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A NEW STRATEGY FOR THE ENANTIOSELECTIVE SYNTHESIS OF ASPIDOSPERMA ALKALOIDS : II - ACHIEVEMENT OF THE PENTACYCLIC SYSTEM.

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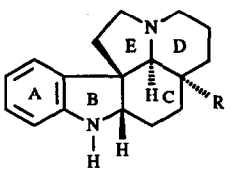
Abstract : *Carbazolone* **5** *has been converted in eleven steps into alkaloid analog* **1** *(R = Me) (13 % overall yield).*

In the preceding paper [1], we proposed a new approach to pentacyclic Aspidosperma alkaloids [(*e.g.* (−)-aspidospermidine, **1**, R = Et], based on the disconnection [**1** → **2** → **3**], in which carbazolones **3** constitute the key [ABC]-type tricyclic subunits.



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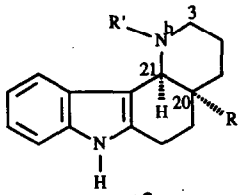

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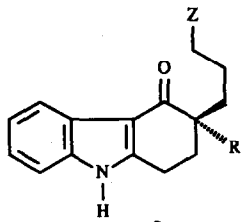

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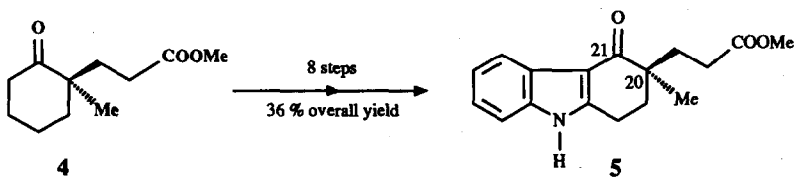
In this respect, the optically active (*R*)-keto-ester **5** was efficiently prepared from cyclohexanone **4**.



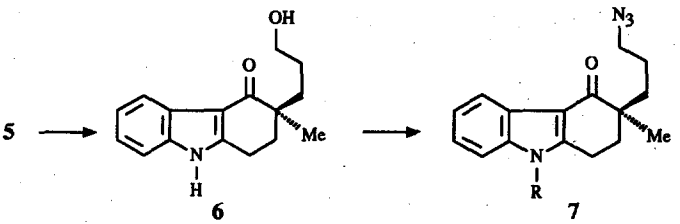
4 **5**

In this paper we report on the conversion of the tricyclic compound **5** into aspidospermidine analog **1** (R = Me). The first problem encountered in the present strategy is the construction of the [ABCD] tetracyclic derivatives of type **2**. This implies a selective ring closure by using the three carbon atoms of the propionate appendage at C-20 of carbazolone **5** (Le Men-Taylor Aspidosperma alkaloids numbering), *bearing in mind that the crucial, "natural", cis CD ring junction must be controlled at this stage.*

Having chosen to create ring D by heterocyclization between the N^b and C-21 centers, an azido group, precursor of the requisite amine function at C-3, was introduced at the end of the side-chain of tricyclic compound **5**, according to the following three steps procedure [**5** → **7a**]. Chemoselective reduction of the ester of carbazolone **5** ($LiEt_3BH$, THF, −10 °C, 1 h, 87 % yield) led to alcohol **6** [2] which was then transformed into azide **7a** [3] (*i* : MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h ; *ii* : NaN_3, DMF, 80 °C, 3 h, 80 % yield).

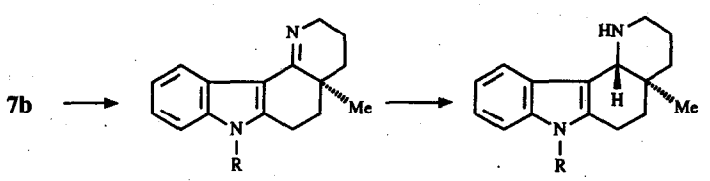
The electrophilic character of the carbonyl function in tricyclic intermediate **7a** is dramatically lowered by conjugation with the electron-rich indole nucleus. Because the achievement of the present annulation requires an enhancement of this electrophilicity, the indole nitrogen atom of compound **7a** was protected with

an electron-withdrawing group, namely by sulfonation (*p* $MeOC_6H_4SO_2Cl$, CH_2Cl_2, NaOH 50 %, tetrabutylammonium hydrogen sulfate, 2 h, 20 °C, 93 % yield).



a R = H
b R = *p* $MeOC_6H_4SO_2$

In the first ring closure route we have explored, the azido group of carbazolone **7b** [4] was reduced (PPh_3, THF, 20 °C, 24 h, 88 % yield)[5], leading directly to tetracyclic imine **8** [6] (probably, *via* an aza-Wittig annulation process which involves an intermediary iminophosphorane) . Unfortunately, all attempts of reduction of this imine ($NaBH_3CN$/AcOH, H_2/PtO_2, BH_3-Me_2S, H_2/Pd-C, $NaBH_4/CeCl_3$) gave amine **9** alone, possessing the undesired, *trans* CD ring junction. Thus, clearly, reduction processes always take place on the less hindered β-face of imine **8**. It should be noted that the catalytic hydrogenation of compound **7b** also gave directly amine **9** [7].

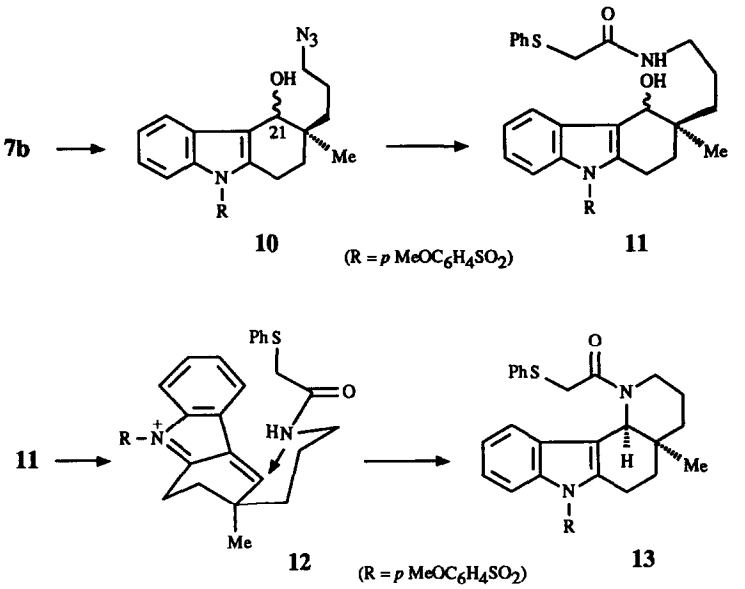


(R = *p* $MeOC_6H_4SO_2$)

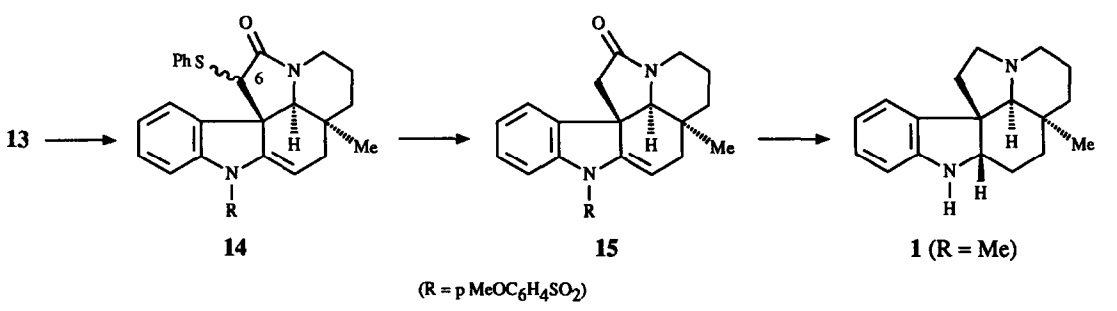
In view of such disappointing results, we turned next to the following alternative annulation procedure, reasoning that the acid-promoted elimination of the hydroxyl group in compound **11** -an elimination assisted by the indole moiety- should give the intermediary iminium ion **12**. The subsequent intramolecular trapping of this iminium ion by the amide nitrogen atom borne by the side-chain should take place on the less hindered β-face of the molecule, leading therefore to the desired *cis* CD ring junction [**12** → **13**].

The requisite alcohol **11** was prepared as follows. Ketone **7b** was first reduced ($NaBH_4$, refluxing EtOH, 10 min, 80 % yield) [8] into a 1.5:1 mixture of epimeric alcohols **10** [9] (the lack of stereocontrol at C-21 at this stage is irrelevant, since the hybridization of this carbon atom becomes sp^2 in iminium ion **12**). Staudinger reduction of compound **10** (PPh_3, THF, 20 °C, 48 h, then H_2O), followed by Schotten-Baumann acylation of the resulting primary amine, with phenylthioacetyl chloride -which introduces the two missing carbon atoms of the future ring E- ($PhSCH_2COCl$, 1 N NaOH, 0 °C, 20 min, 76 % yield from **10**) gave the desired amido-alcohol **11** [10].

As expected, upon acidic treatment (TFA, CH_2Cl_2, 0 °C, 10 min, quantitative yield), compound **11** led to tetracyclic product **13** [11], having the desired *cis* CD ring junction, *as a single derivative*, probably through the intermediary iminium ion **12**.



Completion of the synthesis of compound **1** (R = Me) from tetracyclic **13** now requires the diastereoselective construction of the fifth ring E ; this was efficiently performed by using Magnus' procedure [12]. For this purpose, the phenylthio sulfur atom of compound **13** was first oxidized ($NaIO_4$, THF/MeOH/H_2O, 24 h, 95 % yield) and the resulting sulfoxide submitted to a Pummerer rearrangement (TFAA, 0 °C, then 1 h in refluxing PhCl, 85 % yield), giving the pentacyclic derivative **14**, as an epimeric mixture at C-6. Desulfurization of the latter compound (Ra-Ni in DMF, 20 °C, 10 min, 60 % yield) led to pentacyclic amide **15** [13], as a single isomer. When this compound was treated with a large excess of lithium aluminum hydride [12] (THF, 20 °C, 24 h, 70 % yield), three simultaneous reactions took place : cleavage of the sulfamido group and reduction of both amide and enamine functions, giving the target alkaloid analog **1** (R = Me) [14] [(–)-19-noraspidospermidine].



Tricyclic derivative **5** has been thus converted into compound **1** (R = Me) in eleven steps (13 % overall yield). Enantioselective synthesis of this alkaloid analog from the optically active monocyclic [C]-type subunit **4**, according to the [C → AC → ABC → ABCD → ABCDE] present strategy, has been therefore accomplished in 19 steps, with an overall yield of 5 %. Synthesis of several natural Aspidosperma alkaloids, by using the above methodology are under investigation.

REFERENCES AND NOTES

1 J. d'Angelo, D. Desmaele, *Tetrahedron Lett.*, this Issue, preceding paper.

2 **6** : mp 164 °C, $[\alpha]_D^{20}$ + 70° (c = 1.4, EtOH) ; **IR** (KBr) : 3200 broad, 2960, 1620 cm^{-1}. **^{1}H NMR** (250 MHz, CD_3OD) δ : 8.04 (m, 1H) 7.33 (m, 1H) 7.13 (m, 2H) 3.51 (t, J = 6.1 Hz, 2H) 3.05-2.85 (m, 2H) 2.13 (m, 1H) 1.93 (m, 1H) 1.75-1.45 (m, 14H) 1.16 (s, 3H). **^{13}C NMR** (62,9 MHz, CD_3OD) δ : 201.5 152.8 138.2 126.7 123.9 122.9 121.6 112.3 63.5 45.7 35.8 34.6 28.6 22.9 21.0. **MS** (EI 70 eV) : m/e = 257 (M^+), 199 157 129 102.

3 **7a** : mp 124 °C, $[\alpha]^{20}$ = +61° (c = 2.3, EtOH) ; **IR** (KBr) : 3200 (broad) 2940 2095 1615 1575 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 10.1 (s, 1H) 8.29 (m, 1H) 7.43 (m, 1H) 7.25 (m, 2H) 3.27 (t, J = 5.8 Hz, 2H) 3.07 (t, J = 6.2 Hz, 2H) 2.2 (m, 1H) 2.05 (m, 1H) 1.9-1.6 (m, 4H) 1.30 (s, 3H). **^{13}C NMR** (62.87 MHz, $CDCl_3$) δ : 199.0 150.4 136.4 125.3 123.2 122.3 121.1 111.6 111.3 51.7 44.6 34.5 34.4 24.0 22.5 20.3.

4 **7b** : amorphous solid ; **MS** m/e : 452.1484 (M^+, $C_{23}H_{24}N_4O_4S$) ; **IR** (KBr) : 2950 2095 1660 1655 1590 1570 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 8.24 (m, 1H) 8.14 (m, 1H) 7.84 (d, J = 9 Hz, 2H) 7.33 (m, 2H) 6.91 (d, J = 9 Hz, 2H) 3.79 (s, 3H) 3.34 (dt J = 6.34 2.2 Hz, 2H) 3.24 (m, 2H) 2.2-1.9 (m, 2H) 1.8-1.5 (m, 4H) 1.17 (s, 3H).

5 H. Staudinger, I. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919). P.H. Lambert, M. Vaultier and R. Carrié, *J. Chem. Soc.*, 1224 (1982).

6 **8** : mp 150° (dec) ; $[\alpha]^{20}_D$ -56° (c = 0.95, $CHCl_3$) ; **IR** (KBr) : 2900 1620 1590 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 8.30 (m, 1H) 8.15 (m, 1H) 7.70 (d, J = 9 Hz, 2H) 7.25 (m, 2H) 6.85 (d, J = 9 Hz, 2H) 4.05 (dd, J = 17.5 5 Hz, 1H) 3.75 (s, 3H) 3.65 (m, 1H) 3.2 (m, 3H) 1.9-1.4 (m, 6H) 1.05 (s, 1H).

7 **9** : amorphous solid ; **^{1}H NMR** (90 MHz, $CDCl_3$) δ : 8.10 (m, 2H) 7.70 (d, J = 9 Hz, 2H) 7.15 (m, 2H) 6.82 (d, J = 9 Hz, 2H) 3.75 (s, 3H) 3.68 (t, J = 2.5 Hz, 1H) 3.4-2.8 (m, 4H) 1.8-1.2 (m, 6H) 0.78 (s, 3H).

8 E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).

9 **10** : 1.5:1 mixture of epimers ; **IR** (neat) : 3400 2095 1590 1570 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 8.1 (m, 1H) 4.45 (s, 1H) 3.7 (s, 3H) 1.0 and 0.7 (two s in 1:1.5 ratio, 3H).

10 **11** 1.5:1 mixture of epimers ; **IR** (KBr) : 3400 (broad) 2930 1650 1600 1570 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 8.15 (m, 1H) 4.4 (m, 1H) 3.79 and 3.78 (two s in 1.5:1 ratio, 3H) 3.62 and 3.61 (two s in 1.5:1 ratio, 2H) 0.91 and 0.72 (two s in 1:1.5 ratio, 3H). **MS** (EI, 70 eV) m/e : 578 (M^+) 451, 389, 239, 171.

11 **13** : amorphous solid ; **IR** (KBr) : 2920 1635 1595 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) 3/1 mixture of amide rotamers ; *main conformer* : 8.13 (d, J = 8.3 Hz, 1H) 7.66 (d, J = 9 Hz, 2H) 7.55-6.95 (m, 8H) 5.63 (s, 1H) 3.95 (s, 2H) 3.76 (s, 3H) 3.58 (d, J = 14 Hz, 1H) 3.2-2.9 (m, 2H) 2.55 (dt, J = 13 2.5 Hz, 1H) 2.0-1.1 (m, 6H) 1.03 (s, 3H).

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13 **15** : amorphous solid ; $[\alpha]^{20}_D$ -81° (c = 1.2, $CHCl_3$) ; **IR** (KBr) : 1685 1600 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) 7.84 (d, J = 8.2 Hz, 1H) 7.67 (d, J = 8.9 Hz, 2H) 7.30 (m, 1H) 7.12 (t, J = 8.2 Hz, 1H) 7.06 (dd, J = 7.5 1.5 Hz, 1H) 6.88 (d, J = 8.9 Hz, 2H) 6.18 (dd, J = 8.7 3.2 Hz, 1H) 4.2 (m, 1H) 3.80 (s, 3H) 3.60 (d, J = 1.8 Hz, 1H) 2.70 (m, 1H) 2.37 (dd, J = 16 3.2 Hz, 1H) 1.9-1.0 (m, 6H) 0.67 (s, 3H). **MS**, m/e 450.1606 (M^+, $C_{25}H_{26}N_2O_4S$).

14 **1** (R=Me) : mp 120-122 °C, $[\alpha]^{20}_D$ -42° (c = 2.0, EtOH) ; **IR** (KBr) 3300 (broad) 2800 2770 1610 cm^{-1}. **^{1}H NMR** (250 MHz, CD_3COCD_3) δ : 7.07 (d, J = 6.6 Hz, 1H) 6.92 (dt, J = 7.6 1.3 Hz, 1H) 6.60 (dt, J = 7.4 0.9 Hz, 1H) 6.56 (d, J = 7.5 Hz, 1H) 4.6 (s, 1H) 3.38 (dd, J = 6.0 10.8 Hz, 1H) 3.1-2.9 (m, 2H) 2.23 (s, 1H) 2.3-1.6 (m, 6H) 1.5-1.1 (m, 6H) 0.72 (s, 3H). **^{13}C NMR** (62.9 MHz, CD_3COCD_3). δ 151.6 135.9 127.9 123.4 116.6 110.5 71.5 66.0 54.5 54.3 53.1 40.1 38.9 33.8 29.0 28.0 26.9 22.7. **MS** (EI, 70 eV) m/e : 268 (M^+), 240, 110.

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