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Total synthesis of (−)-raumacline

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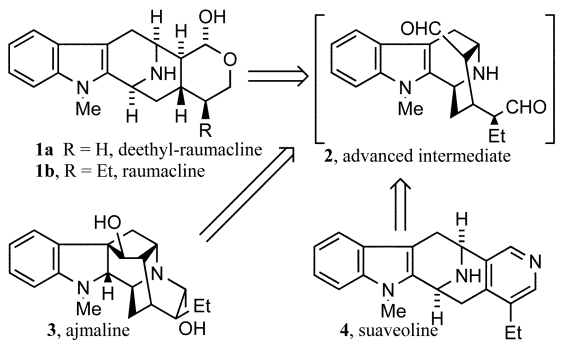
The total synthesis of (−)-raumacline from L-tryptophan was achieved, featuring a *cis*-specific Pictet–Spengler reaction, a stereoselective Dieckmann cyclization, and an epimerization step that allowed complete stereocontrol of five chiral centres.

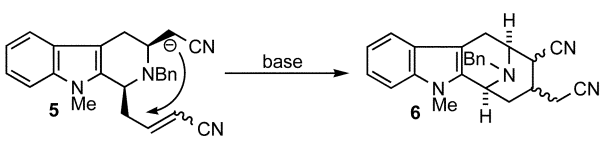
Raumacline **1** was first identified in 1990;[1] it is a bridged indole alkaloid possessing six chiral centres, and is a member of the ajmaline family of alkaloids (see Scheme 1). The important medicinal properties of the indole alkaloids were highlighted in a review in 1988 that contained 359 references,[2] and the ajmaline family have long been used for the treatment of cardiovascular irregularities.[3,4] We have developed stereoselective routes to *cis* 1,3-disubstituted tetrahydro-β-carbolines starting from L-tryptophan,[5] and leading to a number of natural product syntheses,[6a–h] although more complex targets such as raumacline had eluded us until now.

Cook's group has completed the only total synthesis of (−)-raumacline,[7] but their approach required the use of more expensive D-tryptophan as the starting material (using a key epimerization/cyclization step to construct the 1,3-bridge), and also involve recycling of material in an oxy-Cope rearrangement step that generates several isomers. In this communication, we describe a different approach that provides access to the ajmaline family of alkaloids from L-tryptophan,[8] with complete stereochemical control of five chiral centres, and we report the total synthesis of (−)-raumacline.

Our approach was to identify a protected form of the dialdehyde **2**, which would not only be an advanced intermediate in the synthesis of (−)-raumacline, but could also potentially be elaborated to targets such as ajmaline **3** and suaveoline **4** (Scheme 1). In earlier work towards suaveoline,[6f,h] we had found that the dinitrile **5** underwent base induced ring-closure without any significant stereocontrol (Scheme 2), so this route was only of limited use. We had planned to modify the electron-withdrawing nitrile groups of **5** in order to control the stereochemistry, but early stages in the synthesis proceeded with disappointingly poor *cis* stereoselectivity of only 3 : 1 (Scheme 3), and required extensive chromatography at an early stage.

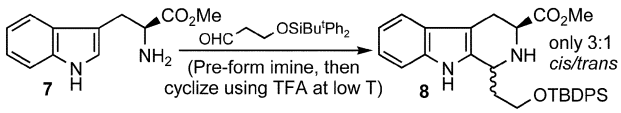


Scheme 1 RSA reveals **2** as an advanced intermediate for **1b**, **3** and **4**.

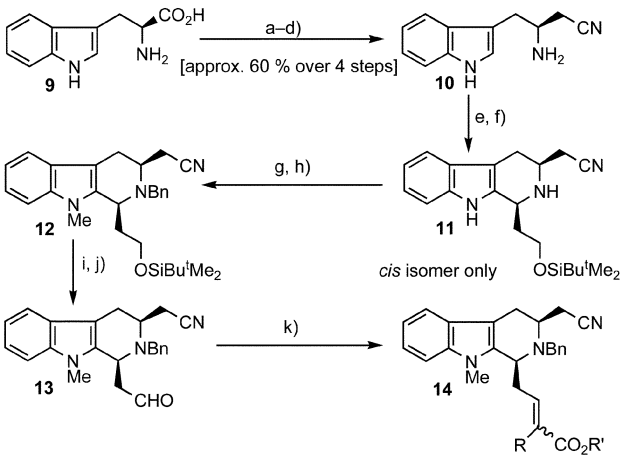


Scheme 2 Dieckmann cyclization of dinitrile **5**.

We therefore returned to our original route,[6h] improving the procedures for the preparation of the advanced intermediates **14a/b** (Scheme 4). Two features of the improved synthesis are especially noteworthy. Firstly, the initial three steps from L-tryptophan **9** yielded crystalline cyano-sulfonamide,[9] and this could be prepared in pure form without the need for any chromatography; however, we found that the sodium/liquid ammonia deprotection was capricious unless we ran the reaction in THF,[10] which provided the amino-nitrile **10** in pure form. Secondly, the kinetically controlled Pictet–Spengler reaction[5] yielded only the *cis* stereoisomer, and we initially assumed that we had simply failed to observe the minor *trans* isomer. Careful examination of the crude NMR spectra revealed that the reaction was virtually 100% stereoselective; this almost unique observation prompted us to undertake a study of related reactions, and we have now been able to extend the range of *cis* specific Pictet–Spengler reactions.[11] Routine alkylations of **11**, followed by removal of the silyl protection and Swern oxidation provided the cyano-aldehyde **13**, from which the Michael acceptors **14a** and **14b** were prepared using Wittig or Horner–Wadsworth–Emmons methodology respectively.



Scheme 3 Formation of **8** *via* the Pictet–Spengler reaction of **7**.



Scheme 4 a) $LiAlH_4$ (98%); b) TsCl, py (78%); c) KCN (86%); d) Na (3 eq.), NH_3(l), 30 min, THF (88%); e) $TBSOCH_2CH_2CHO$, 3 Å mol. sieves, 24 h; f) CH_2Cl_2, TFA (2 eq.), −78 °C → RT, 6 h (80%); g) BnBr, 70 °C (75%); h) MeI, NaH, 0 °C (87%); i) TBAF (96%); j) Swern (100%); k) $Ph_3P{=}CHCO_2Me$ (82%, **14a**, R = H and R′ = Me, *E*/*Z* = 4 : 1) or $(EtO)_2POCHEtCO_2Et$, NaH (65%, **14b**, R = Et and R′ = Et, *E*/*Z* = 5 : 3).

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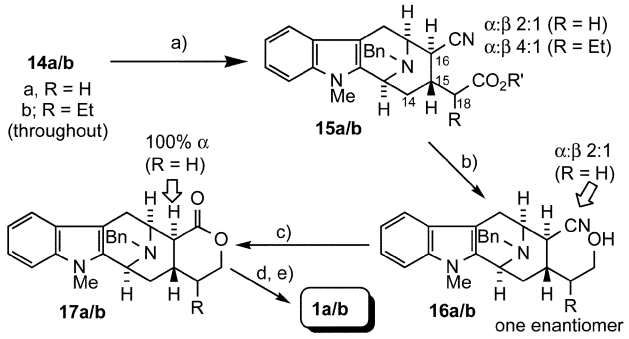

Scheme 5 a) $LiNEt_2$,THF, −78 °C (**15a**, 63%; **15b**, 99%); b) $LiBH_4$ (**16a**, 75%, **16b**, 84%); c) $TsOH{\cdot}H_2O$, THF, reflux (**17a**, 63%; **17b**, 88%); d) DIBAL-H (54%, R = H; 50%, R = Et); e) H_2/Pd–C (100%, R = H or R = Et). [**a**, R = H, R′ = Me; **b**, R = R′ = Et].

We next focused on the deethyl analogue **1a** of raumacline, starting from **14a**. Base induced Michael reaction generated the bridged compound **15a**, with total control of the C-15 chiral centre, but only 2 : 1 selectivity for the α-stereochemistry at C-16; the stereochemistry of the α-isomer **15a** (shown in Scheme 5) was assigned from NMR data,[12] whilst the X-ray crystal structure of the minor β-isomer is shown in Fig. 1.[13]

However, it transpired that the α/β stereochemical problem could be resolved later in the synthesis. Lithium borohydride reduction of either of the epimers gave the cyano-alcohols **16a**, for which derivatisation of the α-isomer as the Mosher's ester[14] allowed us to confirm the optical integrity.[15] Pleasingly, by refluxing EITHER the α- or β-epimer of **16a** with tosic acid hydrate in THF, *trans* decalin pentacycle **17a** was isolated as the ONLY stereoisomer; the β-epimer presumably initally cyclized to the *cis* decalin, which epimerised to the more stable *trans* isomer *via* tautomerisation of the lactone or imidate (*cf.* raumacline in Fig. 2). Reduction with DIBAL, followed by catalytic hydrogenolysis,[7] generated deethyl raumacline **1b**, with complete control of all five chiral centres.

Finally, we repeated the synthetic sequence in Scheme 5, but starting from **14b**. In this case, cyclization *via* Michael reaction generated **15b** in essentially quantitative yield, with α/β selectivity of up to 4 : 1, but composed of a 1 : 1 mixture of C-18 epimers. The latter were separable once the lactone **17b** had been formed, allowing us to complete the synthesis of (−)-raumacline **1b**. Our approach not only exploits a *cis* specific Pictet–Spengler reaction early in the synthesis, and a key stereoselective ring-closure step, but also retains an epimerizable centre that allows us to exploit the thermodynamic stability of the raumacline structure (see Fig. 2). We have therefore not only completed a total asymmetric synthesis of (−)-raumacline, but we have also developed a new stereospecific route to the tetracyclic core of the ajmaline family of indole alkaloids.

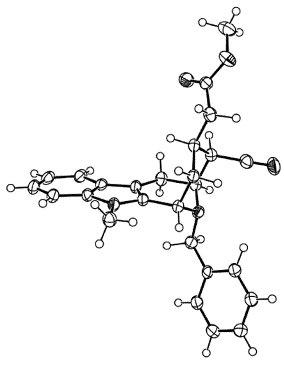

Fig. 1 X-Ray crystal structure of the β-epimer of **15a**.

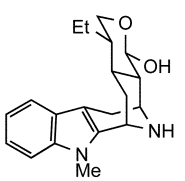

Fig. 2 The predicted 3D structure of (−)-raumacline **1b**, showing the all-equatorial *cis* decalin conformation.

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13 X-Ray data for **15a**. 0.25 × 0.15 × 0.07 mm^3, monoclinic, space group $P2_1$, a = 10.3050(4), b = 7.2730(3), c = 14.2530(8) Å, β = 90.388(2)°, V = 1068.21(9) $Å^3$, Z = 2, ρ_{calcd} = 1.286 Mg m^{-3}, $2\theta_{max}$ = 54.98°, molybdenum radiation, λ = 0.71073 Å, κCCD ϕ and ω scans to full Ewald sphere, temperature = 150(2) K, number of measured/independent reflections 9756/4320 [R(int) = 0.0465], number of reflections included in the refinement 4320 [3530$I > 2\sigma(I)$], Lorentz and polarization corrections were performed, absorption correction semi-empirical from equivalents (m = 0.082 mm^{-1}, max./min. transmission 0.9943/0.9797). The structure was solved by direct methods using SHELXS-97 (G. M. Sheldrick, *SHELXS-97, Program for crystal structure solution*, 1997, University of Göttingen, Germany), refinement method full matrix least squares on F^2 using SHELXL-97 (G. M. Sheldrick, *SHELXL-97, Program for crystal structure refinement* , 1997, University of Göttingen, Germany), no. of parameters = 361, H atoms were subjected to isotopic refinement, final residuals refined against $|F^2|$ were wR^2 = 0.1084 (all data), R_1 = 0.0509 [$I > 2\sigma(I)$], max. and min. residual electron density 0.20 and −0.20 e $Å^{-3}$, and the absolute configuration of **15a** was not determined. CCDC 207148. See http://www.rsc.org/suppdata/cc/b3/b310274b/ for crystallographic data in CIF or other electronic format.
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