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An Efficient Synthesis of (±)-Crinane Using an Intramolecular Azide-Olefin Cycloaddition

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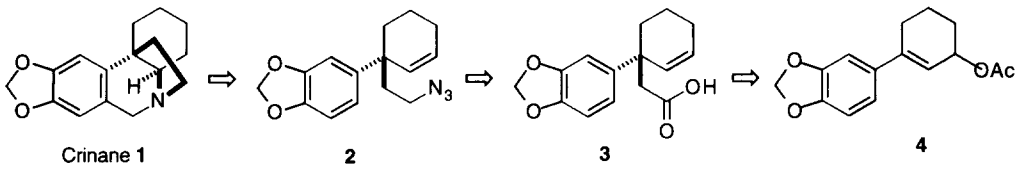
Abstract: Refluxing 3-(2-azidoethyl)-3-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene (**2**) in toluene for 24 hours afforded 3a-[3,4-methylenedioxy)phenyl]-3,3a,4,5,6,7-hexahydro-2*H*-indole (**12**) in quantitative yield. This reaction proceeds by intramolecular 1,3-dipolar cycloaddition of the azide onto the alkene followed by loss of nitrogen from the triazoline intermediate to give an imine. Reduction of the imine **12** with sodium cyanoborohydride in acetic acid / THF gave (3aR*, 7aR*)-3a-[3,4-methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (**13**). Warming **13** with Eschenmoser's salt provided (±)-crinane (**1**). The synthesis of (±)-crinane (**1**) from cyclohexenone was accomplished in 8 steps in 23% overall yield.

INTRODUCTION

The Amaryllidaceae alkaloids have attracted considerable interest from organic chemists due to their diverse structures and wide range of biological activities.[1] We became interested in these alkaloids while studying the generality of the intramolecular azide-olefin cycloaddition reaction (IAOC) for the synthesis of nitrogen-containing natural products.[2-3] Even though crinane (**1**) is not a natural alkaloid, it has been the subject of previous synthetic studies[4] because it has the basic skeleton of the 5,10b-ethanophenanthridine class of Amaryllidaceae alkaloids (e.g., crinine[5a] and pretazettine[5b]). We report herein a short and efficient synthesis of crinane (**1**) in racemic form.

Our retrosynthetic plan is outlined in Scheme 1. Heating **2** should cause 1,3-dipolar cycloaddition, producing a triazoline, which should lose nitrogen to give an imine. Reduction of the imine to an amine followed by Pictet-Spengler[6] reaction should afford (±)-crinane (**1**). The requisite azido-olefin **2** was

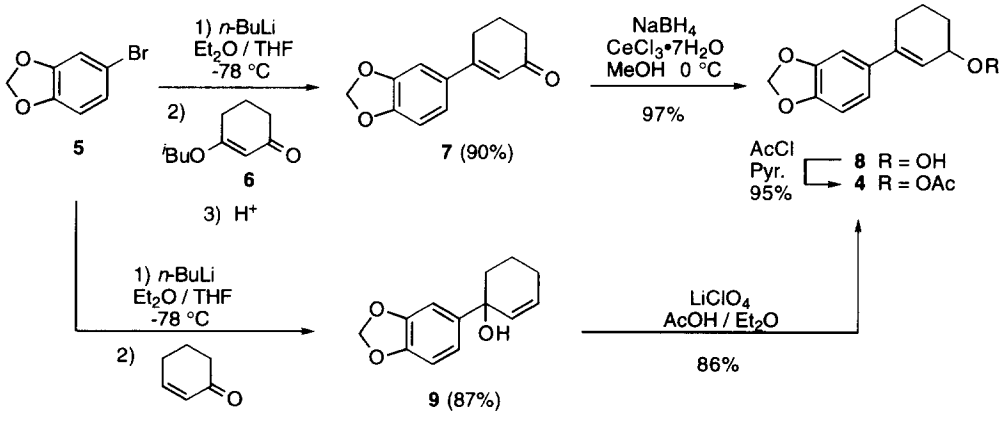


Scheme 1. Synthetic Plan for (±)-Crinane (**1**)

anticipated to be available from the carboxylic acid **3** which, in turn, may be prepared by performing an Ireland-Claisen rearrangement on the acetate **4** as reported by Keck.[4d]

RESULTS AND DISCUSSION

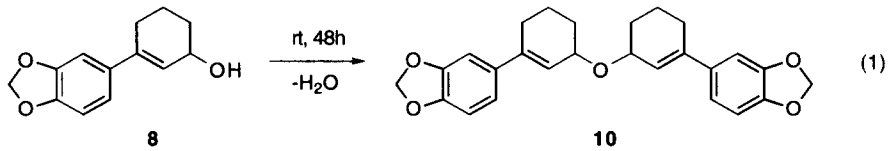
The acetate **4** was prepared by two routes as shown in Scheme 2, the first involving modifications of Keck's methodology,[4d,7] the second involving some recent lithium perchlorate promoted chemistry. Metal-halogen exchange of 4-bromo-1,2-(methylenedioxy)benzene (**5**)[4d] with *n*-butyllithium at -78 °C in an ether / THF mixture[8] gave the aryllithium species. Addition of the aryllithium to 3-isobutoxy-2-cyclohexene-1-one[9] (**6**) followed by aqueous acidic workup afforded enone **7**[4d] in 90% yield. Reduction of enone **7** under the



Scheme 2. Synthesis of the Acetate **9**

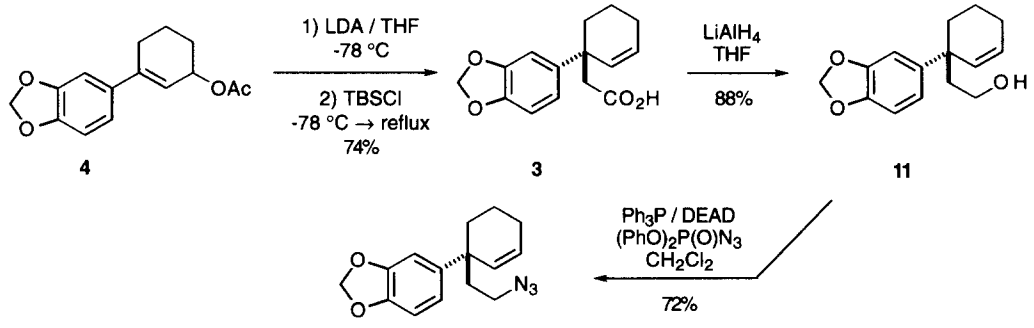
conditions developed by Luche[10] provided the allylic alcohol **8**[4d] in 97% yield (unpurified). The alcohol **8** was usually advanced to the acetate **4**[4d] without purification since, upon standing at room temperature, **8** forms the symmetrical ether **10** (equation 1). Acetylation of **8** gave the acetate **4**. An alternative method for synthesizing the allylic acetate **4** involved the lithium perchlorate promoted substitution reaction of allylic

alcohols and allylic acetates.[11] Alcohol **9** was prepared by addition of the aryllithium derived from **5** to cyclohexenone. Treatment of **9** with acetic acid in ether containing lithium perchlorate provided the desired acetate **4** in 86% yield. This two step protocol, although comparable in yield to the three step sequence, saves a step in the synthetic plan and circumvents proceeding through the unstable alcohol **8**.



8 **10** (1)

Treatment of the acetate **4** with LDA at -78 °C followed by *t*-butyldimethylchlorosilane (TBSCl) according to the procedure of Keck[4d] afforded the carboxylic acid **3** by an Ireland Claisen rearrangement in 74% yield (Scheme 3). Reduction of the acid **3** with lithium aluminum hydride proceeded readily in refluxing THF to provide the alcohol **11** in 88% yield. A one-pot transformation of the alcohol **11** to the azide **2** in 76% yield was accomplished using the Mitsunobu conditions developed by Bose and co-workers.[12]



4 **3** **11** **2**

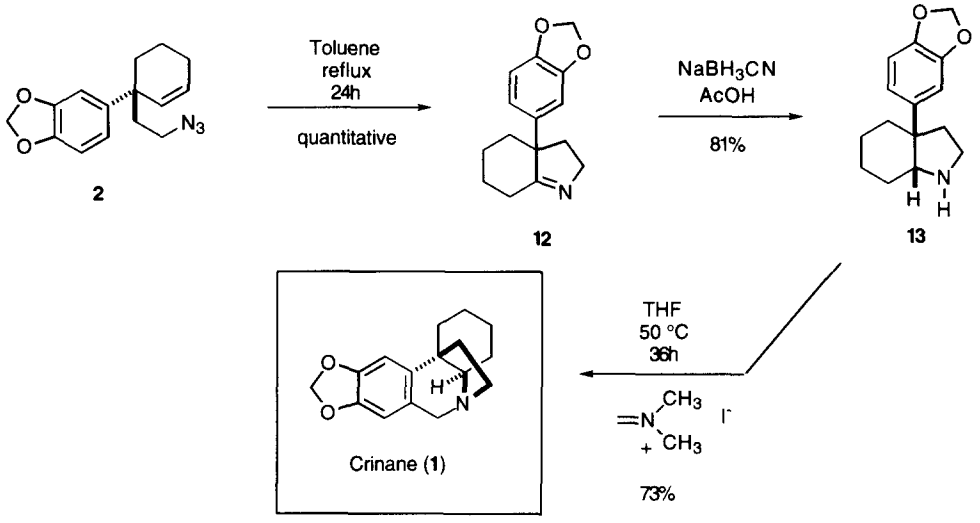
Scheme 3. Synthesis of the Key Azide **2**

Thermolysis of the azide **2** in benzene in a sealed tube (130 °C, 12 h) provided the desired imine **12** in quantitative yield (Scheme 4). A more convenient method for preparing imine **12** involved refluxing azide **2** in toluene under an atmosphere of nitrogen for 24 h. The yield using this procedure was also quantitative. Reduction of the imine **12** with $NaCNBH_3$ in acetic acid occurred stereoselectively to provide the *cis*-octahydroindole **13** in 81% yield after chromatography. Spectra of the hydrochloride salt of **13** matched those

reported in the literature.[4d] Warming the amine **13** with Eschenmoser's salt in THF for 48 h afforded (±)-crinane (**1**) in 73% yield whose spectral data were identical to those reported in the literature.[4d]

CONCLUSION

An efficient synthesis of (±)-crinane (**1**) (8 steps in 23% overall yield) was achieved using an intramolecular azide olefin reaction as the key carbon-nitrogen bond forming reaction. The *cis*-octahydroindole subunit is found in a number of other alkaloid families. We are currently pursuing the synthesis of more complex alkaloids containing this structural subfeature.



Scheme 4. Final Stage of (±)-Crinane Synthesis

EXPERIMENTAL SECTION

General. Reagents and starting materials were obtained from commercial suppliers, and were used without further purification. Commercial *n*-butyllithium was purchased from Lithco and was titrated with diphenylacetic acid prior to use. Tetrahydrofuran and ether were distilled from sodium / benzophenone ketyl. Methylene chloride and triethylamine were distilled from calcium hydride. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to flash column chromatography on silica gel (230-400 mesh) unless otherwise noted. Deactivated silica gel was prepared from flash silica gel and hexamethyldisilazane.[13] Combustion analyses were performed by Spang Microanalytical Laboratories (Eagle Harbor, Michigan) or by the microanalytical facility operated by the University of Michigan. Mass spectra (MS) were obtained on a Finnigan 4500 GC/MS-EI-CI system. High resolution mass spectroscopy (HRMS)

was carried out on a VG-Analytical 70-250 high resolution mass spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker AM-300 (300 MHz) or a Bruker WM-360 (360 MHz) spectrometer in deuterochloroform. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker WM-360 (90 MHz) or a Bruker AM-300 (75 MHz) spectrometer in deuterochloroform. J-Modulated Spin Echo Fourier Transform (JMOD) ^{13}C NMR experiments are reported as (+) (for CH_3 and CH) or (-) (for CH_2 and C) and are used as an alternative to off resonance decoupling experiments.

3-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-one (7). Prepared by a modification of a procedure published by Keck.[4d] *n*-BuLi (50 mL of a 2.20 M solution in hexanes, 0.11 mol) was added in a dropwise fashion to a cold (-78 °C) solution of 4-bromo-1,2-(methylenedioxy)benzene (**5**)[4d] (20.0 g, 99.5 mmol) in ether (200 mL) and THF (100 mL) such that the temperature of the solution (internal thermometer) did not rise above -65 °C. After the mixture was stirred for 30 min at -78 °C, a solution of 3-isobutoxy-2-cyclohexen-1-one (**6**)[9] (18.4 g, 109 mmol) in ether (20 mL) was added in a dropwise fashion. After warming the solution to 23 °C over two hours, 10 % HCl (100 mL) was slowly added. After stirring 1 h, the layers were separated and the aqueous layer was extracted with ether (3 X 100 mL). The combined organic phases were washed with water (100 mL), saturated $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), then dried ($MgSO_4$) and concentrated to give a white solid. Recrystallization from ether/hexane (4 : 1) gave 19.3 g (90 %) of the title compound, mp 101 - 102 °C (lit. mp 100-103 °C[4d]) which had ^{1}H NMR, ^{13}C NMR, and IR spectral data consistent with the literature values.[4d]

3-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-ol (8). Luche's reduction method[10] was used to prepare this compound, which had been previously prepared by Keck with $NaBH_4$ alone.[4d] Sodium borohydride (1.00 g, 26.4 mmol) was added in 0.25 g portions over 5 min to a cool (0 °C) suspension of enone **7** (10.0 g, 46.2 mmol) and $CeCl_3 \cdot 7H_2O$ (11.4 g, 46.2 mmol) in MeOH (27 mL). The solution was stirred for 45 min and water (75 mL) was added. The aqueous layer was extracted with ether (3 X 100 mL) and the combined organic phases were washed with water (2 X 75 mL) and brine (75 mL). After drying ($MgSO_4$), the organic phases were concentrated to give 9.77 g (97 %) of the title compound as a clear oil which solidified on standing in the freezer overnight. This compound was found to decompose to the symmetrical ether **10** in the freezer over several months or more quickly (48 h) when kept at room temperature. R_f = 0.23 (15 % EtOAc / hex eluted three times). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (s, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.02 (m, 1 H), 5.95 (s, 2 H), 4.37 (m, 1 H), 2.40 (m, 2 H), 1.93 (m, 2 H), 1.65 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.42, 146.85, 139.24, 135.76, 125.70, 118.76, 107.87, 105.86, 100.88, 66.11, 31.50, 27.58, 19.37; IR (KBr) 3354 (s), 1643 (w), 1606 (w), 1504 (s) 1443 (s), 1244 (s), 1218 (s), 1158 (m), 1039 (s), 935 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 218 (M^+, 100.0), 200 (23.5), 175 (28.8), 160 (25.5), 141 (10.7), 135 (21.7); HRMS calculated for $C_{13}H_{14}O_3$; 218.0943, found; 218.0943. For an analytically pure sample, the above reaction was run on a smaller scale. Thus **7** (1.98 g, 9.16 mmol), $CeCl_3 \cdot 7H_2O$ (2.26 g, 9.16

mmol) and $NaBH_4$ (35.0 mg, 9.16 mmol) were combined for 45 min in 27 mL MeOH and worked up as above. Flash column chromatography (SiO_2, gradient solvent system, 15 % - 25 % EtOAc / hex) furnished 1.78 g (89 %) of **8** as a white solid (mp 64 - 66 °C). Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found: C, 71.55; H, 6.44.

3,3'-[(3,4-Methylenedioxy)phenyl]-2,2'-oxybiscyclohexene (10). The alcohol **8** was allowed to stand without solvent at room temperature for 48 h, producing a 1 : 1 mixture of diastereomers of the title compound, (mp 120-123 °C), R_f = 0.20 (10 % EtOAc / hex): ^{1}H NMR ($CDCl_3$, 300 MHz)δ 6.93 (s, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 6.06 (s, 0.5 H), 6.03 (s, 0.5 H), 5.94 (s, 2 H), 2.38 (m, 2 H), 1.93 (m, 2 H), 1.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD)δ 147.72 (-), 146.90 (-), 139.68 (-), 139.52 (-), 136.28 (-), 124.82 (+), 118.98 (+), 107.98 (+), 106.16 (+), 101.01 (-), 71.74 (+), 29.48 (-), 29.04 (-), 27.94 (-), 20.06 (-), 19.74 (-); IR (KBr) 1609 (w), 1501 (s), 1444 (s), 1242 (s), 1219 (s), 1036 (s), 934 (m), 803 (s) cm^{-1}; MS (EI, 70 eV) *m/v* (rel int) 418 (M^+, 2.9), 203 (13.9), 202 (100.0), 201 (46.9), 200 (49.3), 169 (7.5), 135 (22.3), 115 (9.3), 79 (7.4), 55 (6.2). Anal. Calcd. for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.80; H, 6.18.

1-Acetyloxy-3-[3,4-(methylenedioxy)phenyl]cyclohex-2-ene (4).[4d] Acetyl chloride (3.42 g, 43.5 mmol) was added to a cool (0 °C) solution of alcohol **8** (4.7 g, 21.8 mmol) and pyridine (3.79 g, 47.9 mmol) in CH_2Cl_2 (50 mL). After 1 h at 0 °C, water (100 mL) and ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with ether (2 X 100 mL). The combined organic phases were washed with water (2 X 100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated to give 5.27 g (93 %) of the title compound as a clear oil which crystallized in the freezer, R_f = 0.49 (25 % EtOAc / hex). The ^{1}H NMR, ^{13}C NMR, and IR spectral data were consistent with the literature values.[4d] See below for an alternative synthesis.

1-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-ol (9). *n*-BuLi (26.1 mL of a 2.0 M in hexane, 52.2 mmol) was added in a dropwise fashion to a cold (-78 °C) solution of 4-bromo-1,2-(methylenedioxy)benzene (**5**) (10.0 g, 49.7 mmol) in ether (100 mL) and THF (50 mL) such that temperature of the solution (internal thermometer) did not rise above -70 °C (approx 15 min) . After 20 min at -78 °C, a solution of cyclohex-2-en-1-one in ether (10 mL) was added in a dropwise fashion. The solution was warmed slowly (over 4 h) to 23 °C and quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with ether (3 X 75 mL), and the combined organic phases were washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated to give a yellow oil. Chromatography (10 % EtOAc / hex) gave 9.40 g (87 %) of the title compound as a white solid, (mp 54.5 - 55.5 °C), R_f = 0.35 (25 % EtOAc / hex): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.0 (d, J = 1.9 Hz, 1 H), 6.92, (dd, J = 1.9, 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.99 (dt, J =

3.4, 10.0 Hz, 1 H), 5.93 (s, 2 H), 5.74 (d, J = 10.0 Hz, 1 H), 2.20-1.53 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.40 (-), 146.25 (-), 142.16 (-), 132.32 (+), 130.30 (+), 107.50 (+), 106.50 (+), 100.80 (-), 72.04 (-), 39.54 (-), 24.88 (-), 19.15 (-); IR (melt) 3404 (s), 1645 (w), 1609 (w), 1484 (s), 1433 (s), 1349 (m), 1239 (s), 1039 (s), 935 (s), 811 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 218 (M^+, 49.9), 190 (41.0), 189 (31.3), 160 (40.9), 149 (26.2), 135 (100.0), 132 (25.4), 122 (23.2), 121 (23.5), 91 (10.9), 77 (15.6), 55 (14.4); HRMS calculated for $C_{13}H_{14}O_3$; 218.0943, found; 218.0940. Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found: C, 71.57; H, 6.41.

1-Acetyloxy-3-[3,4-(methylenedioxy)phenyl]cyclohex-2-ene (4). Lithium perchlorate (1.0 g, 9.4 mmol) was added at 0 °C to a solution of the alcohol **9** (0.54 g, 2.47 mmol) and acetic acid (0.74 g, 12.4 mmol) in 10 mL of ether. After 5 min, water (25 mL) was added and the mixture was extracted with EtOAc (3 X 25 mL). The organic phases were combined and washed with water (2 X 25 mL) and brine (25 mL), then dried (Na_2SO_4). Chromatography (gradient 5-10% EtOAc / hex) provided 0.55 g (86%) of the title compound, which had spectral data consistent with that given above.

[1-(3,4-Methylenedioxy)phenylcyclohex-2-enyl]acetic Acid (3). Prepared according to the procedure published by Keck.[4d] HMPA (3.2 mL, 5 % by volume) was added to a solution of LDA [generated from *n*-BuLi (8.86 mL of a 2.3 M solution in hexanes, 20.4 mmol) and diisopropylamine (2.85 mL) in THF (19 mL)] at -78 °C. Acetate **4** (4.82 g, 18.52 mmol) in THF (70 mL) was then added. After 15 min, *t*-butyldimethylsilyl chloride (4.12 g, 27.3 mmol) in THF (10 mL) was added. The solution was allowed to warm to room temperature over 1 h, then refluxed for 15 h. Water (10 mL) and acetic acid (10 mL) were then added to the solution. After stirring for 3 h, the aqueous phase was separated extracted with ether (3 X 75 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated. Chromatography (5 % THF / hex) afforded 340 mg of the starting acetate **4**. Further elution gave 3.20 g (66 %, 74 % based on recovered starting material) of the title compound as a white solid, mp 127-128 °C (lit. mp 127 °C[4d]) which had ^1H NMR, ^{13}C NMR, IR, and mass spectral data consistent with the literature values.[4d]

3-(2-Hydroxyethyl)-3-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene (11). A solution of the acid **3** (2.67 g, 10.26 mmol) in THF (15 mL) was added in a dropwise fashion to a cool (0 °C) suspension of $LiAlH_4$ (0.39 g, 10.26 mmol) in dry THF (100 mL). The mixture was warmed to reflux for 2 h, then cooled to 0 °C and carefully treated with water (100 mL) and then 12 N HCl (2 mL). The aqueous layer was extracted with ether (3 X 75 mL) and the combined organic phases were washed with water (2 X 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), then dried ($MgSO_4$) and concentrated. Chromatography (25 % EtOAc / hex) afforded 2.33 g (92 %) of the title compound as a clear oil, R_f = 0.21 (25 % EtOAc / hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.85 (s, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.89 (m,

1 H), 5.82 (d, J = 10.3 Hz, 1 H), 3.58 (m, 2 H), 2.10-1.40 (series of multiplets, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.53 (-), 146.36 (-), 141.77 (-), 132.57 (+), 128.34 (+), 120.00 (+), 107.63 (+), 107.45 (+), 100.78 (-), 59.64 (-), 45.24 (-), 41.55 (-), 37.37 (-), 25.27 (-), 18.65 (-); IR (neat) 3336 (m), 1609 (w), 1503 (s), 1486 (s), 1432 (m), 1242 (s), 1040 (s), 934 (m), 810 (m) cm^{-1}; MS (EI, 70 eV) *m/v* (rel int) 246 (M^+, 8.8), 201 (100.0), 135 (37.1), 128 (16.8), 115 (15.8), 86 (27.2), 84 (42.6), 79 (28.6), 77 (16.2), 51 (29.8), 41 (18.9); HRMS calculated for $C_{15}H_{18}O_3$; 246.1246, found; 246.1261.

3-(2-Azidoethyl)-3-[3,4-(methylenedioxy)phenyl]cyclohex-1-ene (2). A solution of the alcohol **11** (0.76 g, 3.09 mmol) in THF (3 mL) was added to triphenylphosphine (0.91 g, 3.45 mmol) and diethyl azodicarboxylate (0.61 g, 3.5 mmol) in THF (10 mL). Diphenylphosphoryl azide (1.0 g, 3.63 mmol) was then added. After 36 h, the volatiles were removed under reduced pressure. Chromatography (gradient, 2.5 % - 5 % EtOAc / hex) gave 0.6 g (72%) of the title compound as a clear oil, R_f = 0.50 (25 % EtOAc / hex): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82 (s, 1 H), 6.75 (s, 2 H), 5.94 (s, 2 H), 5.92 (m, 1 H), 5.75 (d, J = 10.2 Hz, 1 H), 3.14 (m, 2 H), 2.02 (m, 4 H), 1.95-1.25 (series of mult., 4 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 147.68 (-), 145.57 (-), 140.87 (-), 131.60 (+), 129.01 (+), 120.03 (+), 107.75 (+), 107.31 (+), 100.87 (-), 47.59 (-), 41.60 (-), 40.99 (-), 37.19 (-), 25.23 (-), 18.58 (-); IR (neat) 2095 (s), 1610 (w), 1506 (m), 1486 (s), 1242 (s), 1040 (m), 810 (m) cm^{-1}; MS (EI, 70 eV) *m/v* (rel int) 271 (M^+, 1.5), 243 (25.9), 201 (93.8), 149 (29.3), 135 (55.3), 128 (23.4), 115 (19.7), 91 (13.5), 84 (48.3), 79 (50.8), 51 (45.4), 49 (100.0); HRMS calculated for $C_{15}H_{17}N_3O_2$; 271.1321, found; 271.1322.

3a-[3,4-(Methylenedioxy)phenyl]-3,3a,4,5,6,7-hexahydro-2*H*-indole (12). The azide **2** (130 mg, 0.48 mmol) was dissolved in benzene (10 mL), degassed (3 freeze-thaw cycles), and sealed in a glass tubewhich was then immersed in an oil bath at 120 °C for 12 h. After cooling to room temperature, the tube was opened and the solvent was removed *in vacuo* to furnish 116 mg (99 %) of the title compound as a clear oil which solidified on standing in the freezer, mp 65 - 67 °C. Alternatively, azide **2** (0.72 g, 2.65 mmol) was dissolved in toluene (30 mL) and refluxed for 24 h under an atmosphere of nitrogen to afford 0.64 mg (99 %) of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.75 (d, J = 8.1 Hz, 1 H), 6.64 (s, 1 H), 6.55 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 3.88 (m, 1 H), 3.64 (m, 1 H), 2.67 (m, 2 H), 2.25 (m, 1 H), 1.92 (m, 3 H), 1.50 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 180.54 (-), 148.31 (-), 145.84 (-), 137.03 (-), 119.13 (+), 108.38 (+), 106.60 (+), 100.94 (-), 58.58 (-), 57.56 (-), 41.94 (-), 39.30 (-), 30.29 (-), 27.53 (-), 22.49 (-); IR (neat) 1663 (m), 1511 (s), 1486 (s), 1239 (s), 1043 (m), 945 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (rel int) 243 (M^+, 100.0), 242 (49.9), 215 (13.0), 131 (10.5), 122 (35.1), 103 (29.4), 77 (31.8), 45 (92.8); HRMS calculated for $C_{15}H_{17}NO_2$; 243.1259, found; 243.1261. Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.05; N, 5.76. Found: C, 73.73; H, 7.35; N, 5.75.

(3aR*,7aR*)-3a-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (13). Sodium cyanoborohydride (0.33 g, 5.27 mmol) was added to a solution of the imine **12** (0.64 g, 2.63 mmol) in acetic acid (10 mL) at room temperature. After 30 min, 3 N NaOH (50 mL) and ether (100 mL) were added. The aqueous layer was extracted with ether (3 X 75 mL). The combined organic phases were washed with water (2 X 100 mL) and brine (100mL), then dried (Na_2SO_4) and concentrated. Chromatography (deactivated SiO_2, 5 % MeOH / $CHCl_3$) gave 0.52 g (81 %) of the title compound, R_f = 0.51, (deactivated SiO_2, 10 % MeOH / $CHCl_3$): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.85 (s, 1 H), 6.79 (d, J = 8.1 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.89 (s, 2 H), 3.39 (t, J = 4.1 Hz, 1 H), 3.09 (m, 1 H), 2.97 (dt, J = 4.8, 11.0 Hz, 1 H), 2.48 (br s, 1 H), 2.05-1.18 (series of m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.78, 145.40, 141.30, 119.50, 107.80, 107.58, 100.79, 61.16, 48.07, 43.25, 41.54, 34.14, 26.69, 22.27, 21.19; IR ($CDCl_3$) 3348 (w), 1506 (s), 1488 (s), 1432 (m), 1233 (s), 1042 (s), 937 (m), 907 (m) cm^{-1}. **HCl salt**: Prepared by bubbling HCl gas into an ethereal solution of amine **13** and removing the volatiles under reduced pressure: ^1H NMR ($CDCl_3$, 300 MHz) δ 10.35 (br s, 1 H), 9.35 (br s, 1 H), 6.72 (m, 3 H), 5.93 (s, 2 H), 4.05 (s, 1 H), 3.66 (m, 1 H), 3.49 (m, 1 H), 2.25-1.15 (series of mult. 10 H). The data for the HCl salt were consistent with those reported in the literature.[4d]

(±)-Crinane (1). Prepared by a modification of Keck's procedure.[4d] *N,N*-Dimethylmethyleneammonium iodide (Eschenmoser's salt) (0.78 g, 4.24 mmol) was added to a solution of **13** (0.52 g, 2.12 mmol) in THF (100 mL) and the mixture was warmed to 50 °C for 36 h. The THF was removed *in vacuo* and ether (150 mL) was added. 1 N NaOH was added until the solution was basic. The aqueous phase was extracted with ether (3 X 50 mL). The organic phases were combined and washed with water (3 X 50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated. Chromatography (gradient, deactivated SiO_2, 20 % - 30 % THF / hex) afforded 0.40 g (73 %) of the title compound, R_f = 0.31 (deactivated SiO_2, 10 % MeOH / $CHCl_3$): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.65 (s, 1 H), 6.40 (s, 1 H), 5.82 (s, 2 H), 4.30, 3.68 (ABq, J_{AB} = 16.7 Hz, 2 H), 3.27 (m, 1 H), 2.74 (m, 2 H), 2.28 (d, J = 11.4 Hz, 1 H), 2.15 (dt, J = 6.2, 11.7 Hz, 1 H), 1.60 (m, 6 H), 1.18 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 146.20 (-), 145.56 (-), 142.42 (-), 126.31 (-), 106.11 (+), 103.12 (+), 100.48 (-), 67.44 (+), 62.28 (-), 51.94 (-), 42.76 (-), 37.98 (-), 28.96 (-), 27.63 (-), 24.38 (-), 21.73 (-); IR (neat) 1503 (m), 1481 (s), 1232 (s), 1094 (m), 1039 (m), 936 (m), 852 (m) cm^{-1}; MS (EI, 70 eV) *m/v* (rel int) 257 (M^+, 100.0), 256 (24.8), 228 (64.6), 214 (26.9), 201 (35.6), 185 (43.3), 174 (21.6), 115 (30.3), 77 (17.7), 41 (24.7); HRMS calculated for $C_{16}H_{19}NO_2$; 257.1416, found; 247.1406. These spectral data are consistent with those reported.[4d]

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