Total Synthesis of (±)-Crinane from 6,6-Dibromobicyclo[3.1.0]hexane Using a 5-Exo-Trig Radical Cyclisation Reaction to Assemble the C3a-Arylated Perhydroindole Substructure

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(±)-Crinane embodies the tetracyclic framework associated with some of the most common Amaryllidaceae alkaloids. It has now been prepared in ten steps from 6,6-dibromobicyclo[3.1.0]hexane (2). The initial step involves the thermally-induced electrocyclic ring opening of cyclopropane 3 and capture of the resulting π-allyl cation with benzylamine to give an allylic amine that is readily elaborated to the 3°-amine 10. This last compound was engaged in a 5-exo-trig free radical cyclisation reaction to give the C3a-arylated perhydroindole 11. Compound 11 was then converted, over two steps, into (±)-crinane, the hydrochloride salt of which has been subject to single-crystal X-ray analysis.
Introduction

Natural products possessing the 2,3,4,4a-tetrahydro-1\textsubscript{H},6\textsubscript{H}-5,10b-ethanophenanthridine framework \textsuperscript{1} (Figure 1) are defined, depending on their absolute configuration, as either crinine or haemanthamine-type alkaloids. Together they represent a key subclass within the substantial collection of compounds isolated from the Amaryllidaceae family of herbaceous, perennial and bulbous flowering plants.\textsuperscript{1,2}

![Figure 1](image)

Figure 1: The 2,3,4,4a-tetrahydro-1\textsubscript{H},6\textsubscript{H}-5,10b-ethanophenanthridine framework \textsuperscript{1} and the labeling of the associated rings.

A range of significant biological properties has been attributed to such compounds including, for example, anti-viral and anti-tumor properties.\textsuperscript{3} Given this and the often-limited availability of certain of these alkaloids from their natural sources, significant attention has been directed toward their synthesis.\textsuperscript{1,2,4-6} Some of these efforts have been focused on the synthesis of compound \textsuperscript{1}, a.k.a. crinane (which is not itself a natural product).\textsuperscript{4,5} Wildman reported the first synthesis of (±)-crinane in 1956,\textsuperscript{4a} the final step of which involved forming the D-ring by subjecting a C3a-arylated perhydroindole (embodying the ACD-ring system) to a Pictet-Spengler cyclization reaction. Most, if not all, subsequent syntheses have employed the same endgame. However, they often vary considerably in the way in which the C3a-arylated perhydroindole and the associated quaternary carbon are constructed. Enantioselective syntheses of crinane have also been reported, particularly in recent years.\textsuperscript{5}

We have an ongoing interest in the synthesis of crinane-type alkaloids and related compounds and established various means for assembling them, including the use of cyclopropane ring-expansion, intramolecular Alder-ene cyclisation and Claisen-type rearrangement reactions.\textsuperscript{6} In connection with another study we became interested in establishing the viability of a radical cyclisation route to Wildman’s C3a-arylated perhydroindole. Specifically, we imagined that a 2-arylated 2-cyclohexenylamine incorporating an \textit{N}-tethered ethyl radical (Figure 2) might engage in the required 5-\textit{exo-trig} process and thereby establish the critical quaternary carbon center of target \textsuperscript{1} as well as the \textit{cis}-configuration about the newly formed ring-junction. The only variant on this approach to crinane framework that we are aware of involved the
cyclization of trichloroacetamides\textsuperscript{4f} and thus forming, through an atom-transfer radical cyclization (ATRC) process,\textsuperscript{7} the corresponding and isomeric lactam. As a result subsequent reductions were required to remove the carbonyl and chlorines embodied in this product. Accordingly, we now describe the implementation of the approach shown in Figure 2 that has culminated in a total synthesis of (±)-crinane [(±)-1].\textsuperscript{8}

![Proposed radical cyclisation pathway to a C3a-arylated perhydroindole embodying the ACD-ring system of crinane (1) (R = H or amine protecting group).](image)

**Figure 2**: Proposed radical cyclisation pathway to a C3a-arylated perhydroindole embodying the ACD-ring system of crinane (1) (R = H or amine protecting group).
Results and Discussion

The simple and scalable synthetic sequence leading to a C2-arylated cyclohex-2-en-1-amine is shown in Scheme 1. Heating a neat mixture of readily available 6,6-dibromobicyclo[3.1.0]hexane (2) with a four-fold excess of benzylamine (3) at 120 °C afforded the desired (previously unreported) allylic amine 4 in 91% yield. This conversion involved electrocyclic ring-opening of the cyclopropane ring and trapping of the resulting π-allyl cation. Product 4 was reacted with neat tert-butyl dicarbonate (Boc₂O) and thus forming carbamate 5 (96%), spectroscopic analysis of which revealed the presence of rotamers. Suzuki-Miyaura cross-coupling of compound 5 with the commercially available arylboronic acid 6 using triethylamine as base gave the expected C2-arylated cyclohex-2-en-1-amine 7 (90%) and on treatment of this with trifluoroacetic acid (TFA) in dichloromethane the associated Boc-group was cleaved and so forming the 2°-amine 8 in 92% yield. The cross-coupling of amine 4 with acid 6 produced amine 8 directly but only in low yield (<10%) and thus prompting use of the illustrated reaction sequence.

Scheme 1: Synthesis of 2°-amine 8 from precursors 2 and 3.

The conversion of amine 8 into a substrate suitable for studying the proposed free radical cyclization reaction is shown in Scheme 2. Thus, compound 8 was exposed to an excess of ethylene oxide in a pressure tube at 45 °C and thereby affording, through N-alkylation, the amino-alcohol 9 in 92% yield. In this conversion quaternization at nitrogen is not observed. This could be explained by the zwitterionic nature of the species formed, which would readily fragment to regenerate compound 9. The mesylate derived from alcohol 9 was engaged in a Finkelstein reaction using sodium iodide in acetone and thus affording the anticipated halide 10 in 92% yield. Compound 10 was a rather unstable material but on exposure to n-Bu₃SnH and AIBN in toluene at 90 °C under high-dilution conditions the desired reductive radical
cyclization reaction took place. As a result the C3a-arylated perhydroindole 11 was obtained, after flash chromatographic purification, in 40% yield as a clear, colorless oil. NMR and TLC analysis of the crude product mixture arising from this cyclization reaction suggested that this had provided compound 11 as the predominant product and that it was only accompanied by traces of the reductively deiodinated-form of starting material. We thus attribute the low yields of the purified product 11 to the difficulties arising from the separation of tin-containing by-products that have a propensity to complex or react with amines.

Scheme 2: The closing stages, incorporating a 5-exo-trig radical cyclization, of a synthesis of (±)-crinane [(±)-1].

The completion of the synthesis of (±)-crinane involved the hydrogenolysis of benzylamine 11 with dihydrogen in the presence of Pearlman’s catalyst and using 10:1 v/v methanol/TFA as solvent. The spectral data acquired on 2°-amine 12 (75%) matched those reported by Padwa48 (see Supporting Information - SI - for a tabulated comparison of the relevant 13C NMR spectroscopic data sets). Reaction of the latter compound with paraformaldehyde in refluxing formic acid resulted in a Pictet-Spengler cyclization and the formation of (±)-crinane [(±)-1] that was obtained in 74% yield after chromatographic purification. All the spectroscopic data acquired on compound (±)-1 matched those reported previously by Raghavan46 (see SI for a tabulated comparison of the relevant 13C NMR spectroscopic data sets). On allowing a chloroform solution of (±)-crinane to stand at ambient temperatures crystals formed and an X-ray analysis of one of these revealed that this was the hydrochloride salt of (±)-crinane. Details of this analysis are provided in the Experimental Section and the SI.12

Conclusions
The present study has established that a free radical cyclization reaction of the type shown in Figure 2 provides a viable means for constructing the ACD-ring system of the crinane framework. Accordingly, protocols based on the conversion $2 + 3 \rightarrow 4$ shown in Scheme 1 could find utility in the synthesis of crinine and haemanthamine-type alkaloids. An interesting challenge in carrying this work forward is finding means by which cyclohex-2-en-1-amines such as 4 could be obtained in homochiral form from the meso-precursor 2. This would allow for the synthesis of natural products in either enantiomeric series.
Experimental Section

General Experimental Procedures

Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at room temperature in base-filtered CDCl3 on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For 1H NMR spectra, signals arising from the residual protioforms of the solvent were used as internal standards. 1H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual CHCl3 appearing at δH 7.26 and the central resonance of the CDCl3 “triplet” appearing at δC 77.0 were used to reference 1H and 13C NMR spectra, respectively. Infrared spectra (νmax) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F254 plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.13 with silica gel 60 (40–63 µm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.14 Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations

N-Benzyl-2-bromocyclohex-2-en-1-amine (4). A magnetically stirred mixture of cyclopropane 2 (5.00 g, 21 mmol) and benzylamine (10.0 mL, 92 mmol) was heated at 120 °C (oil bath temperature) under an atmosphere of nitrogen for 1 h. The cooled reaction mixture was diluted with ethyl acetate (50 mL) then NH4Cl (50 mL of a saturated aqueous solution) and the separated aqueous phase extracted with ethyl acetate (2 × 40 mL). The combined organics washed with brine (1 × 40 mL), dried (Na2SO4), filtered, and concentrated under reduced
pressure. The ensuing residue was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$ in 5:1 v/v hexane/ethyl acetate) gave allylic amine 4 (5.10 g, 91%) as a pale-yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.40–7.24 (complex m, 5H), 6.21 (t, $J = 4.0$ Hz, 1H), 3.86 (d, $J = 12.9$ Hz, 1H), 3.76 (d, $J = 12.9$ Hz, 1H), 3.36 (m, 1H), 2.11–2.04 (complex m, 2H), 1.92–1.75 (complex m, 3H), 1.63–1.57 (complex m, 1H) (signal due to NH group proton not observed); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.3, 132.4, 128.3, 128.2, 126.9, 126.4, 58.1, 50.8, 29.2, 27.9, 18.3; IR $\nu_{max}$ 3332, 3027, 2928, 2860, 2833, 1641, 1494, 1452, 1331, 1107, 1066, 1028, 986 cm$^{-1}$; MS (EI, 70 eV) $m/z$ 267 and 265 (M$^+$, 95 and 100%, respectively); HRMS M$^+$ calecd for C$_{13}$H$_{16}$BrN 265.0466, found: 265.0461.

**tert-Butyl Benzyl(2-bromocyclohex-2-en-1-yl)carbamate (5).** A mixture of compound 4 (5.00 g, 19 mmol) and tert-butyl dicarbonate (4.74 g, 23 mmol) was stirred at 22 °C for 4 h before being subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$ in 5:1 v/v hexane/ethyl acetate) afforded compound 5 (6.60 g, 96%) as a white, crystalline solid: mp = 78–80 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31–7.21 (complex m, 5H), 6.33 (m, 1H), 5.00 (broad s, 1H), 4.59 (d, $J = 16.5$ Hz, 1H), 4.00 (broadened d, $J = 16.5$ Hz, 1H), 2.02–2.01 (complex m, 4H), 1.64 (complex m, 2H), 1.51 (s, 3H), 1.33 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.7, 140.1, 134.3, 128.3, 128.1, 126.4, 126.2, 124.5, 85.1, 57.4, 47.6, 29.9, 28.2, 27.4, 21.0 (signal broadening and splitting evident due to the presence of carbamate rotamers); IR $\nu_{max}$ 3031, 2974, 2933, 1690, 1495, 1452, 1402, 1365, 1320, 1276, 1252, 1167, 1118, 987 cm$^{-1}$; MS (ESI, +ve) $m/z$ 390 and 388 [(M+Na)$^+$, 98 and 100%, respectively]; HRMS (M+Na)$^+$, calecd for C$_{18}$H$_{24}$BrNO$_2$Na 388.0888, found: 388.0881.

**tert-Butyl (2-(Benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-yl)(benzyl)carbamate (7).** A magnetically stirred solution of carbamate 5 (6.50 g, 17.8 mmol), commercially available benzo[d][1,3]dioxol-5-yl-boronic acid (6) (5.16 g, 35.6 mmol), PdCl$_2$dppf•CH$_2$Cl$_2$ (900 mg, 1.25 mmol) and triethylamine (18 mL) in THF/water (60 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.25 h then heated under reflux for 2 h. The reaction mixture was then cooled, poured into water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions ($R_f = 0.3$ in 5:1 v/v hexane/ethyl acetate), coupling product 7 (6.50 g, 90%) as a colorless foam. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.23–7.19 (complex m, 2H), 7.16–7.12 (complex m, 2H), 7.05 (m, 1H), 6.88–6.85 (complex m, 2H),
6.74 (m, 1H), 6.09 (broad s, 1H), 5.91 (m, 2H), 5.50 (broad s, 1H), 3.99 (d, J = 16.5 Hz, 1H), 3.85 (d, J = 16.5 Hz, 1H), 2.12–2.08 (complex m, 4H), 1.68–1.66 (complex m, 2H), 1.22 (s, 9H; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 156.0, 147.3, 146.3, 140.3, 138.7, 134.7, 130.0, 127.7, 125.9, 119.3, 107.7, 106.8, 100.6, 79.2, 52.8, 46.9, 29.2, 28.3, 27.9, 25.5, 20.9 (signal broadening and splitting evident due to the presence of carbamate rotamers); IR \(\nu_{\text{max}}\) 3028, 2975, 2933, 1690, 1605, 1504, 1488, 1444, 1404, 1365, 1278, 1245, 1225, 1167, 1118, 1040, 1002, 966, 938, 905 cm\(^{-1}\); MS (EI, 70 eV) \(m/z\) 407 (M\(^{+}\), 20%), 351 (20), 200 (100%); HRMS M\(^{+}\) calcd for C\(_{25}\)H\(_{29}\)NO\(_4\) 407.2097, found 407.2095.

2-(Benzo[d][1,3]dioxol-5-yl)-N-benzylcyclohex-2-en-1-amine (8). A magnetically stirred solution of compound 7 (6.50 g, 16 mmol) in anhydrous dichloromethane (100 mL) maintained at 22 °C under an atmosphere of nitrogen was treated with trifluoroacetic acid (15 mL). The resulting solution stirred for 1.25 h then treated with sodium hydroxide (4 M aqueous solution) so as to attain pH 14. The separated aqueous phase was extracted with dichloromethane (3 \(\times\) 75 mL) and the combined organic phases then dried (Na\(_2\)SO\(_4\)), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (\(R_f = 0.4\) in 3:1 v/v hexane/ethyl acetate) amine 8 (4.50 g, 92%) as a clear, colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31–7.21 (complex m, 5H), 6.90–6.81 (complex m, 1H), 6.78–6.71 (complex m, 2H), 5.97 (t, J = 4.0 Hz, 1H), 5.94 (s, 2H), 3.84 (d, J = 13.2 Hz, 1H), 3.68 (d, J = 13.2 Hz, 1H), 3.63 (m, 1H), 2.23–2.13 (complex m, 2H), 2.03–1.96 (complex m, 1H), 1.84–1.72 (complex m, 1H), 1.73–1.60 (complex m, 2H), 1.45 (broad s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 147.6, 146.4, 140.4, 139.1, 135.4, 128.2, 128.1, 127.5, 126.7, 119.3, 108.0, 106.8, 100.8, 52.1, 51.3, 27.3, 26.1, 17.6; IR \(\nu_{\text{max}}\) 3026, 2932, 2829, 1752, 1604, 1502, 1488, 1439, 1244, 1218, 1102, 1039, 936 cm\(^{-1}\); MS (EI, 70 eV) \(m/z\) 307 (M\(^{+}\), 10%), 279 (31), 200 (100), 91 (52); HRMS M\(^{+}\) calcd for C\(_{20}\)H\(_{21}\)NO\(_2\) 307.1572, found 307.1573.

2-((2-(Benzo[d][1,3]dioxol-5-yl)cyclohex-2-en-1-yl)(benzyl)amino)ethan-1-ol (9). A solution of amine 8 (4.00 g, 13 mmol) in methanol (20 mL) was distributed equally between two sealable pressure tubes and these then cooled to 0 °C before ethylene oxide (5 mL, 100 mmol) was added to each tube. The tubes were sealed and the contents of each heated at 45 °C for 8 h before being re-cooled to 0 °C, unsealed and then allowed to warm to 22 °C over 18 h. The residue in each tube was transferred, with the aid of ethyl acetate, to a round-bottomed flask and resulting solution concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:3 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (\(R_f = 0.4\) in 3:1 v/v hexane/ethyl acetate), amino-
alcohol 9 (4.20 g, 92%) as a clear, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29–7.24 (complex m, 3H), 7.02–7.00 (complex m, 2H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.61–6.57 (complex m, 2H), 6.05 (m, 1H), 5.95 (dd, $J = 7.4$ and 1.5 Hz, 2H), 3.83 (broad s, 1H), 3.75 (d, $J = 13.0$ Hz, 1H), 3.51 (m, 1H), 3.40 (d, $J = 13.0$ Hz, 1H), 3.23 (m, 1H), 2.71 (m, 1H), 2.58 (m, 1H), 2.20–2.15 (complex m, 2H), 2.00–1.75 (complex m, 4H), 1.66–1.60 (complex m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.3, 146.2, 139.7, 139.2, 135.6, 130.4, 129.2, 128.1, 127.1, 120.0, 107.7, 107.5, 100.8, 58.3, 54.8, 53.5, 50.8, 25.9, 21.6, 21.0; IR $\nu_{\text{max}}$ 3467, 3026, 2932, 1604, 1502, 1487, 1438, 1370, 1244, 1222, 1123, 1042, 935 cm$^{-1}$; MS (EI, 70 eV) $m/z$ 351 (M$^+$, 7%), 320 (100), 201 (73), 120 (70), 91 (56); HRMS M$^+$ calcd for C$_{22}$H$_{25}$NO$_3$ 351.1834, found 351.1820.

2-(Benzo[d][1,3]dioxol-5-yl)-N-benzyl-N-(2-iodoethyl)cyclohex-2-en-1-amine (10). Step i: A magnetically stirred solution of amino-alcohol 9 (3.90 g, 11 mmol) in anhydrous THF (30 mL) maintained at 22 °C under an atmosphere of nitrogen was treated with triethylamine (2 mL, 14 mmol) then methanesulfonyl chloride (1.50 mL, 14.0 mmol). The resulting solution stirred for 2 h before being filtered through a pad of diatomaceous earth that was washed with Et$_2$O (50 mL). The combined filtrates were concentrated under reduced pressure to give a light-yellow oil.

Step ii: A magnetically stirred solution of the oil obtained from step i in acetone (40 mL) maintained at 22 °C under an atmosphere of nitrogen was treated with sodium iodide (8.00 g, 53.3 mmol). The ensuing mixture was stirred for 3 h then filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 × 60 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained dissolved in ethyl acetate (100 mL) and the solution so-formed washed with Na$_2$S$_2$O$_3$ (50 mL of a 5 % w/v aqueous solution) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to afford the title iodide 10 (4.70 g, 92%) as a pale-yellow oil, $R_f = 0.7$ (in 5:1 v/v hexane/ethyl acetate). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26–7.20 (complex m, 3H), 7.03–7.01 (complex m, 2H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.70–6.67 (complex m, 2H), 6.01 (m, 1H), 5.98 (s, 2H), 3.80 (m, 1H), 3.67 (d, $J = 13.5$ Hz, 1H), 3.52 (d, $J = 13.5$ Hz, 1H), 2.88–2.73 (complex m, 3H), 2.37 (m, 1H), 2.17–2.13 (complex m, 2H), 1.98 (m, 1H), 1.82–1.68 (complex m, 2H), 1.59 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.0, 146.1, 140.1, 139.8, 136.2, 130.1, 128.8, 128.0, 127.0, 120.3, 107.9, 107.5, 100.7, 57.0, 55.0, 53.9, 25.9, 23.1, 21.0, 5.6; IR $\nu_{\text{max}}$ 3025, 2931, 2833, 1604, 1502, 1487, 1436, 1244, 1222, 1196, 1039, 936 cm$^{-1}$; MS (EI, 70 eV) $m/z$ 461 (M$^+$, 5%), 433 (13), 320 (40), 300 (42), 200 (100), 91(56); HRMS M$^+$ calcd for C$_{22}$H$_{24}$INO$_2$ 461.0852, found 461.0840.
This rather light-sensitive and otherwise unstable material was used immediately in the next step of the reaction sequence.

cis-3a-(Benzo[d][1,3]dioxol-5-yl)-1-benzyloctahydro-1H-indole (11). A magnetically stirred solution of iodide 10 (2.00 g, 4.34 mmol) in anhydrous toluene (250 mL) maintained at 90 °C under an atmosphere of nitrogen was treated with AIBN (290 mg, 1.77 mmol, added in three equal portions over 2 h) then, dropwise over 2.5 h, with a solution of tri-n-butyltin hydride (1.92 mL, 7.2 mmol) in anhydrous toluene (50 mL). The reaction mixture thus obtained was then cooled, concentrated under reduced pressure and the ensuing residue dissolved in ethyl acetate (100 mL). The resulting solution was stirred with KF (40 mL of a 1 M aqueous solution) for 0.66 h and the ensuing suspension was filtered through a pad of diatomaceous earth that was washed with ethyl acetate (100 mL). The combined filtrates were washed with brine (1 x 100 mL) before being dried (Na2SO4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:7 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (Rf = 0.5 in 5:1 v/v hexane/ethyl acetate), the title compound 11 (580 mg, 40%) as a clear, colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.41 (m, 2H), 7.35 (m, 2H), 7.28 (m, 1H), 6.94 (broadened s, 1H), 6.89 (dd, J = 8.2 and 1.9 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.95 (s, 2H), 4.17 (d, J = 13.3 Hz, 1H), 3.20 (d, J = 13.3 Hz, 1H), 3.09 (m, 1H), 2.98 (broad t, J = 2.7 Hz, 1H), 2.30 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.85–1.80 (complex m, 3H), 1.69 (m, 1H), 1.55 (m, 1H), 1.42–1.38 (complex m, 1H), 1.31–1.24 (complex m, 1H); 13C NMR (100 MHz, CDCl3) δ 147.5, 145.0, 141.4, 140.5, 128.3, 128.1, 126.5, 119.6, 107.7, 107.6, 100.7, 66.0, 57.8, 51.0, 47.6, 40.6, 35.0, 24.1, 23.0, 20.5; IR νmax 3027, 2930, 2855, 2797, 1607, 1506, 1487, 1452, 1376, 1342, 1233, 1041, 937 cm⁻¹; MS (EI, 70 eV) m/z 335 (M⁺, 100%), 334 (92), 91 (76); HRMS M⁺ calcd for C22H25NO2 335.1885, found 335.1888.

cis-3a-(Benzo[d][1,3]dioxol-5-yl)octahydro-1H-indole (12). A magnetically stirred mixture of benzylamine 11 (160 mg, 0.48 mmol), Pd(OH)2 (50 mg, 20% w/w on charcoal) and trifluoroacetic acid (1 mL, 13 mmol) in methanol (10 mL) was maintained under a balloon of hydrogen for 10 h then flushed with nitrogen. The mixture thus obtained was concentrated under reduced pressure and the residue treated with NaOH (20 mL of a 20% w/v aqueous solution) and methanol (20 mL) before being filtered and the filtrate concentrated under reduced pressure. The ensuing residue was partitioned between water (30 mL) and chloroform (50 mL). The separated aqueous phase was extracted with chloroform (2 x 30 mL) then the combined organic phases dried (Na2SO4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:10 v/v ammonia-saturated methanol/chloroform elution) to afford, after concentration of the appropriate
fractions \((R_f = 0.7)\), the title compound **12** (88 mg, 75%) as a clear, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.86 \((d, J = 1.8\) Hz, 1H), 6.80 \((dd, J = 9.5\) and 1.8\) Hz, 1H), 6.75 \((d, J = 9.5\) Hz, 1H), 5.91 \((s, 2H)\), 3.40 \((t, J = 4.3\) Hz, 1H), 3.15–3.08 \((\text{complex m, 1H})\), 3.01–2.95 \((\text{complex m, 1H})\), 2.16 \((\text{broad s, 1H})\), 2.02–1.95 \((\text{complex m, 1H})\), 1.91–1.82 \((\text{complex m, 1H})\), 1.82–1.72 \((\text{complex m, 3H})\), 1.70 \((m, 1H)\), 1.52–1.42 \((\text{complex m, 3H})\), 1.26–1.20 \((\text{complex m, 1H})\); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 147.5, 145.2, 141.0, 119.3, 107.7, 107.5, 100.8, 61.0, 47.9, 43.1, 41.4, 33.9, 26.3, 22.1, 21.1; IR \(\nu_{\text{max}}\) 3325, 2930, 1687, 1610, 1506, 1488, 1432, 1233, 1204, 1128, 1039, 934 \(\text{cm}^{-1}\); MS (EI, 70 eV) \(m/z\) 245 \((M^{+\bullet}, 100%)\), 244 \((96)\); HRMS \(M^{+\bullet}\) calcd for C\(_{15}\)H\(_{19}\)NO\(_2\) 245.1416, found: 245.1416.

\((\pm)-\)Crinane \([(\pm)-1]\). A magnetically stirred solution of amine **12** (70 mg, 0.29 mmol) in formic acid (10 mL) maintained at 22 °C under a nitrogen atmosphere was treated with paraformaldehyde (150 mg). The resulting mixture was heated under reflux for 18 h then cooled and concentrated under reduced pressure. The residue thus obtained was dissolved in chloroform (20 mL) and the resulting solution treated with NaOH (20% w/v aqueous solution) so as to attain pH 14. The separated aqueous phase was extracted chloroform \((2 \times 50\) mL) and the combined organic phases were dried \((\text{Na}_2\text{SO}_4)\) before being filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash chromatography \((\text{silica, 1:10 v/v ammonia-saturated methanol/chloroform})\) to afford, after concentration of the relevant fractions \((R_f = 0.4)\), compound \((\pm)-1\) (54 mg, 74%) as a clear, colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.60 \((s, 1H)\), 6.37 \((s, 1H)\), 5.79 \((s, 2H)\), 4.34 \((d, J = 16.6\) Hz, 1H), 3.75 \((d, J = 16.6\) Hz, 1H), 3.40 \((m, 1H)\), 2.88–2.76 \((\text{complex m, 2H})\), 2.25–2.15 \((\text{complex m, 2H})\), 1.82 \((m, 1H)\), 1.73–1.64 \((\text{complex m, 3H})\), 1.56–1.38 \((\text{complex m, 2H})\), 1.17 \((m, 2H)\); \(^{13}\)C NMR \((100 MHz, CDCl_3)\) \(\delta\) 146.3, 145.6, 145.6, 140.9, 123.9, 106.0, 103.0, 100.5, 67.2, 61.0, 51.5, 42.7, 36.9, 28.4, 26.6, 23.7, 21.2; IR \(\nu_{\text{max}}\) 2932, 2854, 1504, 1481, 1242, 1232, 1094, 1041, 1000, 938, 909 \(\text{cm}^{-1}\); MS (EI, 70 eV) \(m/z\) 257 \((M^{+\bullet}, 100\%)\), 228 \((70)\); HRMS \(M^{+\bullet}\) calcd for C\(_{16}\)H\(_{19}\)NO\(_2\) 257.1416, found 257.1415.

The hydrochloride salt of \((\pm)-\)crinane was obtained by allowing a chloroform solution of the free base to stand at ambient temperatures in an open vessel until crystals formed. One of these crystals was subjected to single-crystal X-ray analysis (see below and in the SI for details).

*Crystallographic Study on Compound \((\pm)-1\text{•HCl}\)*

**Crystal data**

**Compound \((\pm)-1\text{•HCl}\):** C\(_{16}\)H\(_{19}\)NO\(_2\)•HCl, \(M = 293.79\), \(T = 200(1)\) K, triclinic, space group P1, \(Z = 2\), \(a = 7.0293(3)\), \(b = 9.9371(7)\), \(c = 11.3882(8)\) Å, \(\alpha = 111.307(3)^\circ\), \(\beta = 101.280(4)^\circ\), \(\gamma =\)
92.617(4), \( V = 720.83(8) \) Å³, \( D_x = 1.354 \) g.cm\(^{-3}\), 3294 unique data (\( 2 \theta_{\text{max}} = 55^\circ \)), 2597 with \( I > 2.0\sigma(I) \); \( R = 0.042, R_w = 0.110, S = 1.00 \).

**Structure Determination**

Images were measured on a Nonius Kappa CCD diffractometer (MoK\( \alpha \), graphite monochromator, \( \lambda = 0.71073 \) Å) and data extracted using the DENZO package.\(^{15} \) Structure solution was by direct methods (SIR92).\(^{16} \) The structure of compound (±)-1•HCl was refined using the CRYSTALS program package.\(^{17} \) Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC Deposition number 1840264). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**ASSOCIATED CONTENT**

**Supporting Information**

Cif and anisotropic displacement ellipsoid plot from the single-crystal X-ray analysis of compound (±)-1•HCl. \(^1\text{H} \) and \(^{13}\text{C} \) NMR spectra of compounds 4, 5, 7-12 and (±)-1. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions from all of the authors. All of the authors have given approval to the final version of the manuscript.

**Notes**

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