General Approach to the Synthesis of Sarpagine and Ajmaline Alkaloids. Enantiospecific Total Synthesis of (+)-Ajmaline and Alkaloid G via the Asymmetric Pictet−Spengler Reaction

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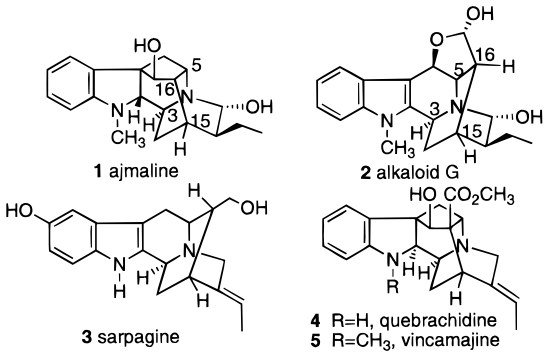
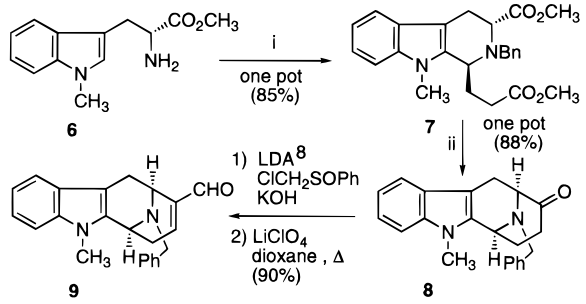
(+)-Ajmaline (**1**), which contains four heteroatoms, six rings, and nine asymmetric centers, is a clinically important indole alkaloid[1,2] with historical significance[3] and is related to the sarpagine **3** bases. Alkaloid G (**2**), which was recently isolated from plant cell cultures of *Rauwolfia serpentina* Benth by Stöckigt et al.[4] after feeding experiments with ajmaline, is also related to **3**. Both of these bases are structurally related by the presence of the quinuclidine ring and the C_5-C_{16} bond linkage. The absolute configurations of the stereogenic centers at C_3, C_5, and C_{15} of members of both the sarpagine and ajmaline class of indole alkaloids are identical.

Three important reports on the synthesis of ajmaline have appeared previously.[5] The first was published by Masamune



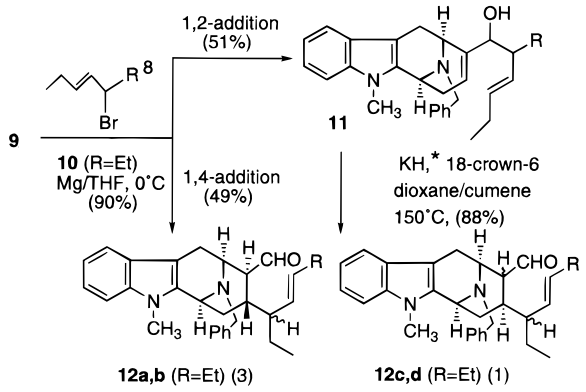
et al. in 1967 and involved 16 steps; this elegant approach was not enantiospecific, and the yields were not reported in some cases. Two years later, Mashimo and Sato converted tryptophan into an intermediate employed by Masamune in the earlier synthesis of ajmaline in order to provide a formal total synthesis of this alkaloid. Van Tamelen in 1970 in his biogenetic approach synthesized deoxyajmaline, and since Hobson et al.[6] had earlier converted deoxyajmaline to ajmaline, another synthesis of **1** was completed. This biogenetic route involved 17 steps, and the overall yield was quite low. We wish to report the first enantiospecific total synthesis of ajmaline that has also resulted in a formal total synthesis of alkaloid G.

Scheme 1[a]



[a] Reagents and conditions: (i) PhCHO, CH_3OH, rt, 2 h; $NaBH_4$; −30 to −10 °C, 3 h; $(CH_3O)_2CHCH_2CH_2COOCH_3$, TFA, $CHCl_3$, Δ, 12 h; (ii) NaH, CH_3OH, $PhCH_3$, Δ, 4 h; HOAc, HCl, Δ 12 h.

Scheme 2



* Ratio of **12a**,**b** to **12c**,**d** from the anionic oxy-Cope rearrangement was 3:2.

The optically active (−)-N_b-benzyltetracyclic ketone **8**[7] was prepared in enantiospecific fashion from D-(+)-tryptophan methyl ester **6** via a stereospecific Pictet−Spengler/Dieckmann protocol in an improved two-pot process. Conversion of the carbonyl function of (−)-**8** into the α,β-unsaturated aldehyde moiety of **9** via the spirooxiranophenylsulfoxide was accomplished in 90% overall yield[8] (Scheme 1). The α,β-unsaturated aldehyde (−)-**9** (>98% ee) serves as the key intermediate for the total synthesis of alkaloids in both the sarpagine and ajmaline series, as illustrated above (Scheme 2).

When (−)-**9** was stirred with 3-bromo-4-heptene **10** (R = Et) at 0 °C under the conditions of a Barbier−Grignard process, the products of 1,2-addition (allylic alcohol **11**, isolated as a mixture of diastereomers) and 1,4-addition (diastereomers **12a**,**b** and **12c**,**d**) were obtained in a combined yield of 90% in a ratio of 51 (**11**):49 (**12**).[8] The ratio of desired to undesired isomers from the 1,4-addition was 3:1 (see **12a**,**b** vs **12c**,**d**). The allylic alcohol **11** was easily separated from the mixture by flash chromatography and underwent the anionic oxy-Cope rearrangement at 150 °C in 88% yield to provide the same C-15-functionalized tetracyclic systems **12a**,**b** and **12c**,**d** in a ratio of 3:2. The key diastereomers could also be obtained by executing the

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(4) Endreb, S.; Takayama, H.; Suda, S.; Kitajima, M.; Aimi, N.; Sakai, S.; Stöckigt, J. *Phytochemistry* **1993**, *32*, 725−730.
(5) For earlier syntheses of ajmaline see: (a) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506−2507. (b) Van Tamelen, E. E.; Oliver, L. K. *Bioorg. Chem.* **1976**, *5* 309−326 . (c) Mashimo, K.; Sato, Y. *Tetrahedron Lett.* **1969**, *11*, 905−906. For a synthesis of isoajmaline see: Mashimo, K.; Sato, Y. *Tetrahedron Lett.* **1969**, *11*, 901−904.
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(7) Cox, E. D.; Hamaker, L. K.; Li, Jin; Yu, Peng; Czerwinski, K. M.; Li, Deng; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 44−61. Yu, Peng; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 6819−6822 and references cited therein.
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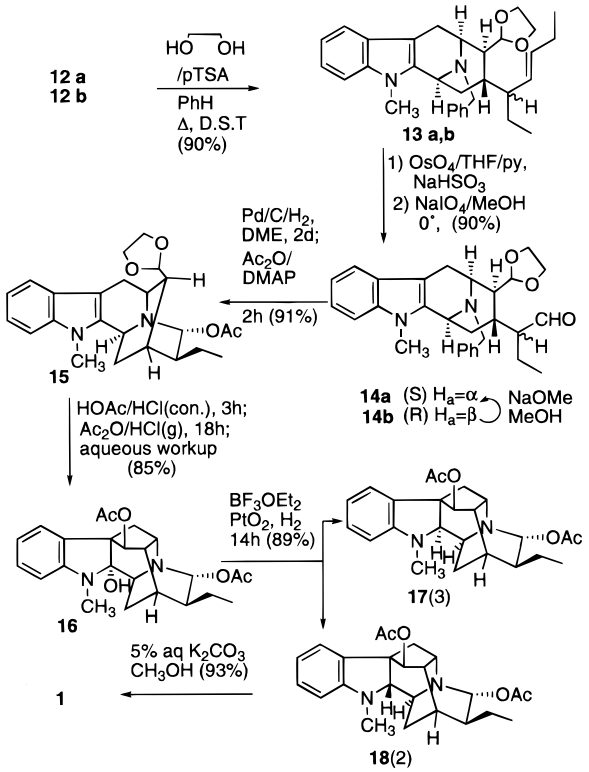
Scheme 3

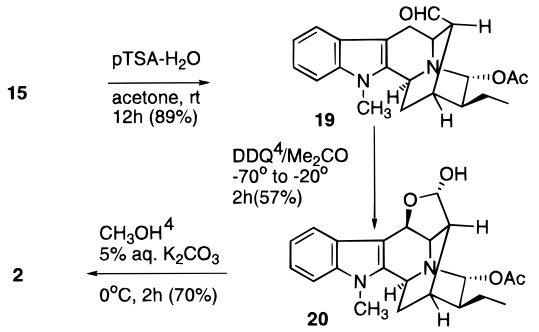


Barbier−Grignard process at 25 °C (only 1,2-addition) followed by the anionic oxy-Cope rearrangement. The desired aldehydes **12a**,**b** were obtained (from **9**) in 63% overall yield and employed for the preparation of **1** and **2**.

The conversion of **9** into aldehydes **12a**,**b**, although not stereospecific, constitutes the first effective solution to the long-standing problem of the stereochemistry at C(16) in the ajmaline series. In earlier work,[5] epimerization of the aldehyde group at C(16) to the unnatural configuration complicated the process; the ratio of desired to undesired diastereomers was reported as 7:43 and 3:7 from different laboratories.[5] In contrast, the presence of the ethyl group in **12a**,**b** (from **10**, R = Et) was found to be critical to retard epimerization of the aldehyde moiety at C(16) to the unnatural configuration. This ultimately permitted the formation of the desired ketal **13** in high yield (see below). Support for the importance of the ethyl group in **10** (R = Et) derives from the following experiment. When the anionic oxy-Cope rearrangement was carried out with the 2-pentenyl derivative (**10**, R = H) rather than the heptene analogue **10** (R = Et), the diasteroselectivity at C(15) was further improved (4:1); however, the ease of epimerization at C(16) to the unnatural diastereomer was increased. The presence of R = Et in **12a**,**b** (from **10**, R = Et) from the anionic oxy-Cope approach retarded isomerization at C(16) to the unnatural isomer, an epimerization process that had hindered earlier work.[5]

As illustrated in Scheme 3, the aldehyde function of **12a**,**b** was protected as the ethylene acetal (see **13a**,**b**) in 90% yield,

Scheme 4



and this was followed by oxidative cleavage (OsO_4, $NaIO_4$) of the olefinic bond to provide the two epimeric aldehydes **14a**,**b** in excellent yield. The desired aldehyde **14a** (*S* configuration) contains the required chirality for the preparation of ajmaline **1**, as well as alkaloid G (**2**). For this reason, the epimeric aldehyde **14b** was treated with base (NaOMe/MeOH) and converted into an equilibrium mixture of **14a** and **14b** (1:1), which was subjected to flash chromatography (silica gel, EtOAc/hexane, 2:8). In this manner, the conversion of **13a**,**b** into the required **14a** could be easily increased to greater than 80%.

The (−)-(*S*)-aldehyde **14a** was converted into the sarpagine system present in **15** in 91% yield by catalytic debenzylation followed by addition of acetic anhydride in a one-pot process. This acetal **15** was then treated with acetic acid and concentrated aqueous HCl for 3 h, after which time this mixture was stirred with acetic anhydride/HCl(g) to effect smooth cyclization to furnish the 2-hydroxyajmaline derivative **16** in 85% yield. The structure of this carbinolamine was determined by NMR spectroscopy and verified by single-crystal X-ray analysis of a derivative **16** (21-OCbz). The alcohol **16** was hydrogenated over platinum oxide in dry CH_2Cl_2 in the presence of BF_3 etherate to afford 2-epidiacetylajmaline **17** and diacetylajmaline **18** in a ratio of 3:2 in 89% yield. Hydrolysis of **18** with aqueous K_2CO_3 in methanol furnished (+)-ajmaline (**1**) in 93% yield. This base was spectrometrically identical (IR, ^1H NMR, ^{13}C NMR, MS, co-TLC) to that of an authentic sample of ajmaline including the optical rotation.[9] Hydrolysis of the intermediate acetal **15** provided the aldehyde **19**. Since aldehyde **19** was previously converted into alkaloid G in two steps, according to the method of Stöckigt et al.,[4] this also serves as a formal total synthesis of alkaloid G in enantiospecific fashion (Scheme 4).

Although reduction of **16** gave only 40% of diacetylajmaline **18**, this still constitutes the highest conversion of alcohol **16** to (+)-**1**[10,11] reported to date. In this caged molecule **16**, the α-face is much less hindered than the *β*-face; consequently, 2-epidiacetylajmaline can be formed with 100% stereoselectivity under certain conditions (Et_3SiH, TFA). This latter reduction process provides a potential route to alkaloids with the 2-epi configuration, including quebrachidine (**4**) and vincamajine (**5**). In addition, the cyclization reaction of **14** to **15** provides facile entry into the substructure of a number of sarpagine alkaloids. The steps described in Schemes 1−3 provide a route (from L-tryptophan) to prepare the (−) enantiomer of ajmaline via the trans transfer of chirality in the asymmetric Pictet−Spengler reaction. The two-pot process for the improved preparation of azabicyclo-[3.3.1]nonane **8** also streamlines this enantiospecific route to **1**.

Supporting Information Available: The X-ray crystallographic coordinates for the derivative (21-OCbz) of **16** (16 pages).

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(9) (**1**): $[\alpha]^{27}_D = +145.8$ (lit.[12] $[\alpha]^{20}_D = +144$).

(10) More than 20 different reaction conditions and reagents were employed to convert alcohol **16** into **18**; however, most of these gave the epi configuration at C(2) of **18**. In fact, the reduction conditions depicted below provide a simple entry (from **16**) into the epiajmaline (see **17**) stereochemistry at C(2) for an approach to bases such as **4** and **5** [9-BBN, PtO_2, H_2 (92%yield); Et_3SiH, TFA (90% yield); Pt/H_2, TFA (80% yield)].

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