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Debenzylation using catalytic hydrogenolysis in trifluoroethanol, and the total synthesis of (−)-raumacline

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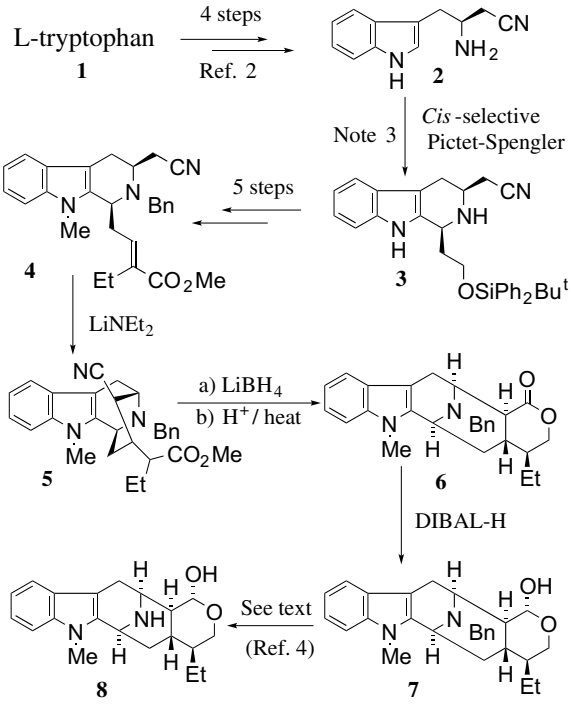
Abstract

N-Debenzylations using catalytic hydrogenolysis often fail to take place unless alcoholic solvents are used, but this can lead to N-alkylation as a side reaction; using trifluoroethanol as the solvent overcomes this problem, and leads to highly reliable hydrogenolyses for a wide range of substrates, including the final deprotection step in our total synthesis of (−)-raumacline.

We have recently completed the total synthesis of (−)-raumacline (Scheme 1).[1] During this work, we encountered an unexpected N-alkylation by the alcoholic solvent when utilizing catalytic hydrogenolysis for the final N-debenzylation step. We believe this observation may be more widespread than is generally acknowledged, because the spectra of alkylated and non-alkylated derivatives are so similar, and the former may be present to the extent of only a few %. We report herein our solution to this problem, our exploration of its wider applicability, and some important observations when applied to our synthesis of (−)-raumacline and related alkaloids.

The synthetic problem related to the final step in our synthesis of (−)-raumacline (**7**→**8** in Scheme 1), in which we simply followed the deprotection procedure published by Cook and Fu.[5,6] All of the data for our intermediates in the synthesis of raumacline were completely consistent with our reported structures, up to and including the protected precursor **7**. The final deprotection failed to take place in non-alcoholic solvents (e.g., ethyl acetate, dichloromethane, THF); Cook had reported that hydrogenolyses



Scheme 1. Our total synthesis of (−)-raumacline.[1] (See above-mentioned references for further information.)

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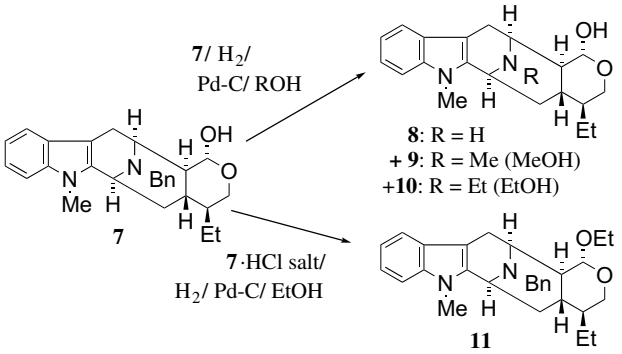


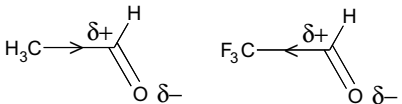
Scheme 2. Attempted deprotections of **11**.

in methanol could be accompanied by N-methylation,[6,7] and indeed, hydrogenolysis of **7** in methanol yielded the *N*-methyl derivative **9** (Scheme 2), and we also observed N-methylation in similar debenzylations.[8]

Cook apparently overcame the problem by using ethanol as the solvent[6,7] but, although this reduced the amount of alkylation, we nevertheless observed significant amounts (ca. 25%) of *N*-ethyl derivative **10**. We also tried hydrogenolysis of the HCl salt of **7** in ethanol (the conditions reported by Cook and Fu[6,7]), but this generated the ethoxy acetal **11** in our hands, without achieving debenzylation (Scheme 2).

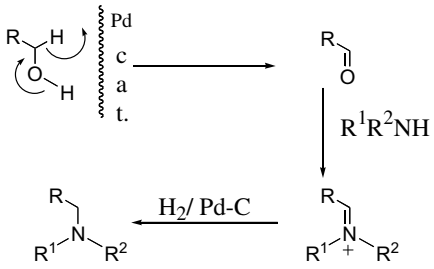
The explanation suggested by Cook for the N-methylation in methanol seems a reasonable one,[6,7] in which the catalyst initially oxidizes the alcohol to the aldehyde, which can then be reductively trapped by the free amine (Scheme 3).

One possible solution, we felt, would be to conduct the hydrogenolysis in an alcoholic solvent for which the corresponding aldehyde was less stable, hopefully raising the activation barrier for dehydrogenation of the alcohol, and thereby blocking the alkylation pathway. We reasoned that trifluoroethanol (TFE) might meet our needs, with the fluorinated aldehyde **13** destabilized by the −I effect of the CF_3 group, relative to non-fluorinated ethanal **12**.

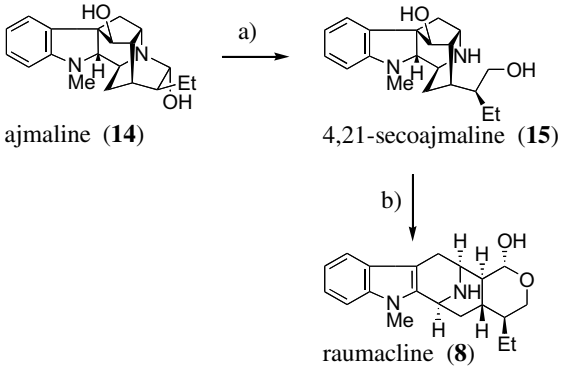


This approach was completely successful, providing (−)-raumacline **8** from **7** in 100% yield, with no hint of N-alkylation.

Although the final outcome was the successful conversion of **7**→**8**, the ^{1}H NMR spectrum of synthetic **8** was initially so different from that reported for the natural product[6,7,9] that we assumed a completely different compound had been formed. We, therefore, set about obtaining (−)-raumacline from natural sources, for comparison; we chose to prepare semi-synthetic **8** from ajmaline, using a slightly modified procedure to that employed by Stöckigt's group,[10] as shown in Scheme 4.



Scheme 3. Mechanism for alkylation.



Scheme 4. Semi-synthesis of (−)-raumacline. Reagents and conditions: (a) $NaBH_4$, (26.8 equiv), MeOH, citrate/NaOH buffer, pH 6.0, 4 °C, 24 h, 100%; (b) (−)-riboflavin, *hν*, MeOH, acetone, citrate/NaOH buffer pH 6.0, 4 °C, 24 h, 78% (see Ref. 10).

As can be seen in Figure 1, the ^{1}H NMR spectra of semi-synthetic raumacline, and our totally synthetic material, were very different. However, it transpired that traces of acid accounted for the differences, as a base wash led to superimposable spectra. Although acids are well known to modify the spectra of basic compounds such as alkaloids, such a dramatic effect is rare.

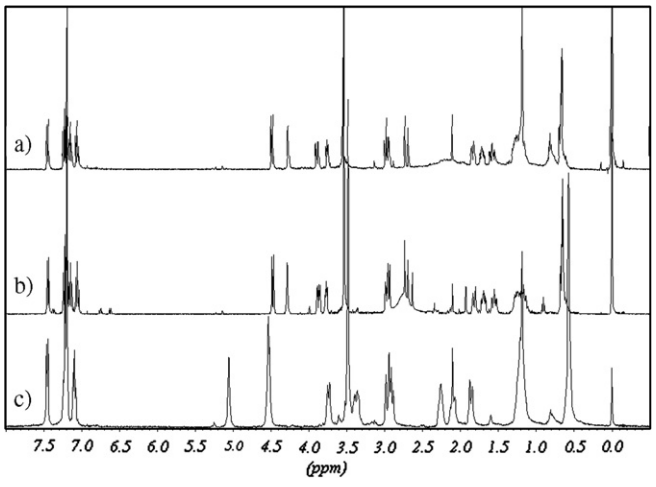


Fig. 1. ^{1}H NMR spectra of (−)-raumacline **8**: (a) our synthetic **8** after base wash; (b) semi-synthetic **8** (Stöckigt method, Scheme 4); (c) our synthetic **8** before base wash.

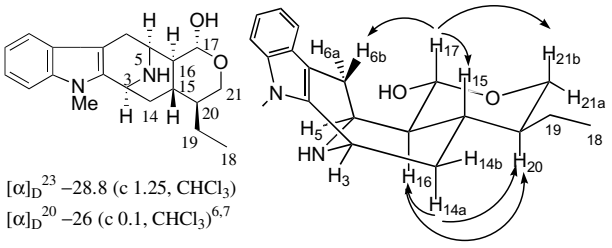


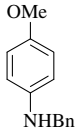
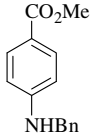
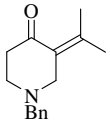
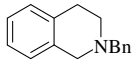
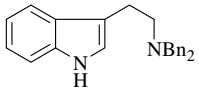
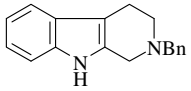
Fig. 2. Key data for our synthetic (−)-raumacline **8**.

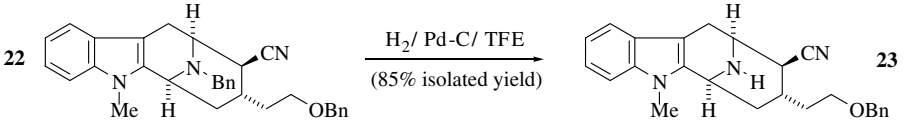
To absolutely confirm the stereochemistry and optical integrity of our synthetic (−)-raumacline, extensive 2D NMR experiments were run, and key NOE and optical rotation results are shown in Figure 2.

Finally, we carried out a limited study on the wider scope/limitations of conducting catalytic hydrogenolysis in a range of alcoholic solvents, including trifluoroethanol, and these results are summarized in Table 1.

The key observations are that debenzylation of anilines usually proceed smoothly in any alcoholic solvent, whilst tetrahydroquinolines and tetrahydro-β-carbolines can be more problematic, and may depend on the activity of the specific batch of catalyst being used. For these latter systems, not only does TFE provide a faster and more reliable deprotection, but it also avoids the potential alkylation of the nitrogen—a problem that may be occurring (perhaps only to the extent of a few %) without people being aware of it (see Ref. 8). Some surprising examples of selectivity were also observed. For example, mono-debenzylation of **20** occurred very efficiently. Moreover, the modified conditions surprisingly allowed a highly efficient N-debenzylation in the presence of an *O*-benzyl group (entry h, **22**→**23**); this selectivity may be of more widespread use, and we are exploiting it in the final stages of the synthesis of ajmaline-related alkaloids. Finally, of course, our conditions have allowed the clean and efficient deprotection of **7**, thereby allowing us to obtain completely pure (−)-raumacline at the end of our total synthesis.

Table 1
Catalytic hydrogenolyses over 10% Pd–C for a range of N-benzylated compounds; for entries **16**–**21**, the time for complete deprotection (confirmed by ^{1}H NMR) is given in each of three solvents (X = no reaction)

Entry	MeOH	EtOH	TFE
16 	>2 h[a]	30 min	10 min
17 	30 min	15 min	24 h
18[b] 	70% after 48 h	24 h	2 h
19 	X	X	24 h
20 	X	X	3 h mono[c]
21 	X	X	5 h



Notes: [a] 70% hydrogenolysis was seen after 2 h.
[b] 100% C=C bond reduction after 24 h in MeOH, after 2 h in EtOH and after 1 h in TFE.
[c] Presence of fully deprotected product (ca. 5%) after 3 h, increasing to ca. 20% after 24 h (identified by multiplet at δ 2.8).

Acknowledgement

We thank the EPSRC for funding.

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5. When we completed our synthesis of (−)-raumacline,[1] we assumed that the final deprotection step following the procedure of Fu and Cook[6,7] would cleanly yield the desired product **8**. Only on subsequent scaleup did we identify the problem of alkylation as a side reaction.
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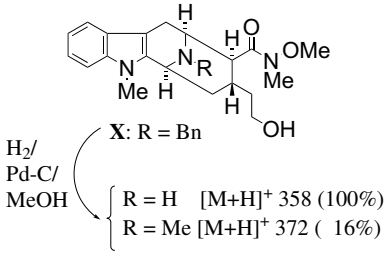
8. We have observed N-alkylation in other cases, as exemplified by the deprotection of the Weinreb amide **X**, for which mass spectrometric evidence indicated the presence of about 15% of the *N*-methyl by-product:



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