoisomer was present (4.5 %), in similar proportion (5 %) as that of one of the two original diastereoisomers which is thus the one related to the diastereoselectivity of the reaction, the other one being related to the enantioselectivity of the reaction (Table, entries 1/3 and Fig. 3).

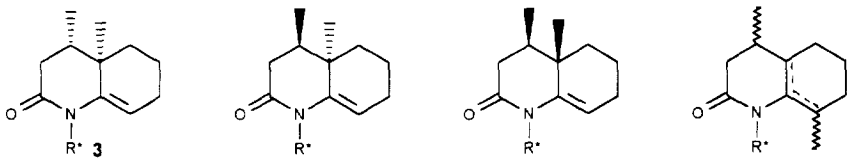


Fig. 3. Isomeric Cyclized Adducts from the Reaction of Imine 1 with Phenyl crotonate 2 (Scheme 5)

When the reaction was performed with methyl methacrylate (Scheme 8) the same discriminative method was used but in this case removal of the chiral moiety was achieved by hydrolysis of imino-ester **16** and its isomers (Table, entries 13/14). The signal of the single diastereoisomer which was initially observed in this instance disappeared upon hydrolysis, showing that it was related to the enantioselectivity of the reaction.

A reverse strategy was used in the reaction with methyl crotonate (Scheme 7) where the GC-MS spectrum of the hydrolyzed then esterified products (**5** and isomers) was compared to the GC-MS spectrum of a chiral amide derivative (**13** and isomers) obtained with (*S*)-1-phenylethylamine (Table, entries 11/12) which showed the appearance of a second diastereoisomer, thus related to the enantioselectivity.

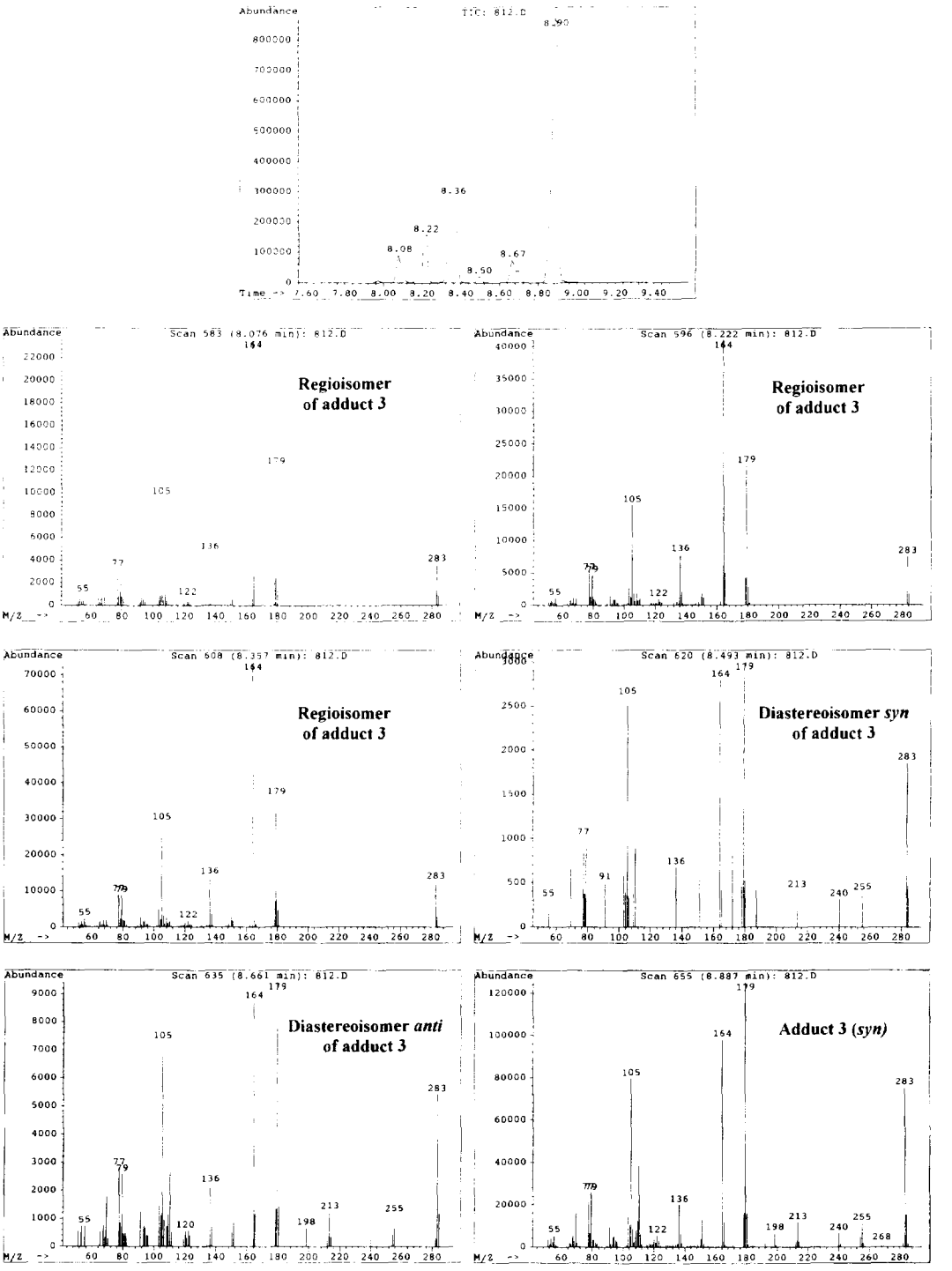
With phenyl methacrylate (Scheme 6) none of the two possible diastereoisomers were detected, *i.e.* the reaction was totally diastereo- and enantioselective (Table, entry 6).

Table. Adducts with Imine 1 (Schemes 5-8)

						"quaternary" adducts					
entry	olefin	reaction conditions	% conversion	% total yield of isomeric adducts	% regio isomers *a*	% **major adduct** (*syn*) *a*	% diastereo isomer *anti* (diastereo-selectivity) *a*	% diastereo isomer *syn* (enantio-selectivity) *a*	diastereo selectivity	% *ee addition reaction*	
1	Ph crotonate	120 °C 4 days	>99	–	36	**3**: 58	5	1	92 : 8[b]	97	*c*
2	**2**		–	84	36	**3**: 58	5	1	92 : 8	97	*d*
3	(Fig. 3)		–	–	40	**6**: 55.5	4.5	–	92.5 : 7.5	–	*e*
4			–	–	5	**6**: 88.5	6.5	–	93 : 7	–	*f*
5			–	–	2.5	**5**: 89.5	8	–	92 : 8	–	*f,g*
6	Ph methacr. **7**	100 °C 7 days	>99	–	27	**8**: 73 (*anti*)[h]	<0.5 *syn*	<0.5 *anti*	>99 : 1	>99	*c*
7			–	74	–	–	–	–	–	–	*d*
8			–	–	26	**9**: 74 (*anti*)	<0.5 *syn*	–	>99 : 1	–	*d,i*
9	Me crotonate **10**	120 °C 30 days	74	–	–	–	–	–	–	–	*j*
10			–	65	–	–	–	–	–	–	*k*
11			–	–	21.5	**5**: 76.5	2	–	97.5 : 2.5[b]	–	*k,l*
12			–	–	24	**13**: 71	1.5	3.5	98 : 2	93[m]	*k,n*
13	Me methacr. **15**	85 °C 24 days	–	–	17	**16**: 80	<0.5	3	>99 : 1	93	*c*
14			–	–	18	**17**: 82	<0.5	–	>99 : 1	–	*c,o*
15			74.5	69	12	**17**: 88	<0.5	–	>99 : 1	–	*p*
16[q]	Me crotonate **10**	120 °C 10 days	91	89	26.5	72	1.5	–	98 : 2	–	
17[q]	Me methacr. **15**	100 °C 3 days	>99	92.5	19	80 (*anti*)[h]	1 *syn*	–	98.8 : 1.2	–	

[a] Relative % by GC-MS determination. [b] See text. [c] Crude mixture of the reaction products. [d] After phenol neutralization and flash chromatography. [e] After cleavage of the chiral moiety from the initial crude mixture of the reaction products. [f] After partial elimination of the regioisomers by flash chromatography. [g] After hydrolysis and esterification. [h] From an acyclic *syn* intermediate. [i] After cleavage of the chiral moiety. [j] Based on distilled 2-methylcyclohexanone after imines hydrolysis of the reaction products. [k] Keto-acid **4** and isomers from total hydrolysis of the reaction products followed by flash chromatography. [l] After esterification. [m] Corrected twice for *ee* = 90.6 %, taking into account the optical purity of the amine (*ee* = 98.5 %). [n] After lactonization giving **12** and isomers, followed by amidation with (*S*)-1-phenylethylamine. [o] After hydrolysis. [p] After distillation of 2-methylcyclohexanone and keto-ester **17** + regioisomers. [q] Adducts with the *N*-benzyl analog of imine **1**; datas from ref. 4.

Fig. 4. GC-MS Spectra of Six Isomeric Cyclic Adducts from the Reaction of Imine 1 with Phenyl crotonate 2 (Scheme 5, Fig. 3)



Influences of the substituents.

The Table enables some relevant facts to be deduced about the influence of the substituents upon the reactivity of the reaction and the proportion of regioisomers as well as the diastereoselectivity and the enantioselectivity of the reaction.

Reactivity. With the methyl esters (**10**, **15**) the reactivity is decreased when the nitrogen atom of the imine bears the bulkier methylbenzyl as compared to the benzyl substituent (entries 9/16, 13/17). Besides, a β-methyl group on these esters (near the methyl group on the double bond of the enamine in the reactive complex) decreases also the reactivity when compared to an α-methyl group (entries 9/13, 16/17). When these factors are both present the decrease in reactivity is reinforced (entries 9/17). On the other hand, as is expected, the reactivity is increased when the phenyl esters (**2** and **7**) are used rather than their corresponding methyl esters **10** and **15** (entries 1/9, 6/13). Moreover, when the methyl substituent is in α-position (**7**) rather than in β-position (**2**), the increase of reactivity is reinforced (entries 6/9). The countereffect of a bulky *N*-substituent is overcome at least with the phenyl ester **2** (entries 1/16) and is even further overcome when phenyl methacrylate 7 is compared with methyl crotonate **10** (entries 6/16).

Regioselectivity. In the reactive complex, crowding around the nitrogen atom and/or the α-position in the ester moiety induces a decrease in the proportion of regioisomers, probably since the nitrogen substituent is also in *anti* relationship with the α-carbon atom bearing the methyl substituent in the enamine, as it is in the reactive complex leading to the "quaternary" adduct[3] (Schemes 3, 4). Indeed a decrease of the regioisomers is observed when the methylbenzyl group rather than the benzyl group is present on the nitrogen (entries 13/17, 11/16), and when the methacrylate esters are used rather than the crotonate ones (entries 13/11, 17/16, 6/1). When both situations are present, the decrease is reinforced (entries 13/16) while when the cross situation is encountered, the proportion of regioisomers is about the same (entries 17/11). On the other hand a phenyl ester (*i.e.* a very reactive electrophile) induces a higher proportion of regioisomers when compared to a methyl ester (entries 1/11, 6/13). This increase effect is reinforced when phenyl crotonate **2** is compared to methyl methacrylate **15** (entries 1/13, 1/17). In the cross situation with phenyl methacrylate **7** and methyl crotonate **10**, the phenyl ester effect is superior to the effect of absence of a methyl group in α-position (entries 6/11), and is also superior to the effect of a less crowded *N*-atom (entries 1/16, 6/17). However when there is both crowding on the *N*-atom and presence of an α-methyl group the phenyl ester effect is overcome (entries 6/16).

Diastereo- and enantioselectivity. The experimental values shown in the Table for the reactions with phenyl crotonate **2** and methyl crotonate **10** should be amended since in fact both contain a small amount of their *cis* counterpart [6% (GC-MS, ^{1}H NMR) and 1% (GC-MS) respectively]. Near the end of the reactions

these values are unchanged for the residual esters. Assuming that the reactivities of the *trans* esters are not very superior to those of the *cis* esters, the corrected values for entries 1, 11, and 16 are thus 98 : 2, 98.5 : 1.5, and 99 : 1, respectively. Thus it appears that in all reactions the diastereoselectivities are extremely good and are not influenced by the substituents on the nitrogen atom and on the esters, *i.e.* that these substituents probably don't affect much the energy difference between the chair and the boat reactive complexes.

In what concerns the enantioselectivity of the reactions, the only significant point which can be noted is the observation of an *ee* increase manifested when the phenyl esters are used rather than the methyl ones (entries 1/12, 6/13).

CONCLUSION

Additions of the chiral imine obtained from (*S*)-1-phenylethylamine and 2-methylcyclohexanone, with crotonate and methacrylate esters, have again confirmed that the geometry of the major adducts is the one which arises from a mechanism including a chairlike complex approach in accordance with the theoretical prediction. As also anticipated, the diastereoselectivities are extremely good (>98 %). These experiments have also shown that the good enantioselectivities usually encountered with electrophilic olefins (*ee* = 90-97 %) are also observed with substituted ones, the example with phenyl methacrylate being particularly remarkable (*de* and *ee* >99 %). The favored diastereofacial selectivity is again in accordance with the rule elaborated previously.

Relevant facts about the influence of the substituents upon the different parameters of the reaction could also be extracted from the results.

EXPERIMENTAL SECTION

General

^{1}H and ^{13}C NMR spectra were recorded, respectively, at 300 and 75.5 MHz ($CDCl_3$). Chemical shifts for hydrogen and carbon resonances are reported in ppm (δ) relative to TMS. 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/or dipped in a Dragendorff solution. Silica gel (230-400 mesh) was used for flash chromatography separations and EtOAc/hexanes (% EtOAc given) was the eluent. Gas chromatography-mass spectrometry (GC-MS) was performed (oven temperature: 140 °C for 2 min, then 16 °C/min to 270 °C) with a Hewlett-Packard 5890 GC apparatus (equipped with a 12 m × 0.20 mm dimethylpolysiloxane capillary column) linked to a Model 5971 EIMS. Uncorrected melting points (mp) were determined with a Fisher-Johns apparatus.

(*S*)-1-phenylethylamine, $[\alpha]_D^{20}$ −40.1 (neat), *ee* ~98.5 %, the chiral auxiliary used in all experiments, was obtained from the commercial amine, $[\alpha]_D^{20}$ −39.1 (neat), *ee* = ~96 %[8].

Crude imine **1**, obtained by azeotropic distillation of a toluene solution of an equimolecular mixture of 2-methylcyclohexanone and (*S*)-1-phenylethylamine[10], was used for all addition reactions which were performed under a nitrogen atmosphere and in the presence of a few hydroquinone crystals.

All extractions were usually followed by water and saturated NaCl aqueous solution washings, $MgSO_4$ drying, filtration and evaporation.

Phenyl crotonate (2): 5 g (58 mmol) of crotonic acid, 5.45 g (1 equiv.) of phenol, 0.2 mL of conc. H_2SO_4, and a trace of hydroquinone, in solution in 50 mL of toluene, were heated at reflux for 24 h in a Dean-Stark apparatus under a nitrogen atmosphere. After toluene removal under reduced pressure, ether was added and the mixture was washed with 10 % NaOH followed by the usual work-up. Distillation of the residue afforded 6.32 g (39 mmol, 67 % yield) of phenyl crotonate: bp 62-65 °C/0.05 Torr; EIMS *m/z* (rel int) 162 (M^+, 13), 69 (base), 41 (14); IR (neat) 1735, 1655 cm^{-1}; ^{1}H NMR δ 1.91 (dd, J_1 = 1.7 Hz, J_2 = 7.0 Hz, 3H), 6.02 (dt, J_1 = 1.7 Hz, J_2 = 15.5 Hz, 1H), 7.07 to 7.22 (m, 4H), 7.31 to 7.38 (m, 2H); ^{13}C NMR δ 18.07, 121.6, 122.0, 125.6, 129.3, 146.8, 150.7, 164.5.

Phenyl methacrylate (7): The procedure used for the preparation of phenyl crotonate [10 mL (118 mmol) of methacrylic acid, 11.07 g (1 equiv.) of phenol, 0.4 mL of conc. H_2SO_4, 100 mL of toluene, and 7 days reflux instead of 24 h in this case] afforded a residue which was flash chromatographed (10 %) in this instance, giving 11.9 g (73 mmol, 62 % yield) of phenyl methacrylate as a colorless liquid: EIMS *m/z* (rel int) 162 (M^+, 72), 134 (25), 94 (45), 69 (base), 66 (15), 65 (26), 41 (31), 39 (39); IR (neat) 1735, 1635 cm^{-1}; ^{1}H NMR δ 2.09 (dd, J_1 = 1 Hz, J_2 = 1.5 Hz, 3H), 5.75 (dt, J_1 = 1 Hz, J_2 = 2 Hz, 1H), 6.40 (s, 1H), 7.13 to 7.17 (m, 2H), 7.23 to 7.29 (m, 1H), 7.38 to 7.45 (m, 2H); ^{13}C NMR δ 18.28, 121.50, 125.61, 127.08, 129.29, 135.78, 150.82, 165.75.

Reaction with phenyl crotonate (2)

(4*S*,4a*R*)-4,4a-Dimethyl-1-[(*S*)-1-phenylethyl]-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (3): 10.2 g of crude imine **1** [obtained from 5.63 mL (46.4 mmol) of 2-methylcyclohexanone] and 8.0 mL (52.3 mmol, 1.1 equiv.) of phenyl crotonate were heated at 120 °C for 4 days and the mixture was then analyzed by GC-MS. Besides a trace of imine **1** at 4.60 min (> 99 % conversion), signals were observed at 8.08, 8.22, and 8.36 min (36 % global, regioisomers of **3**), as well as signals at 8.50 min (1 %, diastereoisomer *syn* of **3**), 8.67 min (5 %, diastereoisomer *anti* of **3**), and 8.90 min (58 %, **3**). Relative amounts are thus 1.5 % / 98.5 % for the diastereoisomer *syn* and **3**, and 8 % / 92 % for the diastereoisomer *anti* and **3**. The mixture was then dissolved in 20 mL of ether, and 8 mL of a 30 % NaOH solution was added. After stirring at room temperature for 30 min and ether extraction followed by the usual work-up, a residue (13.06 g) was obtained. A 1.02 g sample of this residue was flash chromatographed (20 % and 30 %), giving a 0.86 g residue (84 % global yield for **3** and its isomers, from 2-methylcyclohexanone) which was analyzed by GC-MS, showing the same pattern as above. A flash chromatographed fraction yielded an analytical sample of **3**: EIMS *m/z* (rel int) 283 (M^+, 33), 179 (base), 164 (86), 136 (16), 110 (33), 105 (59), 79 (20), 77 (21); ^{1}H NMR δ 0.89 (d, J = 6.7 Hz, 3H), 0.96 (s, 3H), 0.98 to 1.50 (m, 2H), 1.58 (d, J = 7.1 Hz, 3H), 1.69 to 2.06 (m, 5H), 2.26 (dd, J_1 = 12.4 Hz, J_2 = 18.6 Hz, 1H), 2.66 (dd, J_1 = 6.4 Hz, J_2 = 18.5 Hz, 1H), 4.84 (dd, J_1 = 2.6 Hz, J_2 = 5.7 Hz, 1H), 6.28 (q, J = 7.2 Hz, 1H), 7.16 to 7.35 (m, 5H); ^{13}C NMR δ 14.31, 15.21, 15.81, 18.06, 24.93, 35.81, 36.21, 36.42, 37.78, 50.33, 110.2, 125.5, 126.2, 128.2, 140.5, 142.3, 169.0.

(4*S*,4a*R*)-4,4a-Dimethyl-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (6): 5.18 g of the above non-chromatographed mixture was then dissolved in 50 mL of anh. THF, the solution was cooled to −78 °C under a nitrogen atmosphere and *ca.* 120 mL of liquid NH_3 was added. Then, *ca.* 500 mg (71.4 mmol, ~4.5 equiv.) of Li was added and the solution was kept for 1 h at −78 °C, followed by styrene addition up to discoloration. The bath was then removed and NH_3 evaporated. 1 g of NH_4Cl and 20 mL of H_2O were added to the residual solution which was extracted with ether, followed by the usual work-up. The residue (4.85 g) was then analyzed by GC-MS. Signals at 4.21 min (40 %, regioisomers of **6**), 4.65 min (4.5 %, diastereoisomer *anti* of **6**), 4.97 min (55.5 %, **6**) were observed besides non-isomeric impurities. Relative amounts are thus 7.5 % / 92.5 % for the diastereoisomer *anti* and **6**.The mixture was then flash chromatographed (20, 50, and 80 %), yielding a partially purified mixture (1.63 g, *ca.* 8.0 mmol, 43 % yield of **6** from 2-methylcyclohexanone) which was analyzed by GC-MS. Signals at 4.16 min (5 %, regioisomers of **6**), 4.65 min (6.5 %, diastereoisomer *anti* of **6**), and 4.99 min (88.5 %, **6**) were observed, besides a tiny amount of a non isomeric impurity. Relative amounts are thus 7 % / 93 % for the diastereoisomer *anti* and **6**. An analytical sample of **6** was obtained by recrystallization of the flash chromatographed mixture: mp 125 °C (AcOEt / hexanes 40 : 60), $[\alpha]_D^{20}$ +256 (*c* 1.4, EtOH); EIMS *m/z* (rel int) 179 (M^+, base), 178 (19), 165 (10), 164 (99), 151 (16), 137 (12), 136 (63), 122 (11), 110 (58), 109 (17), 108 (20), 94 (14), 93 (15), 91 (13), 79 (17), 77 (13), 69 (24), 67 (11); IR (nujol) 3350, 3170, 1670, 1660, 1610 cm^{-1}; ^1H NMR δ 0.91 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 0.5 Hz, 3H), 1.04 to 1.33 (m, 2H), 1.58 to 1.83 (m, 3H), 2.03 to 2.10 (m, 2H), 2.22 (dd, J_1 = 12.5 Hz, J_2 = 18.5 Hz, 1H), 2.41 (dd, J_1 = 5.5 Hz, J_2 = 18.5 Hz, 1H), 4.87 to 4.90 (m, 1H), 7.83 (br. s, 1H); ^{13}C NMR δ 13.90, 15.96, 18.19, 23.59, 34.14, 34.68, 36.30, 36.93, 104.1, 140.3, 169.5.

Methyl (β*S*,1*R*)-β,1-dimethyl-2-oxocyclohexanepropanoate (5): 240 mg of the above non recrystallized lactam **6** was dissolved in 3 mL of dioxan and 3.4 mL of 10 % HCl was added. The solution was heated under a nitrogen atmosphere at 70 °C for 15 h and after concentration under reduced pressure, the residue was extracted with ether followed by the usual work-up. 250 mg of crude keto-acid **4** was thus obtained and dissolved in 4 mL of methanol. 0.17 mL of 2,2-dimethoxypropane and a catalytical amount of PTS acid were added and the mixture was stirred at room temperature for 1 h. After concentration under reduced pressure, the mixture was flash chromatographed (15 %) yielding 210 mg of a residue which was analyzed by GC-MS. Signals at 3.52 min (2.5 %, regioisomers of **5**), 3.65 (89.5 %, **5**), and 3.71 min (8 %, diastereoisomer *anti* of **5**) were observed. Relative amounts are thus 8 % / 92 % for the diastereoisomer *anti* and **5**. A 1 : 1 mixture of this residue and of an authentic sample of keto-ester **5** (*vide infra*) was also analyzed by GC-MS, displaying a single major signal at 3.72 min for **5**, besides faint signals at 3.58 min (regioisomers of **5**) and 3.78 min (diastereoisomer *anti* of **5**). Moreover, the above residue has $[\alpha]_D^{20}$ +69 (*c* 1.4, EtOH), *i.e.* is indeed dextrorotatory (for $[\alpha]_D^{20}$ as well as spectrographic datas of **5**, *vide infra*).

Reaction with phenyl methacrylate (7)

(3*S*,4a*R*)-3,4a-Dimethyl-1-[(*S*)-1-phenylethyl]-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (8): *ca.* 2.5 mL of crude imine **1** [obtained from 1.04 mL (8.55 mmol) of 2-methylcyclohexanone], and 1.59 mL (10.3 mmol, 1.2 equiv.) of phenyl methacrylate **7** were heated at 100 °C for 7 days and the mixture was then analyzed by GC-MS. Signals at 4.69 min (trace of imine **1**, >99 % conversion), 8.27, 8.31, 8.42 min (27 % global, regioisomers of **8**), and 8.59 min (73 %, **8**) were observed. Then, 10 mL of ether and 10 mL of a 2.5 NaOH aqueous solution were added to the mixture and stirring was applied for 30 min. After ether extraction followed by the usual work-up, the residue was flash chromatographed (15 %, then 20 %) giving 1.8 g (6.4 mmol, 74 % total yield of isomers) of lactam **8** and its regioisomers. Through crystallization at −20 °C followed by several recrystallizations, pure lactam **8** was obtained: mp 91-91.5 °C (hexane). Found: C, 80.6; H, 8.9 ($C_{19}H_{25}NO$ requires C, 80.52; H, 8.89); $[\alpha]_D^{20}$ +63 (*c* 1, EtOH); EIMS *m z* (rel int) 283 (M^+, 84), 255 (26), 213 (43), 198 (12), 180 (13), 179 (base), 178 (17), 164 (63), 151 (27), 136 (10), 110 (18), 105 (42), 103 (10), 79 (13), 77 (15); IR (nujol) 1640 cm^{-1}; ^1H NMR δ 1.15 (s, 3H), 1.34 (d, J = 7 Hz, 3H), 1.44 (dd, $J_1 \approx J_2 \approx$ 13 Hz, 1H), 1.55 to 1.69 and 1.61 (m and d, J = 7.4 Hz, 7H), 1.80 (dd, J_1 = 7 Hz, J_2 = 13.2 Hz, 1H), 1.90 to 2.10 (m, 2H), 2.67 (ddq, J_1 = 7.0 Hz, $J_2 \approx$ 7 Hz, J_3 = 13 Hz, 1H), 4.83 (dd, J_1 = 2.6 Hz, J_2 = 5.2 Hz, 1H), 6.20 (q, J = 7 Hz, 1H), 7.18 to 7.34 (m, 5H); ^{13}C NMR δ 15.34, 18.06, 19.11, 23.19, 24.94, 33.25, 34.23, 38.47, 43.73, 51.05, 109.1, 125.7, 126.2, 128.3, 140.1, 142.6, 172.6; X-ray structure determination: *vide infra*

(3*S*,4a*R*)-3,4a-Dimethyl-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one (9): The mother liquors from the above lactam **8** recrystallization were evaporated, yielding 800 mg of a residue containing **8** and its regioisomers. Cleavage of the chiral moiety was done as described above for the obtention of lactam **6** (15 mL of anh. THF, 20 mL of liquid NH_3, 200 mg of Li, 100 mg of NH_4Cl, and 5 mL of H_2O in this instance) and the residue was analyzed by GC-MS. Signals at 4.10 and 4.35 min (26 % global, regioisomers of **9**) and 4.30 min (74 %, **9**) were observed. The mixture was then flash chromatographed (20 %, 50 %) giving 420 mg (83 % global yield for **9** and its regioisomers) of a residue which was recrystallized twice, yielding an analytical sample of lactam **9**: mp 122 °C (AcOEt/hexanes 40 : 60); $[\alpha]_D^{20}$ +191 (*c* 0.8, EtOH). EIMS *m z* (rel int) 179 (M^+, base), 178 (27), 164 (79), 151 (44), 137 (10), 136 (39), 123 (10), 122 (31), 110 (61), 109 (27), 108 (30), 96 (10), 94 (15), 93 (17), 91 (13), 79 (12), 77 (13), 69 (25), 67 (11), 55 (14), 54 (15), 53 (11); IR nujol) 3180, 1655 cm^{-1}; ^1H NMR δ 1.17 (s, 3H), 1.24 (d, J = 7.5 Hz, 3H), 1.26 to 1.44 (m, 2H), 1.57 to 1.75 (m, 4H), 2.02 to 2.09 (m, 2H), 2.61, (ddq, $J_1 \approx 7.0$ Hz, $J_2 \approx 7$ Hz, $J_3 \approx 13$ Hz, 1H), 4.81 to 4.84 (m, 1H), 7.71 (br. s, 1H); ^{13}C NMR δ 16.75, 17.90, 23.18, 23.34, 31.95, 32.95, 36.55, 43.31, 103.0, 139.6, 172.9.

Reaction with methyl crotonate 10

ca. 10 mL of crude imine **1** [obtained from 5.51 mL (45.4 mmol) of 2-methylcyclohexanone], and 7.2 mL (68.1 mmol, 1.5 equiv.) of methyl crotonate were heated at 120 °C for 30 days and the mixture was then analyzed by GC-MS (initial temperature 130 °C). Besides unreacted imine **1**, unresolved signals were observed from 8.74 min to 9.89 min, accounting for the presence of **11** (9.16 min), the diastereoisomer and regioisomers of **11**, as well as lactam **3** and its isomers (relative % of non-isomeric compounds not reliable). The mixture was then dissolved in 25 mL of methanol and 26 mL of 10 % acetic acid was added under nitrogen. After 15 min at room temperature, the solvent was distilled at normal pressure and the residue was extracted with ether and washed with 10 % HCl followed by the usual work-up. The residue was distilled under reduced pressure, giving 1.30 g (11.6 mmol, 74 % conversion) of 2-methylcyclohexanone and 6.25 g of a mixture which was dissolved in 40 mL of dioxane and 10 mL of 6 N HCl and heated at reflux for 3 days. The solution was then concentrated at reduced pressure and extracted with methylene chloride. Flash chromatography (20 %, then 60 %) gave 4.30 g (21.7 mmol, 65 % total yield based on reacted 2-methylcyclohexanone) of a mixture which was analyzed by GC-MS. Besides a small impurity at 8.34 min, partially resolved signals were observed for keto-acid **4** and its isomers, centered at 4.42 and 4.56 min (**4**); lactam **3** was absent. For analytical purposes, a 37 mg (0.19 mmol) sample of the mixture was added to 0.023 mL (1 equiv.) of 2,2-dimethoxypropane and a trace of PTS acid in 1 mL of methanol and the solution was heated at reflux for 6 h. The mixture was then analyzed by GC-MS and signals at 3.79 and 3.87 min (21.5 %, regioisomers of **5**), 4.05 min (2 %, diastereoisomer of **5**), and 4.01 min (76.5 %, **5**) were observed.

(4*S*,4a*R*)-4,4a-Dimethyl-3,4,4a,5,6,7-hexahydro-2*H*-1-benzopyran-2-one (12): A solution of 2.39 g (12.07 mmol) of the above mixture of keto-acid **4**, its diastereoisomer and its regioisomers, and 149 mg (1.81 mmol, 0.15 equiv.) of sodium acetate in 60 mL of acetic anhydride were heated at reflux under N_2, for 3 h. Acetic anhydride was removed by distillation at reduced pressure and a small amount of water was added to the residue which was extracted with ether and washed with a saturated sodium carbonate solution, followed by the usual work-up. Flash chromatography (15 %) of the residue gave 1.81 g (10.06 mmol, 83 % total yield) of a mixture of lactone **12** (4.11 min) and its isomers (unresolved by GC-MS). An analytical sample of **12** was obtained by crystallization of the mixture, at -20 °C, followed by several recrystallizations in hexane: mp 60 °C (hexane) (Litt.[9], mp 57-60 °C for crude *ent*-**12**). Found: C, 73.1; H, 8.9 ($C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95); $[\alpha]_D^{20}$ +161, $[\alpha]_{579}^{20}$ +169, $[\alpha]_{546}^{20}$ +196, $[\alpha]_{436}^{20}$ +374 (*c* 1, EtOH) (Litt.[9], $[\alpha]_D^{24}$ −144 (*c* 0.15) for crude *ent*-**12**); EIMS *m z* (rel int) 180 (M^+, 38), 152 (10), 137 (22), 111 (61), 110 (35), 109 (10), 69 (base), 67 (13), 55 (20); IR (nujol) 1745, 1675 cm^{-1}; ^1H NMR δ 0.92 (d, J = 6.7 Hz, 3H), 1.03 (s, 3H), 1.36 (ddd, J_1 = 3.7 Hz, J_2 = 13 Hz, J_3 = 13 Hz, 1H), 1.53 to 1.76 (m, 2H), 1.78 to 1.93 (m, 2H), 1.98 to 2.19 (m, 2H), 2.35 (dd, J_1 = 12.6 Hz, J_2 = 18.8 Hz, 1H), 2.66 (dd, J_1 = 6.0 Hz, J_2 = 18.9 Hz, 1H), 5.27 (dd, J_1 = 3.0 Hz, J_2 = 4.8 Hz, 1H); ^{13}C NMR δ 13.82, 15.45, 18.20, 23.48, 34.29, 35.52, 35.54, 35.62, 105.7, 154.9, 167.9.

(βS,1R)-β,1-Dimethyl-*N*-[(*S*)-1-phenylethyl]-2-oxocyclohexanepropanamide (13): 606 mg (3.37 mmol) of the above mixture of lactone **12**, its diastereoisomer and its regioisomers, and 0.87 mL (6.73 mmol, 2 equiv.) of (*S*)-1-phenylethylamine in 4 mL of methylene chloride were heated at 45 °C under nitrogen, for 1 h. Through GC-MS analysis, signals were observed at 9.54, 9.61, and 9.75 min (24 %, regioisomers of **13**),as well as signals at 9.96 and 10.05 min [1.5 % (*anti*), and 3.5 % (*syn*), diastereoisomers of **13**], and 9.89 min (71 %, **13**). After solvent removal under reduced pressure, the residue was flash chromatographed (20 %, then 50 %) giving 800 mg (2.66 mmol, 79 % total yield) of the mixture of keto-amide **13** and its isomers. An analytical sample of **13** was obtained by several recrystallizations: mp 129.5-130 °C (AcOEt/hexanes 30 : 70). Found: C, 75.7; H, 9.1 ($C_{19}H_{27}NO_2$ requires C, 75.71; H, 9.03); $[\alpha]_D^{20}$ −23 (*c* 1, EtOH); EIMS *m/z* (rel int) 301 (M^+, 7), 190 (14), 163 (49), 121 (12), 120 (base), 106 (24), 105 (99), 104 (22), 103 (12), 86 (14), 79 (17), 77 (16), 69 (33), 59 (13), 55 (17); IR (nujol) 3240, 1700, 1635 cm^{-1}; ^1H NMR δ 0.89 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.36 to 1.45 (m, 1H),1.48 (d, J = 7 Hz, 3H), 1.57 to 1.99 (m, 7H), 2.24 (ddd, J_1 = 4 Hz, J_2 = 4 Hz, J_3 = 14 Hz, 1H), 2.51 to 2.73 (ddd and m, J_1 = 6.6 Hz, J_2 = 11.8 Hz, J_3 = 14.3 Hz, 2H), 5.09 (dq, J_1 = 7 Hz, J_2 = 7 Hz, 1H), 5.92 to 6.04 (m, 1H), 7.22 to 7.35 (m, 5H); ^{13}C NMR δ 13.26, 16.92, 20.16, 21.72, 27.75, 32.84, 37.39, 38.66, 39.41, 48.68, 51.57, 126.0, 127.2, 128.5, 143.0, 171.2, 216.9.

(4S,4a*R*)-4,4a-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (14): 0.49 mL (1.23 mmol) of a 2.5 M hexanes solution of n-BuLi was slowly added under nitrogen at −78 °C to a solution of 0.14 mL (1.29 mmol, 1.05 equiv.) of $CH_3P(O)(OCH_3)_2$ in 4 mL of dry THF. After 5 min, a solution of 185 mg (1.03 mmol) of pure lactone **12** in 3 mL of dry THF was added to the mixture which was kept at −20 °C for 4½ h. Then, 0.15 mL of water was added at room temperature and the mixture was directly flash chromatographed (20 %). The solvents were then removed and the residue was dissolved in 3 mL of methanol. 0.5 mL of 10 % NaOH was added and after 20 min at room temperature the methanol was distilled under reduced pressure. A small quantity of water was added and the mixture was extracted with ether. Flash chromatography (20 %) gave 100 mg (55 % yield) of crude octalone **14**. An analytical sample was obtained by crystallization at −20 °C followed by molecular distillation under reduced pressure: mp 31 °C; $[\alpha]_D^{20}$ −215, $[\alpha]_{579}^{20}$ −225, $[\alpha]_{546}^{20}$ −261, $[\alpha]_{436}^{20}$ −484 (*c* 1, EtOH) (Litt.[9], $[\alpha]_D$ +213 (*c* 0.2) for *ent*-**14**); EIMS *m/z* (rel int) 178 (M^+, 59), 163 (17), 137 (12), 136 (base), 135 (20), 122 (10), 121 (58), 109 (19), 108 (24), 107 (36), 94 (10), 93 (22), 91 (20), 79 (22), 77 (16); IR (neat) 1670, 1615 cm^{-1}; ^1H NMR δ 0.95 (d, J = 6.8 Hz, 3H), 1.08 (s, 3H), 1.19 (ddd, J_1 = 5.1 Hz, J_2 = 13 Hz, J_3 = 13 Hz, 1H), 1.29 to 1.45 (m, 1H), 1.55 to 1.72 (m, 2H), 1.86 to 2.03 (m, 3H), 2.17 to 2.48 (m, 4H), 5.74 (d, J = 1.3 Hz, 1H); ^{13}C NMR δ 14.74, 16.12, 21.78, 26.65, 32.94, 38.55, 38.95, 40.17, 42.04, 124.5, 171.5, 199.6.

(βS,1R)-β,1-Dimethyl-2-oxocyclohexanepropanoic acid (4): 100 mg (0.56 mmol) of pure lactone **12** was added under nitrogen to 0.93 mL (1.12 mmol, 2 equiv.) of 10 % HCl in 1 mL of dioxane and the mixture was stirred at room temperature for 20 min. After dioxan removal the residue was flash chromatographed (60 %) giving 108 mg (0.55 mmol, 98 % yield) of keto-acid **4** which was purified by molecular distillation: bp 120 °C (bath)/0.05 Torr; $[\alpha]_D^{20}$ +87, $[\alpha]_{579}^{20}$ +91, $[\alpha]_{546}^{20}$ +106, $[\alpha]_{436}^{20}$ +220 (*c* 1, EtOH) (Litt.[9], $[\alpha]_D^{20}$ −66 (*c* 1.3) for *ent*-**4**; EIMS *m/z* (rel int) 180 (M^+ −H_2O, 3), 154 (66), 113 (10), 112 (base), 111 (13), 110 (39), 109 (14), 97 (13), 95 (25), 84 (10), 83 (43), 82 (13), 81 (12), 69 (26), 67 (14), 55 (31); IR (neat) 3700-2300, 1730, 1705 cm^{-1}; ^1H NMR δ 0.91 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.42 (ddd, J_1 = 4.0 Hz, J_2 = 12.1 Hz, J_3 = 14.3 Hz, 1H), 1.58 to 1.88 (m, 3H), 1.93 to 2.17 (m, 4H), 2.29 to 2.37 (m, 1H), 2.49 to 2.69 (m, 2H), 9.08 to 9.52 (m, 1H); ^{13}C NMR δ 13.46, 17.17, 20.12, 27.43, 32.44, 36.81 (2 C), 38.47, 51.40, 179.1, 216.2.

Methyl (βS,1R)-β,1-dimethyl-2-oxocyclohexanepropanoate (5): A solution of 84 mg (0.42 mmol) of pure keto-acid **4**, 0.057 mL (0.46 mmol, 1.1 equiv.) of 2,2-dimethoxypropane and a trace of PTS acid in 2 mL of methanol, were heated at 80 °C for 5 h. After methanol removal under reduced pressure, the residue was chromatographed (20 %) giving 80 mg (0.38 mmol, 90 % yield) of keto-ester **5** which was purified by molecular distillation (GC-MS showed only one signal, at 3.70 min): bp 80 °C (bath)/0.05 Torr; $[\alpha]_D^{20}$ +77, $[\alpha]_{579}^{20}$ +81, $[\alpha]_{546}^{20}$ +96, $[\alpha]_{436}^{20}$ +196 (*c* 3, EtOH); EIMS *m/z* (rel int) 212 (M^+, 1), 181 (9), 168 (22), 139 (14), 113 (10), 112 (base), 111 (13), 110 (33), 109 (12), 97 (12), 95 (19), 83 (22), 82 (11), 81 (10), 69 (29), 67 (12), 59 (11), 55 (21); IR (neat) 1735, 1700 cm^{-1}; ^1H NMR δ 0.90 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.40 (ddd, J_1 = 3.9 Hz, J_2 = 12.1 Hz, J_3 = 14.1 Hz, 1H), 1.59 to 1.89 (m, 3H), 1.95 to 2.12 (m, 4H), 2.27 to 2.35

(m, 1H), 2.52 to 2.70 (m, 2H), 3.66 (s, 3H). ^{13}C NMR δ 13.60, 17.32, 20.28, 27.63, 32.64, 36.92, 37.03, 38.66, 51.61, 51.65, 173.7, 216.2.

Reaction with methyl methacrylate (15)

ca. 6 g of crude imine **1** [obtained from 3.30 mL (27.2 mmol) of 2-methylcyclohexanone], and 2.80 mL (1 equiv.) of methyl methacrylate were heated at 85 °C for 24 days and the mixture was then analyzed by GC-MS. Besides unreacted imine **1**, three signals were observed: 8.50 min (17 %, unresolved regioisomers of **16**), 8.80 (80 %, **16**), 8.92 [3 %, diastereoisomer (*syn*) of **16**]. The mixture was then diluted with 13 mL of methanol and 10 mL of THF. Hydrolysis was run at room temperature by adding 15.5 mL (1 equiv.) of a 10 % aqueous acetic acid solution. After 20 mn the solvents were removed by distillation at normal pressure and the residue was extracted with ether and washed with a 10 % HCl solution followed by the usual work-up. The residue was analyzed by GC-MS. Besides 2-methylcyclohexanone, signals at 4.14 min (82 %, **17**) and 4.24 + 4.34 (18 %, regioisomers of **17**) were observed. The mixture was then distilled under reduced pressure (0.05 Torr, bath 90 °C) giving 0.776 g (6.93 mmol) of 2-methylcyclohexanone (*i.e.* 74.5 % conversion) and 2.97 g (14 mmol, 69 % total yield of isomers) of a mixture of keto-ester **17** (88 %) and its regioisomers (12 %). 230 mg of this mixture was then dissolved in 2 mL of methanol and the solution was saturated with ammonia, under a nitrogen atmosphere, and kept at room temperature for 85 h. After concentration at reduced pressure and flash chromatography (20 %, then methanol), 50 mg (78 % conversion) of unreacted **17** and 130 mg of the probable hydroxylated intermediate corresponding to lactam **9** were obtained. 120 mg of this intermediate was dissolved in 3 mL of toluene and heated at 100 °C for 2 h. Concentration followed by flash chromatography (60 %) gave 90 mg (*ca.* 75 % yield from reacted keto-ester **17**) of lactam **9**: $[\alpha]_D^{20}$ +150 (*c* 1.2, EtOH), *i.e.* dextrorotatory; GC-MS of this compound, the one obtained from phenyl methacrylate (*vide supra*) as well as that of a 50 : 50 mixture of both, were identical; ^{1}H NMR of both samples are also identical.

(3*S*,4a*R*)- and (3*R*,4a*R*)-3,4a-Dimethyl-3,4,4a,5,6,7-hexahydro-2*H*-1-benzopyran-2-one (19) and (20). The above experiment was repeated at a larger scale and 4.70 g (22.2 mmol) of the non distilled mixture was flash chromatographed (20 %) giving a residue of keto-ester **17** and its regioisomers which was hydrolyzed with 37 mL of a 10 % aqueous HCl solution and 35 mL of dioxane, heated at 50 °C for 5 days. After concentration under reduced pressure, ether extraction followed by the usual work-up and flash chromatography (80 %), 4.40 g (22.2 mmol, quantitative yield) of a mixture of keto-acid **18** and its regioisomers was obtained and analyzed by GC-MS: partially resolved signals were observed for keto-acid **18** and its isomers, centered at 4.46 min (**18**) and 4.52 min. 1.54 g (7.80 mmol) of this mixture and 0.064 g (0.78 mmol) of NaOAc in solution in 39 mL of $(AcO)_2O$ was heated at reflux for 1 h. The mixture was then analyzed by GC-MS: 3.22 min (**20**), 3.44 min (regioisomers of **19**), 3.54 min (**19**), relative % 22 : 5 : 73 [percentages of *non isomeric* intermediates from regioisomers of **18** (5.41 to 5.57 min) are not reliable]. Acetic anhydride was removed with a rotary evaporator and the residue extracted with ether and washed with a saturated Na_2CO_3 aqueous solution followed by the usual work-up. Flash chromatography (10 %) yielded an analytical sample of pure *cis*-lactone **20** and 1.16 g (6.40 mmol, 83 % yield) of a mixture of **20**, the regioisomers of **19**, and *trans*-lactone **19** (~22 : 5 : 73). This mixture was crystallized in hexane at –20 °C, giving *trans*-lactone **19** which was recrystallized several times.

19: mp 61-63 °C (hexane); $[\alpha]_D^{20}$ +113 (*c* 1, EtOH). EIMS *m z* (rel int) 180 (M^+, 37), 137 (10), 124 (11), 111 (base), 110 (93), 109 (22), 108 (12), 95 (15), 93 (14), 81 (15), 69 (54), 67 (24), 55 (44), 53 (10), 43 (42), 41 (40); IR (nujol) 1745, 1675 cm^{-1}. ^{1}H NMR δ 1.20 (s, 3H), 1.32 (d, J = 7.1 Hz, 3H), 1.42 to 1.51 and 1.46 (m and dd, J_1 = 13 Hz, J_2 = 13 Hz, 2H), 1.63 to 1.74 (m, 3H), 1.80 (dd, J_1 = 6.6 Hz, J_2 = 13.2 Hz, 1H), 2.05 to 2.12 (m, 2H), 2.81 (ddq, J_1 = 7 Hz, J_2 = 7 Hz, J_3 = 13 Hz, 1H), 5.21 (dd, J_1 = 3.2 Hz, J_2 = 4.6 Hz, 1H); ^{13}C NMR δ 17.27, 17.91, 22.69, 23.16, 32.22, 33.05, 37.28, 42.04, 105.0, 154.1, 171.4.

20: EIMS *m z* (rel int) 180 (M^+, 32), 137 (11), 124 (12), 111 (base), 110 (87), 109 (20), 108 (11), 95 (15), 93 (13), 81 (16), 69 (51), 67 (21), 55 (40), 53 (11), 43 (43), 41 (39). ^{1}H NMR δ 1.17 and 1.19 (d and s, J = 7 Hz, 6H), 1.26 to 1.40 (m and dd, J_1 = 13 Hz, J_2 = 13 Hz, 2H), 1.62 to 1.70 (m, 3H), 1.86 (dd, J_1 = 7.4 Hz, J_2 = 13.3 Hz, 1H), 2.07 to 2.12 (m, 2H), 2.48 (ddq, J_1 = 7 Hz, J_2 = 7 Hz, J_3 = 12 Hz, 1H), 5.35 (dd, J_1 = 4 Hz, J_2 = 4 Hz, 1H); ^{13}C NMR δ 15.02, 18.72, 23.35, 26.94, 33.67, 34.39, 37.54, 41.84, 108.7, 153.3, 174.8.

(αS,1R)-α,1-Dimethyl-2-oxocyclohexanepropanoic acid (18). 76 mg (0.42 mmol) of lactone **19**, 0.7 mL of a 10 % aqueous HCl solution and 1 mL of dioxane were stirred under a nitrogen atmosphere at room temperature for 2 h. The solvent was then removed with a rotary evaporator and the residue flash chromatographed (20 %, then 80 %), giving 78 mg (0.39 mmol, 94 % yield) of keto-acid **18** as a colorless oil; an analytical sample was obtained by molecular distillation: bath temperature 110 °C/0.02 Torr; $[\alpha]_D^{20}$ +61 (*c* 2, EtOH); EIMS *m z* (rel int) 180 ($M^+ - H_2O$, 1), 154 (20), 125 (11), 112 (base), 109 (25), 97 (30), 83 (24), 81 (12), 74 (15), 69 (18), 55 (27); IR (neat) 3600-2300, 1735, 1705 cm^{-1}; ^1H NMR δ 1.11 (s, 3H), 1.23 (d, J = 7 Hz, 3H), 1.46 (dd, J_1 = 3.0 Hz, J_2 = 14.4 Hz, 1H), 1.63 to 1.89 (m, 6H), 2.25 to 2.59 (m, 4H), 9.80 to 10.70 (m, 1H); ^{13}C NMR δ 20.12, 20.92, 22.97, 27.41, 35.51, 38.66, 39.94, 41.41, 48.69, 182.5, 216.0.

Methyl (αS,1R)-α,1-Dimethyl-2-oxocyclohexanepropanoate (17). A solution of 65 mg (0.33 mmol) of keto-acid **18**, 0.045 mL (0.36 mmol) of 2,2-dimethoxypropane and a trace of PTS acid in 2 mL of methanol were heated at 80 °C for 5 h. The solvent was then removed with a rotary evaporator and the residue flash chromatographed (20%) giving 60.3 mg (0.28 mmol, 86 % yield) of keto-ester **17**: a colorless oil analytical sample was obtained by molecular distillation: bath temperature 90 °C/0.02 Torr; $[\alpha]_D^{23}$ +81 (*c* 2, EtOH); EIMS *m z* (rel int) 181 ($M^+ - CH_3O$, 10), 125 (11), 112 (base), 109 (19), 97 (26), 95 (12), 88 (50), 83 (22), 81 (11), 69 (21), 67 (13), 59 (10), 55 (37); IR (neat) 1730, 1700 cm^{-1}; ^1H NMR δ 1.06 (s, 3H), 1.17 (d, J = 7 Hz, 3H), 1.41 (dd, J_1 = 2.9 Hz, J_2 = 14.3 Hz, 1H), 1.58 to 1.92 (m, 6H), 2.27 to 2.40 (m, 2H), 2.44 to 2.60 (m, 2H), 3.62 (s, 3H); ^{13}C NMR δ 20.07, 20.84, 22.73, 27.33, 35.48, 38.50, 40.27, 41.71, 48.39, 51.43, 177.2, 215.3.

X-ray structure determination of lactam 8

$C_{15}H_{25}NO$, MW = 283.4. A suitable crystal was investigated on a *Siemens* P3 diffractometer (M_oK_α radiation, λ = 0.71069 Å, graphite monochromator). Orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.009(3), b = 11.966(6), c = 17.245(7) Å, d_c = 1.14 g·cm^{-3}, $F(000)$ = 616, μ = 0.37 mm^{-1}. 2786 reflections up to 2θ = 60° of which 692 with $I > 4\sigma(I)$ were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[10] and refined by least-squares with SHELX76[11], minimizing the quantity $\sum w(F_o - F_c)^2$; all non-hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located in difference Fourier maps and refined at observed positions with isotropic temperature factors. Final $R = \sum(F_o - F_c)/\sum F_o = 0.046$, $W_R = [\sum w(F_o - F_c)^2/\sum w \cdot F_o^2]^{1/2} = 0.050$ with $w = 1/\sigma^2(F_o)$. The final difference density shows no features up to 0.136 e·Å^{-3} and down to 0.135 e·Å^{-3}. Lists of the fractional atomic coordinates, isotropic thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK, as supplementary material.

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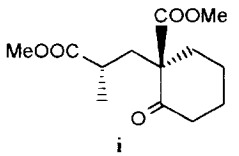
5 Two examples dealing with the imine obtained from 2-methylcyclohexanone and (*R*)-1-phenylethylamine have already been reported[6]. In the first one, crotonyl cyanide was the electrophile and two related chiral diastereoisomers were obtained but with less than 50% combined yield. Moreover they were possibly formed by a different mechanism[1b]. In the second example, methyl 2-phenylthioacrylate was used. The major adduct which was obtained in 80% yield and 90% *ee*, has a diastereoisomeric relationship of the substituents which could arise from a chairlike approach of the reactants, but only if the sulfur atom rather than the carbon atom of the carbonyl group is included in the chair. A third example recently reported, also concerning a particular case, dealt in this instance with a secondary enaminoester obtained from 2-carbomethoxycyclohexanone and (*R*)-1-phenylethylamine[7]. This chiral compound was reacted with excess methyl methacrylate in the presence of 1.2 equivalents of $MgBr_2$, leading after hydrolysis to a single compound claimed to be the diastereoisomer **i** (86% yield, *de* and *ee* > 95%). Surprisingly, this compound has the opposite diastereoselective relationship (*anti*) than that of compound **17** (scheme 8) which we have obtained in this work, as expected, by reaction of the imine from 2-methylcyclohexanone and (*S*)-1-phenylethylamine with methyl methacrylate, under the usual reaction conditions without catalyst. The same diastereoselective relationship was already observed in the (cyclized) racemic compound obtained by the reaction of the imine from 2-methylcyclohexanone and benzylamine with methyl methacrylate[4] (*vide supra*).



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