

Total Synthesis of (\pm)-8-Oxotabersonine via the Indole-2,3-quinodimethane Strategy

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The enecarbamate (**9**) on treatment with the Vilsmeier reagent is converted into the aldehyde (**10**), which was transformed into (\pm)-8-oxotabersonine (**1**).

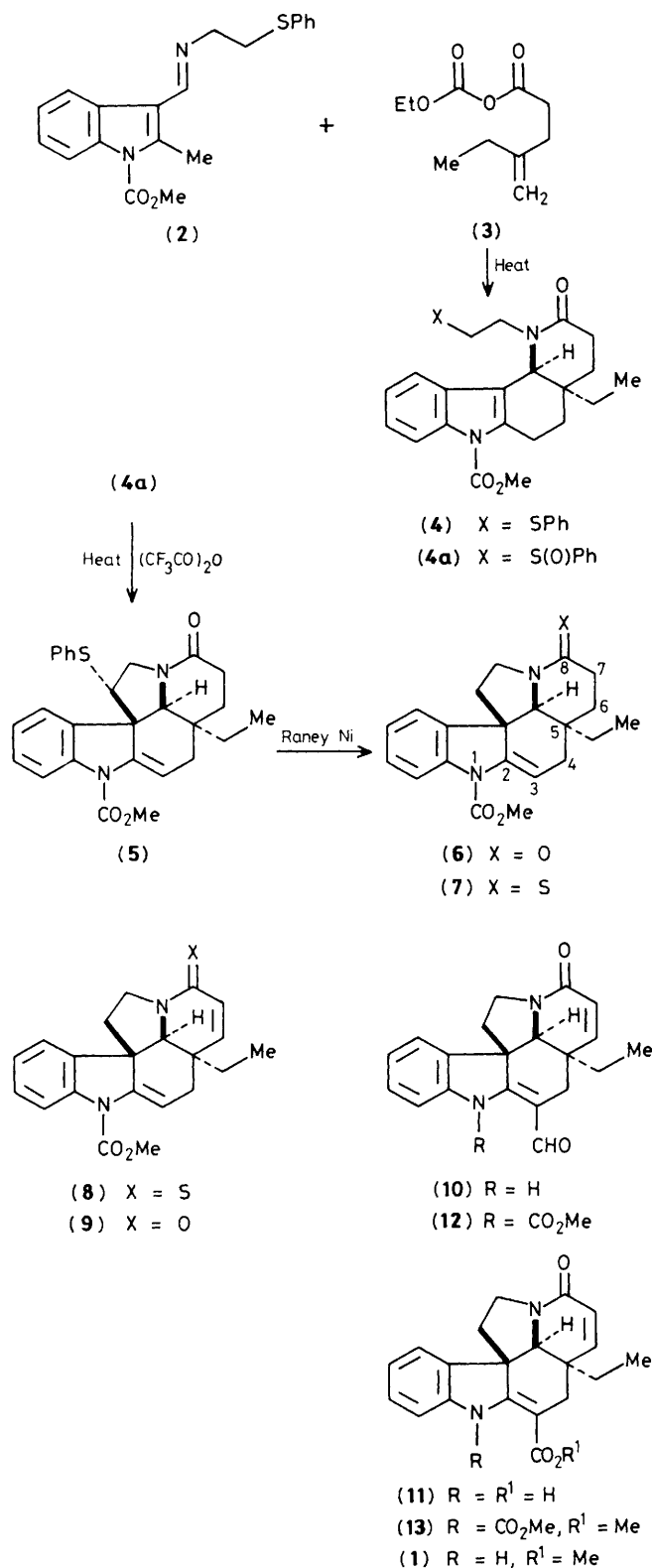
If the indole-2,3-quinodimethane strategy for the synthesis of indole alkaloids¹ is to be successful as a method for assembling complex alkaloids, it is essential that procedures are developed for the introduction of the peripheral functionality.² In this paper we report a direct method for introducing the 3-methoxycarbonyl group of *Aspidosperma* alkaloids in the context of the total synthesis of (\pm)-8-oxotabersonine (**1**).^{3,4} 8-Oxotabersonine (**1**) was isolated from the seeds of *Amsonia elliptica* Roem et Schult, and its synthesis from (\pm)-8-oxovincadifformine was described by Lévy.⁵

The imine (**2**)⁶ was treated with the mixed anhydride (**3**) in PhCl containing Pr_2NEt_2 heated at reflux to give the tetracyclic adduct (**4**) (58%). While this reaction works in the cited yield on a mmol scale, we were not able to increase the scale without drastic reductions in yields despite extensive experimentation. This problem has been discussed, and a solution described in a recent full paper from this laboratory.⁶ Although the above restriction exists, nevertheless, (**4**) is

available in ≥ 10 g quantities, because both (**2**) and (**3**) are readily available, and the production of (**4**) is the first step in a highly convergent sequence. Oxidation of (**4**) [*m*-chloroperbenzoic acid (MCPBA), CH_2Cl_2 , 0 °C] to give the derived sulphoxide (**4a**), followed by intramolecular Pummerer reaction gave (**5**), which was desulphurised with Raney nickel in EtOAc to give (**6**) [82%, from (**4**)].

There are only two methods which directly introduce the 3-methoxycarbonyl group into substrates such as (**6**), and both proceed in low yield.⁷ As a consequence, we were particularly interested in examining the electrophilic substitution chemistry of enecarbamates with carbon electrophiles.⁸

Conversion of (**6**) into the thioamide (**7**) was achieved using Belleau's reagent⁹ in tetrahydrofuran (THF) (-3 to 25 °C over 1.25 h) in 80% yield. The thioamide (**7**) was treated with *p*-toluenesulphonyl chloride (2.5 equiv.)- Pr_2NEt (5.0 equiv.) in PhCl at reflux for 15 min to give the α,β -unsaturated thioamide (**8**) (86%), m.p. 160.5–161.5 °C.



Oxidation of (8) with MCPBA¹⁰ (1.2 equiv.) in CH_2Cl_2 at -20°C gave (9) (77%), m.p. $122\text{--}123^\circ\text{C}$. When (9) was exposed to the Vilsmeier reagent POCl_3 –dimethylformamide (DMF) (20 equiv.), 24°C , 1 h, then 65°C for 15 min, followed by a basic work-up (2 M NaOH), the α,β -unsaturated aldehyde (10) (76%) was isolated, m.p. $224\text{--}226^\circ\text{C}$ (EtOAc), δ_{H} 9.21(CHO). The Viehe reagent¹¹ ($\text{Cl}_2\text{C}=\text{N}^+\text{Me}_2\text{Cl}^-$) did not react with (9).

All attempts to oxidise the aldehyde (10) to give the corresponding carboxylic acid (11) or 8-oxotabersonine (1) (AgO ; MnO_2 , KCN, MeOH; NaOCl_2 , etc.) failed, because of the reactivity of the 2,3-double bond. To overcome this difficulty, (10) was treated with NaH, ClCO_2Me , THF to give (12) (84%). This compound is also directly available from (9) by Vilsmeier formylation, followed by mild work-up to avoid hydrolysis of the N– CO_2Me group; but it is contaminated with (10), and consequently, it is better to reintroduce the carbamate. Oxidation of (12) using NaClO_2 , $\text{H}_2\text{NSO}_3\text{H}$, acetone, isopropenyl acetate, 10% aqueous NaH_2PO_4 , followed by diazomethane, gave the methyl ester (13) (88%). Mild basic hydrolysis of (13) with 1 M NaOMe–MeOH gave (\pm)-8-oxotabersonine (1) (97%) [m.p. $161\text{--}163^\circ\text{C}$, (lit.,⁴ $151\text{--}153^\circ\text{C}$); u.v. λ_{max} (EtOH) 202 (ϵ 15700 $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$), 292 (9600) nm; ^1H n.m.r. (300 MHz, CDCl_3) δ 9.05 (1H, bs), 7.24 (1H, d, J 8.0 Hz), 7.23 (1H, t, J 8.0 Hz), 6.94 (1H, d, J 7.7 Hz), 6.89 (1H, d, J 7.7 Hz), 6.45 (1H, d, J 9.9 Hz), 5.96 (1H, J 9.9 Hz), 4.31 (1H, dd, J 11.7 and 6.3 Hz), 3.98 (1H, s), 3.79 (3H, s), 3.39 (1H, ddd, J 11.7, 6.3, and 6.3 Hz), 2.62 (1H, dd, J 15.6 and 1.9 Hz), 2.07 (1H, d, J 15.6 Hz), 1.91 (2H, m), 1.10 (1H, q, J 7.3 Hz), 1.01 (1H, q, J 7.3 Hz), 0.73 (3H, t, J 7.3 Hz)].

Thermolysis of (13) at 240°C did not produce any retro-Diels–Alder processes that may have eventually resulted in rearrangement to give the iboga-type indole alkaloids, or fragmentation to give 5-ethylpyridine and a carbazole.^{12†}

The National Institutes of Health are gratefully thanked for their financial support of this research.

Received, 28th July 1986; Com. 1063

References

- For a general description of the indole-2,3-quinodimethane strategy see: P. Magnus, T. Gallagher, P. Brown, and P. Pappalardo, *Acc. Chem. Res.*, 1984, **17**, 35.
- P. Magnus and P. Pappalardo, *J. Am. Chem. Soc.*, 1986, **108**, 212.
- P. Magnus, P. Pappalardo, and I. Southwell, *Tetrahedron*, 1986, **42**, 3215.
- N. Aimi, Y. Asada, S.-I. Sakai, and J. Haginiwa, *Chem. Pharm. Bull.*, 1978, **26**(4), 1182.
- J.-Y. Laronze, J. Laronze-Fontaine, J. Lévy, and J. Le Men, *Tetrahedron Lett.*, 1974, 491; J. Lévy, J.-Y. Laronze, J. Laronze-Fontaine, and J. Le Men, *ibid.*, 1978, 1579.
- P. Magnus and P. M. Cairns, *J. Am. Chem. Soc.*, 1986, **108**, 217.
- L. E. Overman, M. Sworin, and R. M. Burk, *J. Org. Chem.*, 1983, **48**, 2685; E. Wenkert, B. Porter, D. P. Simmons, J. Ardisson, N. Kunesch, and J. Poisson, *ibid.*, 1984, **49**, 3733. *Added in proof.* Professor Bau has recently described a new procedure using Vilsmeier chemistry: K. Yoshida, S. Nomura, and Y. Bau, *Tetrahedron*, 1985, **41**, 5495.
- T. Shono, Y. Matsumura, K. Tsubata, and Y. Sugihara, *Tetrahedron Lett.*, 1982, 1201; H. Fritz and S. H. Eggers, *Liebigs Ann. Chem.*, 1970, **736**, 33; H. Fritz and G. Rubach, *ibid.*, 1968, **715**, 135.
- G. Lajoie, F. Lépine, L. Maziak, and B. Belleau, *Tetrahedron Lett.*, 1983, 3815.
- K. S. Kochlar, D. A. Cottrell, and H. W. Pinnick, *Tetrahedron Lett.*, 1983, 1323.
- Z. Janousek and H. G. Viehe, Part 5 in the series 'Iminium Salts in Organic Chemistry,' *Adv. Org. Chem.*, 1976, **9**, 343.
- E. Wenkert, *J. Am. Chem. Soc.*, 1962, **84**, 98; R. Thomas, *Tetrahedron Lett.*, 1961, 544; A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 1968, 945; A. I. Scott, *Acc. Chem. Res.*, 1970, **3**, 151; A. I. Scott and C. C. Wei, *Tetrahedron*, 1974, **30**, 3003.

† All new compounds were fully characterised by elemental analyses and physical and spectroscopic data.