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

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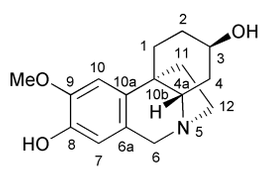
The racemic modifications of the crinine alkaloids 1 and 2 have been synthesized for the first time and by a pathway that involves silver(I)-promoted electrocyclic ring-opening of the ring-fused *gem*-dichlorocyclopropane 3 and trapping of the resulting π-allyl cation by the tethered carbamate moiety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



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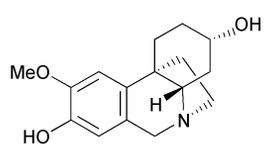

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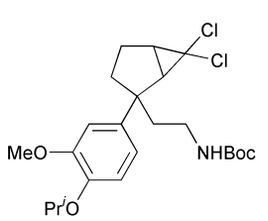

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For some time we have been interested in exploiting π-allyl cation cyclisations initiated by electrocyclic ring-opening of *gem*-dihalocyclopropanes as a method for the assembly of heterocyclic compounds[7] and now describe the application of this 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–

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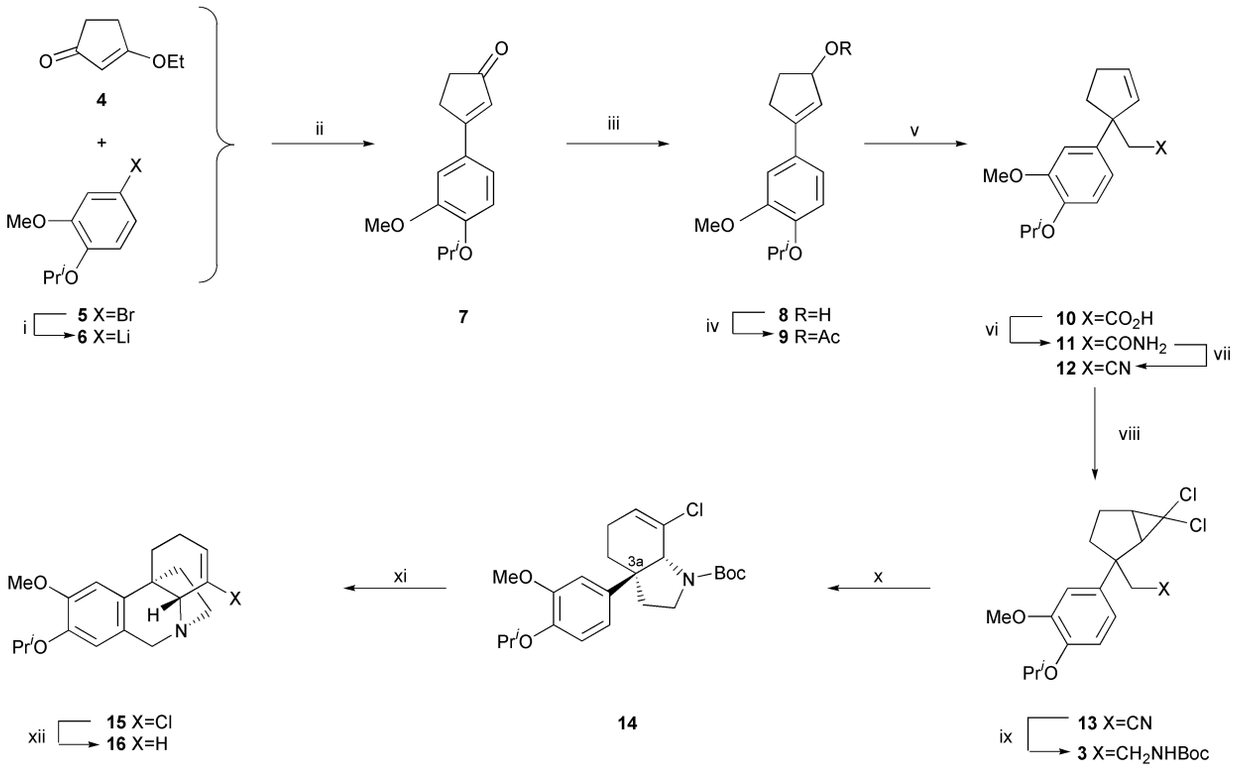


Scheme 1 *Reagents and conditions*: (i) *t*-BuLi (2.0 mol equiv.), THF, −78 °C, 10 min then compound **4** (0.84 mol equiv.), 1.5 h; (ii) *p*-TsOH (cat.), THF, 25 °C, 14 h; (iii) $NaBH_4$ (2.5 mol equiv.), $CeCl_3 \cdot 7H_2O$ (2.5 mol equiv.), 2,6-lutidine (10 mol equiv.), MeOH, 0–25 °C, 10 min; (iv) 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.

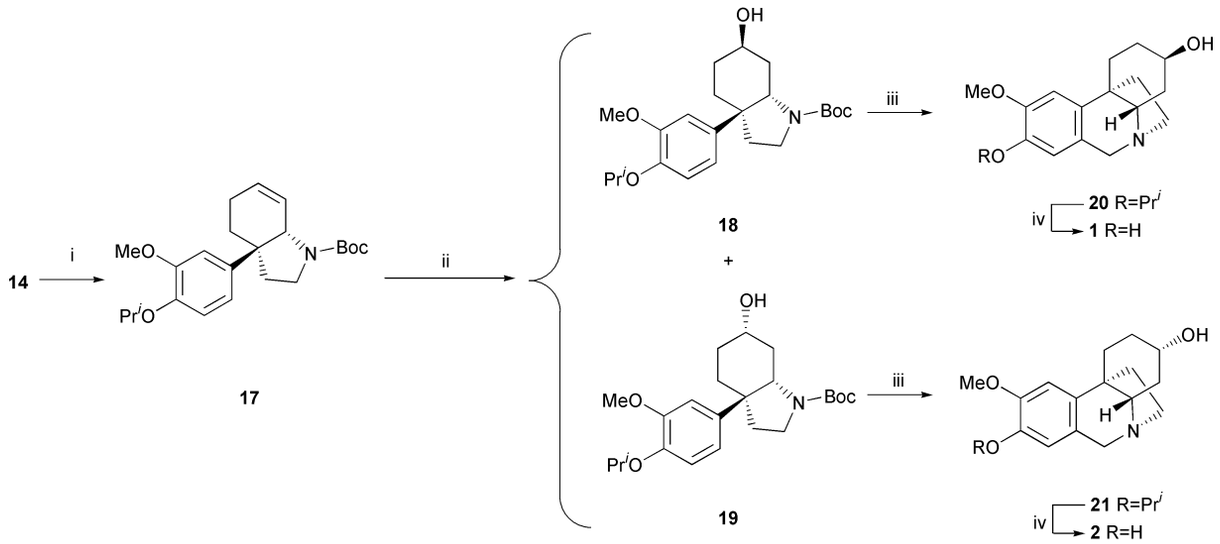
π-allyl cation cyclisation sequence with the major isomer, **3a**, being completely consumed within 8 hours and the minor isomer taking three times longer. Subjection of compound **14** to a Pictet–Spengler reaction,[15] involving its treatment with a mixture of formic acid and paraformaldehyde at 80 °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).

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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).

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