SHORT SYNTHETIC ROUTE TO 5,6-DIHYDROFLAVOPEREIRINE AND FLAVOPEREIRINE

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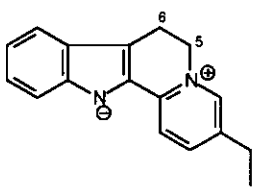
Abstract - A short synthetic route to 5,6-dihydroflavopereirine (**1**) and flavopereirine (**2**) is described.

5,6-Dihydroflavopereirine (**1**) and flavopereirine (**2**) belong to a small group of indole alkaloids of the *Corynanthé*-type which lack the generally present three-carbon unit [C-16, C-17, and C-22 (biogenetic numbering),[1] e.*g*. in geissoschizine (**3**)].[2]



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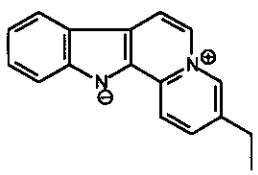

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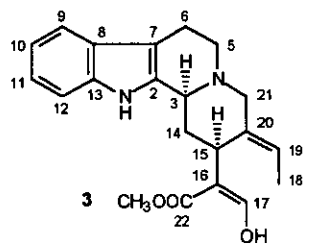

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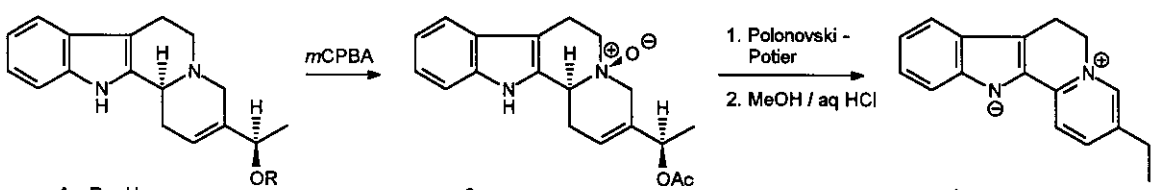
5,6-Dihydroflavopereirine (**1**) was first isolated by Angenot and Denoël[3] from the African *Strychnos usambarensis* Gilg. (Loganiaceae) and flavopereirine (**2**) was isolated almost simultaneously by Janot *et al*.[4] and Rapoport *et al*.[5] from the South American *Geissospermum laeve* (Vellozo) Baillon [=*Geissospermum vellosii* F. Allem.][6] (Apocynaceae), and by Schmid *et al*.[7] from the South American *Strychnos melinoniana* Baillon (Loganiaceae).

Several syntheses (total or partial) are known[2] for compounds (**1**) and (**2**), but most of them are relatively long and tedious. In the present paper we describe a short and easy route to 5,6-dihydroflavopereirine (**1**) and flavopereirine (**2**), which allows the main transformations to be done in one-pot (*vide infra*). This procedure would appear to represent the *méthode de choix* for the easy preparation of these two compounds, especially for 5,6-dihydroflavopereirine (**1**).

Our recently described[8] allylic alcohol (**4**) was acetylated and the acetate (**5**)[9] converted by *m*-chloroperbenzoic acid (*m*CPBA) treatment to the corresponding *trans*-N_b-oxide (**6**)[10] (small amounts of the *cis*-N_b-oxide were detected). The N_b-oxide (**6**) was allowed to react with trifluoroacetic anhydride (TFAA) under Polonovski-Potier conditions.[11-13] The mixture obtained after evaporation was stirred in $MeOH/HCl_{aq}$ for 6 h at room temperature. After normal work-up, the main component, compound (**1**),[14] was purified by flash chromatography (Scheme 1).

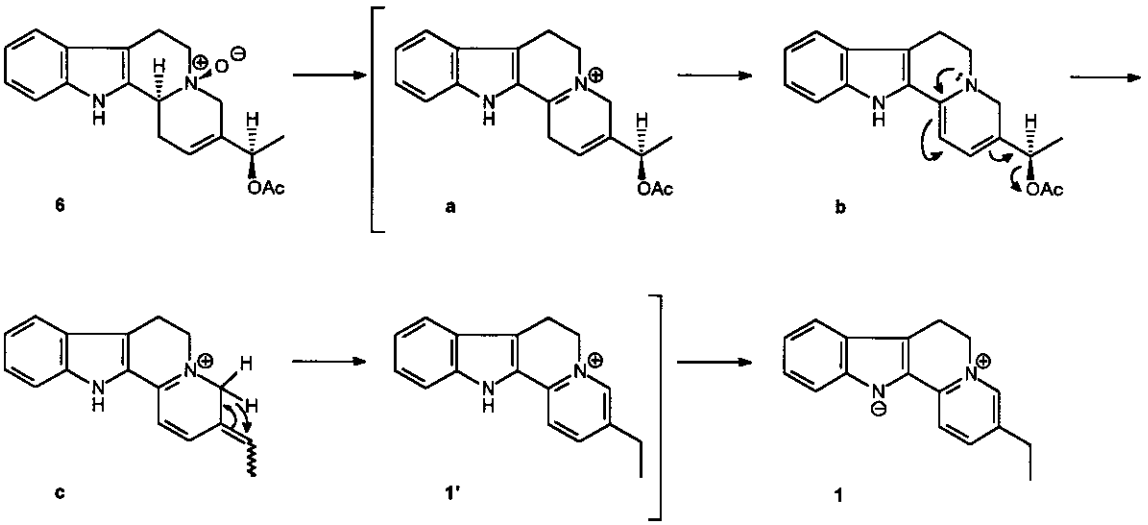


4 R = H
5 R = Ac

6 **1**

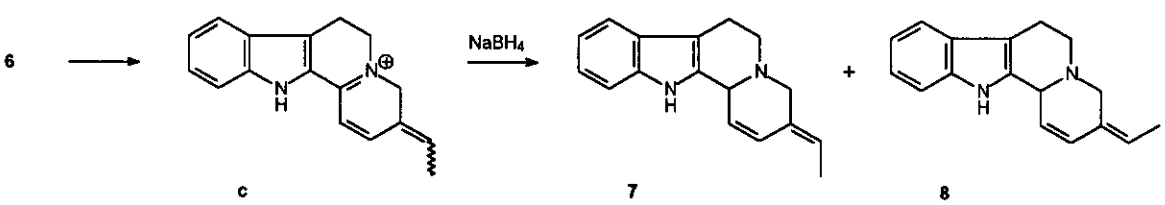
Scheme 1.

The formation of compound (**1**) can be presented in the following manner: Formation of the iminium ion (**a**) from N_b-oxide (**6**), followed by proton cleavage, leads to the enamine (**b**). Conjugated *retro*-Mannich reaction then affords the iminium ion (**c**). Double bond migration completes the formation of compound (**1´**), which exists after basification in zwitterionic form (anhydronium base) (**1**) (Scheme 2).



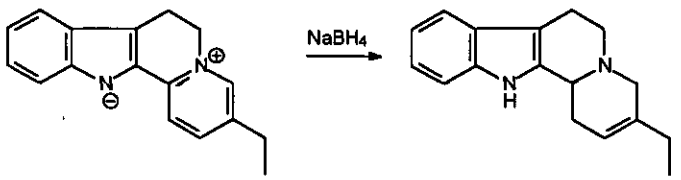
Scheme 2.

We have recently shown[15] that the reaction of the malono ester analogue of compound (**6**) (compound (**7**) in Ref. 15) with TFAA under Polonovski-Potier reaction conditions, followed by $NaBH_4$ treatment, leads to 14,15-didehydro-*E*-deplancheine (**7**)[16] and 14,15-didehydro-*Z*-deplancheine (**8**).[17] The same compounds (**7** and **8**) were obtained from compound (**6**) under identical conditions (Scheme 3).[18] This is a supplementary proof for the intermediacy of the iminium ion (**c**) in the formation of 5,6-dihydroflavopereirine (**1**) (*vide supra*).



Scheme 3.

Moreover, treatment of 5,6-dihydroflavopereirine (**1**) with $NaBH_4$/MeOH afforded compound (**9**),[19] thus confirming the structure (**1**) (Scheme 4).



1 9

Scheme 4.

Finally, oxidation of compound (**1**), for example with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), is known to lead to compound (**2**).[2,20]

In sum, a short synthetic route to indole alkaloids 5,6-dihydroflavopereirine (**1**) and flavopereirine (**2**), utilizing an easily accessible starting material [allylic alcohol (**4**)],[8] is now available.

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9. Compound (**5**). Yield: 80%. Amorphous material. Ir: 1720 cm^{-1} (C=O). ^1H Nmr (200 MHz, $CDCl_3$): 1.35 (3H, d, J=6.5 Hz, H-18), 2.04 (3H, s, CH_3COO-), 3.38 (1H, br d, J≈10 Hz, H-3), 3.45 (1H, d, J=16 Hz, H-21β), 5.36 (1H, q, J=6.5 Hz, H-19), 5.79 (1H, br, H-15), 7.0-7.2 (2H, m, H-10, H-11), 7.24 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.01 (1H, s, NH). ^{13}C Nmr (50 MHz, $CDCl_3$): 18.6 (C-18), 21.2 (C-6), 21.3 (CH_3COO-), 30.7 (C-14), 52.2 (C-5), 53.7 (C-21), 55.2 (C-3), 72.0 (C-19), 108.2 (C-7), 110.7 (C-12), 118.1 (C-9), 119.3 (C-10), 121.3 (2C, C-15, C-11), 127.0 (C-8), 134.5 (C-2), 136.3 (C-20), 136.5 (C-13), 170.5 (C=O). Ms (EI, *m/z*): 310 (M^+), 309, 251 (100%), 250, 170, 169. HRms: Calcd for $C_{19}H_{22}N_2O_2$: 310.1681. Found: 310.1663. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52, H, 7.14, N, 9.03. Found: C, 73.40, H, 7.06, N, 8.90.

10. Compound (**6**). Yield: 52%. Amorphous material. Ir: 1725 cm^{-1} (C=O). ^1H Nmr [200 MHz, $CDCl_3$ + CD_3OD (5 drops)]: 1.39 (3H, d, J=6.5 Hz, H-18), 2.08 (3H, s, CH_3COO-), 4.13 (1H, d, J=16 Hz, H-21β), 4.48 (1H, m, H-3), 5.30 (1H, q, J=6.5 Hz, H-19), 5.89 (1H, br, H-15), 7.0-7.2 (2H, m, H-10, H-11), 7.33 (1H, d, J=7 Hz, H-12), 7.49 (1H, d, J=7 Hz, H-9). ^{13}C Nmr [50 MHz, $CDCl_3$ + CD_3OD (5 drops)]:[21] 17.6 (C-6), 18.1 (C-18), 20.8 (CH_3COO-), 24.5 (C-14), 65.5 (C-5), 65.7 (C-3), 67.3 (C-21), 71.0 (C-19), 105.6 (C-7), 111.4 (C-12), 118.0 (C-9), 119.4 (C-10), 121.5 (C-11), 121.8 (C-15), 125.9 (C-8), 130.8* (C-20), 130.9* (C-2), 136.6 (C-13), 170.7 (C=O). Ms (EI, *m/z*): 326 (M^+,<2%), 310, 251 (100%), 170, 169. HRms: Calcd for $C_{19}H_{22}N_2O_3$: 326.1630. Found: 326.1627. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92, H, 6.79, N, 8.58. Found: C, 69.82, H, 6.90, N, 8.42.

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14. Compound (**1**). Yield: 42%. Yellowish mass [corresponding perchlorate mp 276-280°C (EtOH) (lit., 281-282°C,[20] 278-281°C[22])]. ^{1}H Nmr (200 MHz, DMSO-d_6): 1.38 (3H, t, J=7.5 Hz, H-18), 2.88 (2H, q, J=7.5 Hz, H-19), 3.45 (2H, m, H-6α, H-6β), 4.98 (2H, m, H-5α, H-5β), 7.26 (1H, t, J=8 Hz, H-10), 7.45 (1H, t, J=8 Hz, H-11), 7.64 (1H, d, J=8 Hz, H-12), 7.82 (1H, d, J=8 Hz, H-9), 8.33 (1H, d, J=8 Hz, H-15), 8.58 (1H, d, J=8 Hz, H-14), 9.01 (1H, s, H-21), 12.58 [<1H (only partly protonated), s, NH]. ^{13}C Nmr (50 MHz, DMSO-d_6):[21] 14.3 (C-18), 18.8 (C-6), 24.8 (C-19), 55.8 (C-5), 112.7 (C-12), 116.8 (C-7), 120.6* (2C, C-9, C-10), 120.7* (C-11), 124.8** (C-8), 125.3** (C-20), 126.1 (C-14), 139.2*** (C-2), 139.6*** (C-13), 141.1 (C-3), 144.3 (C-15), 145.2 (C-21). Ms (EI, *m/z*): 248 (M^+), 247 (100%).

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16. Compound (**7**). Yield 28%. For the analytical data, see Ref. 15.

17. Compound (**8**). Yield 12%. For the analytical data, see Ref. 15.

18. The fact that the acetate N_b-oxide (**6**) and its malonate analogue [*Cf.* compound (**7**) in Ref. 15] yield the same compounds (**7** and **8**)(*vide supra*), argues for similar mechanisms. This similarity, it may be added, furnishes supplementary evidence for the correctness of our preferred mechanism for the malonate analogue (*Cf.* Ref. 15, alternative two).

19. Compound (**9**). Yield 54%. For the analytical data, see Ref. 23.

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21. ^{13}C Nmr signals marked with asterisks may be interchanged.

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