COMMUNICATION

π-Allyl cation cyclisations initiated by electrocyclic ring-opening of *gem*-dihalocyclopropanes: application to the first total syntheses of the crinine-type alkaloids maritinamine and *epi*-maritinamine

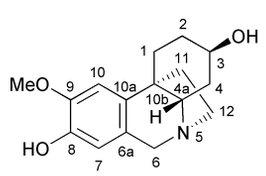
Martin G. Banwell,* Joanne E. Harvey and Katrina A. Jolliffe

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

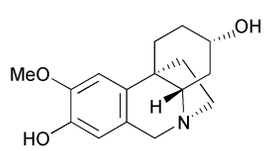
Received (in Cambridge, UK) 17th July 2001, Accepted 30th July 2001
First published as an Advance Article on the web 13th August 2001

The racemic modifications of the crinine alkaloids 1 and 2 have been synthesized for the first time and by a pathway that involves silver(I)-promoted electrocyclic ring-opening of the ring-fused *gem*-dichlorocyclopropane 3 and trapping of the resulting π-allyl cation by the tethered carbamate moiety so as to form the pivotal C3a-arylated hexahydroindole 14.

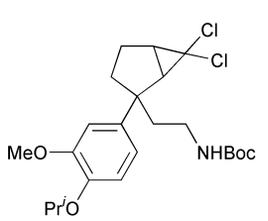
The crinine alkaloids[1,2] embody the 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-ethanophenanthridine skeleton and represent an important sub-class within the large family of *Amaryllidaceae* alkaloids. Many members of this sub-class display interesting biological properties including immuno-stimulatory, cytotoxic and anti-malarial activities. As a consequence, these natural products have been the subject of numerous synthetic studies.[3–6] Broadly speaking, two major routes have been developed. One of these, reported by Schwartz and Holton,[3] employs an intramolecular oxidative coupling of linked aryls (to form the C10a–C10b bond of the crinine skeleton – see structure **1**) followed by an intramolecular hetero-Michael addition reaction (to form the C4a–N5 bond) and may be regarded as a biomimetic synthesis. Variations on this basic approach have been exploited by a number of workers[4] and even executed using polymer-supported reagents.[5] The second and more common route employs an appropriate C3a-arylperhydroindole that is subject to a Pictet–Spengler reaction so as to install C6 of the target framework with accompanying formation of the N5–C6 and C6–C6a bonds. The requisite C3a-arylperhydroindoles have been prepared in a remarkably diverse number of ways.[6] In all of these approaches, construction of the sterically congested quaternary carbon centre (C10b) carrying the aryl group has proved especially challenging.



1



2



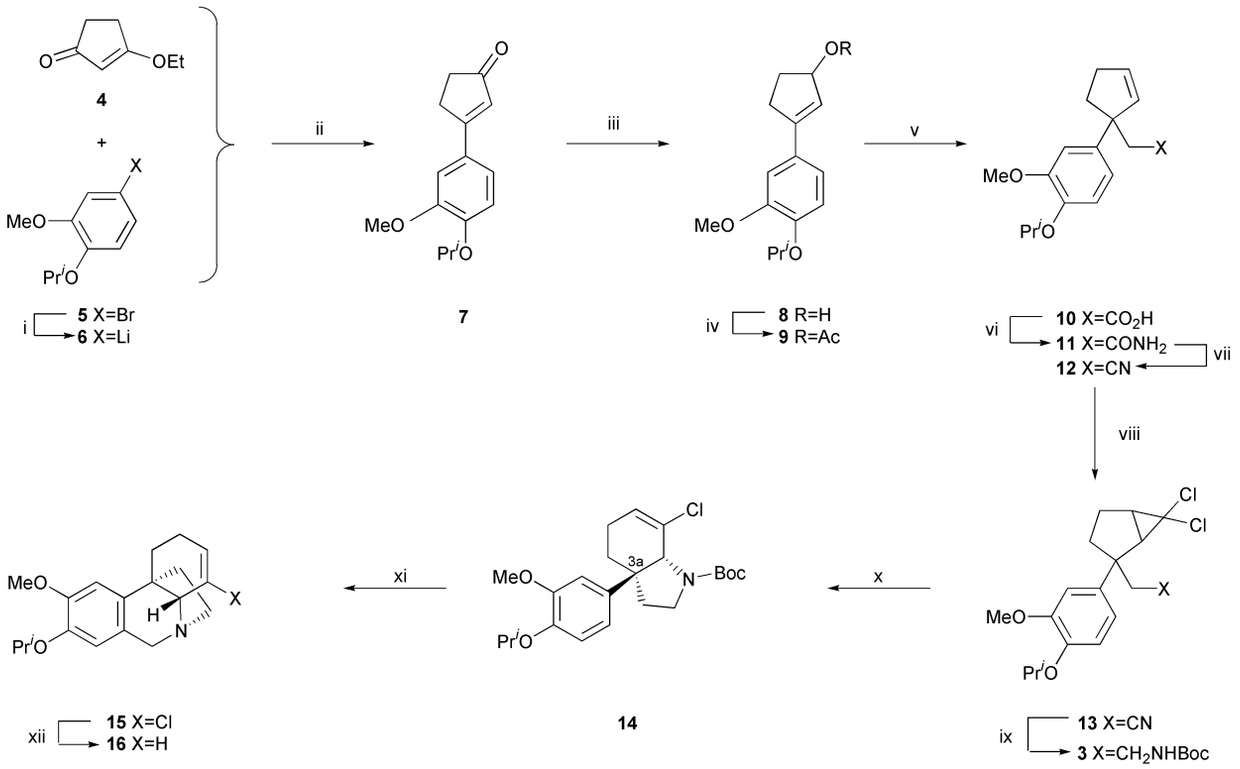
3

For some time we have been interested in exploiting π-allyl cation cyclisations initiated by electrocyclic ring-opening of *gem*-dihalocyclopropanes as a method for the assembly of heterocyclic compounds[7] and now describe the application of this protocol to a new synthesis of C3a-arylhexahydroindoles. We also report on the exploitation of this methodology in the first total syntheses of the racemic modifications of maritinamine (**1**) and *epi*-maritinamine (**2**), two crinine alkaloids isolated by Shamma and co-workers[8] from *Sternbergia lutea* found in Turkey. Natural products **1** and **2** differ from most other members of the crinine alkaloid class in that they possess a C9-methoxy and a C8-hydroxy group rather than the usual (and less synthetically demanding) methylenedioxy unit spanning these positions.[9]

The early stages of the synthesis leading to the pivotal *gem*-dichlorocyclopropane **3** (Scheme 1) rely upon a similar strategy to that employed by Keck and Webb[6e] for construction of the quaternary carbon centre associated with (±)-dihydromaritidine. Thus, β-ethoxycyclopentenone (**4**)[10] was treated with the lithio-species **6** derived from metallation of bromoarene **5**[11] with *t*-BuLi at −78 °C. The resulting alkoxide was subjected to acidic work-up thereby providing the β-arylcyclopentenone **7**† (67%). Smooth and selective 1,2-reduction of this last compound could be effected with the Luche reagent[12] but the reaction had to be carried out in the presence of 2,6-lutidine because of the exceptional acid-sensitivity of the product alcohol **8** (99%). The readily derived acetate **9** (98%) then underwent an Ireland–Claisen rearrangement[13] so as to provide, after acidic work-up, the γ,δ-unsaturated acid **10** (83%) embodying the pivotal quaternary carbon centre associated with targets **1** and **2**. The methyl and ethyl ester derivatives of compound **10** failed to undergo effective reaction with dibromocarbene (generated under phase transfer conditions)[14] and such outcomes are attributed to the high level of steric congestion at the cyclopentenyl double-bond resulting from the presence of the adjacent quaternary carbon center. In an effort to relieve such congestion, the acid moiety within compound **10** was converted, *via* the intermediate amide **11**, into the corresponding nitrile **12** (76% from **10**). Whilst compound **12** also failed to engage in reaction with dibromocarbene, on prolonged exposure to dichlorocarbene a *ca.* 2 : 1 mixture of the epimeric adducts **13a**–**b** (50% combined yield) was obtained.‡ These chromatographically separable adducts were each subjected to hydrogenation in the presence of chloroform and PtO_2 and the ensuing amine hydrochlorides were immediately treated with Boc_2O in the presence of triethylamine so as to deliver the corresponding carbamates **3a** and **3b** (75% in each case).

Independent subjection of each of the epimeric forms of compound **3** to reaction with silver tetrafluoroborate in THF at 40 °C resulted in smooth electrocyclic ring-opening of the cyclopropane and accompanying π-allyl cation cyclisation. The ensuing mixture of the C3a-arylhexahydroindole **14** and the corresponding free amine (arising from loss of the Boc-group) was treated with Boc_2O and in this manner clean samples of compound **14** could be obtained in yields of 65–75%. Interestingly, the epimeric forms of the *gem*-dichlorocyclopropane **3** react at rather different rates in the electrocyclic ring-opening–

 DOI: 10.1039/b106369n



Scheme 1 *Reagents and conditions*: (i) *t*-BuLi (2.0 mol equiv.), THF, −78 °C, 10 min then compound **4** (0.84 mol equiv.), 1.5 h; (ii) *p*-TsOH (cat.), THF, 25 °C, 14 h; (iii) $NaBH_4$ (2.5 mol equiv.), $CeCl_3 \cdot 7H_2O$ (2.5 mol equiv.), 2,6-lutidine (10 mol equiv.), MeOH, 0–25 °C, 10 min; (iv) Ac_2O (4 mol equiv.), pyridine, 25 °C, 24 h; (v) LDA (1.2 mol equiv.), THF, DMPU, −78 °C, 0.5 h then TBDMSCl (2.7 mol equiv.), −78 °C, 10 min then heat at 66 °C, 3.5 h then H_3O^+; (vi) NH_4Cl (4 mol equiv.), EDCI (1.6 mol equiv.), HOBt (1.6 mol equiv.), DMF, 0–25 °C, 18 h; (vii) Cl_3CCOCl (1.2 mol equiv.), Et_3N (2 mol equiv.), CH_2Cl_2, 0 °C, 0.66 h; (viii) $CHCl_3$, 50 % aq. NaOH, TEBAC (cat.), 18 °C, 24 d; (ix) H_2 (3 atm), PtO_2 (cat.), EtOH–$CHCl_3$, 25 °C, 12 h then $(Boc)_2O$ (2 mol equiv.), Et_3N (5 mol equiv.), THF, 25 °C, 15 h; (x) $AgBF_4$ (6 mol equiv.), THF, 40 °C, 21 h, then $(Boc)_2O$ (2 mol equiv.), Et_3N (5 mol equiv.), THF, 25 °C, 15 h; (xi) $(CH_2O)n$ (11 mol equiv.), HCO_2H, 80 °C, 18 h; (xii) Na (6 g atom equiv.), *t*-BuOH (14 mol equiv.), THF, 66 °C, 3 h. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and TEBAC = triethylbenzylammonium chloride.

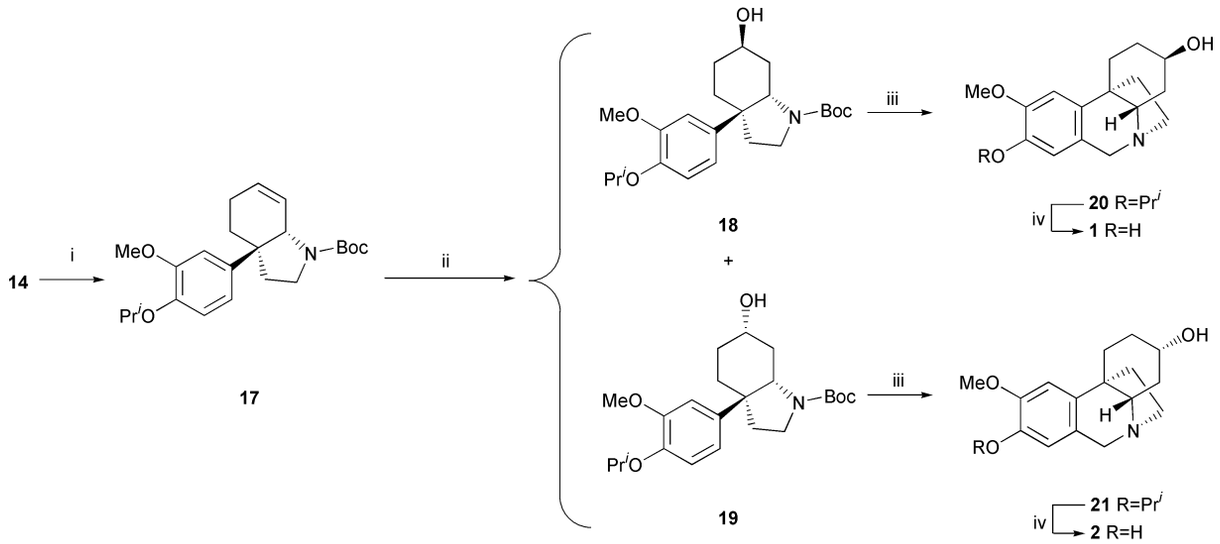
π-allyl cation cyclisation sequence with the major isomer, **3a**, being completely consumed within 8 hours and the minor isomer taking three times longer. Subjection of compound **14** to a Pictet–Spengler reaction,[15] involving its treatment with a mixture of formic acid and paraformaldehyde at 80 °C for 18 h, resulted in the smooth formation of compound **15** (76%) incorporating the crinine framework and with seemingly appropriate functionality for elaboration to the target compounds **1** and **2**. However, whilst the chloroalkene **15** readily underwent reductive dechlorination reaction under Bouveault–Blanc conditions, the ensuing non-chlorinated alkene **16** (98%) could not be manipulated (*e.g. via* attempted oxymercuration or hydroboration–oxidation of the double bond) in any useful manner. On the basis that such difficulties may arise because of steric congestion within the rigid crinine framework, a re-ordering of the reaction sequence, wherein the Pictet–Spengler cyclisation was delayed, seemed appropriate. To such ends, the C3a-arylated hexahydroindole **14** (see Scheme 2) was subject to reductive dechlorination under the same conditions as used earlier and in this manner alkene **17** (98%) was obtained. Subjection of the latter material to oxymercuration with $Hg(OAc)_2$ under conditions described by Burk and Overman[6j] gave, after reductive work-up with alkaline sodium borohydride, a chromatographically separable mixture of the epimeric alcohols **18** (25%) and **19** (71%). Independent subjection of each of these products to a Pictet–Spengler reaction (using formic acid and paraformaldehyde as before) gave, after hydrolytic work-up with methanolic potassium carbonate, the corresponding crinines **20** (72%) and **21** (58%), respectively. Whilst selective de-isopropylation of compounds **20** and **21** could not be effected with $AlCl_3$ in dichloromethane,[16] such conversions could be achieved with BCl_3 in dichloromethane at 0 °C. Under these conditions compound **20** afforded (±)-maritinamine **1**§ (70%) and congener **21** led to (±)-*epi*-maritinamine **2**¶ (70%). The spectroscopic data derived from the synthetic samples of (±)-**1** and (±)-**2** are completely consistent with the assigned structures. Further, there is reasonable agreement between these data and those reported by Shamma *et al.*[8] for the corresponding natural materials. The consistent *ca.* 0.1 ppm difference in chemical shifts between the appropriate sets of ^{1}H NMR data is attributed to variations in both solvent acidity and sample concentration. Related differences have been observed between the ^{1}H NMR spectroscopic data sets obtained for 4a-dehydroxycrinamabine.[17]

Since the C3a-arylperhydroindole moiety is also a basic structural element associated with *Sceletium* alkaloids such as mesembrine and pretazettine,[6l] the strategy described here could also serve as a useful means of accessing these interesting types of compounds. In addition, any capacity to effect enantioselective 1,2-reduction of the prochiral enone **7** should enable ready adaptation of the chemistry described above to the synthesis of the (+)- and (−)-forms of the title alkaloids.[18]

Experimental

Compound 14

A magnetically stirred solution of carbamate **3a** (90 mg, 0.20 mmol) in THF (5 mL) was treated with silver tetrafluoroborate (0.23 g, 1.2 mmol). The resulting solution was protected from light and heated at 40 °C under an atmosphere of nitrogen for 21 h then cooled and poured into H_2O (20 mL). After the addition of aq. NH_3 (2 mL) the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting pale-yellow oil was re-dissolved in THF (2 mL) and triethylamine (0.19 mL, 1.4 mmol) added. The ensuing mixture was stirred for 10 min, treated with di-*tert*-butyl dicarbonate (0.12 g, 0.54 mmol), stirred at 18 °C for 15 h then poured into H_2O (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were dried



Scheme 2 *Reagents and conditions*: (i) Na (6 g atom equiv.), *t*-BuOH (14 mol equiv.), THF, 66 °C, 3 h; (ii) $Hg(OAc)_2$ (2 mol equiv.), 1 : 1 v/v THF–H_2O, 25 °C, 24 h then $NaBH_4$ (2 mol equiv.), 3 M aq. NaOH, 25 °C, 0.5 h; (iii) $(CH_2O)n$ (10 mol equiv.), HCO_2H, 80 °C, 18 h then K_2CO_3 (6 mol equiv.), MeOH, 25 °C, 1 h; (iv) BCl_3 (5 mol equiv.), CH_2Cl_2, 0 °C, 0.25 h.

($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this material to flash chromatography (1 : 4 v/v ethyl acetate–hexane elution) gave, after concentration of the appropriate fractions (R_f 0.3), the *carbamate* **14** (60 mg, 72%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.83 (s, 2H), 5.91 (m, 1H), 4.92 (broad m, 1H), 4.50 (septet, *J* 6.1 Hz, 1H), 3.85 (s, 3H), 3.38–3.02 (complex m, 2H), 2.40–1.80 (complex m, 6H), 1.42 (broad s, 9H), 1.35 (d, *J* 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (C), 150.1 (C), 145.8 (C), 138.4 (C), 133.6 (C), 125.6 (CH), 117.8 (CH), 115.5 (CH), 109.9 (CH), 79.6 (C), 71.3 (CH), 56.0 (CH_3), 49.7 (C), 43.7 (CH_2), 31.3 (CH_2), 28.4 (CH_3), 23.3 (CH_2), 22.1 (CH_3), two signals obscured or overlapping; IR (KBr) 2975, 2931, 1693, 1517, 1389, 1262, 1174, 1111 cm^{-1}; MS (EI) *m*/*z* 421.2019 ($C_{23}H_{32}$ $^{35}ClNO_4$ requires 421.2020, $M^{+\bullet}$, 65%), 367 (6), 365 (18), 325 (39), 323 (71), 288 (23), 235 (53), 57 (100).

Acknowledgements

We thank the Institute of Advanced Studies for financial support including the provision of an IAS post-Doctoral Fellowship to KAJ and a PhD Scholarship to JEH.

Notes and references

† All new and stable compounds had spectroscopic data [IR, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ The major and chromatographically more mobile epimer **13a** is tentatively assigned as possessing an *anti*-relationship between the cyclopropyl and aryl rings. This epimer leads, *via* hydrogenation and carbamate formation, to compound **3a**.

§ *Selected spectral data for compound* **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.57 (s, 1H), 4.47 (d, *J* 16.5 Hz, 1H), 4.28 (m, 1H), 3.88 (s, 3H), 3.87 (d, *J* 16.5 Hz, 1H), 3.53 (m, 1H), 3.47 (dd, *J* 12.5 and 5.5 Hz, 1H), 2.94 (ddd, *J* 12.5, 9.0 and 7.0 Hz, 1H), 2.28 (m, 1H), 2.25–2.10 (complex m, 3H), 1.92–1.73 (complex m, 3H), 1.35 (ddd, *J* 12.5, 12.0 and 2.5 Hz, 1H), signals due to hydroxy group protons not observed; ^{13}C NMR (125 MHz, CD_3OD) δ 147.1 (C), 145.3 (C), 138.1 (C), 121.8 (C), 112.8 (CH), 106.3 (CH), 65.2 (CH), 63.8 (CH), 60.0 (CH_2), 55.4 (CH_3), 51.5 (CH_2), 42.6 (C), 36.2 (CH_2), 32.1 (CH_2), 27.1 (CH_2), 22.0 (CH_2); IR (neat, NaCl plates) 3369, 2917, 1558, 1507, 1443, 1277, 1131, 1013 cm^{-1}; MS (EI) *m*/*z* 275.1520 ($C_{16}H_{21}NO_3$ requires 275.1521, $M^{+\bullet}$, 100%), 258 (26), 247 (15), 246 (18), 228 (14), 204 (16), 203 (41), 202 (17), 187 (19).

¶ *Selected spectral data for compound* **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.58 (s, 1H), 4.42 (d, *J* 16.6 Hz, 1H), 3.88 (s, 3H), 3.82 (d, *J* 16.6 Hz, 1H), 3.64 (m, 1H), 3.47 (m, 1H), 3.11 (dd, *J* 12.0 and 5.1 Hz, 1H), 2.93 (m, 1H), 2.45 (dt, *J* 13.8 and 3.3 Hz, 1H), 2.31 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 1.84–1.74 (complex m, 2H), 1.60 (m, 1H), 1.35 (app. q, *J* 12.0 Hz, 1H), signals due to hydroxy group protons not observed; ^{13}C NMR (150 MHz, CD_3OD) δ 148.5 (C), 146.8 (C), 138.3 (C), 122.2 (C), 114.0 (CH), 107.7 (CH), 68.9 (CH), 68.2 (CH), 60.9 (CH_2), 56.5 (CH_3), 52.6 (CH_2), 43.7 (C), 37.3 (CH_2), 36.0 (CH_2), 31.3 (CH_2), 27.1 (CH_2); IR (neat, NaCl plates) 3306, 2920, 1562, 1509, 1447, 1277, 1128, 1071, 1029 cm^{-1}; MS (EI) *m*/*z* 275.1519 ($C_{16}H_{21}NO_3$ requires 275.1521, $M^{+\bullet}$, 100%), 258 (18), 247 (16), 246 (21), 228 (16), 204 (39), 203 (37), 202 (18), 187 (19), 79 (46).

1 S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987; vol. 30, pp. 251–376.
2 J. R. Lewis, *Nat. Prod. Rep.*, 1998, **15**, 107.
3 M. A. Schwartz and R. A. Holton, *J. Am. Chem. Soc.*, 1970, **92**, 1090.
4 (*a*) H. Irie, S. Uyeo and A. Yoshitake, *J. Chem. Soc. C*, 1968, 1802; (*b*) T. Fushimi, H. Ikuta, H. Irie, K. Nakadachi and S. Uyeo, *Heterocycles*, 1979, **12**, 1311; (*c*) I. H. Sánchez, F. J. López, J. J. Soria, M. I. Larraza and H. J. Flores, *J. Am. Chem. Soc.*, 1983, **105**, 7640.
5 S. V. Ley, O. Schucht, A. W. Thomas and P. J. Murray, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1251.
6 For representative examples see (*a*) H. Muxfeldt, R. S. Schneider and J. B. Mooberry, *J. Am. Chem. Soc.*, 1966, **88**, 3670; (*b*) H. W. Whitlock Jr. and G. L. Smith, *J. Am. Chem. Soc.*, 1967, **89**, 3600; (*c*) R. V. Stevens, *Acc. Chem. Res.*, 1977, **10**, 193; (*d*) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 2579; (*e*) G. E. Keck and R. R. Webb II, *J. Org. Chem.*, 1982, **47**, 1302; (*f*) I. H. Sánchez, F. J. López, H. J. Flores and M. I. Larraza, *Heterocycles*, 1983, **20**, 247; (*g*) O. Hoshino, S. Sawaki, N. Shimamura, A. Onodera and B. Umezawa, *Chem. Pharm. Bull.*, 1987, **35**, 2734; (*h*) S. F. Martin and C. L. Campbell, *J. Org. Chem.*, 1988, **53**, 3184; (*i*) J. P. Michael, A. S. Howard, R. B. Katz and M. I. Zwane, *Tetrahedron Lett.*, 1992, **33**, 6023; (*j*) R. M. Burk and L. E. Overman, *Heterocycles*, 1993, **35**, 205; (*k*) W. H. Pearson and F. E. Lovering, *J. Org. Chem.*, 1998, **63**, 3607; (*l*) A. Padwa, M. A. Brodney, M. Dimitroff, B. Liu and T. Wu, *J. Org. Chem.*, 2001, **66**, 3119.
7 See, for example (*a*) M. Banwell, A. Edwards, J. Harvey, D. Hockless and A. Willis, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2175; (*b*) M. G. Banwell, J. E. Harvey, D. C. R. Hockless and A. W. Wu, *J. Org. Chem.*, 2000, **65**, 4241.
8 V. Pabuccuoglu, P. Richomme, T. Gozler, B. Kivcak, A. J. Freyer and M. Shamma, *J. Nat. Prod.*, 1989, **52**, 785.
9 The crinine alkaloids 8-*O*-demethylmaritidine (M. Kihara, T. Koike, Y. Imakura, K. Kida, T. Shingu and S. Kobayasi, *Chem. Pharm. Bull.*, 1987, **35**, 1070), siculine,[8] narcidine (E. Tojo, *J. Nat. Prod.*, 1991, **54**, 1387), 8-hydroxy-9-methoxycrinine (B. Sener, S. Könükol, C. Kruk and U. K. Pandit, *Nat. Prod. Lett.*, 1993, **1**, 287) and macowine (J. J. Nair, A. K. Machocho, W. E. Campbell, R. Brun, F. Viladomat, C. Codina and J. Bastida, *Phytochemistry*, 2000, **54**,

945) each possess a C8-hydroxy and a C9-methoxy group. 9-*O*-Demethyl-1,2-dihydromaritidine (J. Bastida, J. M. Llabrés, F. Viladomat, C. Codina, M. Rubiralta and M. Feliz, *Planta Med.*, 1988, **54**, 524) and cantabricine (L.-Z. Lin, S.-F. Hu, H.-B. Chai, T. Pengsuparp, J. M. Pezzuto, G. A. Cordell and N. Ruangrungsi, *Phytochemistry*, 1995, **40**, 1549) each possess a C9-hydroxy and a C8-methoxy group.

10 B. B. Kikani, J. R. McKee and M. Zanger, *Synthesis*, 1991, 176.

11 M. F. Comber and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2783.

12 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.

13 For a useful review of the Ireland–Claisen rearrangement see: P. Wipf in *Comprehensive Organic Synthesis*, vol. 5, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, pp. 840–847.

14 M. G. Banwell and M. E. Reum, in *Advances in Strain in Organic Chemistry*, ed. B. Halton, JAI Press, Greenwich, Connecticut, 1991, vol. 1, pp. 19–64; and references cited therein.

15 M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903.

16 M. G. Banwell, B. L. Flynn and S. G. Stewart, *J. Org. Chem.*, 1998, **63**, 9139.

17 J. J. Nair, A. K. Machocho, W. E. Campbell, R. Brun, F. Viladomat, C. Codina and J. Bastida, *Phytochemistry*, 2000, **54**, 945.

18 For a commentary on the generation of quaternary stereocentres using the enantioselective 1,2-reduction of an enone followed by chirality transfer *via* an Ireland–Claisen rearrangement see E. J. Corey, A. Guzman-Perez and S. E. Lazerwith, *J. Am. Chem. Soc.*, 1997, **119**, 11769.