SHORT SYNTHETIC ROUTE TO 5,6-DIHYDROFLAVOPEREIRINE AND FLAVOPEREIRINE

Mauri Lounasmaa*, Pirjo Hanhinen, and Sami Lipponen

Laboratory for Organic and Bioorganic Chemistry, Technical University of Helsinki, FIN-02150 Espoo, Finland

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 Corynanthē-type which lack the generally present three-carbon unit [C-16, C-17, and C-22 (biogenetic numbering), e.g. in geissoschizine (3)].

5,6-Dihydroflavopereirine (1) was first isolated by Angenot and Denoël from the African Strychnos usambarensis Gilg. (Loganiaceae) and flavopereirine (2) was isolated almost simultaneously by Janot et al. and Rapoport et al. from the South American Geissospermum laeve (Vellozo) Baillon [=Geissospermum vellosii F. Allem.] (Apocynaceae), and by Schmid et al. from the South American Strychnos melinoniana Baillon (Loganiaceae).
Several syntheses (total or partial) are known 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 allylic alcohol (4) was acetylated and the acetate (5) converted by m-chloroperbenzoic acid (mCPBA) treatment to the corresponding trans-\(\text{N}_6\)-oxide (6) (small amounts of the cis-\(\text{N}_6\)-oxide were detected). The \(\text{N}_6\)-oxide (6) was allowed to react with trifluoroacetic anhydride (TFAA) under Polonovski-Potier conditions. 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), was purified by flash chromatography (Scheme 1).

\[4 \quad \text{R} = \text{H} \]
\[5 \quad \text{R} = \text{Ac} \]

Scheme 1.

The formation of compound (1) can be presented in the following manner: Formation of the iminium ion (a) from \(\text{N}_6\)-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).
We have recently shown\textsuperscript{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\textsubscript{4} treatment, leads to 14,15-didehydro-\textit{E}-deplancheine (7)\textsuperscript{16} and 14,15-didehydro-\textit{Z}-deplancheine (8).\textsuperscript{17} The same compounds (7 and 8) were obtained from compound (6) under identical conditions (Scheme 3).\textsuperscript{18} This is a supplementary proof for the intermediacy of the iminium ion (c) in the formation of 5,6-dihydroflavopereirine (1)(vide supra).

Moreover, treatment of 5,6-dihydroflavopereirine (1) with NaBH\textsubscript{4}/MeOH afforded compound (9),\textsuperscript{19} thus confirming the structure (1) (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).\textsuperscript{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)],\textsuperscript{8} is now available.

REFERENCES AND NOTES


9. Compound (5). Yield: 80%. Amorphous material. Ir: 1720 cm\(^{-1}\) (C=O). \(^1\)H Nmr (200 MHz, CDCl\(_3\)): 1.35 (3H, d, J=6.5 Hz, H-18), 2.04 (3H, s, CH\(_3\)COO-), 3.38 (1H, br d, J=10 Hz, H-3), 3.45 (1H, d, J=16 Hz, H-21\(\beta\)), 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\(_3\)COO-), 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\(_2\)O\(_2\): 310.1681. Found: 310.1663. Anal. Calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_2\): 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). \(^1\)H Nmr [200 MHz, CDCl\(_3\)+CD\(_3\)OD (5 drops)]: 1.39 (3H, d, J=6.5 Hz, H-18), 2.08 (3H, s, CH\(_3\)COO-), 4.13 (1H, d, J=16 Hz, H-21\(\beta\)), 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\(_3\)OD (5 drops)]: 17.6 (C-6), 18.1 (C-18), 20.8 (CH\(_3\)COO-), 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\(^\ast\) (C-20), 130.9\(^\ast\) (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\(_2\)O\(_3\): 326.1630. Found: 326.1627. Anal. Calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_3\): C, 69.92, H, 6.79, N, 8.58. Found: C, 69.82, H, 6.90, N, 8.42.


Compound (1). Yield: 42%. Yellowish mass [corresponding perchlorate mp 276-280°C (EtOH) (lit., 281-282°C, \textsuperscript{20} 278-281°C\textsuperscript{22})]. \textsuperscript{1}H Nmr (200 MHz, DMSO-d\textsubscript{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-6\textalpha, H-6\textbeta), 4.98 (2H, m, H-5\textalpha, H-5\textbeta), 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]. \textsuperscript{13}C Nmr (50 MHz, DMSO-d\textsubscript{6}):\textsuperscript{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\textsuperscript{*} (2C, C-9, C-10), 120.7\textsuperscript{*} (C-11), 124.8\textsuperscript{**} (C-8), 125.3\textsuperscript{**} (C-20), 126.1 (C-14), 139.2\textsuperscript{***} (C-2), 139.6\textsuperscript{***} (C-13), 141.1 (C-3), 144.3 (C-15), 145.2 (C-21). Ms (EI, m/z): 248 (M\textsuperscript{+}), 247 (100%).


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\textsubscript{6}-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.


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


Received, 29th February, 1996