Tetrahedron: Asymmetry Vol. 2, No. 6, pp. 407-410, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

The Use of 3-Alkyl-2,4-Diketopiperidines in Asymmetric Michael Additions

Lydia Ambroise, Claude Chassagnard, Gilbert Revial and Jean d'Angelo*

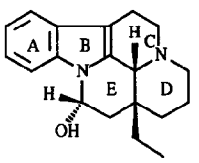
Unité de Chimie Organique Associée au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05 (France).

(*Received* 19 *April* 1991)

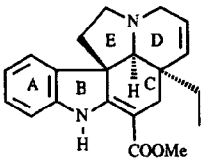
***Key-words** : 2,4-diketopiperidines, chiral enamines, asymmetric Michael addition, imine ⇄ enamine tautomerism, indole alkaloids.*

***Abstract** : Chiral enamine **12**, derived from 2,4-diketopiperidine **11** added to methyl acrylate, leading, after hydrolytic work-up to adduct **15** (94 % stereoselectivity).*

The biogenetically related eburnamine-type and tabersonine-type alkaloids both possess a rearranged secologanin skeleton derived from a common precursor [1a]. These two families are among the largest groups of indole alkaloids [1a-b].

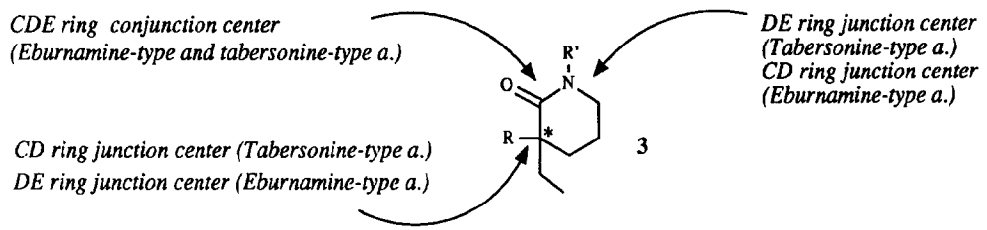


1 : EBURNAMINE



2 : TABERSONINE

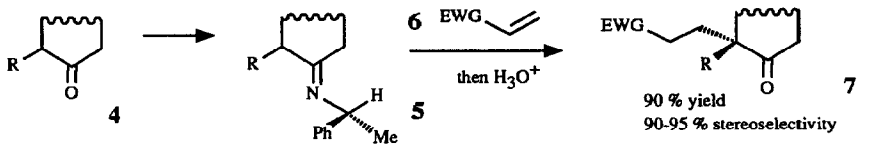
One of the most simplifying disconnective analyses of the aforementioned molecules generates lactam **3**, a precursor of ring D, as a common target subunit [2]. Indeed, as indicated below, such an appropriately substituted lactam might be converted specifically into either preceding alkaloid series, by alternative ordering of the subsequent annulation steps.



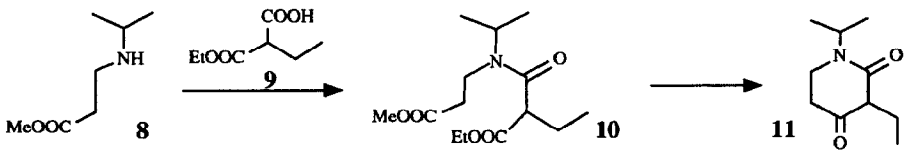
Piperidone **3** contains a single stereogenic center, namely a quaternary carbon atom bearing two geminal appendages. Such a species might be elaborated by using the very efficient asymmetric Michael process which we have disclosed, typified by conversion [**4** → **7**] [3]. Thus chiral imines **5**, derived from α-substituted cyclanones **4** and optically active 1-phenylethylamine, add to electrophilic alkenes **6**, leading to adducts **7** with a high yield and a high degree of regio and stereoselectivity.

In this paper we show that chiral enamine **12**, derived from 2-4-diketopiperidine **11**, reacted with methyl acrylate, giving with a high stereoselectivity (94 %) adduct **15**, a synthetic equivalent to lactam **3**.

Preparation of 2,4-diketopiperidine 11



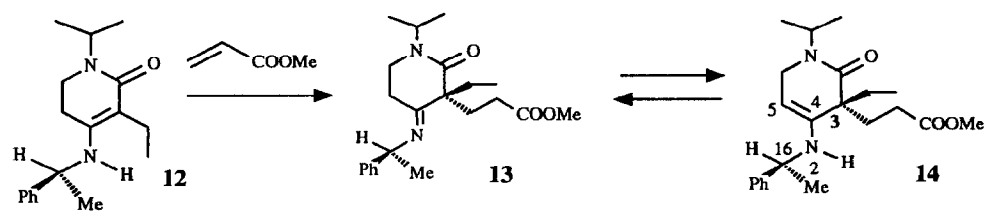
Several key intermediates in the synthesis of emetine [4], likewise certain antiepileptic agents [5] or herbicides [6] contain the 2,4-diketopiperidine nucleus. We have prepared the requisite keto-lactam **11**, essentially according to the methodology developed by Sugasawa and Fujii [4a]. For this purpose isopropylamine was first added to methyl acrylate [7] (48 h at 20 °C), giving adduct **8** [8] in a 80 % yield. Acylation of compound **8** by means of monoethyl ethylmalonate **9** [9] (1 eq of **8**, 1.2 eq of **9**, 1.1 eq DCC, 0.1 eq of DMAP, CH_2Cl_2, 24 h at 20 °C) [10] led to derivative **10** [11] (85 % yield). Dieckmann-type ring closure of diester **10**, followed by acid hydrolysis, furnished finally keto-lactam **11** [12] (powdered Na in refluxing xylene, 2 h, then 6 N HCl, 2 h at 100 °C, 85 % yield).



Formation of chiral enamine 12 and Michael addition

Enamine **12** [13] was prepared from keto-lactam **11** and (*S*)-(−)-1-phenylethylamine (93 % ee) (1.1 eq of amine, refluxing toluene with azeotropic removal of water, 24 h, quantitative). In $CDCl_3$ solution, compound **12** was found to be homogeneous by ^1H and ^{13}C NMR spectroscopy, revealing thus that the imine ⇄ enamine tautomeric equilibrium is completely displaced towards the conjugate enamine form **12**.

Addition of enamine **12** to methyl acrylate proceeded smoothly (2 eq of methyl acrylate, 2 weeks at 20 °C), giving adduct **13** ⇄ **14**. *Surprisingly only the secondary enamine tautomer* ***14*** [14] *was observed in the crystalline state*, as established by X-ray diffraction analysis (see Fig. 1 and 2). In addition *these crystals proved to be astonishingly stable*, having been exposed to the laboratory atmosphere for several weeks at room temperature without any significant alteration (by contrast scrupulous precautions must be taken to exclude all traces of moisture in the crystal structure analyses of most enamines) [15]. X-ray analysis of **14** deserves the following comments. (**a**) *The enamine structure* was definitively established, in view of the good agreement between the bond lengths and angles of the enamine part (see **14** for the atom numbering) and the mean corresponding values published by Dunitz and Eschenmoser [15] (D.E.) for several crystalline enamines : C4-C5 : 1.30 Å (D.E. 1.34 Å), C3-C4 : 1.50 Å (D.E. 1.50 Å), N2-C4 : 1.41 Å (D.E. 1.40 Å), N2-C16 : 1.46 Å (D.E. 1.46 Å), C3-C4-C5 : 122.3° (D.E. 121.2°), C3-C4-N2 : 113.4° (D.E. 115.6°), C5-C4-N2 : 124.3° (D.E. 123.3°), C4-N2-C16 : 120.7° (D.E. 119.5°). (**b**) The absolute configuration at the newly created stereogenic center at C-3 is *R*. (**c**) The heterocycle is *nearly planar*, as shown in Fig. 2. It is worthy of note that the tautomeric equilibrium **13** ⇄ **14** was observed *in solution*, the ratio between the two tautomeric forms, measured by ^1H NMR, being highly solvent-dependent (see below).



13/14 ratio (solvent) : 0 : 100 (DMSO-d_6) 50 : 50 (C_6D_6) 50 : 50 (CD_3COCD_3) 20 : 80 (CD_3OD)

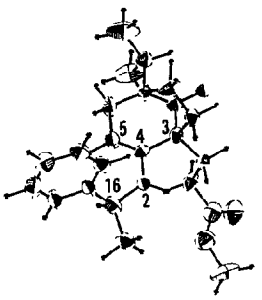


Fig. 1

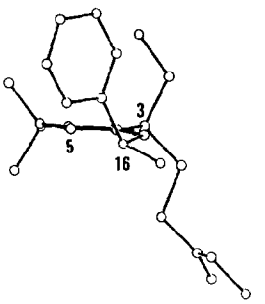
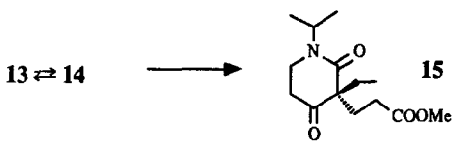


Fig. 2

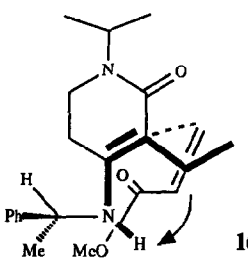
Hydrolysis of *crude* adduct **13** ⇄ **14** (H_2O, AcOH, MeOH, 24 h at 60 °C) led to (*R*)-compound **15** [16] (70 % overall yield from **11**). The enantiomeric excess (88 % ee) in derivative **15** was established by ^1H NMR, by using Eu $(hfc)_3$ as chiral shift reagent. Based upon the ee of the chiral auxiliary amine being 93 %, *the stereoselectivity of the present Michael process is 94 %.*



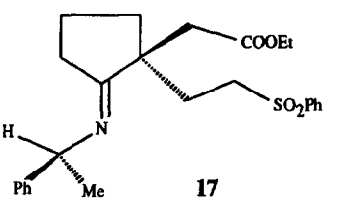
Discussion

The stereochemical outcome observed in reaction [**12** → **14**] may be rationalized, invoking that the reaction proceeds through the compact transition state **16**, in which the enamine nitrogen atom of **12** is transferred to the α-carbon center of methyl acrylate (arrow) *concertedly* with the creation of the new C-C bond (dotted line) [3b]. According to such a transition state, the alkylation takes places predominandly on the *Re* π-face of the enamine, *opposite to the phenyl ring of the amine moiety* (when this depected in its energetically preferred conformation, namely the C-H bond roughly eclipsing the six-membered ring) [3c].

The following comments can be made concerning adduct **13** ⇄ **14** (*a*). The tautomeric equilibrium in this adduct is strongly displaced towards secondary enamine form **14**, though no *apparent* factor may stabilize this enamine structure (thus, by comparison, *no* tautomeric equilibrium can be detected spectroscopically in the structurally related imine **17** [3g]. (*b*) This adduct proved to be much more resistant to hydrolysis than imine **17**. (*c*) The heterocycle in crystalline enamine **14** shows a considerable flattening (see Fig. 2). It is manifest that these three related phenomena should be attributed to the presence of the lactam moiety, imine **17** exhibiting none of these unexpected behaviors. Works are in progress to identify the factor of stabilization of the enamine structure in compound **14**.



16



17

Preparation of appropriately substituted adducts **15** and their conversion into alkaloids of type **1** and **2** are currently under investigation [17].

References and Notes

1 (*a*) Kisakürek, M.V. ; Leeuwenberg, A.J.M. ; Hess, M. in *Alkaloids : Chemical and Biological Perspectives*, Pelletier, S.W., Ed., Wiley-Interscience : New York, **1983**, vol 1, Chapter 5. (*b*) Saxton, J.E. *Nat. Prod. Reports*, **1989**, *6*, 433-474, *Ibid.*, **1990**, *7*, 191-243.

2 For examples of synthetic approaches to indole alkaloids using ring D as the target subunit see : (*a*) Takano, S. ; Sato, S. ; Goto, E. ; Ogasawara, K. *J. Chem. Soc., Chem. Comm.*, **1986**, 156-158. (*b*) Node, M. ; Nagasawa, H. ; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517-521. (*c*) Ihara, M. ; Yasui, K. ; Taniguchi, N. ; Fukumoto, K. *Heterocycles* **1990**, *31*, 1017-1020. (*d*) ref 3g.

3 (*a*) Pfau, M. ; Revial, G. ; Guingant, A. ; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273-274. (*b*) d'Angelo, J. ; Guingant, A. ; Riche, C. ; Chiaroni, A. *Tetrahedron Lett.* **1988**, *29*, 2667-2670. (*c*) d'Angelo, J. ; Revial, G. ; Guingant, A. ; Riche, C. ; Chiaroni, A. *Ibid.*, **1989**, *30*, 2645-2648. -*d*) d'Angelo, J. ; Desmaele, D. *Ibid.* **1990**, *31*, 879-882. (*e*) Desmaele, D. ; d'Angelo, J. *Ibid.*, **1990**, *31*, 883-886. (*f*) Desmaele, D. ; d'Angelo, J. ; Bois, C. *Tetrahedron : Asymmetry* **1990**, *1*, 759-762. (*g*) d'Angelo, J. ; Revial, G. ; Costa, P.R.R. ; Castro, R.N. ; Antunes, O.A.C. *Ibid.*, **1991**, *2*, 199-202.

4 (*a*) Sugasawa, S. ; Fujii, T. *Pharm. Bull. (Japan)* **1955**, *3*, 47-52. (*b*) Ban, Y. *Ibid.*, **1955**, *3*, 53-59. (*c*) Barash, M. ; Osbond, J.M. ; Wickens, J.C. *J. Chem. Soc.* **1959**, 3530-3543.

5 Masset, E. U.S. Pat., 2, 525, 231, Oct. 10, 1950 (*Chem. Abstr.* **1951**, 3426 a).

6 Geach, N.J. ; Gilmour, J. ; Hatton, L.R. ; Smith, P.H.G. *Eur. Pat. Appl.* EP 278,742, 17 Aug 1988 (*Chem. Abstr.* **1989**, *110*, 38898 b).

7 Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, 1117-1125.

8 **8** : oil ; bp 40 °C (0.01 mm Hg) ; *IR* (neat) 3300, 1730 cm^{-1} ; ^1H *NMR* (90 MHz, $CDCl_3$) δ 1.0 (d, J = 6 Hz, 6H), 1.15 (br s, 1H), 2.25-2.6 (m, 2H), 2.6-3.0 (m, 3H), 3.6 (s, 3H).

9 Compound **9** was prepared according to : *Org. Synth.* vol. 37, **1957**, pp 34-36, Cason, J. Ed., John Wiley, New-York.
9 : oil ; *IR* (neat) 3600-2400, 1730 cm^{-1} (br) ; ^1H *NMR* (90 MHz, $CDCl_3$) δ 0.9 (t, J = 7.5 Hz, 3H), 1.3 (t, J = 7.2 Hz, 3H), 1.9 (m, 2H), 3.3 (t, J = 7.5 Hz, 1H), 4.2 (q, J = 7.2 Hz, 2H), 11.0 (br s, 1H).

10 Neises, B. ; Steglich, W. *Angew. Chem. Int.* **1978**, *17*, 522-523.

11 **10** : oil, bp 120 °C (0.01 mm Hg) ; *IR* (neat) 1730, 1630 cm^{-1} ; ^1H *NMR* (90 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 1.22 (d, J = 7.5 Hz, 6H), 1.25 (t, J = 7.0 Hz, 3H), 1.95 (m, 2H), 2.6 (m, 2H), 3.5 (m, 3H), 3.65 (s, 3H), 4.13 (q, J = 7.0 Hz, 2H), 4.2 (m, 1H).

12 **11** : oil, purified by flash chromatography on silica gel ; *IR* (neat) 1727, 1654 cm^{-1} ; ^1H *NMR* (250 MHz, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 2.00 (m, 2H), 2.4-2.7 (m, 2H), 3.12 (t, J = 5.9 Hz, 1H), 3.50 (m, 2H), 4.90 (m, 1H) ; ^{13}C *NMR* (20 MHz, $CDCl_3$) δ 205.6, 167.6, 59.3, 44.3, 38.6, 35.6, 19.8, 19.5, 18.3, 11.9.

13 **12** oil (crude) ; $[\alpha]^{20}_D$ -7.0 (c = 3.8, MeOH) ; IR (neat) 3340, 1630, 1580 cm^{-1} ; ^1H *NMR* (250 MHz, $CDCl_3$) δ 1.00 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H), 1.49 (d, J = 6.75 Hz, 3H), 2.00 (m, 1H), 2.37 (m, 3H), 3.00 (m, 2H), 4.25 (m, 1H) 4.55 (m, 1H) 4.8 (m, 1H) 7.2-7.4 (m, 5H). ^{13}C *NMR* (63 MHz, $CDCl_3$) 167.0, 149.0, 145.0, 128.7, 127.0, 125.0, 103.7, 52.3, 42.5, 36.7, 25.1, 25.0, 19.6, 17.2, 12.7.

14 **14** : solid, mp 154 °C (from methyl acrylate) ; *IR* (KBr) 3400, 1730, 1690, 1615 cm^{-1} ; ^1H *NMR* (250 MHz, DMSO-d_6), *enamine form* **14** : δ 0.46 (t, J = 7.2 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.7 Hz, 3H), 1.6-2.2 (m, 6H), 3.56 (s, 3H), 3.5-3.6 (m, 2H), 4.16 (m, 2H), 4.64 (m, 1H), 4.81 (d, J = 6.5 Hz, 1H), 7.1-7.4 (m, 5H). Crystallographic data of compound **14** have been deposited at the Cambridge crystallographic Data Centre, U.K.

15 Brown, K.L. ; Damm, L. ; Dunitz, J.D., Eschenmoser, A. ; Hobi, R. ; Kratky, C. *Helv. Chim. Acta* **1978**, *61*, 3108-3135.

16 **15** : oil ; $[\alpha]_D^{20}$ + 5.9 (c = 4.8, MeOH) ; *IR* (neat) 1735, 1720, 1640 cm^{-1} ; ^1H *NMR* (250 MHz, $CDCl_3$) δ 0.80 (t, J = 7.5 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.88 (q, J = 7.5 Hz, 2H), 2.20 (m, 4H), 2.62 (t, J = 6.5 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.65 (s, 3H), 4.98 (m, 1H) ; ^{13}C *NMR* (20 MHz, $CDCl_3$) 208.9, 173.1, 170.5, 60.7, 51.6, 44.8, 39.8, 35.3, 31.1, 30.5, 29.8, 19.53, 19.44, 9.5.

17 For a related approach to *Aspidosperma* alkaloids, see ref. 3d, 3e.