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A short synthesis of (±)-cytisine †

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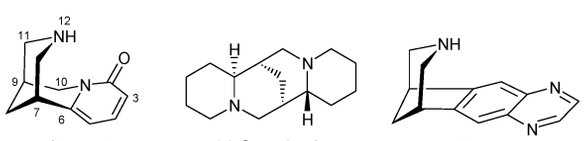
The synthesis of racemic cytisine 1 has been completed using *(i)* *N*-selective alkylation of 6-bromopyridone with bromide 6 and *(ii)* Pd(0) mediated intramolecular α-arylation of lactam 8 as key steps to achieve rapid assembly of the tricyclic core skeleton of the lupin alkaloids.

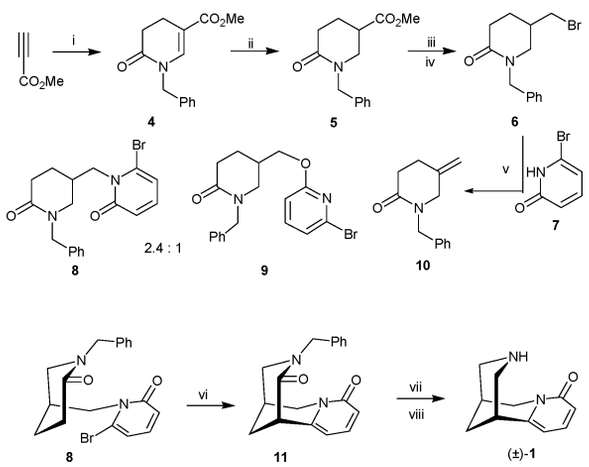
(−)-Cytisine **1** [1a,b] is an important representative member of the lupin class of alkaloids,[2] which also includes (+)-sparteine **2**, a molecule that has found broader application as a ligand within asymmetric synthesis.[3] Cytisine, which is a potent nicotinic agonist[4] with specificity for the α4β2 subtype and is currently marketed as Tabex™ for use as a smoking cessation aid, was first synthesised by van Tamelen,[5a,b] followed closely by both Bohlmann[5c] and Govindachari,[5d] but there was little further activity in this area for almost fifty years. In 2000, the Pfizer groups of O'Neill[6a] and Coe[6b] each described new routes to (±)-cytisine, as part of a broader drug discovery project aimed at exploiting the therapeutic potential of nicotinic agonists that has led to analogues such as **3**.[7] This resurgence of interest in this area has continued at pace with the first asymmetric synthesis of (−)-cytisine **1** being reported very recently.[8]



In this paper we describe a novel strategy for the synthesis of cytisine **1** that has, we believe, potential for more general application to the assembly of a range of other, more complex lupin alkaloids, as well as unnatural, but potentially important variants such as **3**.

Our approach to racemic cytisine has relied on two key steps: *(i)* the *N*-selective alkylation of a 6-halopyridone (to establish C(10)–N(1) bond) and *(ii)* the intramolecular α-arylation of a lactam to establish the C(6)–(7) bond and complete the tricyclic core of the target. This provides a direct and highly convergent entry to cytisine, and this paper reports the implementation of this strategy, together with a discussion of the key issues involved.

The synthetic route is outlined in Scheme 1. The 5-substituted piperidinone **5** was assembled in 55% overall yield *via* **4**, an intermediate that was available from commercially available materials using the three component coupling procedure described by Stille.[9] $LiAlH_4$ reduction of **5** followed by halogenation gave bromide **6** in 57% overall yield. The first key transformation requires an *N*-selective alkylation of 6-bromopyridone **7**[10] using bromide **6**. While this chemistry has good precedent, use of Curran's[11] optimised conditions for *alkyl* halides [6-bromopyridone (1 equiv.), alkyl halide (2 equiv.), LiBr (4 equiv.), DME/DMF (10 : 1), NaH (1 equiv.), rt to 65 °C] gave no conversion after 6 days. We then examined conditions similar to those previously used by Curran for more reactive alkylating agents [(6-bromopyridone (1 equiv.), alkyl halide (1 equiv.), LiBr (2 equiv.), DME/DMF (4 : 1), NaH (1 equiv.), rt to 65 °C]. Under these conditions a poor yield (20%) of the desired *N*-alkylated product **8** was obtained. The major adduct isolated was the *O*-alkylated isomer **9** (57%), and the elimination product **10** (23%) was also observed.



Scheme 1 *Reagents and conditions:* i, $BnNH_2$, Et_2O, rt, then CH_2=CH_2COCl, THF, 70 °C (56%) ref. 9; ii, H_2 (1 atm), Pd/C, Na_2CO_3, EtOH, 20 °C (95%); iii, $LiAlH_4$, THF, −10 °C; iv, PBr_3, PhMe, 110 °C (57% over two steps); v, **7** (1 equiv.), NaH (2 equiv.), LiBr (4 equiv.), DME/DMF (24 : 1), concentration of both **6** and **7** = 0.2 M, 10 days (**8**: 61%; **9**: 25%; **10**: 14%) vi, $Pd(OAc)_2$ (5 mol%), (±)-BINAP (7.5 mol%), KHMDS (2 equiv.), THF, 70 °C (44%); vii, BH_3·THF, THF, 0 °C to rt (55%); viii, HCl in MeOH (1 equiv.), H_2 (1 atm), $Pd(OH)_2$/C, MeOH (88%).

Two strategies were adopted to address this problem. We screened a wide range of other reaction conditions to improve access to **8**, but with little success. This included examination of different substrates, and full details of these attempts will be described at a later date. Our second approach was to refocus on the direct reaction between **6** and **7** and explore this process using factorial experimental design methods.[12] Following our initial studies, a number of parameters were recognised as potentially important in terms of determining *N*- *vs.* *O*-selectivity, as well as pyridone alkylation *vs.* elimination. These included reaction temperature, substrate concentration, DMF/DME ratio, and the number of equivalents of both LiBr and NaH.‡ Using this statistical approach, we have identified modified conditions (details are presented in Scheme 1) that serve to suppress elimination (<15% of this pathway is observed) and provides a 2.4 : 1 ratio of *N*- to *O*-alkylated adducts **8** and **9** respectively, with **8** being obtained in 61% yield. This represents a comparatively minor adjustment to Curran's original conditions, but using **6** as the alkylating agent these changes are significant in practical terms. This exercise

† Electronic supplementary information (ESI) available: Characterization data for key intermediates. See http://www.rsc.org/suppdata/ob/b4/b405275g/

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illustrates further the highly sensitive nature of this type of alkylation and work continues to improve this process, since one drawback is the requirement for extended reaction times (7–10 days) for the conversion of **6** to **8**.

The second key step, the intramolecular lactam α-arylation of **8**, was achieved using Hartwig's original conditions (KHMDS, (±)-BINAP)[13] and the arylated adduct **11** was isolated in 44% yield. This transformation has yet to be fully optimised but we have examined briefly other general conditions for α-arylation,[14] such as those reported by Buchwald,[14a] but these were less effective in our case. One possible issue here relates to the conformational requirements associated with this cyclisation step. Intermediate **8** must adopt the axial conformation shown in Scheme 1 in order for cyclisation to take place. The fate of the equatorial conformer of **8** under these conditions is unknown, but may involve intermolecular reactions leading to oligomer formation. To date, the only characterisable product from this reaction is the tricycle **8**.

The final steps to complete the synthesis of racemic cytisine are shown in Scheme 1 and involved selective lactam reduction of **11**, which was achieved after some experimentation with BH_3·THF, followed by *N*-debenzylation to provide (±)-**1** in 21% overall yield from **8**.§ This final deprotection step was employed by O'Neill,[6a] although we have used somewhat different conditions to those described earlier.

One aspect of this chemistry merits further comment. The asymmetric synthesis of cytisine has only very recently been achieved.[8] Earlier, Coe[6b] used the asymmetric variant of the Heck reaction that underpins his very direct and elegant approach to cytisine, but this only proceeded in 22% ee. We have investigated various methods for the catalytic asymmetric reduction of the unsaturated ester **4** (as well as the corresponding carboxylic acid), but to date we have also only achieved modest enantiomeric excesses of the order of ≤24% ee.¶ An efficient asymmetric entry to cytisine *via* an intermediate such as **5** remains a goal of this programme.

In summary, we have described a novel strategy for the synthesis of cytisine **1**, which has been achieved in a total of 8 steps from commercially available starting materials. The route is also highly convergent but it should be stressed that this sequence has not yet been optimised in terms of the key transformations involved. Nevertheless, we anticipate that the strategy outlined above, and exemplified for cytisine, will be applicable to a range of other related targets.

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Notes and references

‡ We explored the alkylation of pyridone **7** with bromide **6** using Design Expert program (www.statease.com). This generated an eight factorial set of 20 experiments including 4 centre points which were carried out using a carousel reactor assembly, and analysis to determine the extent of conversion and product distribution was carried out by ^{1}H NMR.

§ Synthetic material was compared directly (TLC, IR, ^{1}H and ^{13}C NMR) to a commercially available sample of (−)-cytsine.

¶ Reduction of **4** was carried out in 24% ee (based on chiral HPLC) using H_2 (4 atm), Ru[(*R*,*R*)-Me-Duphos]Cod·BF_4, in MeOH at 45 °C.

1 (*a*) A. Partheil, *Arch. Pharm. (Weinheim, Ger.)*, 1894, **232**, 161; (*b*) H. Ing, *J. Chem. Soc.*, 1932, 2778.
2 N. J. Leonard, in *The Alkaloids*, ed. R. H. F. Manske and H. L. Holmes, Academic Press, New York, 1953, vol. 3, Chapter 19, p. 119; K. A. Aslanov, Y. K. Kushmuradov and A. S. Sadykov, *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1997, vol. 31, Chapter 5, p. 117; H. C. S. Wood and R. Wrigglesworth, *Rodd's Chemistry of Carbon Compounds*, 2nd Edn., ed. S. Coffey, Elsevier, Amsterdam, 1978; Vol. IV, Part H, Chapter 38, p. 285.
3 T. Schütz, *Synlett*, 2003, 901.
4 (*a*) L. A. Pabreza, S. Dhawan and K. J. Kellar, *Mol. Pharmacol.*, 1991, **39**, 9; (*b*) S. F. Heinemann and R. L. Papke, *Mol. Pharmacol.*, 1994, **45**, 142; (*c*) D. J. Anderson and S. P. Arneric, *Eur. J. Pharmacol.*, 1994, **253**, 261.
5 (*a*) E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, 1955, **77**, 4944; (*b*) E. E. van Tamelen and J. S. Baran, *J. Am. Chem. Soc.*, 1958, **80**, 4659; (*c*) F. Bohlmann, A. Englisch, N. Ottawa, H. Sander and W. Weise, *Chem. Ber.*, 1956, **89**, 792; (*d*) T. R. Govindachari, S. Rajadurai, M. Subramanian and B. S. Thyagarajan, *J. Chem. Soc.*, 1957, 3839.
6 (*a*) B. T. O'Neill, D. Yohannes, M. W. Bundesmann and E. P. Arnold, *Org. Lett.*, 2000, **2**, 4201; (*b*) J. W. Coe, *Org. Lett.*, 2000, **2**, 4205. A formal total synthesis based on ref. 6*a* has also been reported: P. Nshimyumukiza, D. Cahard, J. Rouden, M.-C. Lasne and J.-C. Plaquevent, *Tetrahedron Lett.*, 2001, **42**, 7787.
7 J. W. Coe and P. R. P. Brooks, *U.S. Patent 6,605,610*, 2003.
8 B. Danieli, G. Lesma, D. Passarella, A. Sacchetti, A. Silvani and A. Virdis, *Org. Lett.*, 2004, **6**, 493.
9 G. R. Cook, L. G. Beholz and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 3575.
10 G. R. Newkome, J. Broussard, S. K. Staires and J. D. Sauer, *Synthesis*, 1974, 707.
11 H. Liu, S. B. Ko, H. Josien and D. P. Curran, *Tetrahedron Lett.*, 1995, **36**, 8917. A variety of different conditions are presented in this paper, and a number of these were examined in our study. Alkyl halides tend to show lower *N*-selectivities under conditions suited to more reactive allyl and propargyl halides.
12 M. R. Owen, C. Luscombe, L.-W. Lai, S. Godbert, D. L. Crookes and D. Emiabata-Smith, *Org. Process Res. Dev.*, 2001, **5**, 308.
13 K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546. See also T. Hama, X. Liu, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 11176; D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234.
14 (*a*) Buchwald has described the arylation of a vinylogous amide: T. Hamada, A. Chieffi, J. Ahman and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1261; (*b*) We also evaluated an alternative zinc-based variant that was recently reported, but without success. See, J. Cossy, A. de Filippis and D. G. Pardo, *Org. Lett.*, 2003, **5**, 3037; (*c*) δ-Lactams have been produced by intramolecular α-arylation of amide enolates, see T. Honda, H. Namiki and F. Satoh, *Org. Lett.*, 2001, **3**, 631.