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A New Asymmetric Bridging Annulation Reaction Involving the Intramolecular Michael Addition of Chiral Imines to Enoates

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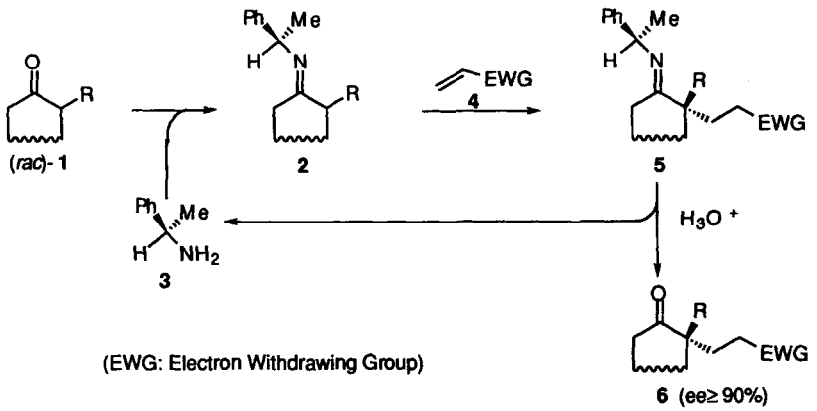
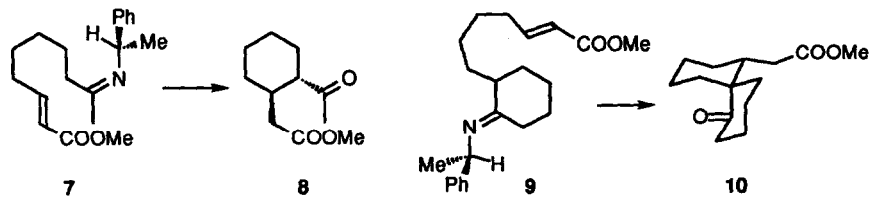
*Abstract : Thermal cyclization of imine **12b** led ,after hydrolytic work-up, to bicyclic derivative **13b** with a very high control of the three newly created stereogenic centers. In contrast adducts **13a** and **13c**, resulting from the cyclization of imines **12a** and **12c** respectively, were obtained as complex mixtures of stereomers.*

A few years ago we have reported that chiral imines **2** derived from *racemic* 2-alkylcyclanones **1** and optically active 1-phenylethylamine **3**, add to electrophilic alkenes **4**, giving adducts **5**. Acidic hydrolysis of **5** led to 2,2-dialkylcyclanones **6**, obtained with an excellent overall yield and with a high degree of regio- and stereoselectivity, along with the recovered, unchanged chiral auxiliary amine.[1]



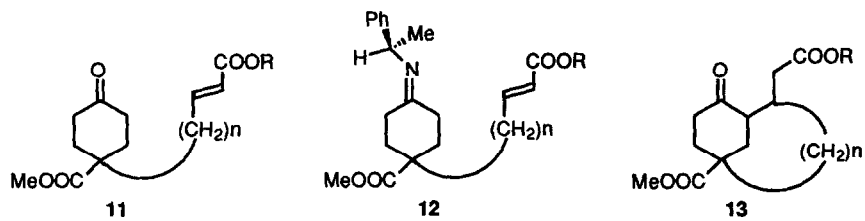
Several intramolecular variants of this highly potent asymmetric Michael reaction have been recently explored. Thus, for example, *carbocyclization* of iminoester **7** gave the cyclohexane derivative **8** with a 92 % ee.[2] Likewise iminoester **9** underwent a *spiroannulation*, furnishing adduct **10** with a high level of control (≥ 90 %) of the relative and absolute configurations of the two newly created stereogenic centers.[3]



7 8 9 10

The purpose of the present paper is to report the *bridging annulation* of keto-enoates **11**[4] into **13**, *via* their corresponding chiral imines **12**. It is worthy of note that, due to the C_2-symmetry of the molecule, the centers in the α-position to the carbonyl group in ketone **11** are *enantiotopic*. The same centers becoming *diastereotopic* in the corresponding imine derivatives **12**, they would now be differentiated during the annulation process, thereby allowing control of the absolute configuration of the three newly created stereogenic centers in bicyclic adducts **13**.

In fact the efficacy of this ring closure, as well as its stereoselectivity, were found to be highly dependent on the length of the enoate appendage in starting compounds **11**. Thus, although cyclization of imino-esters **12 a, b, c** proved to be efficient, giving the expected bridged derivatives **13 a, b, c** respectively, all efforts to annulate **12d** were fruitless. On the other hand, of the three successful bridging annulations, only the process leading to the [3,3,1]-type bicyclic derivatives **13b** was found to be highly stereoselective, adducts **13a** and **13c** having been obtained as complex mixtures of stereomers.



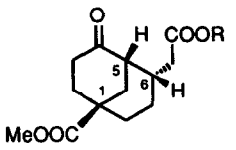
11 12 13

a: n = 1 ; **b**: n = 2 ; **c**: n = 3 ; **d**: n = 4 (R = Me or Bn)

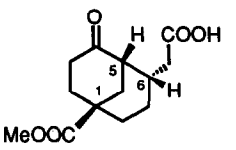
Imine **12b** (R = Me) was prepared in an almost quantitative yield by stirring an equimolar mixture of keto-enoate **11b** (R = Me) and (*R*)-1-phenylethylamine (cyclohexane, 1 h at 20° in the presence of a catalyst[5]). This imine cyclized under relatively mild thermal conditions (3h, 80°C, in toluene), leading after acidic work-up (10 % AcOH in water, 20°C, 1h), the bicyclo-[3,3,1]-nonane derivative **13b** (R = Me)[6] with a 80 % yield. A complete *relative* control of the three newly created stereogenic centers in the bicyclic adduct was obtained, this compound proving to be homogeneous by (non-chiral) CPV analysis, and by ^{13}C and ^{1}H NMR spectroscopy (including in the latter case experiment using Eu (FOD)$_3$ as shift reagent). The ee in this adduct was found to be 90 % (by ^{1}H NMR, using Eu (hfc)$_3$ as shift reagent, by comparison with a *racemic* specimen, prepared from *racemic* 1-phenylethylamine). Similar findings were obtained in the conversion of keto-enoate **11b** (R = Bn) into **13b** (R = Bn).

The *relative* stereochemistry in adducts **13b** was determined by X-ray analysis of the corresponding acid **14**[7] (molecular structure **16**), itself resulting from the hydrogenolysis of **13b** (R = Bn)

(3 bars of H_2, Pd/C, quantitative). The *absolute* configuration in adducts **13b** was established as being predominantly 1*S*, 5*S*, 6*S*, by chemical correlation of acid **14** with olefin (1*S*, 5*S*)-**15**[8] ($PhI(OAc)_3$, $Cu(OAc)_2$, pyridine)[9]. The configuration of this olefin was assigned by CD spectroscopy, the molecule exhibiting a negative Cotton effect, as predicted by the octant rule.[10]



13 b (R = Me or Bn)



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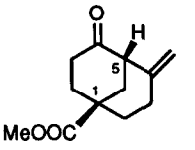
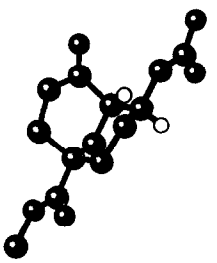
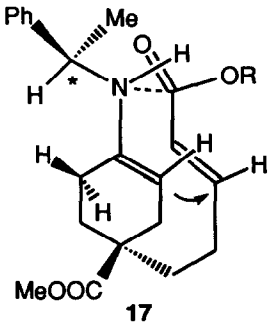


15

The stereochemical outcome observed in the conversion [**12b** → **13b**] may be interpreted, assuming that the reaction proceeded through the "all-boat", compact approach **17**, in which the nucleophilic species was a secondary enamine in tautomeric equilibrium with the imine function.[1] In such an approach, the *syn* arrangement of the enamine part and of the enoate moiety (a conformation stabilized by the N··· C=O bonding interaction) accounted for the relative configuration of resulting adducts **13b** (acetate appendage *anti* to the bridge). The *absolute* configuration of these adducts may be rationalized, considering that the alkylation took place preferentially on the less hindered enamine π-face, *anti* to the phenyl nucleus (α-side of the molecule), having depicted the chiral amine moiety in its putative reactive conformation[1], namely the N-H *syn* to the enamine double bond (geometry required for a more or less concerted proton transfer), and the C*-H bond nearly eclipsing an *equatorial* hydrogen atom of the cyclohexene ring.



16 (= **14**)

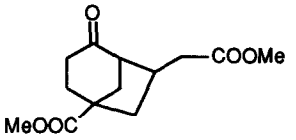


17

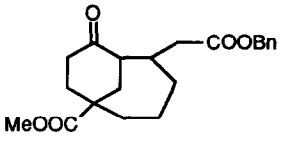
(only H's on stereogenic centers shown for clarity)

Cyclization of imine **12a** (R = Me) (6 h in refluxing toluene) led, after hydrolytic work-up, to bicyclo-[3,2,1]-octane derivative **13a** (R = Me) with a 70 % yield. This was obtained as a mixture of diastereomers (60 % de), both exhibiting a low optical purity (30 % ee). Annulation of **12c** (R = Bn) required somewhat more drastic conditions (48h in refluxing toluene) affording, after hydrolytic work-up, the bicyclo-[4,3,1]-decane derivative **13c** (R = Bn) with a 50 % yield (20 % de, ee not determined). This compound proved to be rather unstable, since regenerating partially starting keto-enoate **11c** (R = Bn) by

flash chromatography on silicagel, as the result of a facile retro-Michael-type fragmentation. In contrast, all attempts to prepare bicyclo-[5,3,1]-undecane derivative, starting from imine **12d** (R = Bn), were uniformly unsuccessful, because delivering the unreacted starting imine and/or polymeric materials.



13 a



13 c

The striking decrease of stereoselectivity observed in the formation of compounds **13a** and **13c**, compared to **13b**, clearly reflected a dramatic change in the mechanism of this bridging annulation (possibly due to competition between *syn* and *anti* approaches, and reversibility of the addition process). Work is in progress in our laboratory to continue the study of this interesting asymmetric annulation.

Acknowledgments : *We thank L. Leroy and J. Bolard (LPCB, Université Pierre et Marie Curie, Paris) for providing us the CD spectrum of compound* ***15***.

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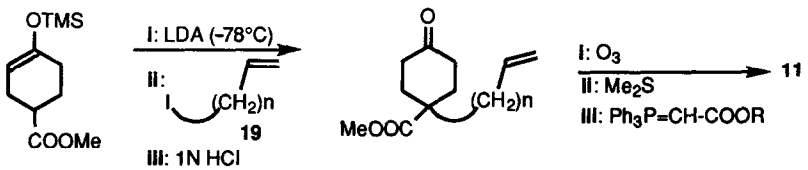
2. Dumas, F.; d'Angelo, J. *Tetrahedron : Asymmetry* **1990**, *1*, 167-170.
3. d'Angelo, J.; Ferroud, C.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1989**, *30*, 6511-6514.
4. Keto-enoates **11** were prepared as follows. Alkylation of compound **18** (Jung, M.E.; Mc Combs, C.A. *Tetrahedron Lett.* **1976**, 2935-2938) with iodo-alkenes **19** led to derivatives **20** with a 70 % yield. Ozonolysis of **20**, followed by Wittig condensation then gave **11** with a 80 % yield.



18 **20**

5. This catalyst was prepared by calcinating with a free flame under vacuum (O.1 Torr) before use, a mixture of powdered 5 Å molecular sieves (10 parts), silica gel 60 (0.04-0.063 mm) (1 part) and aluminium oxide neutral (type T) (2 parts).
6. **13b** (R = Me) : colorless oil; IR(neat) 1722 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ : 1.25–1.48 (m, 1H) 1.68–2.65 (m, 13H) 3.68 (s, 3H) 3.72 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ : 212.9 177.5 172.7 52.1 51.6 48.4 40.0 38.7 38.1 36.1 34.6 34.5 30.1 26.8; $[\alpha]^{20}_D$ + 6.1 (c = 3.5, MeOH).
7. **14** : solid, mp : 122°C ($CHCl_3$); $[\alpha]^{20}_D$ + 13.0 (c = 2.3, MeCN).
8. **15** : colorless oil ; ^1H NMR (200 MHz, $CDCl_3$) δ : 0.76–2.66 (m, 10H) 3.15 (t, J = 2.9 Hz, 1H) 3.63 (s, 3H) 4.77 (dd, J = 7.8 , 1.2 Hz, 1H) 4.84 (br d, J = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ : 210.3 177.2 142.8 112.6 54.9 52.2 40.0 37.3 35.4 34.5 31.1 29.3; $[\alpha]^{20}_D$ + 64.0 (c = 1.12, MeCN); CD: $\Delta\varepsilon_{318}$ = -33.6 (MeOH).
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