Pergamon

Tetrahedron Letters, Vol. 35, No. 21, pp. 3585-3586, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0538-9

Stereospecific Reduction of a β-Keto-Nitrile: Formation of a Single Indolic β-Hydroxy-Nitrile from a Mixture of Tautomers and Diastereoisomers

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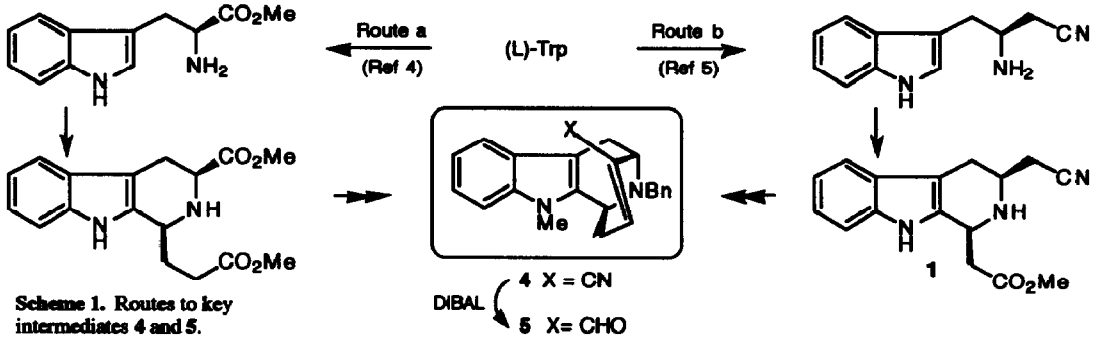
Abstract: The β-keto-nitrile **2**, which is an advanced intermediate for the synthesis of several indole alkaloids, is composed of a mixture of enol/keto tautomers, and of diastereoisomers; nevertheless, reduction with sodium borohydride yields essentially a single diastereoisomer **3**.

The bridged indole alkaloids of the ajmaline-sarpagine family possess a valuable range of biological properties, and they have received much attention from synthetic organic chemists.[1] We have developed two tactics that utilise (L)-tryptophan as a chiral building block for the synthesis of the advanced intermediates **4** and **5**, which have been used by Cook[2] and Magnus[3] to prepare a range of bridged indole alkaloids (Scheme 1). During work on the second approach (Scheme 1, route b), we encountered a stereospecific reduction that is remarkable in its own right, and which might have wider applications in the formation of multiple chiral centres.



Scheme 1. Routes to key intermediates **4** and **5**.

Both routes start with diastereoselective kinetically controlled Pictet-Spengler reactions which afford *cis*-tetrahydro-β-carbolines.[6] In route b, the key bridging unit was then generated by a Dieckmann/Thorpe cyclisation of **1** mediated by lithium diethylamide. Although the yield of the apparently homogeneous product **2** was 90%, the spectroscopic data (e.g. broad multiple peaks in the ^{13}C NMR) indicated that the compound was a mixture of tautomers and diastereoisomers (see Scheme 2); we hoped that reduction of the carbonyl group followed by dehydration might generate the desired α,β-unsaturated nitrile **4** as a single compound.

However, instead of the expected mixture of four diastereoisomers on reduction of **2** with sodium borohydride, the reaction yielded essentially one isomer **3**, which was homogeneous after a single

recrystallisation.[7] Structural assignment of **3** was initially based on extensive NMR data (Figure 1), but was later confirmed by single crystal X-ray structure determination of the TMS derivative **6** (Figure 2).

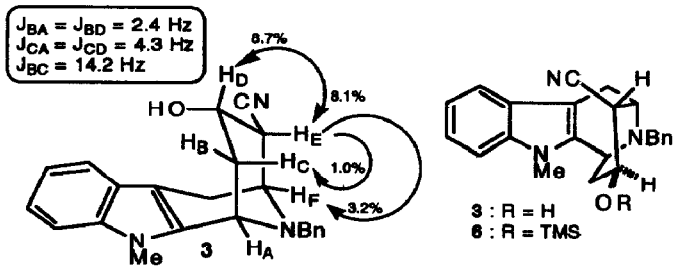


Figure 1. 360 MHz NMR data for **3**; couplings indicate H_A and H_D are both equatorial; NOE data reveals that H_E is axial.

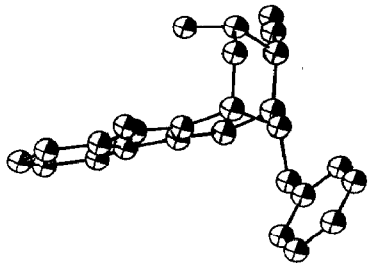
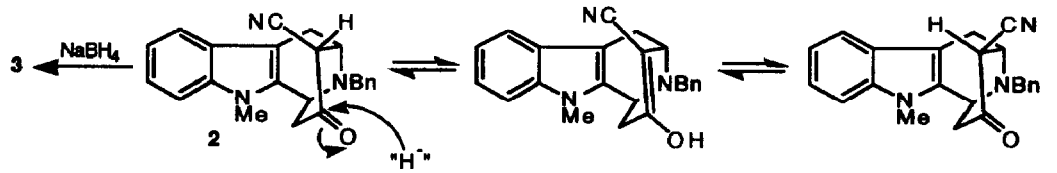


Figure 2. X-Ray crystal structure for **6** minus the TMS; data deposited with CCDC.



Scheme 2. Stereospecific sodium borohydride reduction of the β-keto-nitrile **2**. From molecular models, it would appear that the *re* face of the ketone (i.e. away from the indole system) is the less hindered, and we infer that reduction from this side occurs most rapidly when the nitrile is *anti* (rather than *syn*). Thus, a single keto-nitrile diastereoisomer is continuously removed from the enol/keto equilibrium mixture, allowing the single diastereoisomer **3** to be obtained in excellent yield.[8]

In principle, displacement of the "OH" group of **3** by a C_4 nucleophile would generate the correct skeleton and stereochemistry for a large number of indole alkaloids. More straightforward was dehydration of **3** ($POCl_3$/pyridine) to α,β-unsaturated nitrile **4**, reduction of which with DIBAL generated the α,β-unsaturated aldehyde **5**;[5] this was used by Cook in his recent synthesis of (-)-suaveoline and related alkaloids, starting from (D)-tryptophan.[2] More importantly, these results indicate that a chiral auxiliary can control the absolute stereochemistry of two new chiral centres during the reduction of an enol/keto mixture of isomers, and this principle should be applicable to the synthesis of other β-hydroxy esters and nitriles.

We would like to thank the SERC NMR service at Sheffield, SERC for a studentship (to SPH) and SWPRD and SERC for a CASE studentship (to KMM).

References and Notes:

1. For example, the landmark syntheses of ajmaline by: a) Masamune, S.; Ang, S. K.; Engli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Amer. Chem. Soc.* **1967**, *89*, 2506; b) van Temelen, E. E.; Oliver, L. K. *J. Amer. Chem. Soc.* **1970**, *92*, 2136.
2. For example, Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661.
3. For example, Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Amer. Chem. Soc.* **1990**, *112*, 5220.
4. Bailey, P. D.; McLay, N. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 441.
5. Bailey, P. D.; Hollinshead, S. P.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vernon, J. M. *submitted for publication.*
6. a) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K. M.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431; b) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177.
7. The reaction was extremely clean, generating up to 95% isolated yields of (3). However, some unreacted starting material (2) was always also generated on work-up (between 5-50%, depending on the exact reaction conditions); presumably this was caused by deprotonation of the enol, to generate enolate that was stable to $NaBH_4$, and which reformed (2) on work-up.
8. We favour this mechanism over Michael attack on the enol followed by protonation - c.f. extensive attempts at conjugate nucleophilic addition to **4** have proved impossible (Hollinshead, S. P. *D. Phil. Thesis*, York, 1987), and to **5** is very rare.[2]

(*Received in UK* 7 *February* 1994; *revised* 14 *March* 1994; *accepted* 17 *March* 1994)