Pergamon

Tetrahedron Letters 40 (1999) 161–164

TETRAHEDRON LETTERS

A Novel Route to (±)-Aspidospermidine: First Application of "Radical-Polar Crossover" Reactions to Total Synthesis

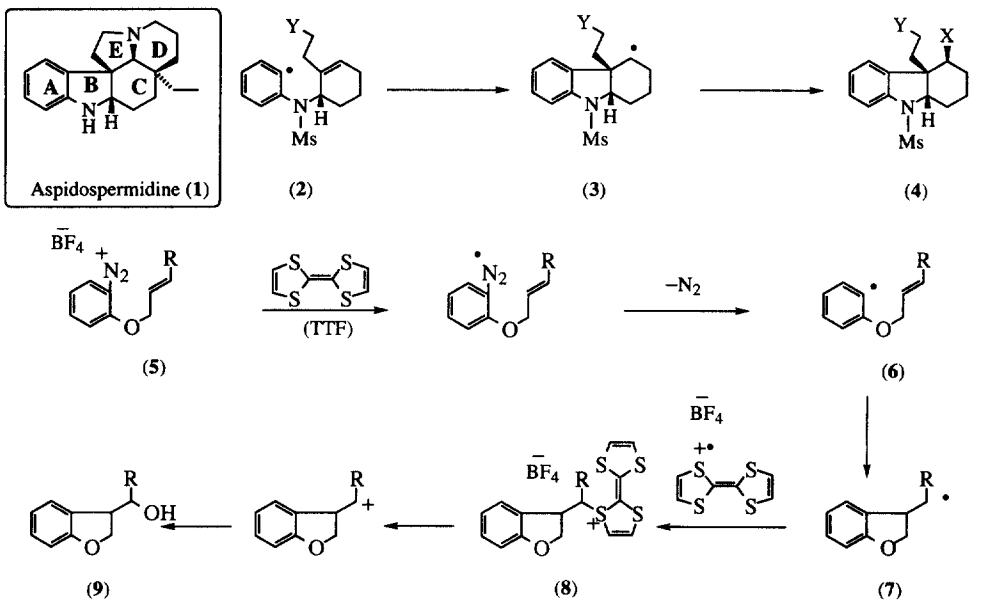
Owen Callaghan, Christopher Lampard#, Alan R. Kennedy and John A. Murphy*

Department of Pure and Applied Chemistry,University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, U.K.

Received 8 October 1998; accepted 19 October 1998

Abstract: Aspidospermidine has been prepared by a novel route featuring TTF-induced cyclisation of a diazonium salt.

The *Aspidosperma* alkaloids pose a severe challenge to the synthetic chemist[1,2]. The two principal difficulties in synthesising aspidospermidine (**1**) are the generation of the tetrasubstituted, spiro centre at the **BCE** ring junction and the control of stereochemistry at the four contiguous chiral centres. Radical chemistry is well suited to the generation of tetrasubstituted carbon atoms[3], and so a radical approach to the synthesis merits scrutiny.



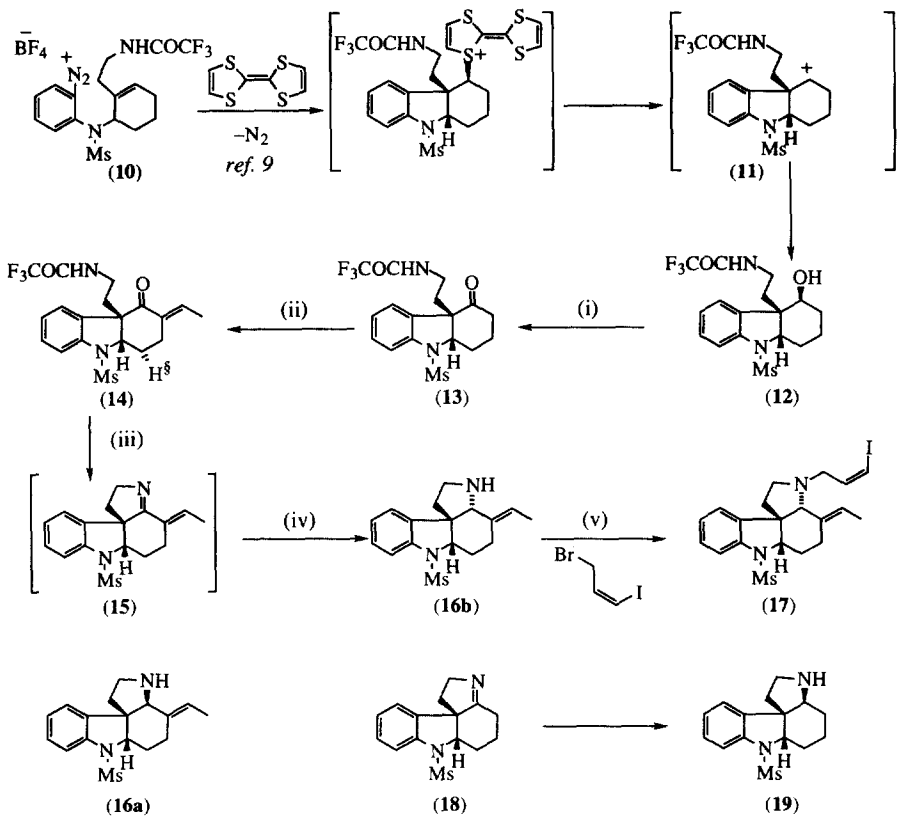
Radical cyclisations leading to [6.5]-fused ring systems, in which a bond to the ring-junction is formed, are well established to give a *cis* ring junction[4], and so cyclisation of the aryl radical (**2**) might afford a useful opening for the synthesis. This places the "Y" side-chain above the new cyclohexyl ring which would be appropriate for the formation of ring **E**. However, functionalising the alkyl radical (**3**) with a functional group "X" which would permit the completion of the synthesis is much more challenging. As shown below, the ideal

#*Current address: Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG, Scotland.*

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02256-4

functional group would be an alcohol (X = OH), but there is no *direct* way to introduce an alcohol *via* radical chemistry[5,6]. An iodide group (X = I) could be efficiently introduced[7], but as this would be a secondary neopentyl iodide, subsequent conversion into an alcohol would be extremely difficult.

We have recently shown[8] that alcohols can be formed in high yield through TTF-mediated radical-polar crossover reactions performed in moist acetone. This process permits an ordered sequence of radical and ionic steps to be followed in one pot. Specifically, electron transfer from TTF to a diazonium salt (**5**) is followed by loss of dinitrogen; the aryl radical (**6**) cyclises rapidly and the resulting alkyl radical (**7**) then couples to TTF+• to form a sulfonium salt (**8**). This salt undergoes unimolecular solvolysis in moist acetone yielding the corresponding alcohol (**9**). Accordingly diazonium salt (**10**)[9] had been treated with TTF under these conditions to form the alcohol (**12**)[9] as a single isomer.



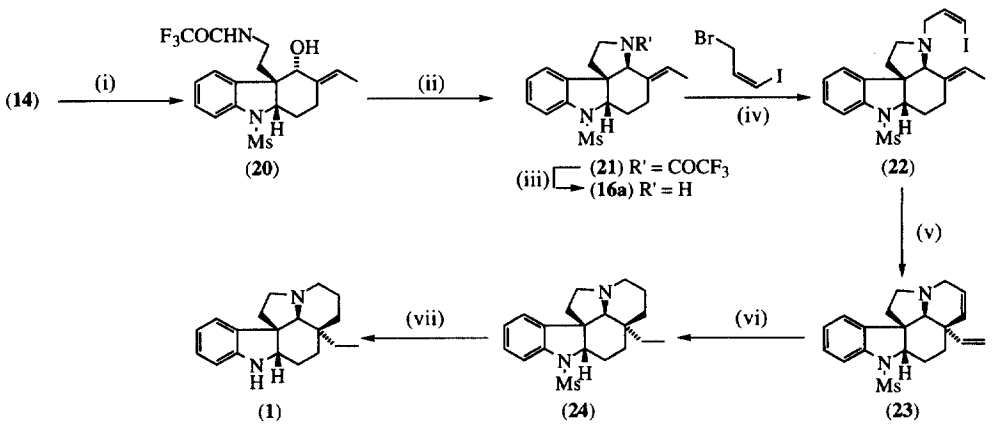
Reagents and conditions: (i) PCC, SiO_2, DCM, 18h, 82%; (ii) TMSCl, Et_3N, DMF, 80°C, 48h, ; $TiCl_4$, paraldehyde, DCM, -78°C 0.5h, then r.t. 48h, 51%; (iii) K_2CO_3, MeOH, H_2O, 18h, (iv) $NaBH_4$, $CeCl_3$, 15 min, 79%; (v) K_2CO_3, Bu_4NCl, DMF, 46%.

The stereochemistry at the alcohol in this compound has not been established, but our previous studies led us to expect complete stereoselectivity in favour of top-face attack on carbocation (**11**). Oxidation of the alcohol cleanly afforded the ketone (**13**), which could now be used to introduce the two carbons which would ultimately form the ethyl side-chain of aspidospermidine. Aldol reaction[10] followed by spontaneous dehydration afforded

(**14**). Hydrolysis of the trifluoroacetamide group was carried out efficiently under mild conditions to afford the unstable imine (**15**). We had previously investigated[9] the stereochemistry of reduction of the imine (**18**) which afforded (**19**) as principal product[11]. Luche reduction of imine (**15**) *in situ* afforded exclusively what we initially assumed to be (**16a**). However alkylation of this amine with *Z*-3-bromo-1-iodopropene afforded an alkylated product which was unable to undergo ring closure by Heck reaction. Hence the stereochemistry of this alkylated compound was investigated by performing a single-crystal X-ray structure determination, which showed it to be compound (**17**)[11], implying that the reduction had afforded (**16b**). The difference in stereochemistry of reduction of (**15**) and (**18**) was intriguing[12].

To overcome this problem, we reduced the ketone (**14**), and were delighted to find that Luche conditions afforded exclusive top-face delivery of hydride to afford alcohol (**20**)[13]. Intramolecular Mitsunobu reaction of this alcohol, exploiting the inherent acidity of the trifluoroacetamide group, neatly closed ring **E** affording (**21**). Reductive cleavage of the trifluoroacetamide and alkylation[14] of the resulting amine (**16a**) yielded the *Z*-iodoalkene (**22**) and ring closure under the conditions[15] of Kuehne *et al.* gave the pentacycle (**23**). Hydrogenation proceeded rapidly for the terminal alkene and more slowly for the ring alkene to afford (**24**). Deprotection of the mesyl group occurred cleanly to afford aspidospermidine (**1**), with the data in agreement with literature[1].

This novel synthesis of aspidospermidine allows all of the stereochemistry to be controlled by the configuration of the single stereocentre[16] in (**10**). It also demonstrates for the first time the synthetic utility of the radical-polar crossover reaction. The unique property of the radical-polar sequence in allowing direct formation of the key neopentyl alcohol (**12**) demonstrates a crucial advance in methodology.



Reagents and conditions: (i) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0°C, 100%; (ii) DEAD, PPh_2Me, THF, 0°C → r.t. 99%; (iii) $NaBH_4$, EtOH, 60°C, 82%; (iv) K_2CO_3, dry THF, 80%; (v) $Pd(OAc)_2$, Et_3N, PPh_3, dry CH_3CN, reflux, 37%; (vi) 10% Pt / C, 40psi, EtOH, 5 days, 58%; (vii) Red-Al, toluene, 100°C, 84%.

We thank the EPSRC for funding and the EPSRC National Mass Spectrometry Laboratory, Swansea, for high resolution mass spectra.

References.

1. Previous syntheses of aspidospermidine: A. Camerman, N. Camerman, J. P. Kutney, E. Piers and J. Trotter, *Tetrahedron Lett.*, **1965**, 637. T. Gallagher, P. Magnus and J. C. Huffman, *J. Am.*

Chem. Soc., **1983**, *105*, 4750. S. B. Mandal, V. S. Giri, M. S. Sabeena and S. C. Pakrashi, *J. Org. Chem.*, **1988**, *53*, 4236. P. Le Ménez, N. Kunesch, S. Liu and E. Wenkert, *J. Org. Chem.*, **1991**, *56*, 2915. D. Desmaële and J. d'Angelo, *J. Org. Chem.*, **1994**, *59*, 2292. P. Forns, A. Diaz and M. Rubiralta, *J. Org. Chem.*, **1996**, *61*, 7882.

2. For synthesis of *N*-benzylaspidospermidine, see: N. Benchekroun-Mounir, D. Dugat, J.-C. Gramain and H.-P. Husson, *J. Org. Chem.*, **1993**, *58*, 6457.
3. D. L. J. Clive, Y. Tao, A. Khodabocus, Y.-J. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, G. Kleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson and P. G. Vernon, *J. Amer. Chem. Soc.*, **1994**, *116*, 11275.
4. D. L. J. Clive, H. W. Manning and T. L. B. Boivin, *J.Chem. Soc., Chem. Commun.*, **1990**, 972.
5. For an alternative method, see V. F. Patel and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2703. H. Bhandal, V. F. Patel, G. Pattenden and J. J. Russell, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2691.
6. Diazonium salts can be converted to phenols. *e.g.* P. Hanson, R. C. Hammond, P. R. Goodacre, J. Purcell and A. W. Timms, *J. Chem. Soc. Perkin Trans. 2*, **1994**, 691, but our attempts to perform an analogous transformation to produce aliphatic alcohols after cyclisation of an aryl radical did not yield good results (R. Palin, unpublished work).
7. A. L. J. Beckwith and G. F. Meijs, *J. Org. Chem.*, **1987**, *52*, 1922. A. N. Abeywickrema and A. L. J. Beckwith, *J. Org. Chem.*, **1987**, *52*, 2568.
8. C. Lampard, J. A. Murphy and N. Lewis, *J.Chem. Soc., Chem. Commun.*, **1993**, 295. R. J. Fletcher, C. Lampard, J. A. Murphy and N. Lewis, *J. Chem. Soc., Perkin Trans 1*, **1995**, 623.
9. R. Fletcher, M. Kizil, C. Lampard, J. A. Murphy and S. J. Roome *J. Chem. Soc., Perkin Trans 1*, **1998**, 2341.
10. K. Narasaka, K. Soai and T. Mukaiyama, *Chem Lett.*, **1974**, 1223. T. Yanami, M. Miyashita and A. Yoshikoshi, *J. Org. Chem.*, **1980**, *45*, 607.
11. Crystal data for (**17**). Monoclinic, C2/c, colourless crystal, a = 32.972(5), b = 11.611(4), c = 11.161(5), β = 108.51(2), V = 4046(2), z = 8, R = 0.059, GOF = 1.54.
12. For related studies, see: A. Azzouzi, B. Perrin, M.-E. Sinibaldi, J.-C. Gramain and C. Lavaud, *Tetrahedron Lett.*, **1993**, *34*, 5451. A. Azzouzi, B. Perrin, M.E. Sinibaldi, D. Gardette, C. Lavaud, D. Vallée-Goyet, J.-C. Gramain, A. Kerbal, *Bull. Soc. Chim. Fr.*, **1995**, *132*, 681.
13. This is in line with modelling studies which show that the cyclohexyl ring in the most stable conformer of (**14**) adopts a boat conformation, but inverted with respect to that of (**18**). Approach to the lower face of the ketone in (**14**) is impeded by $H^{\S}$.
14. E. Piers and J. Renaud, *J. Org. Chem.*, **1993**, *58*, 11.
15. M. E. Kuehne, T. Wang and P. J. Seaton, *J. Org. Chem.*, **1996**, *61*, 6001.
16. Enantiomerically pure aspidospermidine should be accessible by this route using a single enantiomer of 2-allylcylohex-2-en-1-ol, the ultimate source of this chiral centre [rather than the racemic compound used here]. This compound has been prepared[17] in >96% e.e. , and Mitsunobu reactions on cyclohex-2-enols have been found to proceed with clean inversion[18] of stereochemistry.
17. C. Y. Hong, N. Kado and L. E.Overman, *J. Amer. Chem. Soc.* **1993** *115*, 11028.
18. K. A. Parker and D. Fokas, *J. Amer. Chem. Soc.* **1993**, *114*, 9688; *J. Org. Chem.*, **1994**, *59*, 3933.