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ASYMMETRIC MICHAEL ADDITION OF CHIRAL IMINES TO PHENYLVINYLSULFONE : PREPARATION OF KEY CHIRAL BUILDING BLOCKS FOR THE SYNTHESIS OF *ASPIDOSPERMA* AND *HUNTERIA* ALKALOIDS.

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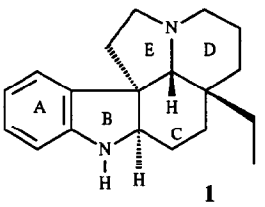
Abstract : Addition of chiral imine 8 to phenylvinylsulfone 9 led, after hydrolytic work-up to adduct 11 (91 % stereoselectivity). This derivative has been converted into target cyclopentanones 14 and 16.

Presence of an ethyl substituent at an angular quaternary carbon center is a common structural feature among the naturally occuring *Aspidosperma* and *Hunteria* alkaloids [1]. It is worthy of note that both opposite configurations at this quaternary center are found in the above indole alkaloids, as exemplified by (+)-aspidospermidine **1** and (+)-vincamine **2** [2].



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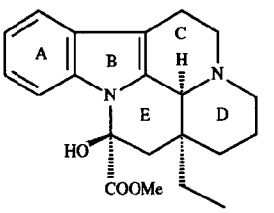
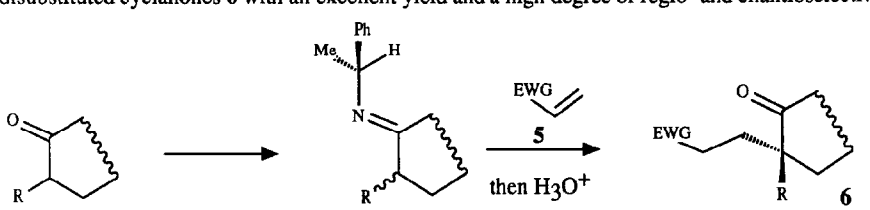


2

Several efficient enantioselective approaches to these molecules have been recently developed, using appropriately substituted butyrolactones or valerolactones as key chiral segments, precursors of the future ring D [3]. In this paper we report on a short and efficient asymmetric synthesis of cyclopentanones **14** and **16** which possess, similarly to the foregoing lactones, the skeleton as well as the functional groups required for a concise approach to alkaloids **1**, **2** and related compounds.

Cyclopentanones **14** and **16** bear a single stereogenic center, namely a quaternary carbon atom in the α-position to the carbonyl function of the ring. This particular molecular arrangement is encountered in adducts **6** which result from the very efficient asymmetric Michael process which we have disclosed, typified by equation [**3** → **6**] [4]. Thus chiral imines **4**, derived from *racemic* α-substituted cyclanones **3** and optically active 1-phenylethylamine, react with electron-deficient alkene **5** to lead, after hydrolytic work-up, to α,α-disubstituted cyclanones **6** with an excellent yield and a high degree of regio- and enantioselectivity.



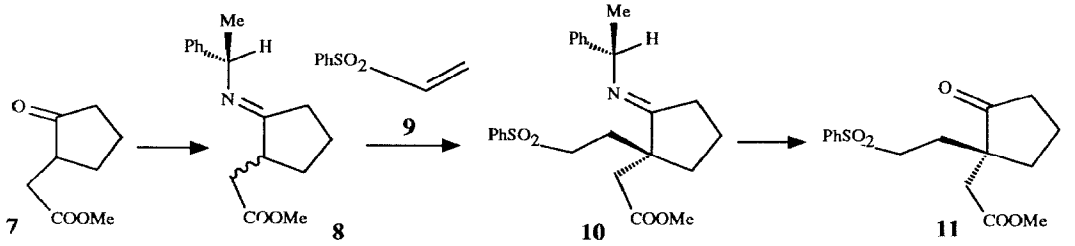
3 **4** **6**

90 % yield
90-95 % stereoselectivity

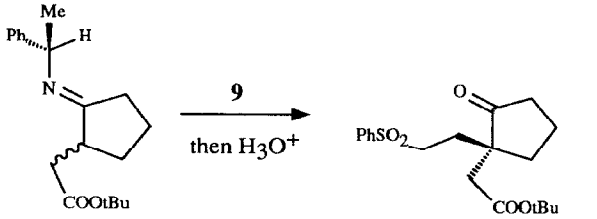
Two geminal appendages -an acetate and an ethyl group- are borne on the quaternary carbon

center of target cyclopentanones **14** and **16**. In the present strategy, ketone **7**, which contains the requisite acetate side-chain, is used as starting material, the ethyl group being next introduced, in an indirect manner, through the aforementioned Michael reaction. For this purpose the corresponding chiral imine **8** was added to phenylvinylsulfone **9**, and the ethyl group, "masked" in the resulting adduct **11**, was then generated by reductive cleavage of the phenylsulfonyl function [**11** → **14** or **16**].

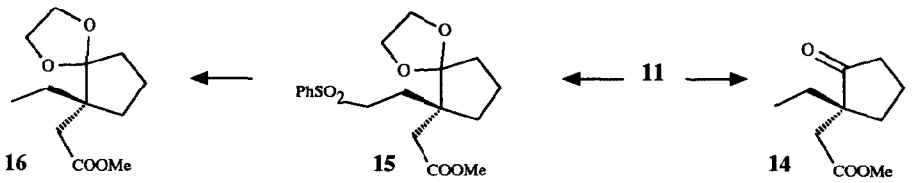
Chiral imine **8** was obtained quantitatively, as nearly equivalent mixture of diastereoisomers, from keto-ester **7** and *R*(+)-1-phenylethylamine ($[\alpha]_D^{20}$ + 39.1 , neat, 96 % ee), (powdered 4 Å molecular sieves, cyclohexane, 20 °C, 72 h). This crude imine was added to phenylvinylsulfone **9** (toluene, 80 °C, 24 h) to lead to imine **10** [5]. The selectivity of the reaction (91 % de) could be determined at this stage by ^{1}H NMR on an analytic sample of this imine (purified by flash chromatography on silica gel, eluent : hexane/AcOEt : 4/1 in the presence of a few amount of Et_3N). Hydrolysis of crude imine **10** (10 % acetic acid in water, 36 h at 20 °C) gave (*S*)-compound **11** [6] (74 % overall yield from **7**, 86 % ee, 91 % stereoselectivity). The ee of adduct **11** was established by ^{1}H NMR, using Eu $(hfc)_3$ as chiral shift reagent, and its absolute configuration was determined by chemical correlation (*vide infra*).



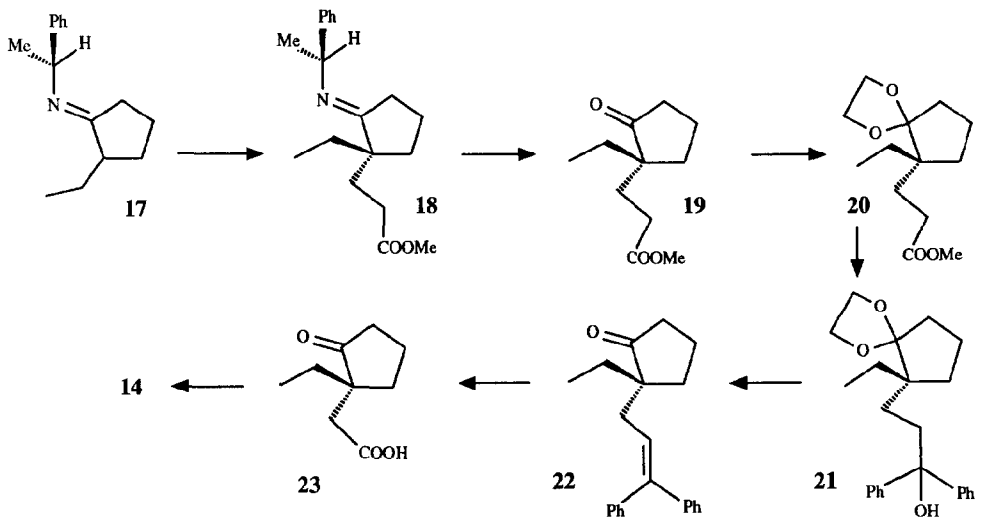
Similarly, addition of imine **12** to phenylvinylsulfone (toluene, 80 °C, 24 h) led, after hydrolytic work-up, to (*S*)-adduct **13** [7] (55 % yield, 86 % ee, 90 % stereoselectivity)



With the desired cyclopentanone **11** in hand, we turned next to its transformation into target compound **14** by reductive cleavage of the phenylsulfonyl function. Cleavage of a phenylsulfonyl group borne on a "non-activated" carbon center requires usually drastic reduction conditions. In the present case this conversion was performed by using a large excess of 6 % sodium amalgam in dry methanol [8], followed by acidification at pH 4 with acetic acid. The desired (*R*)-keto-ester **14** [9] was thus obtained, though with a low yield (30-35 %). Having attributed this low yield to the presence of the highly electrophilic ketonic function in starting material **11**, this carbonyl was protected by ketalization [**11** → **15**], (10 eq of ethylene glycol, *p* TsOH in refluxing toluene with azeotropic removal of water, 24 h, 90 % yield). As expected, cleavage of the phenylsulfonyl group in ketal **15** proceeds efficiently since, when submitted to the operating conditions of reduction of parent compound **11**, the (*R*)-ketal-ester **16** [10] was produced in a satisfactory yield (65-70 %).



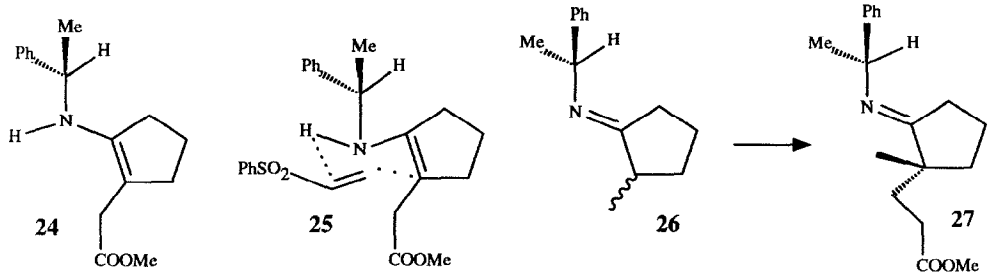
The *R* configuration in target compound **14** was established by the following chemical correlation, using the Barbier-Wieland one-carbon degradation of (*R*)-keto-ester **19**. Imine **17**, prepared from 2-ethylcyclopentanone and *S*-(−)-1-phenylethylamine ($[\alpha]^{20}_{D}$ -40.1 , neat, 98.5 % ee) was added to methyl acrylate (neat, 40 °C, 24 h), leading to adduct **18** (91 % de by capillary VPC). This adduct was hydrolyzed (10 % acetic acid in water) and the ketonic group in the resulting (*R*)-keto-ester **19** [11] was protected by ketalization (ethylene glycol, *p*-TsOH, 24 h in refluxing benzene with azeotropic removal of water). Ketal-ester **20** was converted into alcohol **21** (excess PhLi, THF, 0 °C) which was transformed into olefin **22** (refluxing acetic acid, 12 h). This olefin was next oxidized into acid **23** (RuO_4 cat, $NaIO_4$, CCl_4/H_2O, 45 °C, 12 h) which was finally methylated by CH_2N_2 into desired (*R*)-keto-ester **14**.



Discussion

It is clear that the nucleophilic species implied in addition [**8** → **10**] is the secondary enamine **24**, in tautomeric equilibrium with imine **8**. The related cyclic, chair-like transition state **25** should be invoked in this addition, in which the proton borne by the nitrogen atom of enamine **24** is transferred to the α-carbon center of acceptor **9**, *concertedly* with the creation of the new C-C bond (*"aza-ene-synthesis-like"* transition state) [4b]. The present stereochemical outcome can be easily rationalized, assuming that the alkylation process takes place mainly on the π-face of enamine **24** opposite to the phenyl ring of the chiral amine moiety, when this depicted in its energetically preferred conformation (C-H nearly eclipsing the five-membered ring) [4c]. In other respects, one should note that, somewhat surprisingly, *an increasing of the reaction temperature has no appreciable effect on the stereoselectivity of these Michael additions ;* thus, though performed respectively at

20 °C, 40 °C and 80 °C, the three closely related reactions **[26 → 27]** [4a], **[17 → 18]** and **[8 → 10]** exhibit the same order of diastereoselectivity (90-92 % de). Likewise, presence of a bulky *t*-butyl acetate substituent in imine **12** does not modify significantly the stereoselectivity, when compared with the parent methyl ester compound **8**.



The aforementioned Michael additions use 1-phenylethylamine as chiral inductor ; seeing that both isomers of this amine are readily available, inexpensive chemicals (which, in addition, can be easily and quantitatively recovered without any loss of optical activity), *the two enantiomers of target cyclopentanones,* **14** *and* **16** *are therefore of comparable accessibility.* Conversion of these chiral building blocks into *Aspidosperma* and *Hunteria* alkaloids is currently under investigation [12].

Acknowledgments *: The National Research Council of France (CNRS), the National Research Council of Brazil (CNPq) and the Foundation for Research of Rio de Janeiro (FAPERJ) are gratefully acknowledged for financial support of this work.*

References and Notes

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5 **10** : pair of diastereoisomers in the 21:1 ratio, determined (250 MHz ^{1}H NMR) by integration of the doublets corresponding to the methyl group of the amine moiety ; *IR* (neat) 1675, 1730 cm^{-1} ; *^{13}C NMR* (63 MHz, $CDCl_3$) major isomer, δ 20.2 24.5 26.6 27.9 28.5 35.4 40.0 46.4 50.8 51.3 61.2 126.1 127.6 127.8 129.0 133.2 139.1 145.1 171.3 177.7.

6 **11** : white solid ; mp 73-74 °C (ether) ; $[\alpha]^{20}_D$ -1.0 (c = 5, CH_3OH) ; *IR* (KBr) 1730 cm^{-1} ; *^{13}C NMR* (63 MHz, $CDCl_3$) δ 18.2 27.2 33.7 37.0 38.4 47.8 51.1 51.4 127.7 129.1 133.6 138.7 170.7 219.2.

7 **13** : solid ; mp 72-73 °C (ether) ; $[\alpha]^{20}_D$ -0.6 (c = 5, MeOH) ; *IR* (KBr) 1730 cm^{-1}.

8 Trost, B.M. ; Arndt, H.C. ; Strege, P.E. ; Verhoeven, T.R. *Tetrahedron Lett.*, 3477 (1976). Brimble, M.A. ; Officer, D.L. ; Williams, G.M. *Ibid.* **29**, 3609 (1988).

9 **14** : oil ; $[\alpha]^{20}_D$ -2.3 (c = 6.2, CCl_4) ; *IR* (neat) 1730 cm^{-1} ; *^{1}H NMR* (250 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H) 1.4-1.5 (m, 2H) 1.8-2.1 (m, 4H) 2.3-2.5 (m, 2H) 2.48 (d, J = 16.4 Hz, 1H) 2.66 (d, J = 16.4 Hz, 1H) 3.63 (s, 3H) ; *^{13}C NMR* (20 MHz, $CDCl_3$) δ 8.4 18.7 28.6 32.3 37.6 39.3 49.8 51.5 172.0 221.5.

10 **16** : oil ; $[\alpha]^{20}_D$ -1.9 (c = 10.5, CCl_4) ; *IR* (neat) 1737 cm^{-1} ; *^{1}H NMR* (250 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H) 1.45 (m, 2H) 1.6-1.8 (m, 6H) 2.31 (d, J = 14.3 Hz, 1H) 2.41 (d, J = 14.3 Hz, 1H) 3.62 (s, 3H) 3.8 (m, 4H) ; MS (m/e) 228 (M^+) 197 185 169 155 139 127 113 99 86.

11 **19** (90 % ee) : oil ; $[\alpha]^{20}_D$ -8.4 (c = 3, EtOH). The *R* configuration was attributed to this keto-ester, assuming that the stereochemical courses in reactions **[17 → 18]** and **[26 → 27]** [4a] are the same.

12 For a related approach to *Aspidosperma* alkaloids, see ref 4d, 4e.