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AN EFFICIENT ASYMMETRIC SPIROANNULATION PROCESS

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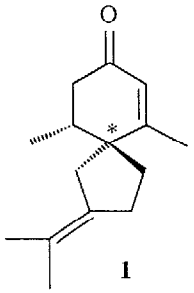
Abstract : *After hydrolytic work-up, intramolecular Michael-type alkylation of imine* **11** *gave spiro adduct* **13** *with a high degree of control of the two newly created asymmetric centers.*

Although spiro centers are widely distributed in natural products (e.g. in sesquiterpenes β-vetivone **1**, α-cedrene **2**, α-chamigrene **3**, ...)[1], very few methods have been devoted to the enantioselective construction of such carbon units[2].



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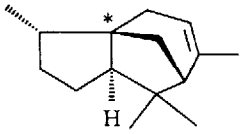

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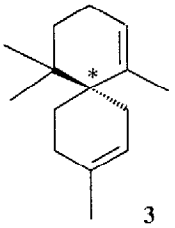

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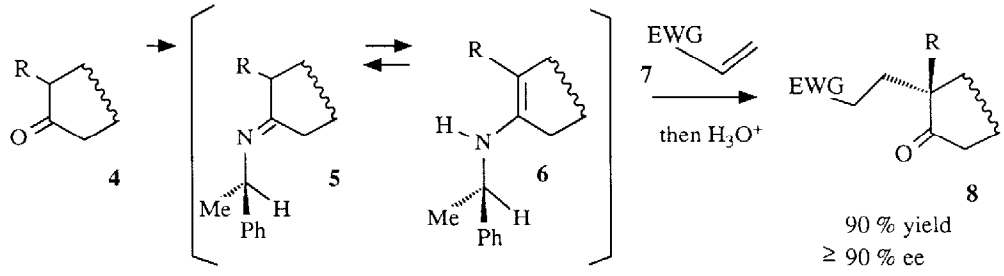
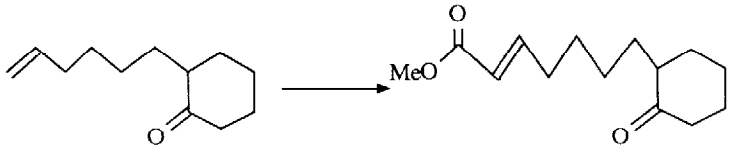
Spiro centers –which are, in fact, particular cases of quaternary carbon atoms– might easily be created by using an *intramolecular variant* of the highly potent asymmetric Michael alkylation that we disclosed[3], epitomized by the conversion [**4** → **8**]. Thus, imines **5**, derived from *racemic* α-substituted cyclanones **4** and optically active 1-phenylethylamine, add to electron-deficient alkenes **7** (the reactive nucleophilic species being tautomeric enamines **6**) to give, after hydrolytic work-up, regio- and stereoselectively α-disubstituted cyclanones **8** with high yields and excellent enantiomeric excesses.



In this paper we report the successful intramolecular application of this method to the preparation of the spiro [5.5] undecane derivative **13**, with a very high level of control of the (*relative and absolute*) configurations of the two newly created asymmetric centers.

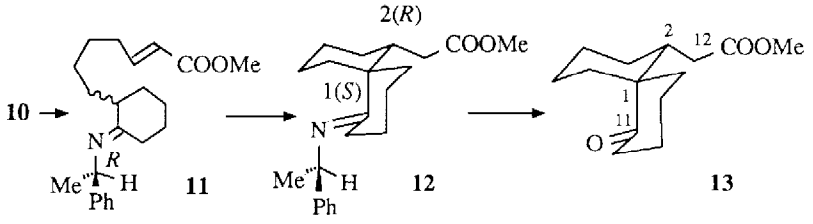
The requisite starting material **10** –a cyclohexanone α-substituted by a methyl heptenoate side-chain– was readily prepared as follows. The lithio salt of the imine derived from cyclohexanone and cyclohexylamine (LDA, THF, –78 °C, 0.5 h) was first alkylated with 1-bromo-5-hexene (20 °C, 12 h, then aqueous AcOH), giving quantitatively ketone **9**. Ozonolysis of the latter compound (CH_2Cl_2, –78 °C, then Me_2S), followed by Wittig condensation (Ph_3P=CH–COOMe, 20 °C, 24 h) gave the desired (*E*) keto-ester **10** (65 % overall yield)[4].



9 **10**

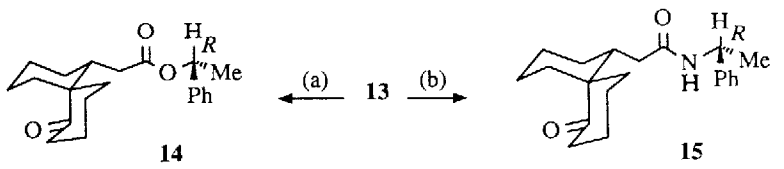
Imine **11**, prepared from this keto-ester and (*R*) 1-phenylethylamine (3 h in refluxing cyclohexane, in the presence of an activated catalyst[5]), was obtained quantitatively, as an equimolar mixture of diastereoisomers (^{1}H NMR)[6]. Thermally-induced cyclization of this imine (DMF, 120 °C, 12 h) led to the spiro derivative **12** (85 % yield) with a high stereocontrol of the two newly created adjacent asymmetric centers (^{1}H NMR)[7]. Hydrolysis (aqueous AcOH) of this imine then gave quantitatively keto-ester **13**. This compound exhibits *a high stereochemical homogeneity*, as established by the inspection of its ^{1}H and ^{13}C NMR spectra[8].

Note that the "one pot" conversion [**10** → **13**] could easily been performed, by heating an equimolar mixture of keto-ester **10** and chiral auxiliary amine in refluxing toluene (24 h, with azeotropic removal of water), followed by hydrolytic work-up.



The virtually complete control of the two asymmetric centers in keto-ester **13** was definitively proved by the following experiments, which established the homogeneity of its ester **14**[9] and amide **15**[10] derivatives. These were obtained by *quantitative* derivatization of adduct **13**, using (*R*) 1-phenylethanol or (*R*) 1-phenylethylamine as chirality markers, respectively. Careful HPLC analysis of ester **14** thus revealed the presence of only two minor accompanying isomers (each accounting for less than 5 % of the mixture), while the melting point of crude amide **15** was found to be almost unchanged, by fractional recrystallization in three different solvents (Et_2O, cyclohexane, iPr_2O).

The absolute configurations of the two contiguous asymmetric centers created during this spiroannulation reaction (1*S*,2*R*, as shown in compounds **12**, **13**, **14**, **15**) were unambiguously established by



(a) i : LiOH then H_3O^+ ii : (*R*) 1-phenylethanol, DCC, DMAP
(b) i : LiOH then H_3O^+ ii : $(COCl)_2$ iii : (*R*) 1-phenylethylamine

the X-ray structure determination of amide **15**[11] (Fig. 1), taking advantage of the (*R*) 1-phenylethylamine moiety as an *internal stereochemical probe.*

Discussion

The spiroannulation process described here shows that the *intramolecular* Michael addition of imines to a crotonate-type acceptor proceeds smoothly, compared to the related *intermolecular* alkylation[3d]. Moreover, in close analogy with the aforementioned intermolecular reaction [**4** → **8**], intramolecular addition in compound **11** is highly regioselective, taking place at the *more substituted* α-position of the imine, with the formation of spiro derivative **12** alone.

The *relative configuration* of the two newly created asymmetric centers in this adduct (C2-C12 bond of the acetate side-chain *syn* to the C1-C11 bond of the ring system) may easily be rationalized by assuming that this spiroannulation proceeds through the compact approach **16** (the reactive tautomeric enamine form of imine **11**). This approach involves a *gauche* (synclinal) arrangement between the ethylenic ester and the enamine parts, thereby allowing the transfer of the proton borne by the enamine nitrogen atom to the vinylic carbon center in the α-position to the ester, *concertedly* with the creation of the C-C bond (aza-ene-synthesis-like cyclic transition state)[3d]. Stereocorrelation model **16** also takes into account the observed *absolute configurations* of the two newly asymmetric centers in adduct **12**, making the assumption that this intramolecular Michael addition occurs, as indicated, on the π-face of the enamine *opposite* the phenyl ring of the chiral auxiliary amine appendage, the latter being depicted in its energetically preferred conformation[3d,3g].

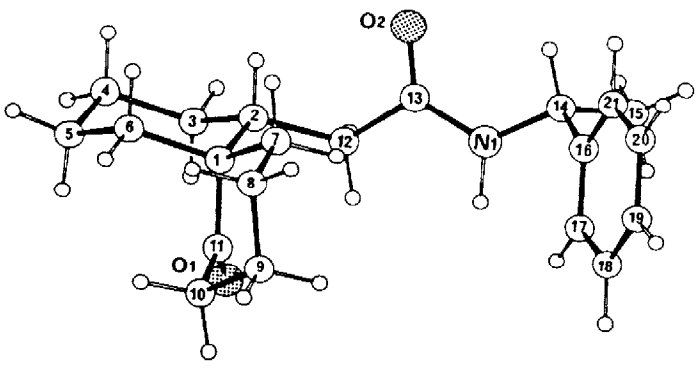
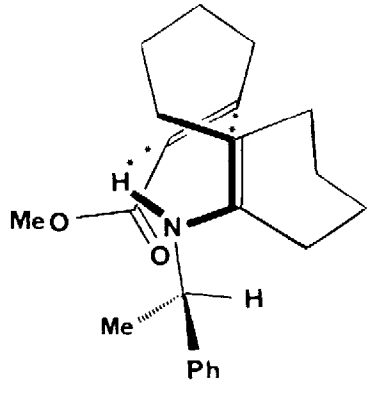


Fig. 1 : Molecular structure of amide **15**



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4. **9** : bp 130 °C (20 torr). **10** : IR (neat) 1740, 1710, 1660 cm^{-1}.

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6. **11** : ^1H NMR (90 MHz, CCl_4) δ 1.35 (d) 1.33 (d).

7. **12** : ^1H NMR (90 MHz, CCl_4) δ 1.33 (d).

8. **13** : oil ; $[\alpha]^{20}_D$ + 43.3° (c = 6.66, EtOH) ; IR (neat) 1735, 1700 cm^{-1} ; ^1H NMR (90 MHz, $CDCl_3$) δ 3.55 (s, 3H) ; ^{13}C NMR (20 MHz, $CDCl_3$) δ 215.3 (s) 174.2 (s) 51.7 (s) 51.5 (q) 39.4 (t) 38.2 (d) 37.3 (t) 35.0 (t) 32.9 (t) 27.7 (t) 27.0 (t) 23.4 (t) 21.4 (t) 20.4 (t).

9. **14** : oil ; ^1H NMR (90 MHz, $CDCl_3$) δ 1.50 (d, 3H) 5.85 (q, 1H) 7.30 (m, 5H) ; HPLC : Spherisorb S5W, 4.9 mm ID x 25 cm, AcOEt/cyclohexane 3:97.

10. **15** : mp 133 °C ; ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (d, J = 6.9 Hz, 3H) 5.10 (m, 1H) 5.97 (d, J = 7.60 Hz, 1H) 7.30 (m, 5H).

11. **15** Crystallographic study. C21 H29 N O2, M = 327.47. Crystals belong to the orthorhombic system (iPr_2O), space group $P2_12_12_1$ Z = 4. Cell parameters : a = 8.921 (4), b = 9.852 (5), c = 21.777 (8) Å, V = 1913.97 $Å^3$, d_c = 1.14 gcm^{-3}, λ(CuKα) = 1.5418 Å, μ = 4.9 cm^{-1} (absorption ignored).
Diffractometric intensity data were obtained from a very small crystal of 0.35 x 0.30 x 0.05 mm. From the 3080 unique reflections collected by the θ - 2θ scan-technique up to θ = 60 °, only 1161 were considered as observed having I ≥ 2.0σ (I) −σ(I) from counting statistics − and kept in refinement calculations. The structure was solved by direct methods[(1)] and refined by least-squares minimizing the function $\Sigma w(\Delta F)^2$ [(2)].
Most of the hydrogen atoms were located on difference Fourier maps. All of them were introduced in the refinement at theoretical positions (d C-H= 1.00 Å), except that one linked to nitrogen atom N-1, refined. They were assigned the equivalent isotropic thermal factor more 10 % of the bonded carbon atom. Final conventional R factor was 0.071, R_w was 0.083 with $w = 1/\sigma^2(Fo)+0.0095\ Fo^2$, residual electron density between −0.25 and 0.21 $eÅ^{-3}$.
In the crystal, the molecules are linked in infinite chains by means of hydrogen bonds built between the hydrogen atoms H-1 and the oxygen atoms O-2 of the nearest molecules (-x, +0.5+y, 1.5-z) (bonds N-1...O-2 = 2.93 (1), H-1...O-2 = 1.84 (2) Å, angle N-1..H-1...O-2 = 168.6°).
Lists of the atomic coordinates, bond distances and angles, torsion angles, have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material.
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