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A NEW STRATEGY FOR THE ENANTIOSELECTIVE SYNTHESIS OF ASPIDOSPERMA ALKALOIDS : I - CONSTRUCTION OF THE [ABC]-TYPE TRICYCLIC INTERMEDIATES.

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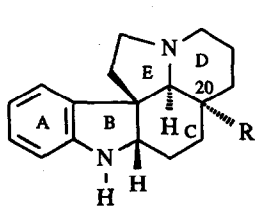
Abstract : *Carbazolone* **19** *has been prepared in eight steps from cyclohexanone* **11** *(36 % overall yield).*

A great amount of work has been devoted to the synthetic approaches to pentacyclic Aspidosperma alkaloids [1] [exemplified by (–)-aspidospermidine, **1**, R = Et]. Thus, for example, in the strategies developed by Magnus [2], Ziegler [3], and others [4], the [ABCD]-type tetracycles **2** are elaborated in the penultimate stage. Although unused in the foregoing tactics, the tricyclic carbazolones **3** constitute *a priori* particularly well-suited subunits for the construction of such tetracyclic entities.



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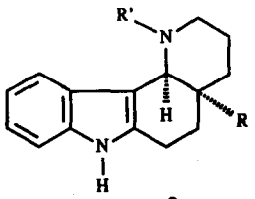

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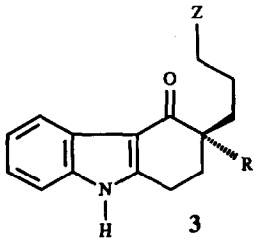
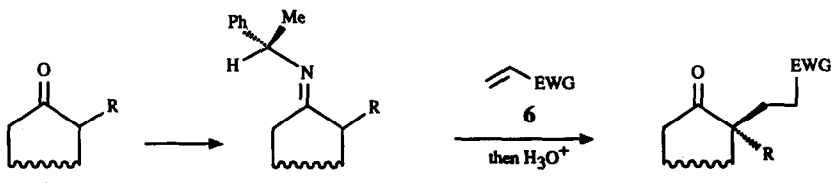


3

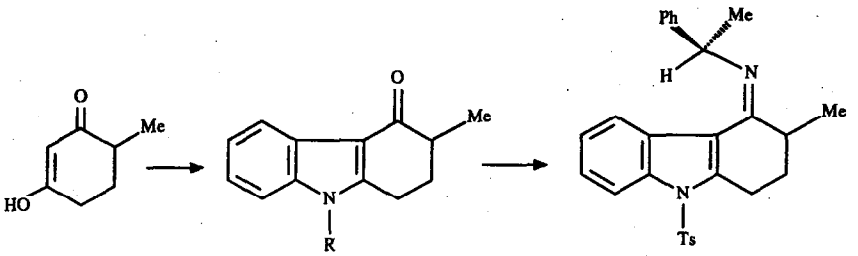
In fact, tricyclic compounds **3** bear *a single asymmetric center* (future C-20 center in alkaloids **1**), namely a quaternary carbon atom in the α-position to the carbonyl group of a cyclanone. This particular structural feature is encountered in adducts **7**, resulting from the very efficient asymmetric Michael process we have described [5], summarized by the transformation [**4** → **7**]. Thus chiral imines **5** derived from *racemic* α-substituted cyclanones **4** and optically active 1-phenylethylamine react (as their tautomeric secondary enamine forms) with electron-deficient alkenes **6** to produce, after hydrolysis, α-disubstituted cyclanones **7** with high yields and excellent enantiomeric excesses.



4 **5** **7**

90 % yield
≥ 90 % ee

In this communication, we report the successful application of this method to the enantioselective synthesis of tricyclic compound of type **3**. The first and *a priori* simplest route for the preparation of compound **3** which we have explored was the addition of electrophilic alkenes to the tricyclic imine **10**. The latter compound was obtained in three steps, starting from 4-methyl-1,3-cyclohexanedione **8**. This diketone was first transformed by regioselective Fischer indole synthesis [6] into the carbazolone **9** (R = H), (*i* : phenylhydrazine, *ii* : H_2SO_4 50 %, 100 °C, 2 h, 45 % yield). The nitrogen atom of the latter compound was then tosylated by the use of phase transfer catalysis (50 % aqueous NaOH, CH_2Cl_2, tetrabutylammonium hydrogen sulfate, TsCl, 85 % yield). Imine **10**, derived from ketone **9** (R = Ts) [7] and R(+)-1-phenylethylamine was prepared by using the titanium chloride-catalyzed procedure [8] ($TiCl_4$, toluene, 20 °C, 12 h, 92 % yield). Unfortunately this imine proved to be completely unreactive toward electrophilic alkenes, even under drastic conditions, a failure reflected by the complete lack of secondary enamine form in tautomeric equilibrium with imine **10** [9].

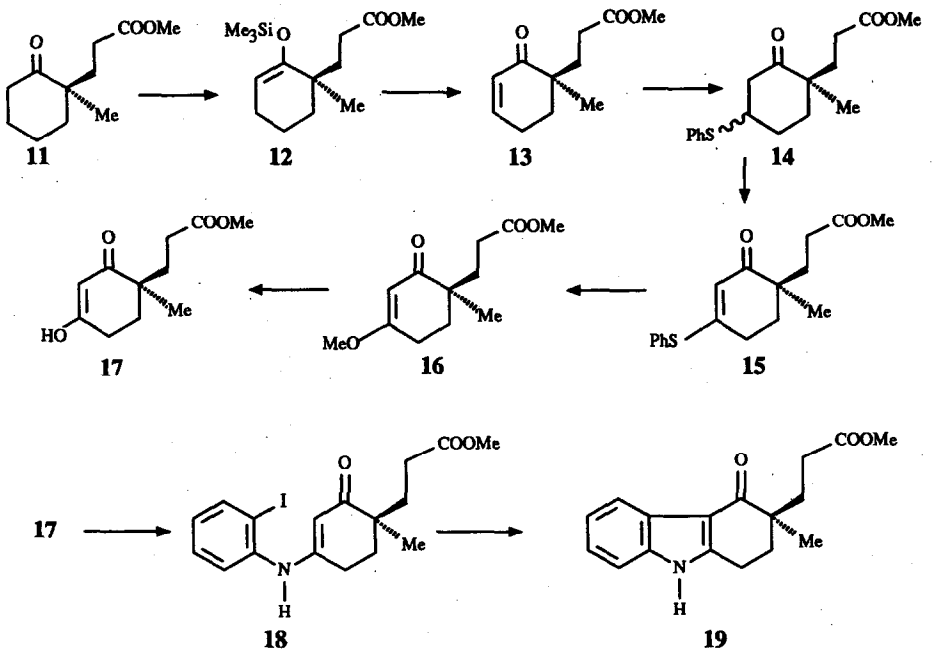


8 **9** **10**

In view of such frustrating results, we turned then to the following indirect route, reasoning that the indole moiety of tricyclic compound **3** could be subsequently elaborated by the regioselective introduction of an appropriately substituted aniline onto the monocyclic 1,3-dione **17** [**17** → **18**], followed by ring closure of the resulting enaminone **18** [**18** → **19**].

(*R*)-keto-ester **11**, prepared through the aforementioned asymmetric Michael process [5], was used as chiral starting material in the present strategy. This keto-ester was transformed into the required dione **17**, in six steps, with an overall yield of 50 %, according to the following oxidation state adjustement sequence. Keto-ester **11** was first converted into silyl enol ether **12** (TMSCl, Et_3N, 80 °C, 48 h in DMF) which was oxidized [10] into cyclohexenone **13** [11] (DDQ, toluene, collidine, 20 °C, 72 h, 82 % yield from **11**). Thiophenol was next added to the cyclohexenone (PhSH, Et_3N cat) and the resulting thio-adduct **14**, by chlorination [12] (NCS, CCl_4, 5 % cyclopentene), gave the thio-enone **15** [13] (80 % yield from **13**). Having established that direct hydrolysis of thio-enone **15** into dione **17** proved to be troublesome, we turned to the following two-steps procedure. Addition of methanol to the thio-enone (MeONa, MeOH, 60 °C, 2 h, then AcOH) afforded the methoxy derivative **16** [14] which was next converted into the target dione **17** [15] (1 N HCl in THF, 75 % yield from **15**).

With the desired dione **17** in hand, we then proceeded with its conversion into our tricyclic synthetic goal **3**. For this purpose, *ortho*-iodoaniline was first added to this dione (refluxing toluene, TsOH cat, 2 h), giving regioselectively enaminone **18** [16] (95 % yield). Copper-mediated cyclization [17] of the sodio derivative of this enaminone (NaH, HMPA, then CuI, 120 °C, 2 h) led to the desired indole derivative **19** [18] with a 75 % yield.



Synthesis of optically active (*R*)-carbazolone **19** has been thus achieved in eight steps, with an overall yield of 36 %, starting from keto-ester **11**. The conversion of this tricyclic derivative into a pentacyclic alkaloid analog of type **1** is presented in the following paper [19].

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7 **9** (R=Ts) : mp 166 °C ; **IR** (KBr) : 3040, 2950, 1660, 1590 cm^{-1} ; **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 8.24 (1H, m) 8.18 (1H, m) 7.74 (2H, d, J = 8.4 Hz) 7.32 (2H, m) 7.24 (2H, d, J = 8.5 Hz) 3.47 (1H, ddd, J = 18.7 4.6 4.6 Hz) 3.18 (1H, ddd, J = 18.7 10.3 5.1 Hz) 2.55 (1H, m) 2.33 (3H, s) 2.26 (1H, m) 1.92 (1H, m) 1.22 (3H, d, 6.9 Hz).

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11 **13** : $[\alpha]_D^{22}$ −3° (c = 10, EtOH ; ee 90 %) ; **IR** (neat) : 2920, 1735, 1670 cm^{-1} ; **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 6.89 (1H, dt, J = 10 4.1 Hz) 5.91 (1H, dt, J = 10 2.1 Hz) 3.66 (3H, s) 2.5-2.1 (4H, m) 2.0-1.7 (4H, m) 1.09 (3H, s) ; **^{13}C NMR** (20.1 MHz, $CDCl_3$) δ 203.1 (s) 173.9 (s) 148.8 (d) 128.4 (d) 51.5 (q) 43.9 (s) 33.6 (t) 31.4 (t) 29.1 (t) 23.1 (t) 21.6 (q) ; **Anal.** Calculated for $C_{11}H_{16}O_3$: C 67.32 H 8.21, found : C 67.28 H 8.14.

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13 **15** : $[\alpha]_D^{22}$ +32° (c = 3.8, EtOH) ; **IR** (neat) : 2950, 1740, 1655, 1585, 1440 cm^{-1} ; **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 7.3-7.4 (5H, m) 5.29 (1H, s) 3.54 (3H, s) 2.47 (2H, m) 2.17 (2H, m) 1.95-1.65 (4H, m) 0.98 (3H, s) ; **^{13}C NMR** (62.87 MHz, $CDCl_3$) δ : 197.5 (s) 172.0 (s) 162.3 (s) 133.6 (d) 128.2 (d) 128.0 (d) 126.4 (s) 118.1 (d) 49.6 (q) 41.3 (s) 32.2 (t) 29.8 (t) 27.3 (t) 25.2 (t) 20.0 (q). **MS** (70 eV) m/e : 304 (M^+), 273, 218, 176, 147.

14 **16** : $[\alpha]_D^{22}$ = +7° (c = 3, EtOH ; ee 90 %) ; **IR** (neat) : 2940, 1735, 1655, 1600 cm^{-1} ; **^{1}H NMR** (90 MHz, $CDCl_3$) δ : 5.27 (1H, s) 3.70 (3H, s) 3.65 (3H, s) 2.5-1.8 (8H, m) 1.10 (3H, s).

15 **17** : mp 95 °C (Et_2O) ; $[\alpha]_D^{22}$ −5.3° (c = 5.5, EtOH) ; **IR** (KBr) : 2940, 2500 (broad), 1725, 1580 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) : 1/4 keto-enol mixture. *Enol form* δ 10.33 (1H, broad s) 5.35 (1H, s) 3.62 (3H, s) 2.43 (2H, t, J = 6 Hz) 2.23 (2H, t, J = 8 Hze) 1.4-1.2 (4H, m) 1.10 (3H, s). *Keto form* δ : 3.63 (3H, s) 3.52 (1H, d, J = 16 Hz) 3.36 (1H, d, J = 16 Hz) 1.15 (3H, s). **^{13}C NMR** (62.86 MHz, $CDCl_3$) : *Enol form* δ : 199.0 185.6 174.3 103.5 51.6 40.9 32.4 32.3 29.2 27.9 22.4. *Keto form* δ : 207.1 204.0 173.4 55.9 51.6 46.5 36.3 31.7 30.7 28.7 21.4. **Anal.** Calculated for $C_{11}H_{16}O_4$: C 62.24 H 7.59, found : C 62.60 H 7.42.

16 **18** : mp 116°C ; **IR** (KBr) : 3200 (broad), 2950, 2900, 1735, 1570 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ : 7.86 (1H, d, J = 7.8 Hz) 7.30 (2H, d, J = 4.0 Hz) 6.91 (1H, m) 6.06 (1H, broad s) 5.23 (1H, s) 3.65 (3H, s) 2.59 (2H, m) 2.30 (2H, m) 2.0-1.8 (4H, m) 1.12 (3H, s).

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18 **19** : mp 122 °C (Et_2O) ; $[\alpha]_D^{22}$ +46° (c = 2, EtOH) ; **IR** (KBr) : 3200 (broad), 2950, 1740, 1620, 1585, 1470 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ : 9.9 (1H, broad s) 8.22 (1H, m) 7.4-7.15 (3H, m) 3.63 (3H, s) 3.01 (2H, m) 2.42 (2H, m) 2.25-1.90 (4H, m), 1.24 (3H, s). **^{13}C NMR** (20.1 MHz, $CDCl_3$) δ : 198.8 (s) 174.4 (s) 150.9 (s) 136.6 (s) 125.3 (s) 123.2 (d) 122.3 (d) 121.0 (d) 111.6 (d) 111.5 (s) 51.6 (q) 44.3 (s) 34.8 (t) 32.3 (t) 29.6 (t) 22.5 (q) 20.3 (t). **Anal.** Calculated for $C_{17}H_{19}O_3N$: C 71.55 H 6.71 N 4.91, found C 71.53 H 6.44 N 4.89.

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