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THE ASYMMETRIC MICHAEL ADDITION PROCESS INVOLVING CHIRAL IMINES : STEREOCHEMICAL DATA IN SUPPORT OF A CYCLIC-LIKE TRANSITION STATE

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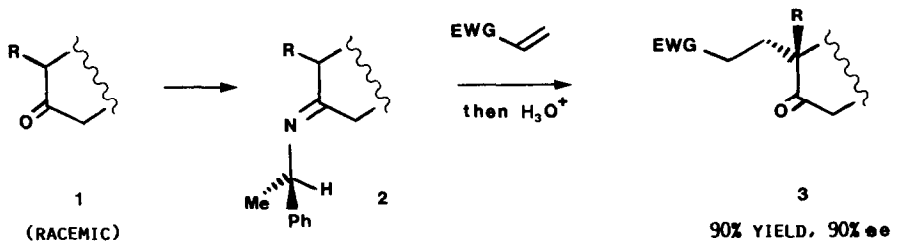
Summary : *Additions of imine 4 to Michael acceptors 5 and 8 are both highly selective processes. The observed stereocontrol of the newly created asymmetric centers in the resulting adducts strongly supports cyclic-like transition states.*

Two of us have recently published a very efficient method for the enantioselective synthesis of compounds bearing a quaternary carbon center, 3 [1a]. This new reaction involves the regioselective "*deracemizing alkylation*" of α-substituted cyclanones 1, through the conjugate addition of their chiral imines derivatives 2 to electron-deficient alkenes. Already used in steroid chemistry [1b], this extremely promising method is currently applied to the enantioselective approaches to many other natural compounds : terpenes, alkaloids ..., by ourselves and others [2].

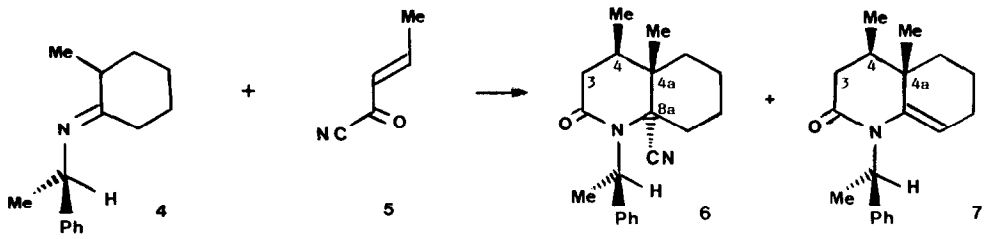


A compact, chair-like transition state has been proposed for such a process, on the basis of a theoretical study involving *ab initio* SCF calculations [3]. In this paper, we report two sets of experimental results that both strongly support the above mentioned mechanism, namely the high stereocontrol level of two newly asymmetric centers, created at α and β to the quaternary carbon center respectively, by using appropriately substituted electron-deficient olefins.

Simultaneous creation of a second asymmetric center at α to the quaternary one

β-Substituted Michael acceptors, which are required for such a study, are in general strongly deactivated partners, compared to their unsubstituted counterparts [1]. Thus, for example, (*E*) methyl crotonate does not react with imine 4 [prepared from 2-methylcyclohexanone and (*R*)-(+)-1-phenylethylamine [1a]], even under forced conditions. However, this

imine adds smoothly to very reactive (*E*) crotonyl cyanide 5 [4] ; in cyclohexane the alkylation takes place exclusively at the *more* substituted α-side of the imine, giving a mixture of closely related bicyclic lactams 6 and 7 [5].



The *cis* relationship between the methyl groups at C-4 and C-4a centers in products 6 and 7 was unequivocally assigned from their ^{1}H NMR spectra, the analysis of the H_3-H_4 coupling constants establishing in both cases that the C-4 Me group is *equatorial*. Moreover, the absolute configurations of the three newly created asymmetric centers in bicyclic adduct 6 (4*R*,4a*S*,8a*R*) were established by an X-ray diffraction analysis of this compound (Fig. 1).

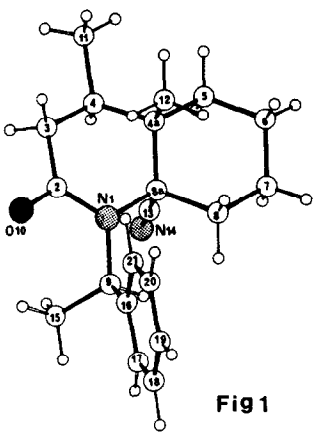
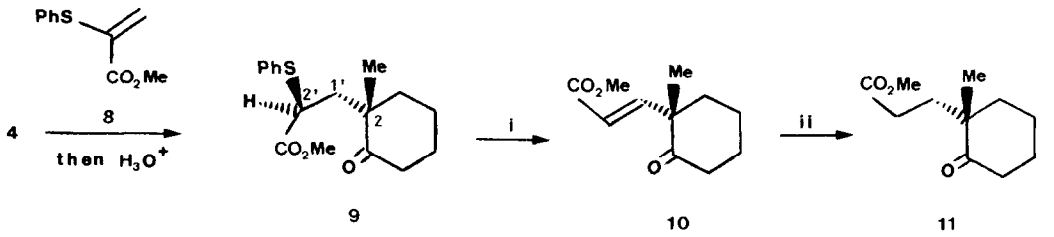


Fig 1

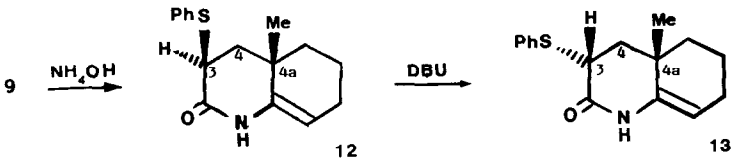
Simultaneous creation of a second asymmetric center at β to the quaternary one

Such a study requires a disymmetrically *gem*-disubstituted electron-deficient olefin as a Michael acceptor ; for this purpose we used the highly versatile methyl α-(phenylthio)acrylate 8 [6]. Imine 4 adds very smoothly to this acceptor leading exclusively, after hydrolytic work-up, to "quaternary" adduct 9 [7] (major diastereoisomer depicted). The *S* configuration (90 % ee) at the created C-2 quaternary carbon center was unambiguously determined by the conversion of adduct 9 into (*S*) keto-ester 11, enantiomer of a compound we have previously described [1a], through the unsaturated intermediate 10.



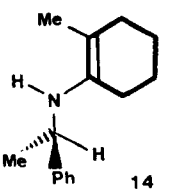
i MCPBA THEN HEAT ii H_2/PtO_2

The *S* configuration at C-2' center was easily established by the following transformations. Treatment of adduct 9 with aqueous ammonia led to bicyclic ene-lactam 12 [8], which was then converted, under basic conditions, into the thermodynamically more stable epimer 13 [9], thus establishing that the phenylthio group is *axial* in compound 12 and *equatorial* in isomer 13. More data in support of these stereochemical assignments were obtained from the ^{1}H NMR spectra of these diastereoisomers (H_3-H_4 coupling constants analysis and nOe measuring experiments).

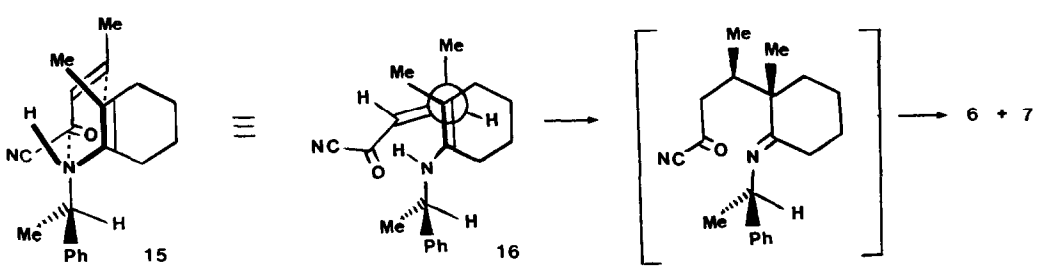


Discussion

Let us first consider the tautomeric equilibrium between the starting imine 4 and secondary enamine 14 which is in fact, the reactive nucleophilic species in this Michael addition process [1-3]. A brief examination of molecular models shows that the energetically preferred conformation for compound 14 is the one depicted here, in which the main steric repulsions are minimized. This qualitative assessment is supported by extended Hückel calculations that, in addition, assign important barrier energies to internal rotation about the two C-N single bonds ; the present enamine conformation should therefore be preferentially taken into account in the corresponding transition states.

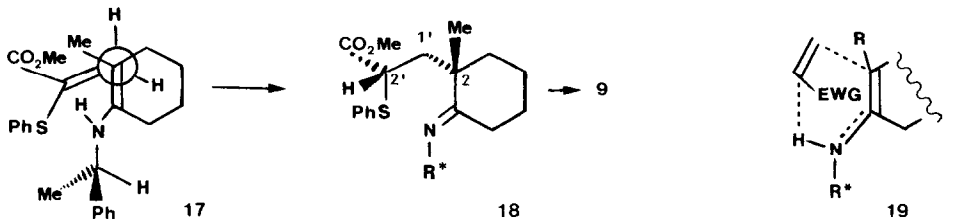


As suggested by the theoretical study [3], the formation of bicyclic lactams 6 and 7 probably involves the chair-like structure of compact approach 15, and consequently a *gauche* (synclinal) arrangement of reactant partners 14 and 5, as depicted in the corresponding Newman projection 16. Reactants approach structure 16 takes into account the observed *cis* relationship between the C-4 and C-4a Me groups in products 6 and 7 ; moreover in agreement with our previous findings [1], the starting chiral inductor (*R*)-1-phenylethylamine leads to an *S* configuration at the C-4a created quaternary carbon center (the alkylation process being *synplanar* -as depicted- to the methyl group borne by the chiral amine moiety). Furthermore, owing to the favorable geometry of the NH (*syn* to the double bond in enamine 14) a facile, more or less concerted proton transfer may be expected in this process.



A cyclic transition state involving the *gauche* approach of reactants 17 can be also adequately postulated for the addition : 4+8 → [18] → 9. It is clear that the high stereocontrol level observed at C-2' center in product 9 involves that the proton borne by the nitrogen atom of enamine partner 14 should be transferred to the α carbon atom of acceptor 8 (future C-2' center in compound 9), *concertedly* with the formation of the C_2-C_1, bond. Moreover, to take into account the *S* configuration at C-2' center, the electron-deficient olefin 8 must be arranged as depicted in approach 17. It should also be noted that, once again, the starting (*R*)-1-phenylethylamine induces an *S* configuration at the C-2 quaternary carbon center.

To conclude, as a consequence of the above mentioned concerted proton transfer, the transition state of the present Michael addition process is best represented by the "*aza ene synthesis-like*" cyclic activated complex 19 [10].



References and Notes

1(a) Pfau M., Revial, G. ; Guingant, A. ; d'Angelo, J. J. Am. Chem. Soc. **1985**, (107), 273-274. **(b)** Volpe, T. ; Revial, G. ; Pfau, M. ; d'Angelo, J. Tetrahedron Lett. **1987**, (28), 2367-2370.

2. An interesting *intramolecular* application of our methodology has been reported : Hirai, Y. ; Terada, T. ; Yamazaki, T. J. Am. Chem. Soc. **1988** (110), 958-960.

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

4. Compound 5 was prepared according to : Normant, J.F. ; Piechucki, C. Bull. Soc. Chim. Fr. **1972**, 2402-2403. Use of this compound in synthesis : El-Abed, D. ; Jellal, A. ; Santelli, M. Tetrahedron Lett. **1984**, (25), 4503-4504 and ref. cit. therein.

5. An equimolar mixture of 4+5 was stirred for 24 h at 5 °C. Combined yield of 6+7 : 40-50 %. Any other definite compounds could be detected by careful analysis (HPLC) of the crude. 6 : crystals, mp 140 °C. 7 : crystals, mp 69 °C.

6. Compound 8 was prepared according to : Leyendecker, F. ; Comte, M.T. Tetrahedron Lett. **1982**, (23), 5031-5034.

7. An equimolar mixture of 4 and 8 was stirred for 24 h at 20 °C in THF ; the crude was then hydrolyzed with 1.5 N AcOH. Compound 9 was obtained as an oil in a 80 % yield.

8. 12 : crystals, mp 217 °C ; $[\alpha]_D^{20}$ -245°(c 1.16, $CHCl_3$).

9. 13 : oil : $[\alpha]_D^{20}$ -160 ° (c 1.02, EtOH).

10. The present mechanism agrees with the "topological rules" proposed by D. Seebach : Seebach, D. ; Beck, A.K. ; Golinski, J. ; Hay, J.N. ; Laube T. Helv. Chim. Acta, **1985** (68), 162-172 (and ref. cited therein). Other recent examples of enantioface differentiating Michael addition process : Enders, D. ; Papadopoulos, K. ; Rendenbach, B.E.M. Tetrahedron Lett. **1986** (27), 3491-3494. Tomioka, K. ; Yasuda, K. ; Koga, K. J. Chem. Soc., Chem. Comm., **1987**, 1345-1346.

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