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Alkaloid Synthesis: Stereoselective Approach Towards Fawcettimine-Serratinine Group of Lycopodium Alkaloids

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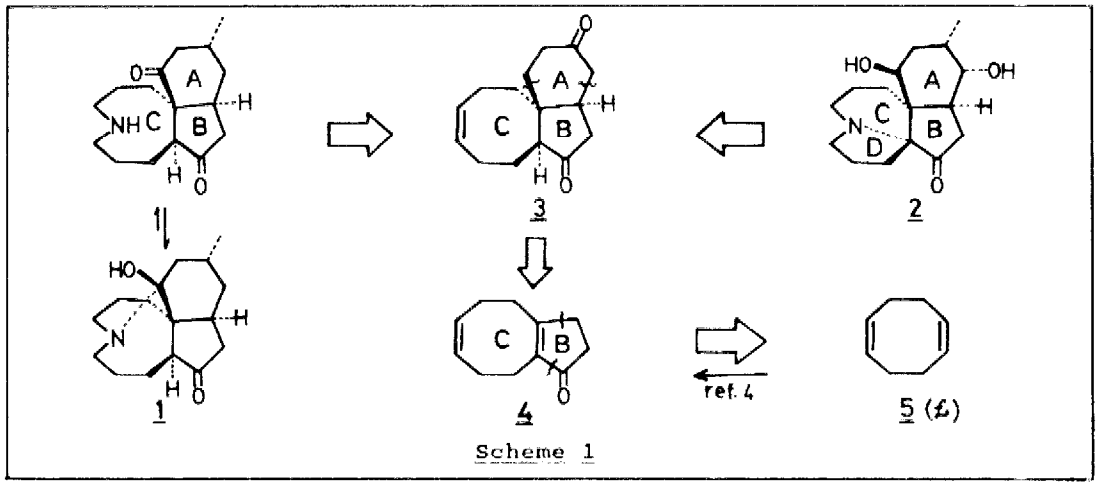
Key Words: Lycopodium alkaloids, Azacyclononane, Transannular cyclisation.
Abstract: The concept of carbocycle-heterocycle equivalency has been utilised to assemble the framework of fawcettimine-serratinine group of alkaloids from 1,5-cyclooctadiene through a common tricarbocyclic intermediate **3**.

Lycopodium alkaloids exhibit a fascinating spectrum of structural variation and biological activity and have, therefore, emerged as challenging and popular targets of synthesis in recent years.[1] Among them, fawcettimine **1** from Lycopodium fawcetti[2a] and serratinine **2** from Lycopodium serratum THUNB.,[2b] having close structural and biogenetic kinship, are prototypes of a growing family.[2c,d] The synthetic appeal of these alkaloids emanates from their unusual framework, embellished with stereochemical intricacies and considerable functionalisation.[3] Herein we describe the attainment of the complete framework present in **1** and **2**, with desired stereochemical disposition and adequate level of functionalisation, following an approach based on carbocycle-heterocycle equivalency.

From a retrosynthetic perspective, the key element was the recognition that the indolizidine moiety in **2** was equivalent to the azacyclo-

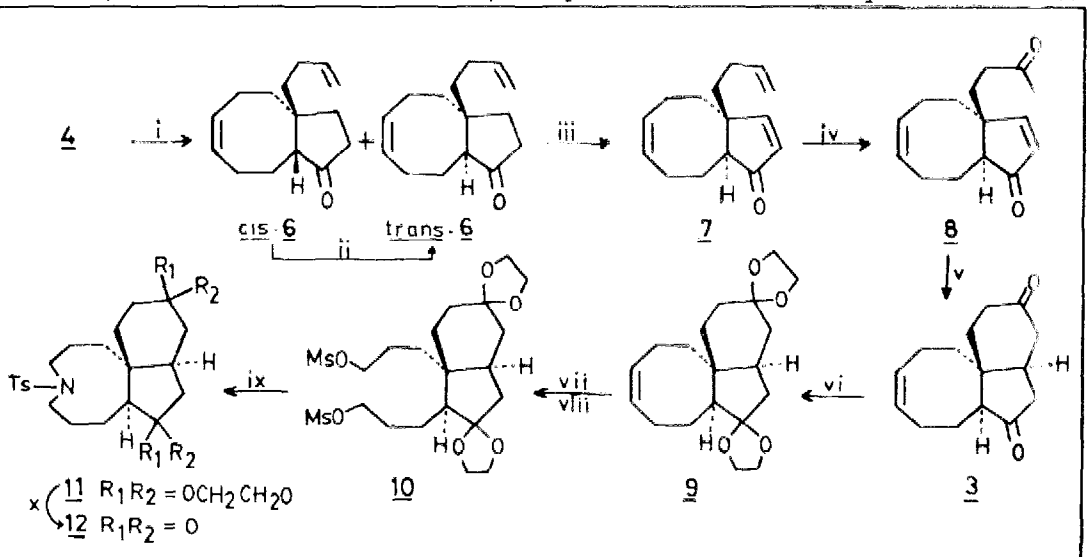


1 3 2 4 5 (±)

Scheme 1

nonane moiety (ring C) in **1**, which in turn was considered equivalent to cyclooctene (ring C) in **3**. Thus, the tricarbocyclic framework **3** was identified as the advanced common intermediate for **1**, **2** and other alkaloids of this group. Further bond disconnections in **3** led to bicyclic dienone **4** (BC rings) and then to 1,5-cyclooctadiene **5**(f), Scheme 1. Dienone **4** is readily available from **5** through a cyclopentenone annulation methodology that we developed some years ago[4] and our first objective was to elaborate it to the 'common core' **3**.

Conjugate 1,4-addition of the Grignard reagent prepared from 4-bromo-1-butene to **4** in the presence of Cu(I) complex and BF_3-etherate furnished a 5 : 1 mixture of cis-**6** and trans-**6** in good yield. The cis-**6** could be readily and completely converted to the desired trans-**6** on exposure to base. The trans-**6** was transformed to enone **7** via phenylselenylation-selenoxide elimination sequence and the butenyl side chain was then subjected to regioselective Wacker-type oxidation[5] with Pd^{+2} to furnish diene-dione **8**, Scheme 2. On exposure to base, **8** underwent the contemplated intramolecular Michael addition to furnish the key tricarbocyclic dione **3**.[6] The cyclooctene ⟶ azacyclononane equivalency in **3** was established through conversion to bis-acetal **9**, reductive ozonolysis to diol and double (inter- and intramolecular) displacement with N-tosylamide in the

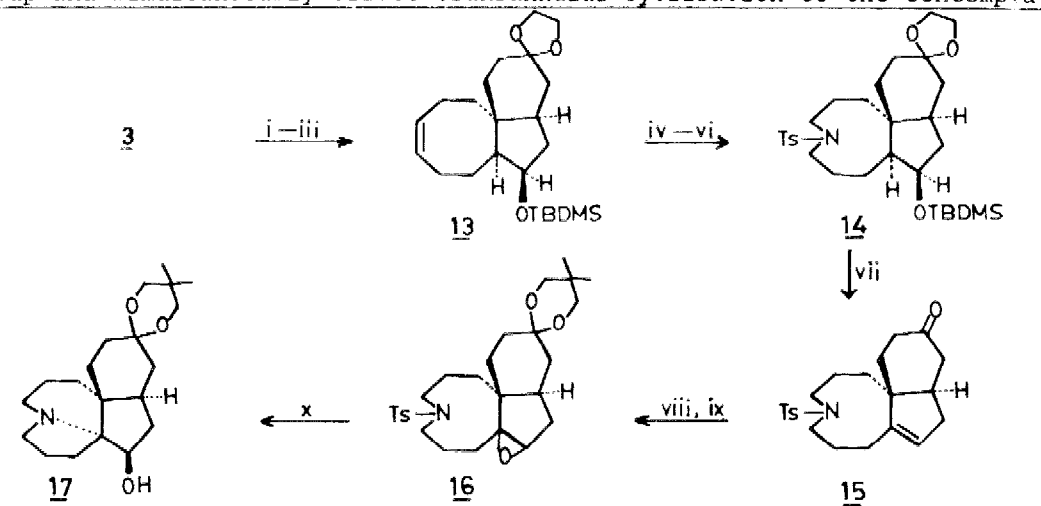


Reagents and Yield: (i)  MgBr, CuBr-Me_2S, BF_3OEt_2, Me_2S, THF, -78°C ⟶ 0°C, 75%; (ii) 2% KOH/MeOH, RT, 91%; (iii) Li-hexamethyldisilazide, PhSeCl, THF, -78°C ⟶ RT; 30% H_2O_2, pyridine-DCM, 0°C ⟶ RT, 60%; (iv) $PdCl_2$-O_2, CuCl,aqDMF, RT, 86%; (v) NaH, THF, 50°C, 78%; (vi) $HOCH_2CH_2OH$, camphorsulphonic acid, benzene, 90°C, 88%; (vii) O_3, MeOH, -78°C, $NaBH_4$, -78°C ⟶ RT; (viii) $MeSO_2Cl$, Et_3N, DCM, -23°C ⟶ RT, 70% from **9**; (ix) $TsNH_2$, n-Bu_4NI, NaOH, benzene, H_2O, 90°C, 48%; (x) Pyridinium-p-toluenesulphonate, acetone, 65°C, 89%.

Scheme 2

derived dimesylate **10** to furnish **11**.[6] Stereostructure of **11** was secured through a single crystal X-ray structure determination.[7] Deprotection in **11** led to the diketone **12**, which has the fawcettimine framework.

For elaboration into serratinine framework, the common intermediate **3** was chemoselectively monoprotected, reduced with sodium borohydride and converted into the t-butyldimethylsilylether **13**. Cyclooctene ring in **13** was now elaborated to the N-tosylazacyclononane moiety in a three step sequence (vide supra) to furnish **14**, Scheme 3. Brief exposure of **14** to BF_3-etherate resulted in carbonyl deprotection as well as the unexpected but desirable hydroxyl elimination to furnish the tricyclic enone **15**.[6] The indolizidine moiety was now generated to complete the serratinine framework. The carbonyl group in **15** was protected and the resulting acetal was epoxidised to furnish a mixture of epoxides **16**. The crude epoxide mixture was treated with sodium-naphthalenide to remove N-tosyl group and simultaneously effect transannular cyclisation to the contempla-



Reagents and Yield: (i) $HOCH_2CH_2OH$, PPTS, benzene, 90°C; (ii) $NaBH_4$, MeOH, RT; (iii) TBDMSCl, DBU, DMAP, DCM, RT, 64% from **3**; (iv) O_3, MeOH, -78°C, $NaBH_4$, -78°C ⟶ RT; (v) $MeSO_2Cl$, Et_3N, DCM, -23°C ⟶ RT, 73% from **13**; (vi) $TsNH_2$, n-Bu_4NI, NaOH, benzene, H_2O, 50%; (vii) BF_3OEt_2, $CHCl_3$, RT, 82%; (viii) $HOCH_2C(CH_3)_2CH_2OH$, PPTS, benzene, 90°C; (ix) MCPBA, DCM, 0°C ⟶ RT; (x) Na-naphthalene, DME, -78°C, (18% from **15**).

Scheme 3

ted tetracyclic framework **17**, Scheme 3. The stereochemical assignment at the newly generated quaternary centre follows largely from the previous precedence for such cyclisation.[3b]

Having accomplished the construction of the tri- and tetracyclic systems **12** and **17**, representing the frameworks of **1** and **2**, respectively, we hope to exploit the carbonyl handle present in ring A to generate the requisite functionalisation of the natural products of this lycopodium family.

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