A total asymmetric synthesis of (−)-suaveoline

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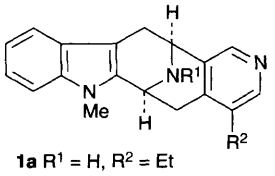
A new total synthesis of (−)-suaveoline from L-tryptophan is reported (overall yield *ca.* 14%); key steps include a high yielding *cis*-specific Pictet–Spengler reaction, a one-pot Horner–Wadsworth–Emmons/alkylation procedure, a vinylogous Thorpe cyclization and the direct formation of a pyridine from a 1,5-dinitrile.

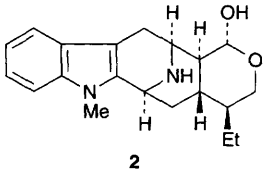
Because of their wide-ranging medicinal properties, indole alkaloids (and analogues thereof) continue to be attractive synthetic targets.[1] The indole alkaloid (−)-suaveoline **1a** was first isolated from the bark of *Rauwolfia suaveolens* in 1972,[2] but has since been found in other Rauwolfia species,[3,4] along with structural analogues such as macrophylline **1b**.[4] Biotransformations in *Rauwolfia serpentina* cell cultures convert ajmaline **3** into a range of alkaloids including (−)-suaveoline **1a**[5] and raumacline **2**.[6] Indeed, chemical modifications of ajmaline to the suaveoline derivative **1c** were used in the initial structural assignment of suaveoline.[2] The biosynthetic interconversion of members of the ajmaline family emphasises the fact that advanced intermediates can often be exploited in the synthesis of several alkaloids and analogues.

The first total synthesis of racemic suaveoline was achieved by Trudell and Cook in 1989; the key steps in this ingenious synthesis from D/L-tryptophan (overall yield 2.3%) included a *trans*-specific Pictet–Spengler reaction to gain access (after epimerisation) to the bridged ketone **4**, an unusual homologation to the α,β-unsaturated aldehyde **5**, and an anionic Cope rearrangement in order to introduce the final carbons of the suaveoline skeleton.[7] Cook's asymmetric synthesis of (−)-suaveoline started from D-tryptophan, and included modified procedures to improve the overall yield significantly.[8] Nevertheless, the synthesis uses non-proteinogenic D-tryptophan as the starting material, and the construction of the carbon skeleton is lengthy and awkward. We achieved a formal asymmetric synthesis of (−)-suaveoline in 1993 starting from L-tryptophan,[9] by exploiting the *cis*-selective kinetically-controlled Pictet–Spengler reaction;[10] our route gave access to the bridged ketone **4** used by Cook.[7,8] We also developed an independent asymmetric route to the α,β-unsaturated aldehyde **5**[11] (also an intermediate in Cook's synthesis of suaveoline[7,8]), in which the aldehydic carbon was introduced at the start of the synthesis by homologation of L-tryptophan to the nitrile **7**.

In this paper, we report a short, efficient total synthesis of (−)-suaveoline. Starting from L-tryptophan **6**, the homologous nitrile **7**[12] could be prepared in multigram quantities without chromatography.[13] Reaction of **7** with the silyl protected aldehyde **8** under conditions of kinetic control[10] afforded the *cis*-1,3-disubstituted tetrahydro-β-carboline **9** in 80% isolated yield, with none of the *trans*-isomer apparently generated. Similarly high *cis*-selectivity (>10:1) has been observed in only two other cases,[14,15] also involving aldehydes of the type



1a R^1 = H, R^2 = Et
b R^1 = H, R^2 = CH_2CH_2OH
c R^1 = Me, R^2 = Et



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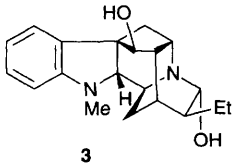

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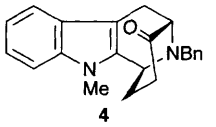

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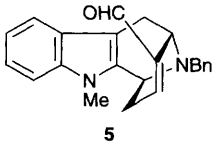

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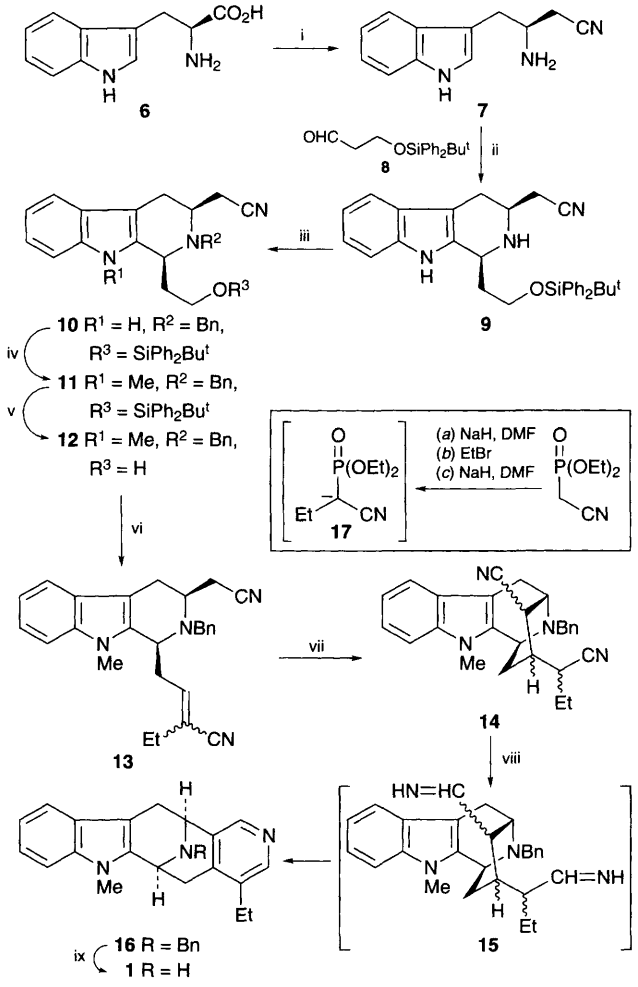

Scheme 1 *Reagents and conditions:* i, LAH, THF, then TsCl, py, then KCN, MeOH, then Na, NH_3 (liq.) (80% over 4 steps);[12] ii, **8**, CH_2Cl_2, 3 Å molecular sieves, 0 °C then TFA, −78 °C to room temp., 6 h (80%); iii, BnBr (neat), 70 °C, 24 h (79%); iv, MeI, NaH, DMF, 0 °C, 1 h (100%); v, TBAF, THF, room temp., 2 h (100%); vi, $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 °C, 20 min, then NEt_3, −60 °C to room temp., 1 h, then **17** (generated *in situ*) in DMF (83% overall); vii, $KOBu^t$, THF, 0 °C, 10 min, (67%); viii, DIBAL-H, CH_2Cl_2, 0 °C to room temp., 24 h (53%); ix, EtOH, HCl then evaporate; H_2, Pd–C, EtOH (96%)

RCH_2CHO (where R is bulky). After benzylation of the *N*-2 nitrogen (79% yield), N^{in}-methylation and removal of silyl protection proceeded quantitatively. The introduction of all remaining carbons of the suaveoline skeleton was accomplished by Swern oxidation to the aldehyde, followed by a one-pot Horner–Wadsworth–Emmons/alkylation procedure that generated the dinitrile **13** in 83% overall yield. The bridged skeleton of suaveoline was constructed by a vinylogous Thorpe cyclization (67%), giving **14** as a mixture of diastereoisomers. Reduction of **14** with DIBAL-H followed by an aqueous acid work-up led directly to the formation of *N*-benzyl-(−)-suaveoline **16** in 53% yield {$[\alpha]_D^{17}$ −149 (*c* 0.33, $CHCl_3$); lit,[8] $[\alpha]_D^{24}$ −127 (*c* 0.33, $CHCl_3$),}† presumably *via* oxidative cyclization of the diimine **15**. Debenzylation of **16**.HCl (H_2, Pd–C, EtOH, 96%) yielded (−)-suaveoline **1**, identical in all respects to the natural product.

We have therefore achieved a total asymmetric synthesis of (−)-suaveoline from L-tryptophan in *ca.* 14% overall yield.

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Footnote

† Compound **16** was initially obtained as an oil, with $[\alpha]_D$ close to that reported by Cook[8] (*ca.* −120); after careful purification, **16** was obtained as a white solid foam, with $[\alpha]_D^{17}$ −149.

References

1 (*a*) J. P. Kutney, *The Total Synthesis of Natural Products*, ed. J. A. Simon, Wiley-Interscience, New York, 1977, vol. 3; (*b*) J. E. Saxton, *Specialist Periodical Reports, The Alkaloids*, The Royal Society of Chemistry, London, 1983, vol. 13; (*c*) C. Szantay, C. Blasko, K. Honty and G. Dornyei, *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1986, vol. 27.
2 S. P. Majumbar, P. Potier and J. Poisson, *Tetrahedron Lett.*, 1972, 1563.
3 M. A. Amer and W. E. Court, *Phytochemistry*, 1981, **20**, 2569.
4 A. M. A. G. Nasser and W. E. Court, *Phytochemistry*, 1983, **22**, 2297.
5 S. Enders, H. Takayama, S. Suda, M. Kitajima, N. Aimi, S. Sakai and J. Stockigt, *Phytochemistry*, 1993, **32**, 725.
6 L. Polz, J. Stockigt, H. Takayama, N. Uchida, N. Aimi and S. Sakai, *Tetrahedron Lett.*, 1990, **31**, 6693.
7 M. L. Trudell and J. M. Cook, *J. Am. Chem. Soc.*, 1989, **111**, 7504.
8 X. Fu and J. M. Cook, *J. Am. Chem. Soc.*, 1992, **114**, 6910.
9 P. D. Bailey and N. R. McLay, *J. Chem. Soc., Perkin Trans 1*, 1993, 441.
10 P. D. Bailey, S. P. Hollinshead, N. R. McLay, K. M. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds and S. D. Wood, *J. Chem. Soc., Perkin Trans 1*, 1993, 431.
11 P. D. Bailey, I. D. Collier, S. P. Hollinshead, M. H. Moore, K. M. Morgan, D. I. Smith and J. M. Vernon, *J. Chem. Soc., Perkin Trans 1*, 1994, 1559.
12 J. P. Kutney, G. K. Eigendorf, H. Matsu, A. Murai, K. Tanaka, W. L. Sung, K. Wada and B. R. Worth, *J. Am. Chem. Soc.*, 1978, **100**, 938. This is the only example of the synthesis of bridged indole alkaloids using the homologated nitrile of tryptophan.
13 K. M. Morgan, D.Phil. Thesis, York, 1993.
14 G. Massiot and T. Mulamba, *J. Chem. Soc., Chem. Commun.*, 1983, 1147.
15 N. de la Figuera, I. Rozas, T. Garcia-Lopez and R. Gonzalez- Muniz, *J. Chem. Soc., Chem. Commun.*, 1994, 613.

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