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Studies on the synthesis of the indole alkaloids paucifloríne A and B

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Abstract

A double Bischler–Napieralski reaction of the 11-membered ring carbamate **15** gave the homoannular diene **17** in a single step.

In 1996 the structures of the *Kopsia* alkaloids pauciflorine A and B **1/2** were published,[1] and apart from their unusually strained structure, it was claimed that they selectively "inhibited melanin synthesis of B16 melanoma cells at 13 μg mL^{-1} without any cytotoxicity towards the cultured cells". Consequently, we have embarked upon a strategy for their synthesis, which is in part, based on a biogenetic speculation. While there have not been any published proposals concerning the speculated biosynthesis of **1/2**, it appears reasonable to consider **3** as a very plausible immediate precursor. The structurally similar *Kopsia* alkaloid kopsidasine **8** is known.[2] Grob fragmentation of **3** leads to **1/2**. The structure of **3** is the classical *kopsia* skeleton,[3] which can be derived from **4** (Scheme 1).[4] Two transannular cyclizations of **5** have the potential to provide a concise route to the homoannular diene **4**. Isogramine-type fragmentation of **6** should provide access to **5**,[5] and **6** is available from the classical Pictet–Spengler reaction of a tryptamine derivative and a pyruvate ester **7**.[6]

We have opted to test the above strategy for the synthesis of **4** starting with tryptamine rather than the far less accessible 6,7-dioxygenated tryptamine derivative. Consequently, our initial studies have focused on the synthesis of **15**. Oxidative cleavage of **9** using in situ generated RuO_4 gave the pyruvate **10** (60%). Also ozonolysis of **9** followed by reductive work-up provided **10** (95%). Pictet–Spengler condensation of **10** with tryptamine (containing 0.05 equiv. of tryptamine.HCl) gave **11** which was converted into the lactam **12**. It should be noted that the use of the dimethyl ester derivative of **10** was unsuccessful because the methyl ester derivative of **11** could not be converted into **12**, and as a consequence the reactions in Scheme 2 are required. Belleau's reagent[7] converted **12** into **13**, and Ni_2B/H_2 desulfurization[8] gave **14**. Treatment of **14** with $PhOCOCl/ClCH_2CH_2Cl$ heated at reflux resulted in **15**, whose structure was confirmed by X-ray crystallography.[9]

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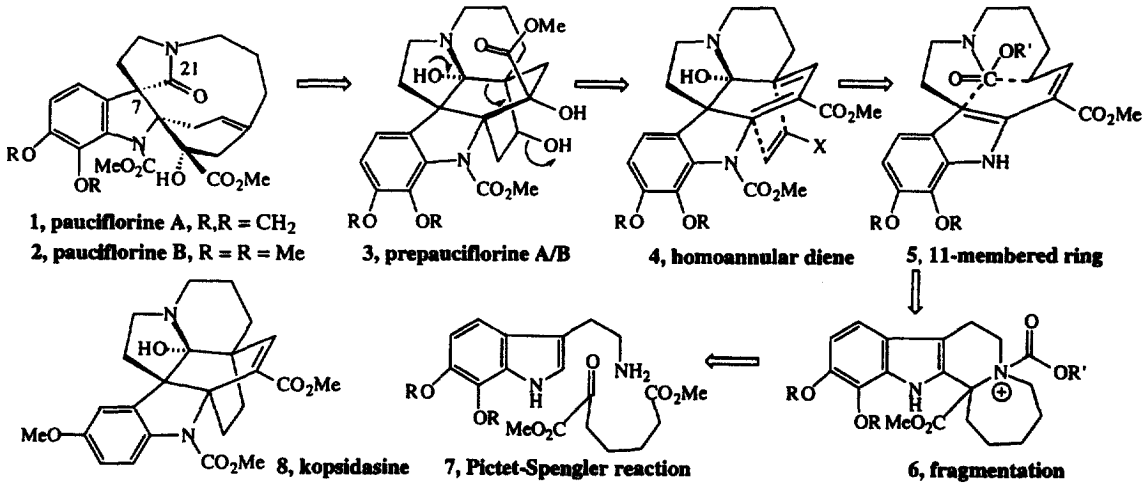
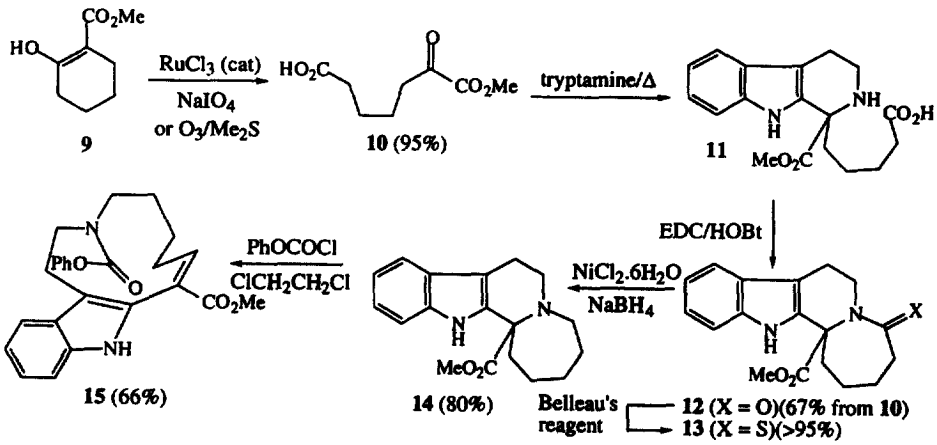
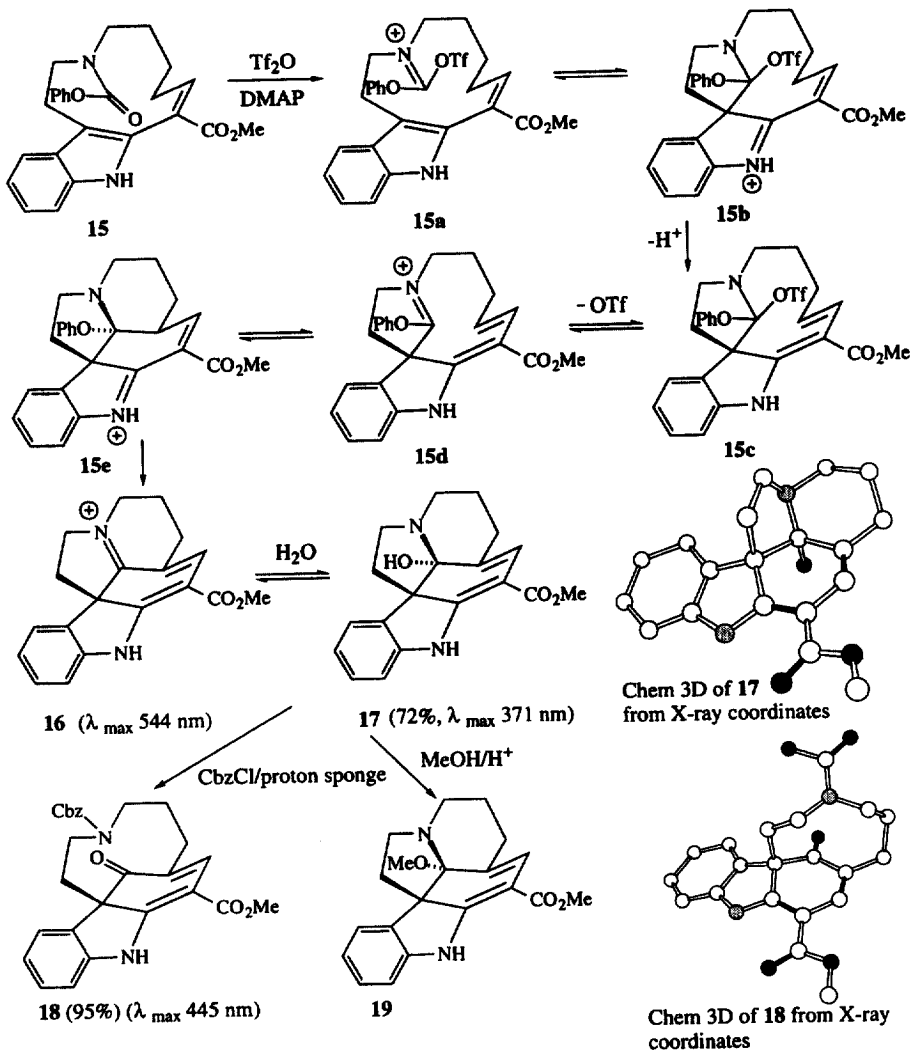


Scheme 1. Structure and proposed biogenetic origin of pauciflorine



Scheme 2. Synthesis of tetracyclic amine **14** and fragmentation to give **15**

It was anticipated that treatment of **15** with a powerful electrophile had the potential to cause both transannular reactions (**5**, Scheme 1) to take place resulting in **17** (Scheme 3). Activation of **15** to give **15a** should result in **15b**, which on proton loss to **15c** and iminium ion formation generates **15d**, which can cyclize to give **15e**. The iminium ion **15e** can lose a proton and eliminate –OPh to give **16**. In the event treatment of **15** with triflic anhydride in dichloromethane containing 4-dimethylaminopyridine heated at reflux,[10] eventually gave a deep purple solution of the iminium ion **16**. Quenching the purple solution with aqueous $NaHCO_3$ gave **17** as yellow crystals whose structure was confirmed by X-ray crystallography.[11] Dissolving **17** in trifluoroacetic acid gave a purple solution (λ_{max} 544 nm), and treatment of **17** with MeOH/TsOH gave **19**, thus providing strong evidence for the intermediacy of the iminium ion **16**. The carbinolamine **17** was readily cleaved by treatment with benzyl chloroformate to provide the orange conjugated dienone **18** (X-ray).[12] The homoannular diene **17** is available in only seven steps from **9**. Currently we are examining the cycloaddition chemistry of **17** and **18** along with asymmetric versions of the key transannular cyclization reaction. The double Bischler–Napieralski reaction strategy has some analogy to the so-called 'crisscross' annulation reaction recently described by the Bonjoch group.[13]



Scheme 3. Formation of the homoannular diene **17**

Acknowledgements

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11. Mp 184–185°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (1H, br s), 7.53 (1H, dd, *J*=7.5, 0.6 Hz), 7.21 (1H, td, *J*=7.5, 1 Hz), 6.97 (1H, td, *J*=7.5, 1 Hz), 6.88 (1H, d, *J*=7.5 Hz), 6.18 (1H, d, *J*=2.1 Hz), 3.78 (3H, s), 3.34 (1H, q, *J*=8.7 Hz), 3.28 (1H, td, *J*=13.6, 2.8 Hz), 3.03–2.86 (2H, m), 2.51 (1H, tdd, *J*=13.7, 4.7, 2.2 Hz), 2.5–2.3 (2H, m), 1.92–1.65 (3H, m), 1.53 (1H, ddd, *J*=13.1, 4.7, 2.3 Hz); IR (film) 3354, 2928, 2851, 1678 cm^{-1}; UV ($CHCl_3$, 4.93×10^{-5} M) λ_{max} 371 (ε 11,300), 297 (ε 6900); (1% v/v TFA in $CHCl_3$, 6.16×10^{-5} M) λ_{max} 544 (ε 1800), 370 (ε 11,500), 330 (ε 7900), 306 (ε 7300); HRMS (CI^+) calcd for $C_{19}H_{20}N_2O_3$ (M^+) 324.1474, found 324.1473.
12. Mp 185–188°C (decomp, softens at 170°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, br s), 7.92 (0.6H, d, *J*=7.5 Hz), 7.73 (0.4H, d, *J*=7.5 Hz), 7.45–7.3 (6H, m), 7.42 (0.6H, s), 7.40 (0.4H, s), 7.15–7.93 (2H, m), 5.25–4.95 (2H, m), 3.88 (3H, s), 3.82–3.65 (1H, m), 3.60 (0.6H, dd, *J*=14.8, 5.7 Hz), 3.50 (0.4H, dd, *J*=14.8, 5.7 Hz), 3.27 (0.4H, dd, *J*=14.8, 9.8 Hz), 3.17 (0.6H, dd, *J*=14.8, 9.8 Hz), 3.00–2.68 (2.6H, m), 2.50 (0.4H, dd, *J*=14.3, 10.0 Hz), 2.35–2.10 (1H, m), 2.1–1.6 (3H, m); IR (film) 3313, 2923, 2853, 1652, 1612 cm^{-1}; HRMS (CI^+) calcd for $C_{27}H_{27}N_2O_5$ (MH^+) 459.1920, found 459.1913.
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