Tetrahedron Letters 54 (2013) 1726–1729

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselectivity and conformational control in the synthesis of ajmaline and *epi*-ajmaline alkaloids

Patrick D. Bailey [a,*], Mark A. Beard [b], Mark Cresswell [a], Hoa P. T. Dang [b], Ravindra B. Pathak [a], Theresa R. Phillips [a], Richard A. Price [b]

[a] *EPSAM Research Institute, Keele University, Keele, Staffordshire ST5 5BG, UK*
[b] *School of Chemistry, University of Manchester, Manchester M13 9PL, UK*

ARTICLE INFO

Article history:
Received 9 June 2012
Revised 4 January 2013
Accepted 17 January 2013
Available online 25 January 2013

Keywords:
Stereoselective synthesis
Indole alkaloids
Ajmaline

ABSTRACT

Careful choice of the N-protecting group provides crucial conformational control, allowing ring-closure to the indole 3-position in the late stages of the synthesis of ajmaline alkaloids; the choice of protecting group and reducing agent can also provide access to either the natural or *epi* configuration at the indole 2-position.

Despite its modest molecular weight (M_r 326), the alkaloid ajmaline (**1**) has nine contiguous chiral centres packed into a tetracyclic cage-like structure.[1] The synthetic challenge of this polycyclic region, combined with the important medicinal properties of ajmaline as an antiarrhythmic agent,[2] have led to claims of total syntheses and numerous partial syntheses over the past 45 years.[3–6] Of these, only Cook[6] has actually completed the preparation of a synthetic sample of ajmaline, with other 'total syntheses' relying on comparison with semi-synthetic intermediates which could themselves be transformed into ajmaline (sometimes called 'relay syntheses').

All of the synthetic approaches have essentially involved two phases (see Scheme 1):

(a) construction of an advanced core **4** that is common to the family of ajmaline/sarpagine alkaloids, but lacking the bond to the indolic 3-position;
(b) introduction of the bond to the indolic 3-position (creating 3 new chiral centres), which can be carried out earlier (route a) or towards the end (route b), before relatively simple transformations to complete the synthesis.

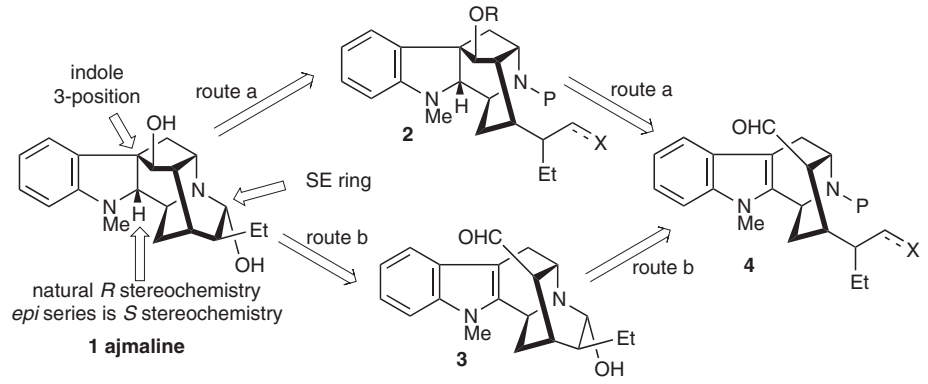
One important consideration has been whether the closure of the 3-indolyl bond should precede or follow the formation of the south-east (SE) ring (see Scheme 1). Bartlett et al.[7] carried out studies on compounds derived from ajmaline, and found that prior closure of the SE ring led to the *epi*-ajmaline series when reductive ring-closure to the 3-indolyl position was carried out. Cook's group also chose to close this SE ring fairly early in their total synthesis, as this facilitates 3-indolyl ring-closure (see Scheme 4); they observed either totally or partially selective reduction to the *epi*-ajmaline stereochemistry, although they managed to develop conditions in which the desired isomer was only disfavoured by a factor of 3:2.[6]

With this in mind, our approach was to leave the formation of the SE ring until the end of the synthesis, and this Letter describes our findings on the 3-indolyl ring-closure, which would set three of the chiral centres in ajmaline; our results also have an important bearing on some previous synthetic claims.

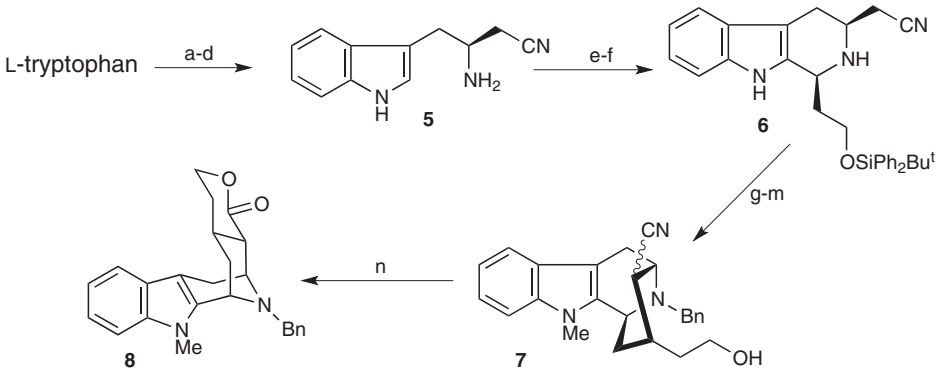
The synthetic studies described herein were directed at a de-ethyl derivative of ajmaline (i.e., ethyl absent from SE ring of **1**), for which the aldehyde **9** (see Scheme 3) was a key advanced intermediate (cf. structure **4** in Scheme 1). The synthesis of **9** involved a homologation sequence starting from L-tryptophan (Scheme 2) to generate the nitrile **5**,[8] followed by a kinetically controlled Pictet–Spengler reaction[9] to generate **6**, with complete stereo-control of two of the chiral centres; fairly standard steps allowed conversion into **7** in which a third chiral centre was installed, and lactonization of this involved an epimerization such that **8** had four asymmetric centres installed with complete control of the stereochemistry (Scheme 2).[10] Ring-opening of **8** to give the Weinreb amide,[11] protection of the OH as the methyl ether, then reduction with $LiAlH_4$ gave aldehyde **9** (Scheme 3). Using this *N*-benzyl derivative **9**, we investigated a series of ring-closure conditions based on early work using ajmaline derivatives,[7] and modified subsequently

* Corresponding author. Tel.: +44 01782 734583; fax: +44 01782 734593.
E-mail address: p.bailey@natsci.keele.ac.uk (P.D. Bailey).

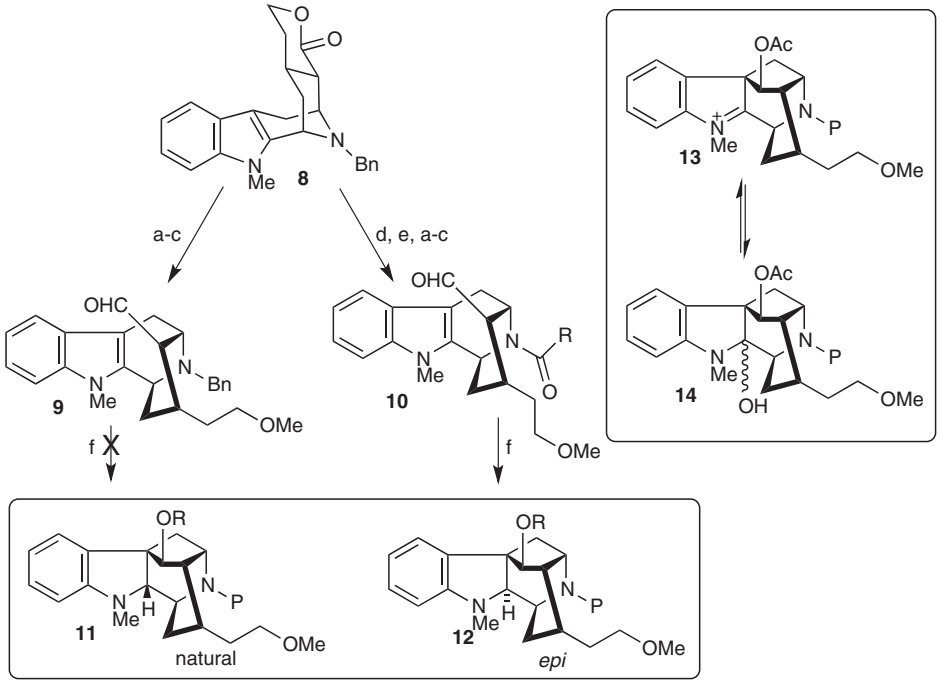
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.01.074



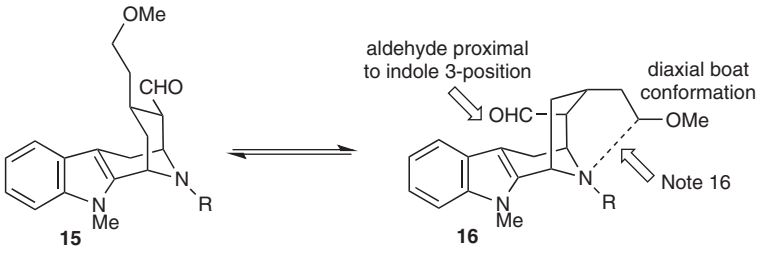
Scheme 1. Late stage retrosynthetic analysis of ajmaline (**1**).



Scheme 2. Synthesis of advanced intermediate **8**. Reagents and conditions: (a) $LiAlH_4$, THF, rt, 16 h, 100%; (b) TsCl, py, 0 °C to rt, 16 h, 90%; (c) KCN, MeOH, 65 °C, 2 h, 77%; (d) Na, liq NH_3, THF, −78 °C, 30 min, 79%; (e) $TBDPSO(CH_2)_2CHO$, 3 Å MS, CH_2Cl_2, rt, 16 h; (f) TFA, CH_2Cl_2, −78 °C to rt, 6 h, 62% (over 2 steps); (g) DIPEA, BnBr, CH_3CN, 80 °C, 40 h, 95%; (h) NaH, MeI, DMF, 0 °C to rt, 1.5 h, 91%; (i) TBAF, THF, rt, 2 h, 89%; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C to rt, 15 min, 100%; (k) Ph_3PCHCO_2Me, CH_2Cl_2, 0 °C to rt, 5 h, 89%; (l) ^{n}BuLi, Et_2NH, THF, −78 °C, 2 h, 63%; (m) $LiBH_4$, THF, 66 °C, 16 h, 75%; (n) *p*-TSA, THF, 66 °C, 16 h, 63%.



Scheme 3. Synthesis of the pentacyclic compounds **11** (natural) and **12** (*epi*). Reagents and conditions: (a) HN(Me)OMe·HCl, $AlMe_3$, CH_2Cl_2, rt, 16 h, 86%; (b) NaH, MeI, THF, 0 °C to rt, 16 h, 92%; (c) $LiAlH_4$, THF, −78 to 10 °C, 3.5 h, 94%; (d) $Pd(OH)_2/C$ (20%), H_2, CF_3CH_2OH, rt, 16 h, 100%; (e) RCOCl, Et_3N, CH_2Cl_2, rt, 16 h, 71–84%; (f) see Table 1.



Scheme 4. Chair-boat equilibrium in the cyclization to the indolic 3-position.

Table 1
Reducing agents for the conversion of **9** or **10** into the pentacyclic compounds **11**/**12** (see Scheme 3 and Ref. 13); yields are quoted for isolated products that were fully characterized, whilst the natural/*epi* ratio was determined from the NMR spectra of the crude products

Compound	R (in **10**)	Reduction	Yield (%)	Natural/*epi* (**11**:**12**)
9	—	Various conditions	No cyclization	—
10a	Ph	For example, $NaBH_4$; H_2/Pd-C; BH_3·THF; N-selectride; H_2/PtO_2, 6 M HCl[17]	10–60	0:100
10b	*cy*-C_6H_{11}	H_2/PtO_2, 6 M HCl	70	22:78
10b	*cy*-C_6H_{11}	H_2/Pd-C, 6 M HCl	68	59:41
10c	Bu^t	$NaBH_4$	32	0:100
10c	Bu^t	H_2/Pd-C	47	45:55[18]
10c	Bu^t	$LiAlH(OBu^t)_3$	37	58:42
10d	Adamantyl	$NaBH_4$	100	0:100
10d	Adamantyl	H_2/Pd-C	69	42:58
10d	Adamantyl	$LiAlH(OBu^t)_3$	48	72:28

For related substrates, Masamune[3] reported a natural/*epi* ratio of 2:1, whilst Cook[6] achieved a 40:60 ratio for the reductive cyclization step in his total synthesis of ajmaline.

by Cook[6]—this essentially involved the use of AcOH/Ac_2O/HCl to trap the alcohol as the acetate **13** (which could be isolated as the hydroxy-amine **14**), followed by reduction of this iminium intermediate. However, no hint of cyclization was observed until the conditions became so forcing (>60 °C) that the starting aldehyde was degrading faster than cyclization was occurring, and no significant amounts of ring-closed product could be isolated. Of course, pre-closure of the SE ring facilitates this ring-closure, but leads to stereochemical problems at the reduction step (loc. cit.). It occurred to us, however, that replacing the benzyl by benzoyl might aid the cyclization in two ways associated with the nitrogen becoming sp^2 hybridized (see Scheme 4):

(a) increasing the conformational flexibility of the boat conformer **16**, allowing a closer approach to the indole 3-position;
(b) lowering the energy of the boat conformer **16** relative to the chair **15**, thereby increasing the concentration of **16** in the appropriate conformation for ring-closure.

Removal of the benzyl group was accomplished by catalytic hydrogenation in trifluoroethanol,[12] followed by *O*-methylation and *N*-benzoylation; Weinreb amide formation and $LiAlH_4$ reduction yielded the aldehyde **10a**. To our delight, relatively mild conditions led to cyclization,[13] for which reduction by $NaBH_4$ gave a single diastereomeric product[14] with three new chiral centres. The stereochemistry at the 2-indolyl position is characterized by the coupling constant—ca. 5 Hz in the *epi*-ajmaline series, but a broad singlet (J <1 Hz) in the ajmaline series.[15] To our dismay, it was the *epi*-ajmaline derivative **12** that we had obtained, and this remained the case under a wide range of hydrogenation and hydride reducing conditions; this is in contrast to results obtained by Masamune,[3] in which preferential reduction to the ajmaline stereochemistry (natural/*epi*, 2:1) was reported.

One result did however give us hope. Using platinum oxide as the catalyst, some reduction of the phenyl ring of the benzoyl group occurred, and the resulting cyclohexyl derivative clearly showed the presence of the singlet (ca. δ 2.6) characteristic of the ajmaline series.[17] We reasoned that the bulkier protecting group was partially blocking the *si* face of the imine, allowing reduction to the ajmaline series. We therefore tried to optimize this with bulkier protecting groups and reducing agents, eventually leading to a 72:28 preference for the ajmaline series—the best selectivity ever reported for this cyclization.

We believe these results are important for three reasons:

(a) We now have a clearer insight into the subtle conformational factors that affect ring-closure to the indole 3-position (Scheme 3), for which the functionalization of the remote piperidine nitrogen is a crucial factor (see Scheme 4 and Ref. 16).
(b) The stereoselectivity that we observed for the reductive cyclization of the benzoyl derivative **10a** (exclusively *epi*) is in contrast to that reported by Masamune.[3]
(c) These results clearly take us very close to a synthesis of ajmaline itself, with seven of the nine chiral centres installed; introduction of the ethyl group and closure of the SE ring are the steps still required.

Acknowledgment

We thank the EPSRC and the Mass Spectrometry Service at Swansea, and Keele University for ACORN funding (M.C.).

References and notes

1. (a) Siddiqui, S.; Siddiqui, R. *J. Indian Chem. Soc.* **1931**, *8*, 677–680; (b) Woodward, R. B. *Angew. Chem.* **1956**, *68*, 13–20.
2. Brugada, J.; Brugada, P. *Am. J. Cardiol.* **1996**, *78*, 69–75.
3. Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506–2507.
4. Mashimo, K.; Sato, Y. *Chem. Pharm. Bull.* **1970**, *18*, 353–355.

5. van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136–2137.
6. (a) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998–7010; (b) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett.* **2001**, *3*, 345–348.
7. Bartlett, M. F.; Sklar, R.; Taylor, W. I.; Schlittler, E.; Amai, R. L. S.; Beak, P.; Bringi, N. V.; Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 622–630.
8. Kutney, J. P.; Eigendorf, G. K.; Matsue, H.; Murai, A.; Tanaka, K.; Sung, W. L.; Wada, K.; Worth, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 938–943.
9. Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431–439.
10. Bailey, P. D.; Clingan, P. D.; Mills, T. J.; Price, R. A.; Pritchard, R. G. *Chem. Commun.* **2003**, 2800–2801.
11. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
12. Bailey, P. D.; Beard, M. A.; Dang, H. P. T.; Phillips, T. R.; Price, R. A.; Whittaker, J. H. *Tetrahedron Lett.* **2008**, *49*, 2150–2153.
13. *Typical reaction conditions were*: (a) Cyclization with HCl(g) in AcOH, Ac_2O, 0 °C, 3 h then warming to rt overnight, followed by; (b) reduction with $NaBH_4$, THF, 0 °C, 4 h; or H_2, Pd-C, CH_2Cl_2, rt, 16 h; or $LiAl(OBu^t)_3H$, THF, −78 °C warming to rt over several hours.
14. Initially we thought that **11a/12a** had been formed as a 50:50 mixture, as ^1H NMR spectra clearly showed the presence of two fully resolved compounds with all of the key structural features, but it transpired that these were in fact rotamers, despite the fact that **10a** did not show a similar feature (just slight broadening of a few peaks).
15. For example, the pivaloyl products displayed H-2 for **11c** at δ 2.58 (1H, s) and H-2 for **12c** at δ 2.92 (1H, d, J 4.9 Hz); similarly, the adamantoyl products displayed H-2 for **11d** at δ 2.57 (1H, s) and H-2 for **12d** at δ 2.90 (1H, d, J 4.7 Hz).
16. Without prior formation of the SE ring, the boat conformation must be adopted if ring-closure to the indolic 3-position is to occur; if the SE ring is already closed (see dashed line), as in semi-synthetic studies[7] and Cook's synthesis,[6] then the boat conformation is locked, facilitating ring-closure, but directing reduction of the iminium intermediate **13** to the *epi*-ajmaline series.
17. Using platinum oxide, about 40% of the *epi*-benzoyl product **12** was obtained, and about 10% of a crude cyclohexylcarbonyl derivative **11** with the natural stereochemistry (R = Ac, P = CO-*cy*-C_6H_{11}).
18. We have also carried out cyclization and catalytic hydrogenation of the 2,2-dimethyl-2-(2-nitrophenyl)ethanoyl protected analogue of **10**, with ca. 60:40 selectivity of natural/*epi*; this provides further evidence for the bulk of the protecting group influencing the stereochemistry of the reduction.