Pergamon

Tetrahedron Letters, Vol. 38, No. 13, pp. 2263-2266, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00293-1

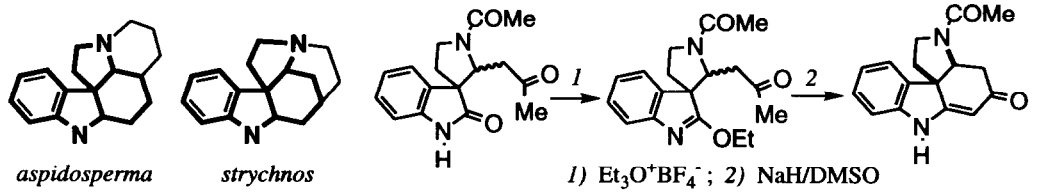
Intramolecular Acid-Catalyzed Aldolization of Oxindolic Methylketones

Catherine Mirand, Mario Papa, Dominique Cartier and Jean Lévy*

Laboratoire de Transformations et Synthèse de Substances Naturelles, associé au CNRS,
Université de Reims Champagne-Ardenne, Faculté de Pharmacie, 51 rue Cognacq-Jay,
F-51096 Reims France§

Abstract : The oxindolic methylketones **13**, **15**, **20** and **22** were cyclized in one step with para-toluene-sulfonic acid to the tetracyclic enaminoketones **16**, **17**, **23** and **24**, respectively.

As a part of the framework of a number of indole alkaloids in the *aspidosperma* and *strychnos* series (Scheme 1), the pyrrolo[*2,3-c*]-carbazole ring system has been constructed by a variety of approaches[1]. Tetracyclic indole compounds containing this ring system have been synthesized, either as intermediates or as model systems.[2]



aspidosperma *strychnos* *1)* $Et_3O^+BF_4^-$; *2)* NaH/DMSO

Scheme 1

In this context, Ban's methodology[2a] is based on the obtention of an enaminoketone through the cyclization of a suitable oxindolic methylketone derived from 2-hydroxytryptamine (Scheme 1). However, to prevent the imino double bond from deactivation through a Grob's fragmentation, the oxindolic lactam has to be transformed into an iminoether while the basic nitrogen has to be acylated. Furthermore, although the starting compound was a mixture of stereoisomers, the reaction was stereospecific because of the necessary *cis* junction of the pyrrolidine and cyclohexenone rings in the resulting enaminoketone.

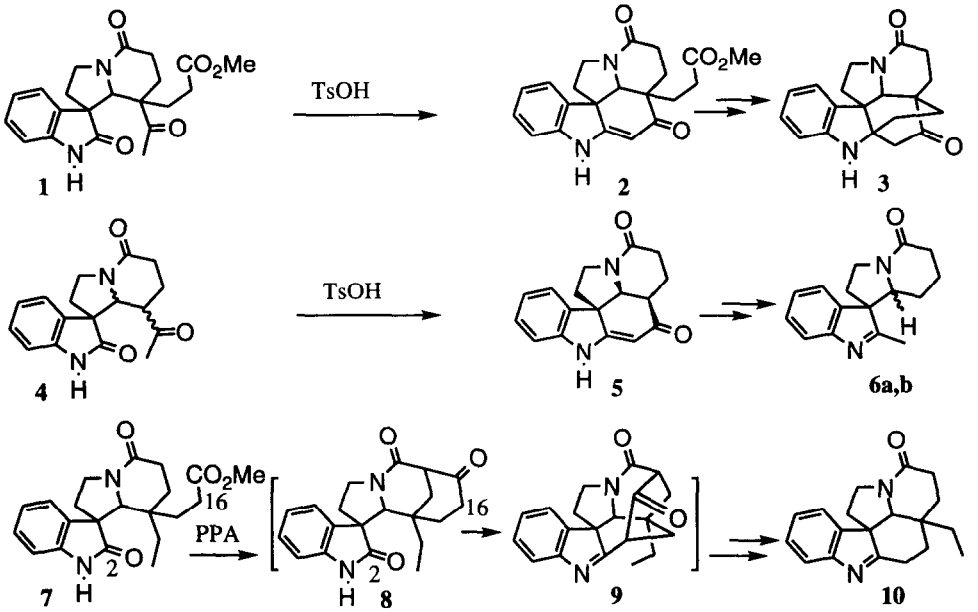
We have found that direct cyclization of such oxindolic methylketones avoids both the preparation of an imino ether and the strong basic conditions used by Ban. This result is a consequence of the following observations made during our previous syntheses[3] in the *aspidosperma* series (Scheme 2), which bring to light acid-catalyzed intramolecular aldolizations of a ketone onto an oxindolic carbonyl group:

§ fax: 03 26 05 35 52; e-mail: jean levy@univ-reims.fr

(1) The synthetically highly efficient double cyclization, hydrolysis and decarboxylation of **1** to dioxoaspidofractinine **3** (TsOH, toluene)[3e]in which enaminoketone **2** was isolated and shown to be an intermediate.

(2) The treatment of the oxindolic methylketone **4** under identical conditions afforded[3e] the enaminoketone **5**, that had suffered further fragmentation to **6a,b**, resulting in the amazing transfer of the methyl group of the methylketone to the initial lactamic carbon of the oxindole.

(3) The concise synthesis of dehydrooxoaspidospermidine **10** under heating of **7** with PPA[3a] is thought§ to involve a Dieckman-like cyclization to **8**, followed by formation of the 2-16 bond[4], fragmentation and decarboxylation.



Scheme 2

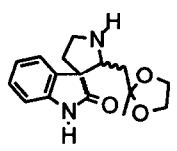
The tricyclic oxindolic methylketones **13a,b**, **15a,b**, **20a,b**, and **22a,b** for the present study(Scheme 3) were prepared as follows: 2-hydroxytryptamine was reacted with the dioxolane derivative of 3-oxobutanal[2a,5] (MeOH/H_2O 1:1; NaOH, 1.2 eq, rt, 24 h) to yield **11a,b** as a diastereomeric mixture. These compounds were immediately acylated in dichloromethane, with AcCl in the presence of DMAP, or with TFAA in the presence of Et_3N. Chromatography of each mixture then allowed separation of (±)**12a** (30%) and (±)**12b**(50%) on one hand, and of (±)**14a**(30%) and (±)**14b**(40%) on the other. The ketogroup of each compound was then deprotected (HCl/MeOH, rt, 1h; 96-98%). Compounds **18a,b-22a,b** were obtained under similar conditions from the dioxolane derivative of 5-oxohexanal (that was prepared by reduction of the related nitrile[6] with DIBAH) and 2-hydroxytryptamine: **20a**(30%), **20b**(30%), **22a**(25%),**22b**(25%).

Treatment of the mixture **15a,b** with PPA (120°C, 1h) afforded the tricyclic compound **25** (30%). Refluxing compounds **15** in dioxane or in benzene in the presence of 5eq of TsOH was ineffective, while

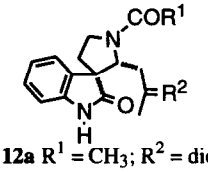
§ After a suggestion of M.E. Kuehne

TsOH in refluxing toluene (18-24h) induced cyclization. Thus, ketones **13a** and **13b** gave the enaminoketone **16**[2a] with modest yields (15% and 11%, respectively), along with **26** (22%). Heating the trifluoroacetamido derivatives **15a** or **15b** with TsOH in toluene, in contrast with the formation of **25** with PPA, gave only the expected enaminoketone **17** (43% from both compounds). Performing the reactions in refluxing xylene did not improve the yields.

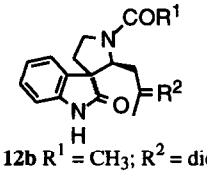
The relative configurations of compounds **13a,b** and **15a,b** were tentatively deduced from the NMR spectra, which showed a significant difference in the chemical shifts for the methyl groups of the methylketones[7]: in each couple of isomers, one compound had its methyl group resonating at 2.08- 2.15 ppm, while the other one gave signal(s) at 1.70 -1.76 ppm. With regard to the constrained ring junction in the tetracyclic enaminoketones **16**, **17**, compounds with their methyl group suffering the most important shielding effect of the aromatic system were ascribed the **b**-series, in agreement with the slight difference in the yields of cyclization observed for **13a** *vs* **13b**. Cyclization of **13b** and of **15b** implies an equilibration, that is ascribed to a retro-Pictet-Spengler reaction favoured by the formation of the resulting enaminoketones **27a,b**.



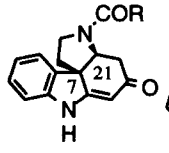
11a,b



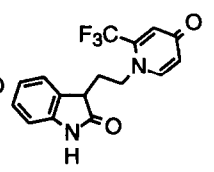
12a $R^1 = CH_3$; R^2 = diox (*)
13a $R^1 = CH_3$; $R^2 = O$
14a $R^1 = CF_3$; R^2 = diox
15a $R^1 = CF_3$; $R^2 = O$



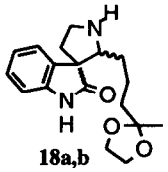
12b $R^1 = CH_3$; R^2 = diox
13b $R^1 = CH_3$; $R^2 = O$
14b $R^1 = CF_3$; R^2 = diox
15b $R^1 = CF_3$; $R^2 = O$



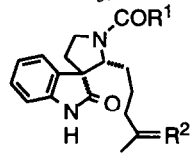
16 R = CH_3
17 R = CF_3



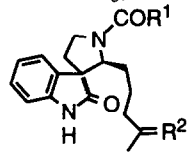
25



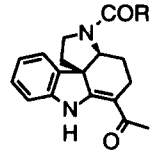
18a,b



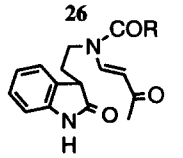
19a $R^1 = CH_3$; R^2 = diox
20a $R^1 = CH_3$; $R^2 = O$
21a $R^1 = CF_3$; R^2 = diox
22a $R^1 = CF_3$; $R^2 = O$



19b $R^1 = CH_3$; R^2 = diox
20b $R^1 = CH_3$; $R^2 = O$
21b $R^1 = CF_3$; R^2 = diox
22b $R^1 = CF_3$; $R^2 = O$



23 R = CH_3
24 R = CF_3



26

27a R = CH_3
27b R = CF_3

(*)diox =

Scheme 3

The cyclization of the four other oxindolic ketones was much more efficient in one series (which is ascribed the **a**-configuration) than in the other (**b**)- series, as a consequence of a less favourable equilibration through the retro-Pictet-Spengler process. Thus, the enamino ketone **23** was produced in 57% yield from **20a**, and in only 5% yield from **20b**. Similarly, **22b** cyclized to **24** (12%) while the most efficient cyclization in this set of experiments was performed from **22a**, yielding **24** (79%).

The spectroscopic data[7] were in full agreement with the structures of the compounds although the NMR spectra were complicated by the existence of rotamers of the N-acyl groups.

Thus *p*-toluenesulfonic acid[8] in boiling toluene allows a one-step intramolecular aldolization (and further dehydration) of suitable oxindolic ketones. The reaction advantageously avoids the transformation of the oxindolic lactam to an iminoether with Meerwein's reagent, and the strongly basic conditions of the further cyclization step, that were used in Ban's methodology.

References and notes

1. a) Cordell, G.A. The Aspidosperma alkaloids. In *The Alkaloids*; Manske, R.H.F.; Rodrigo, R.G.A. Eds; Academic Press: New York, 1979, *17*, pp 199-384. b) Sapi, J.; Massiot, G. The Strychnos Alkaloids. In *Indoles. The Monoterpenoid Indole Alkaloids*; Saxton, J.E. Ed; John Wiley and Sons : New York, 1994, pp 279-355.
2. For leading references see: a) Oishi, T.; Nagai, M.; Ban, Y. *Tetrahedron Lett.* **1968**, 491-495. b) Ban, Y.; Sendo, Y.; Nagai M.; Oishi ,T. *Tetrahedron Lett.* **1972**, 5027-5030. c) Ban, Y.; Sekine, Y.; Oishi, T. *Tetrahedron Lett.* **1978**, 151-154. d) Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880-6881. e) Takano, S.; Shishido, K; Matsuzaka, J.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, *13*, 307-320. f) Doë de Maindreville, M.; Lévy, J. *Bull. Soc. Chim. Fr.* **1981**, II-179-183. g) Vercauteren, J.; Massiot, G.; Lévy, J. *J. Org. Chem.* **1984**, *49*, 3230-3231. h) Overman, L.E.; Angle, S.R. *J. Org. Chem.* **1985**, *50*, 4021-4028. i) Kuehne, M.E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490-7497. j) Kuehne, M.E.; Brook, C.S.; Frasier, D.A.; Xu, F. *J. Org. Chem.* **1994**, *59*, 5977-5982. k) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J.C., Husson, H.P. *J. Org. Chem.* **1993**, *58*, 6457-6465. l) Rawal, V.H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685-2686.
3. a) Laronze, J.Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, 491-494 b) Laronze, J.Y.; Cartier, D.; Laronze, J.; Lévy, J. *Tetrahedron Lett.* **1980**, *21*, 4441-4444. c) Cartier, D.; Patigny, D.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 1897-1900. d) Cartier, D.; Ouahrani, M.; Hugel, G.; Lévy, J. *Heterocycles* **1988**, *27*, 657-661. e) Cartier, D.; Ouahrani, M.; Lévy, J. *Tetrahedron Lett.* **1989**, *30*, 1951-1954.
4. Biogenetic numbering after Le Men, J.; Taylor, W.I. *Experientia* **1965**, *21*, 508-511.
5. Cartier, D.; Lévy, J. *Tetrahedron* **1990**, *46*, 5295-5304.
6. Lüthy, C.; Konstantin, P.; Untch, K.G. *J. Am. Chem. Soc.* **1978**, *100*, 6211-6217.
7. Salient features of the spectroscopic data of new compounds (NMR spectra were recorded at 300 MHz and 75 MHz, in $CDCl_3$; MS spectra by electron impact; UV spectra in MeOH.)

   15a: ^{1}H NMR 2.15(3H, s), 4.80(1H, dd, J10, J'3.5), 6.80-7.30(4H, m), 7.85(1H, s); MS 340($M^{+\cdot}$), 297, 184, 159, 146, 130; **15b**: ^{1}H NMR 1.70(3H, s), 4.88(1H, dd, J10, J'4.5), 6.90-7.30(4H, m), 9.33(1H, s); MS 340($M^{+\cdot}$), 297, 184, 159, 146, 130.

   17: UV 228, 293, 336; ^{1}H NMR [2 rotamers 55:45], 4.68(0.55H, t, J7.8), 4.88(0.45H, t, J7.8), 5.62-5.65(1H, 2s), 6.85-7.35(4H, m), 9.20-9.26(1H, 2brs); ^{13}C NMR [2 rotamers], [38.2, 38.9], [40.4, 40.7], [44.1, 44.9], [51.7, 54.1], [60.3, 60.6], [97.9, 98.2], 110.8, 116.1(q, J_{CF}286), [121.6, 121.7], [122.5, 122.7], 129.3, [133.0, 133.2], [142.6, 142.7], [155.2, 155.5(q, J_{CF}37)], [170.4, 170.9], [192.4, 192.7]; MS 322($M^{+\cdot}$), 280, 183, 170.

   20a: ^{1}H NMR [2 rotamers 6:4], 2.00(1.8H, s), 2.06(1.2H, s), 2.08(1.2H, s), 2.18(1.8H, s), 3.60-3.80(1.4H, m), 3.92-4.10(1H, m), 4.25(0.6H, dd, J7.5, J'5.5), 6.85-7.25(4H, m), 9.15(0.6H, s), 9.18(0.4H, s); MS 314($M^{+\cdot}$), 272, 187, 159, 146, 130. **20b**: ^{1}H NMR 2.02(3H, s), 2.18(3H, s), 4.40(1H, t, J7.5), 6.90-7.30(4H, m), 9.10(1H, s); MS 314($M^{+\cdot}$), 272, 187, 159, 146, 130.

   22a: ^{1}H NMR 2.02(3H, s), 4.34(1H, dd, J7.8, J'5.5), 6.88-7.30(4H, m), 8.80(1H, m); MS 368($M^{+\cdot}$), 254, 184, 159, 146, 130. **22b**: ^{1}H NMR 2.02(3H, s), 4.45(1H, t, J7.5), 6.90-7.35(4H, m), 9.10(1H, s); MS 368($M^{+\cdot}$), 254, 184, 159, 146, 130.

   23: UV 204, 236, 302, 354; ^{1}H NMR [2 rotamers 6:4], 2.20, 2.22(3H, 2s), 2.26(3H, s), 4.18(0.4H, d, J7.5), 4.50(0.6H, d, J7.5), 6.85-7.30(4H, m), 10.5(1H, brs); ^{13}C NMR [2 rotamers], [21.5, 21.8], [22.7, 23.1], 27.3, [29.0, 30.6], [36.0, 38.3], [44.0, 45.8], [54.4, 55.8], [59.5, 60.4], 110.1, 121.5, 121.8, [128.4, 128.5], [135.3, 135.5], 143.1, [161.4, 162.1], [169.6, 169.8], 196.6; MS 296($M^{+\cdot}$), 269, 211, 198, 168, 154.

   24: UV 206, 232, 300, 352; ^{1}H NMR [2 rotamers 7:3], 2.23(0.9H, s), 2.25(2.1H, s), 4.40-4.48(0.3H, m), 4.58(0.7H, d, J7.8), 6.86-7.30(4H, m), 10.48(1H, s); ^{13}C NMR [2 rotamers], [21.4, 22.5], 27.4, [28.2, 30.1], [34.9, 38.5], [44.7, 45.5], 53.6, 61.9, 104.3, 110.3, 116.2(q, J_{CF}288), 121.5, [121.8, 122.1], 128.9, 134.6, 143.3, 161.2, 196.7; MS 350($M^{+\cdot}$), 324, 323, 307, 212, 198, 168.

   25: ^{1}H NMR 6.48(1H, dd, J8, J'3.5), 6.84(1H, d, J3.5), 6.90-7.30(4H, m), 7.54(1H, d, J8), 8.80(1H, s); MS 322($M^{+\cdot}$), 253, 190, 177, 159, 144, 133.

   26: [diastereoisomeric mixture] ^{1}H NMR 2.12, 2.15(3H, 2s), 5.00, 5.02(1H,2s), 6.86-7.30(4H,m); ^{13}C NMR [20.4, 20.6], [33.4, 33.8], [35.0, 35.9], 46.4, [55.8, 56.4], [65.1, 65.6], [97.9, 98.5], [110.2, 110.7], [122.5, 122.6], [122.4, 124.0], [128.9, 129.0], [127.8, 129.4], [140.8, 141.6], [161.4, 161.7], [177.3, 178.4], [190.5, 191.2]; MS 268($M^{+\cdot}$), 244, 167, 159, 123.
8. For an example of intramolecular acylation induced by TsOH, see Fu, X.; Kubiak, G.; Zhang, W.; Han, W.; Gupta, A.K.; Cook, J.M. *Tetrahedron* **1993**, *49*, 1511-1524.

(*Received in France* 20 *November* 1996; *accepted* 14 *February* 1997)