Radical Cyclizations – Synthesis of γ-Lycorane

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(±)-γ-Lycorane has been synthesized in ten steps from piperonylic alcohol. Two radical reactions were used successively to build the D and B rings. A formal synthesis of (+)-γ-lycorane was achieved via an optically active unsaturated aldehyde intermediate.

Introduction

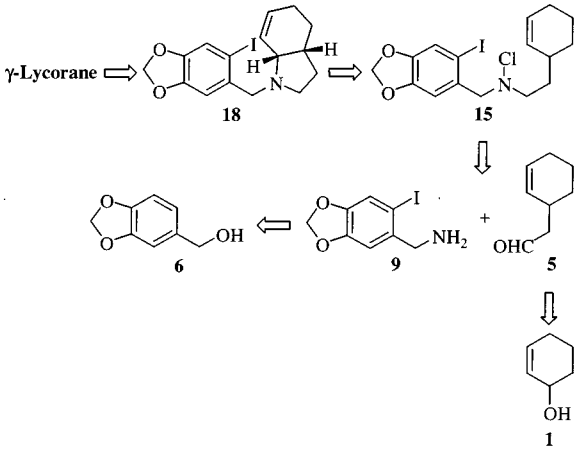
The lycorine-type natural products, which are characterized by the presence of the galanthane ring system represent a significant subclass within the *Amaryllidaceae* alkaloid family.[1] Various lycorine-type alkaloids have been shown to possess antiviral, antineoplastic and antimitotic as well as other pharmacological properties.[2] Others are known to inhibit plant growth or to disrupt the formation of peptidic bonds during protein synthesis or to have insect antifeeding properties. Consequently, considerable effort has been directed towards the total synthesis of these alkaloids. Unlike many of its congeners, the lycorine-derived degradation product, γ-lycorane, does not appear to possess any useful pharmacological properties. Nevertheless, γ-lycorane has become a popular target for illustrating the potential of new strategies for the synthesis of lycorine-type alkaloids.[3]

Results and Discussion

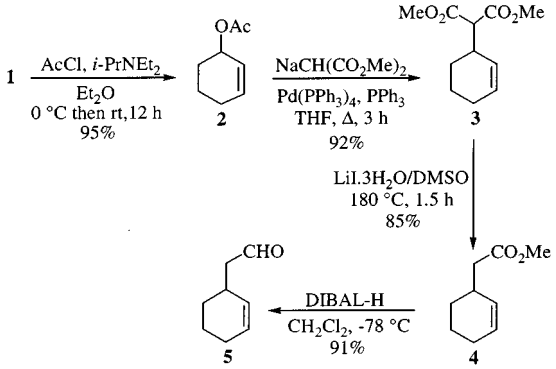
Herein, we give a full account of a practical convergent route to (±)-γ-lycorane[4] and a formal synthesis of (+)-γ-lycorane. It was anticipated that the D and B rings of γ-lycorane can be achieved by using two consecutive radical cyclizations as the key steps. The synthesis was planned according to the retrosynthetic analysis depicted in Scheme 1.

The precursor **18** of (±)-γ-lycorane was synthesized in a convergent manner from piperonylic alcohol (**6**) and cyclohex-2-enol (**1**). Cyclohex-2-enol (**1**) was converted into the corresponding allylic acetate **2**[5] (AcCl, Hünig's base) which was transformed into the diester **3**[6] (92% yield) by treatment with $NaCH(CO_2Me)_2$ in the presence of a catalytic amount of $Pd(PPh_3)_4$ (0.04 equiv.) and triphenylphosphane (0.12 equiv.).[7] After decarboxylation of diester **3** (LiI·3 H_2O, DMSO, 180 °C, 85% yield),[8] unsaturated ester **4**[9] was reduced to aldehyde **5**[10] by DIBAL-H in CH_2Cl_2 at −78 °C (91% yield).

The iodoamine **9** was synthesized from piperonylic alcohol (**6**). The iodination of piperonylic alcohol (**6**) was achieved with I_2 (1.2 equiv.) in the presence of silver trifluoroacetate (1.2 equiv.) in chloroform at 0 °C.[11] With the aim of obtaining amine **9**, alcohol **7** was subjected to treatment with PBr_3 in the presence of triethylamine (CH_2Cl_2/Et_2O, 2:3; 40 °C; 1 h), and the ensuing bromide was treated with hexamethyldisilazane (3 equiv.) in the presence of Na_2CO_3 in refluxing acetonitrile. After purification on silica gel, tribenzylamine **10** was isolated (79%) and no trace of the expected amine **9** was observed. Furthermore, succinimide **11**, which results from the condensation of phthalimide with alcohol **7** (DEAD, PPh_3, THF, 0 °C, 18 h) was not reactive on treatment with hydrazine (EtOH, 85 °C, 48 h) as succinimide **11** was not converted into amine **9** but entirely



Scheme 1. Retrosynthetic scheme



Scheme 2. Synthesis of aldehyde **5**

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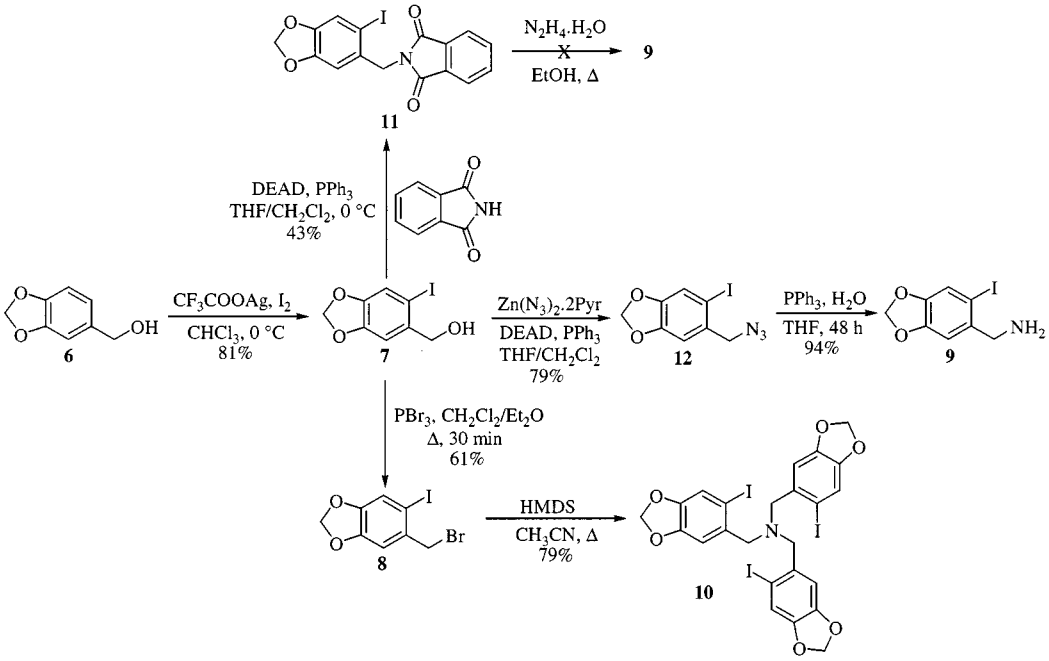
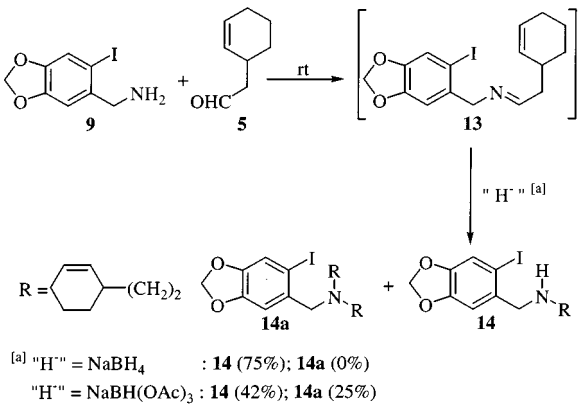
recovered. On the contrary, when a Mitsunobu reaction was applied to iodo alcohol **7**, with $Zn(N_3)_2 \cdot 2\,Pyr$ (0.75 equiv.)[12] in the presence of diethyl azodicarboxylate (1.5 equiv.) and PPh_3 (1.5 equiv.), azide **12** was formed in 79% yield. Following reduction of **12** under standard conditions (PPh_3, H_2O, THF, 72 h)[13] amine **9**[14] was isolated in 94% yield.



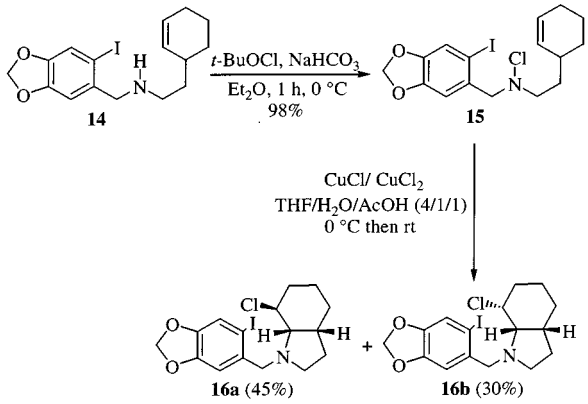
Scheme 3. Synthesis of amine **9**

The coupling product **14** was obtained via imine **13** by reductive amination of homoallylic aldehyde **5** with **9**.[15] When $NaBH(OAc)_3$ in CH_2Cl_2 was used as the reducing agent, the dialkylated amine **14** and the trialkylated amine **14a** were obtained in a 63:37 ratio (yield: 67%). The best yield of **14** (75%) was obtained by reduction of imine **13** with $NaBH_4$ (4 h, room temp.).



Scheme 4. Synthesis of amine **14**

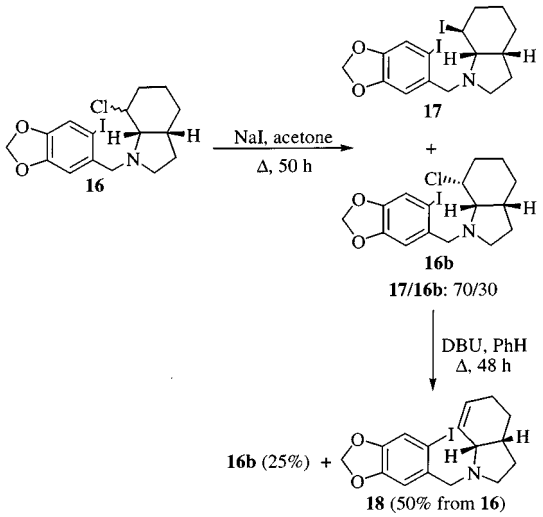
The *N*-chlorination of **14**, with *t*BuOCl in the presence of $NaHCO_3$[16] (Et_2O, 1 h, 0 °C) afforded **15** in 98% yield. When **15** was irradiated[17] (visible light, 1500 W, $CHCl_3$, 40 min), **16b** was the only product of cyclization isolated (23% yield). When **15** was treated with $TiCl_3/TiCl_4$,[18] a mixture of **16**, **14** and **15** was obtained in a 1:5:4 ratio. In contrast, when **15** was treated with $CuCl/CuCl_2$[19] (THF/H_2O/AcOH, 4:1:1; 0 °C → room temp.), a 5-*exo*-trig cyclization of the subsequent aminyl radical species led to the formation of the D ring of (±)-γ-lycorane. Two inseparable isomeric products **16a** and **16b** were obtained in a 60:40 ratio in a yield of 75%.



Scheme 5. Formation of the D ring of (±)-γ-lycorane

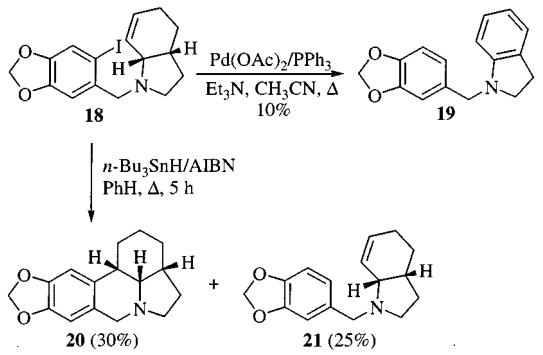
Attempts to form the B ring of (±)-γ-lycorane from intermediate **16** under different conditions such as *n*BuLi/CuI,[20] SmI_2,[21] Mg/CH_2Br_2[22] did not produce the desired product. In the light of these failures, a new approach to the B ring involving either a Heck cyclization or a radical cyclization of the unsaturated derivative **18** was considered. As treatment of **16** with different bases such as DBU, *t*BuOK and *i*Pr_2NEt did not lead to **18**, a halogen exchange (Cl → I) was carried out. Treatment of **16a/16b** with NaI in acetone allowed a stereoselective halogen exchange, as **17** was the only iodo compound formed and **16b** was partially

recovered. The stereoselectivity observed can be explained by the fact that only the *anti* isomer in which departure of chloride can be assisted by the amino moiety[19c] undergoes substitution with NaI in refluxing acetone. After treatment of **17** with DBU (PhH, Δ*T*, 48 h) the unsaturated iodide **18** was isolated (50% from **16**), and compound **16b** was recovered in 25% yield.



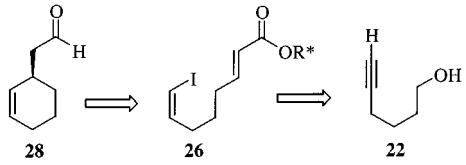
Scheme 6. Synthesis of the precursor **18** of (±)-γ-lycorane

When a Heck reaction was applied to compound **18** in the presence of $Pd(OAc)_2$ (0.1 equiv.), PPh_3 (0.22 equiv.) and triethylamine (2.2 equiv.)[23] in refluxing acetonitrile, amine **19** was obtained in poor yield (10%), and no trace of cyclized product was detected. We thus considered a radical cyclization reaction to build up the B ring of (±)-γ-lycorane. When **18** was treated with tris(trimethylsilyl)silane (1.7 equiv.)[24] in the presence of AIBN in refluxing benzene, only a trace of (±)-γ-lycorane was detected by GC/MS. Furthermore, treatment of **18** with nBu$_3$GeH (1.7 equiv.)[25] did not afford (±)-γ-lycorane. Fortunately, treatment of **18** with nBu$_3$SnH (1.7 equiv.) in the presence of AIBN (0.1 equiv.) in refluxing benzene for 5 h furnished the dehalogenated amino compound **21** (25%) and (±)-γ-lycorane **20** (30%), the spectral data of which were identical in all aspects to those published previously.[3i] The synthesis of (±)-γ-lycorane was thus achieved in ten steps from piperonylic alcohol with two consecutive radical cyclizations that have allowed the construction of the D and B rings of this alkaloid.



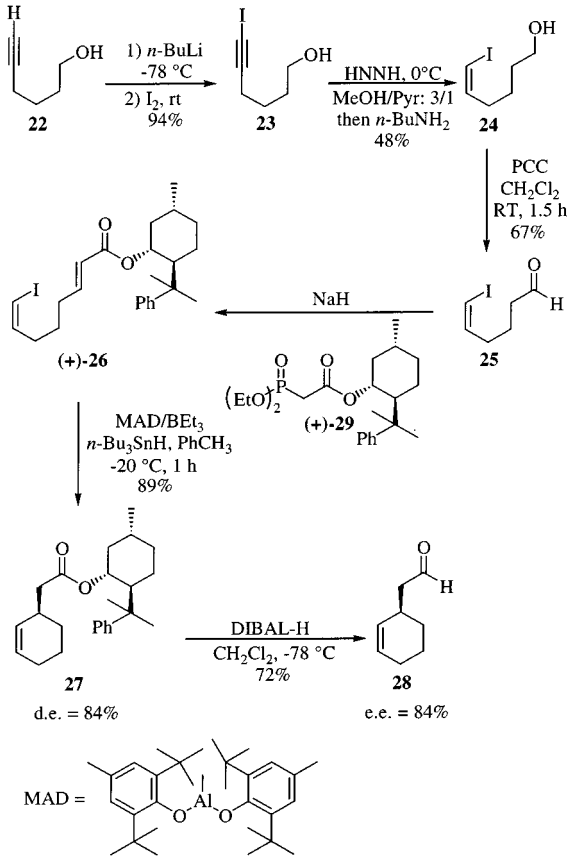
Scheme 7. Formation of the B ring of (±)-γ-lycorane

As the synthesis of (±)-γ-lycorane had been achieved, the synthesis of (+)-γ-lycorane was envisaged from the optically active unsaturated aldehyde **28** which will result from a diastereoselective radical cyclization of the optically active unsaturated iodide **26** in the presence of Lewis acid.[26] The synthesis of **28** was planned from commercially available hex-5-ynol according to the retrosynthetic analysis in Scheme 8.



Scheme 8. Retrosynthetic scheme

Hex-5-ynol **22** was transformed into the unsaturated vinyl iodide **26** in four steps. 6-Iodohex-5-ynol,[27] obtained from iodination of hex-5-ynol (nBuLi, I_2, −78 °C, THF) was reduced with diimide to (*Z*)-6-iodohex-5-en-1-ol (**21**),[28] which was oxidized to form the corresponding aldehyde **25** with PCC (CH_2Cl_2, room temp., 67% yield).[28] The reaction of **25** with the chiral phosphonate (+)-**29**[29] (NaH, THF, room temp.) led to the unsaturated ester (+)-**26** in 89% yield ($[\alpha]_D^{25} = +1.89$; $c = 2.16$, $CHCl_3$). Reaction of (+)-**26** with a Lewis acid such as methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[30] at −20 °C provided the cyclized product **27**[26] in good yield (81%) and



Scheme 9. Synthesis of aldehyde **(−)-28**

high diasteroselectivity as determined by ^{1}H NMR (84% d. e.). After reduction of **27** with DIBAL-H in CH_2Cl_2 at −78 °C, aldehyde **28** was obtained in 72% yield ($[\alpha]_D^{25}$ = −18.3; c = 2.67, $CHCl_3$). As the configuration of this aldehyde is (*R*), (+)-γ-lycorane can be obtained by using the previous route developed for the synthesis of (±)-γ-lycorane.

Conclusion

By using radical cyclizations as key steps, (±)-γ-lycorane as well as (+)-γ-lycorane can be obtained easily from inexpensive starting materials.

Experimental Section

General Remarks: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. − THF and ether were distilled from sodium/benzophenone ketyl immediately prior to use. − Acetone was distilled twice from potassium carbonate. − Methanol and ethanol were distilled from $Mg(OMe)_2$. − All other solvents and amines were distilled from calcium hydride. − Moisture-sensitive reactions were conducted in oven-dried glassware under argon. − Analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230−400 mesh). − Melting points are uncorrected. − IR: Perkin−Elmer 298. − Optical rotations: Perkin −Elmer 241MC polarimeter. − Elemental analyses: Service Régional de Microanalyses de l'Université P. et M. Curie. − HRMS: Centre de Spectrochimie Organique de l'Université P. et M. Curie or Centre de Spectrochimie de l'Ecole Normale Supérieure. − NMR: Bruker AC spectrometer (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively). Chemical shifts (δ) are expressed relative to TMS. − MS: Mass spectra were obtained by GC/MS with electron impact ionization using a 5971 Hewlett Packard instrument at 70 eV; only selected ions are reported.

Cyclohex-2-enyl Acetate (2): To a solution of alcohol **1** (5.0 mL, 51 mmol) in dry ether (100 mL) at 0 °C were successively added Hünig's base (26.5 mL, 153 mmol) and acetyl chloride (4.35 mL, 61.2 mmol). The resulting mixture was stirred at room temperature for 12 h before quenching with 10% aqueous citric acid (30 mL). The ethereal layer was washed with brine (2 × 20 mL), dried with $MgSO_4$ and filtered. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of Et_2O/pentane) to afford 6.8 g (95%) of acetate **2** as a pale yellow oil. − IR (neat): $\tilde{\nu}$ = 3020, 1730, 1650, 1370, 1240 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.95 (ddt, J = 1.1, 3.7 and 9.9 Hz, 1 H), 5.72−5.65 (m, 1 H), 5.28−5.21 (m, 1 H), 2.04 (s, 3 H), 2.10−1.92 (m, 2 H), 1.90−1.80 (m, 1 H), 1.79−1.60 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 170.7 (s), 132.6 (d), 125.6 (d), 68.0 (d), 28.2 (t), 24.8 (t), 21.3 (q), 18.8 (t). − MS (70 eV); *m/z* (%): 140 (9) [$M^{+\bullet}$], 125 (1), 112 (1), 98 (79), 83 (25), 81 (31), 79 (100), 70 (26). − $C_8H_{12}O_2$ (140.08): calcd. C 68.54, H 8.63; found C 68.54, H 8.63.

Dimethyl (Cyclohex-2-enyl)propanedioate (3): To a suspension of NaH (1.48 g, 61.6 mmol) in THF (90 mL) at 0 °C, dimethyl malonate (6.75 mL, 9.10 mmol) was added cautiously. After stirring for 15 min at room temperature, the resulting mixture was transferred to a solution of acetate **2** (6.90 g, 49.3 mmol), $Pd(PPh_3)_4$ (1.88 g, 1.63 mmol) and PPh_3 (1.55 g, 5.91 mmol) in THF (30 mL). The mixture was then refluxed for 4 h. After cooling to room temperature, the solution was diluted with ether (100 mL) and hydrolyzed with a saturated aqueous NH_4Cl solution (50 mL). The organic layer was successively washed with water (2 × 30 mL) and brine (50 mL). After drying with $MgSO_4$ and filtration, the ethereal layer was concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of Et_2O/pentane) to yield 9.66 g (92%) of diester **3** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 1755, 1725, 1650, 1435, 1330, 1015 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.79−5.72 (m, 1 H), 5.54−5.47 (m, 1 H), 3.72 (s, 6 H), 3.27 (d, J = 9.6 Hz, 1 H), 2.94−2.82 (m, 1 H), 2.02−1.93 (m, 2 H), 1.82−1.62 (m, 2 H), 1.61−1.48 (m, 1 H), 1.42−1.29 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 168.7 (s), 129.6 (d), 127.3 (d), 56.8 (d), 52.5 (q), 52.3 (q), 35.3 (d,), 26.6 (t), 24.9 (t), 20.7 (t). − MS (70 eV); *m/z* (%): 212 (0.5) [$M^{+\bullet}$], 181 (4), 152 (100), 137 (8), 133 (23), 121 (17), 101 (20), 93 (22), 81 (38).

Methyl (Cyclohex-2-enyl)acetate (4): A solution of diester **3** (3.90 g, 18.4 mmol) and LiI·3 H_2O (3.46 g, 18.4 mmol) in DMSO (70 mL) was degassed with argon. The mixture was then heated at 180 °C for 90 min. After cooling to room temperature, the mixture was diluted with water (70 mL) and the resulting solution was extracted with ether (3 × 70 mL). The ethereal layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The remaining oil was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of Et_2O/pentane) to afford 2.41 g (85%) of methyl ester **4** as a yellow oil. − IR (neat): $\tilde{\nu}$ = 1740, 1430, 1160 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 5.74−5.67 (m, 1 H), 5.56−5.49 (m, 1 H), 3.67 (s, 3 H), 2.65−2.53 (m, 1 H), 2.37−2.19 (m, 2 H), 2.01−1.92 (m, 2 H), 1.87−1.76 (m, 1 H), 1.75−1.63 (m, 1 H), 1.62−1.48 (m, 1 H), 1.33−1.21 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 173.2 (s), 130.0 (d), 128.1 (d), 51.4 (q), 40.5 (t), 32.2 (d), 28.7 (t), 25.0 (t), 20.9 (t). − MS (70 eV); *m/z* (%): 154 (23) [$M^{+\bullet}$], 139 (1), 122 (49), 94 (63), 80 (100), 75 (29), 74 (11). − $C_9H_{14}O_2$ (154.21): calcd. C 70.09, H 9.09; found C 70.02, H 9.03.

(Cyclohex-2-enyl)acetaldehyde (5): To a solution of methyl ester **4** (4.80 g, 31.2 mmol) in dichloromethane (140 mL) at −78 °C was added dropwise a 1 M solution of DIBAL-H in hexane (35.8 mL, 35.8 mmol). The mixture was stirred at −78 °C for 1 h and was treated with methanol (10 mL) and pH = 7.2 phosphate buffer solution (60 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was filtered through silica gel (Et_2O/pentane, 15:85) to give 3.5 g (91%) of aldehyde **5** as a colorless oil. − IR (neat): $\tilde{\nu}$ = 2720, 1730, 1650, 1450 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 9.78 (t, J = 2.2 Hz, 1 H), 5.78−5.70 (m, 1 H), 5.57−5.49 (m, 1 H), 2.75−2.63 (m, 1 H), 2.44−2.39 (m, 2 H), 2.03−1.94 (m, 2 H), 1.89−1.80 (m, 1 H), 1.77−1.65 (m, 1 H), 1.64−1.50 (m, 1 H), 1.33−1.21 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 202.4 (d), 129.8 (d), 128.4 (d), 50.0 (t), 29.6 (d), 28.5 (t), 24.4 (t), 20.5 (t). − MS (70 eV); *m/z* (%): 124 (33) [$M^{+\bullet}$], 109 (10), 96 (20), 95 (58), 81 (58), 80 (100), 79 (66), 67 (61).

5-(Hydroxymethyl)-6-iodo-1,3-benzodioxole (7): To a solution of piperonylic alcohol (**6**) (6.2 g, 41 mmol) in dry $CHCl_3$ (93 mL) at −5 °C were successively added silver trifluoroacetate (10 g, 45.2 mmol) and iodine (11.5 g, 45.2 mmol). After stirring for 5 min, the resulting heterogeneous mixture was filtered through a Celite pad. The filtrate was then washed with saturated aqueous $Na_2S_2O_3$ (100 mL), dried with $MgSO_4$, filtered and concentrated in vacuo to give a pale yellow solid. Recrystallization from $CHCl_3$ afforded 9.23 g (81%) of iodoalcohol **7** as white needles, m. p. 108−109 °C.

– IR (KBr): $\tilde{\nu}$ = 3300–3100, 1620, 1470, 1240, 925 cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 7.32 (s, 1 H), 7.02 (s, 1 H), 6.02 (s, 2 H), 5.39 (t, *J* = 5.5 Hz, 1 H), 4.31 (d, *J* = 5.5 Hz, 2 H). – ^{13}C NMR ([D$_6$]DMSO): δ = 148.0 (s) 147.0 (s), 137.4 (s), 117.0 (d), 108.0 (d), 101.5 (t), 84.5 (s), 67.2 (t). – MS (70 eV); *m/z* (%): 278 (100) [$M^{+\bullet}$], 261 (12), 149 (10), 121 (10), 93 (40), 65 (23), 63 (11), 53 (10).

5-(Bromomethyl)-6-iodo-1,3-benzodioxole (8): To a solution of alcohol **7** (4.17 g, 15.0 mmol) in dichloromethane (33 mL) and THF (24 mL) at 0 °C were successively added Et_3N (2.1 mL, 15 mmol) and PBr_3 (1.4 mL, 15 mmol). The resulting mixture was then heated at 40 °C for 30 min. After cooling to room temperature, the solution was poured onto ice and the pH of the aqueous layer was adjusted to 7 with a saturated aqueous Na_2CO_3 solution. The aqueous layer was then extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0–7% of EtOAc/cyclohexane) to give 3.1 g (61%) of bromide **8** as a white solid, m. p. 72 °C. – IR (KBr): $\tilde{\nu}$ = 1610, 1480, 1250, 1230, 930, 860 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 7.26 (s, 1 H), 6.97 (s, 1 H), 6.00 (s, 2 H), 4.57 (s, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 148.7 (s) 148.6 (s), 133.3 (s), 119.0 (d), 110.0 (d), 102.0 (t), 88.8 (s), 39.5 (t). – MS (70 eV); *m/z* (%): 342 (8) [$M^{+\bullet}$], 340 (9) [$M^{+\bullet}$], 261 (100), 203 (3), 134 (8), 130 (5), 76 (11).

***N*,*N*-Bis[(6-iodo-1,3-benzodioxol-5-yl)methyl]-6-iodo-1,3-benzodioxole-5-methanamine (10):** To a solution of bromide **8** (102 mg, 0.30 mmol) in dry acetonitrile was added HMDS (0.32 mL, 1.50 mmol). The resulting solution was refluxed for 16 h. After cooling to room temperature, the heterogeneous mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0–10% of Et_2O/petroleum ether) to afford 65 mg (82%) of trialkylated amine **10** as a yellow oil. – IR (neat): $\tilde{\nu}$ = 1615, 1500, 1475, 1230, 930, 860, 730 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 7.18 (s, 3 H), 7.01 (s, 3 H), 5.94 (s, 6 H), 3.67 (s, 6 H). – ^{13}C NMR ($CDCl_3$): δ = 148.4 (s) 147.5 (s), 134.3 (s), 118.4 (d), 110.0 (d), 101.5 (t), 87.9 (s), 62.4 (t). – MS (70 eV); *m/z* (%): 797 (18) [$M^{+\bullet}$], 670 (13), 536 (16), 409 (4), 261 (78), 205 (67), 167 (45), 149 (100), 135 (47), 57 (75). – $C_{24}H_{18}I_3NO_6$: calcd. 796.8268; found 796.8272 (MS).

2-[(6-Iodo-1,3-benzodioxol-5-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (11): To a solution of alcohol **7** (1.11 g, 4.00 mmol) and PPh_3 (1.26 g, 4.80 mmol) in dry THF (10 mL) and dichloromethane (2 mL) was added phthalimide (706 mg, 4.80 mmol). The reaction mixture was cooled to 0 °C and DEAD (0.76 mL, 4.80 mmol) was added dropwise. The mixture was then stirred at 0 °C for 18 h. The organic layer was diluted with ether (10 mL) and successively washed with water (10 mL) and brine (10 mL). The ethereal layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with 10–50% of EtOAc/cyclohexane) to afford 0.7 g (43%) of **11** as a white solid, m. p. 145 °C – ^1H NMR ([D$_6$]DMSO): δ = 7.92–7.80 (m, 4 H), 7.41 (s, 1H), 6.82 (s, 1 H), 6.01 (s, 2 H), 4.61 (s, 2 H). – ^{13}C NMR ([D$_6$]DMSO): δ = 169.2 (s), 167.7 (s), 148.3 (s), 147.6 (s), 134.5 (d), 134.2 (d), 132.6 (s), 131.8 (s), 131.4 (s), 123.2 (d), 122.9 (d), 118.1 (d), 107.9 (d), 101.8 (t), 85.7 (s), 46.2 (t). – MS (70 eV); *m/z* (%): 407 (2) [$M^{+\bullet}$], 280 (100), 150 (12), 139 (8), 133 (5), 130 (70), 104 (9), 102 (8), 76 (14).

5-(Azidomethyl)-6-iodo-1,3-benzodioxole (12): To a solution of iodo alcohol **7** (5.56 g, 20.0 mmol) and PPh_3 (6.29 g, 24.0 mmol) in dry THF (60 mL) and dichloromethane (15 mL) was added ZnN_6·2 Pyr (3.68 g, 12.0 mmol). The reaction mixture was cooled to 0 °C and DEAD (3.8 mL, 24.0 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 15 h and filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography on silica gel (eluting with a gradient of 0–5% of Et_2O/pentane) to give 9.23 g (79%) of azido compound **12** as a yellow oil. – IR (neat): $\tilde{\nu}$ = 2100, 1470, 1355, 1235 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 7.29 (s, 1 H), 6.90 (s, 1 H), 6.01 (s, 2 H), 4.38 (s, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 148.6 (s), 148.4 (s), 131.4 (s), 118.8 (d), 109.6 (d), 101.9 (t), 87.3 (s), 58.8 (t). – MS (70 eV); *m/z* (%): 303 (51) [$M^{+\bullet}$], 275 (12), 261 (100), 247 (4), 148 (4), 134 (6), 120 (6), 90 (10), 63 (11). – $C_8H_6IN_3O_2$: calcd. 302.9505; found 302.9506 (MS).

6-Iodo-1,3-benzodioxole-5-methanamine (9): To a solution of azide **12** (3.49 g, 11.5 mmol) in THF (70 mL) were successively added PPh_3 (4.54 g, 17.3 mmol) and distilled water (1.04 mL, 57.5 mmol). The resulting solution was stirred at room temperature for 4 d and then concentrated under reduced pressure. The remaining residue was dissolved in ethyl acetate (20 mL). The organic layer was extracted with a 1 N aqueous HCl solution (3 × 10 mL) and the pH of the aqueous layer was adjusted to 12 with KOH pellets. After extraction with dichloromethane (3 × 20 mL), the organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo to yield 3 g (94%) of amine **9** as a white solid, m. p. 101–102 °C. – IR (KBr): $\tilde{\nu}$ = 3400–3020, 1580, 1495, 1475, 1235, 925, 860 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 7.21 (s, 1 H), 6.89 (s, 1 H), 5.94 (s, 2 H), 3.75 (s, 2 H), 1.53 (br. s, 2 H). – ^{13}C NMR ($CDCl_3$): δ = 148.5 (s), 147.2 (s), 138.7 (s), 118.5 (d), 108.7 (d), 101.5 (t), 86.3 (s), 51.1 (t). – MS (70 eV); *m/z* (%): 277 (40) [$M^{+\bullet}$], 261 (8), 247 (8), 150 (100), 121 (7), 93 (17), 65 (20). – $C_8H_8INO_2$: calcd. 276.9600; found 276.9599 (MS).

***N*-[2-(Cyclohex-2-enyl)ethyl]-6-iodo-1,3-benzodioxole-5-methanamine (14):** To a solution of aldehyde **5** (2.48 g, 20.0 mmol) in dry methanol (20 mL) was added amine **9** (6.09 g, 22.0 mmol). The resulting solution was stirred at room temperature for 4 h and then cooled to 0 °C. $NaBH_4$ (1.14 g, 30.0 mmol) was slowly added to the reaction mixture. After 4 h, the solution was hydrolyzed with 2.5 M aqueous NaOH (10 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (eluting with a gradient of 10–30% of EtOAc/cyclohexane) to afford 5.75 g (75%) of amine **14** as a yellow oil. – IR (neat): $\tilde{\nu}$ = 3450–3200, 1500, 1475, 1230, 930 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 7.24 (s, 1 H), 6.94 (s, 1 H), 5.94 (s, 2 H), 5.71–5.64 (m, 1 H), 5.60–5.53 (m, 1 H), 3.73 (s, 2 H), 2.68 (t, *J* = 7 Hz, 2 H), 2.23–2.11 (m, 1 H), 2.02–1.93 (m, 2 H), 1.84–1.67 (m, 2 H), 1.61–1.42 (m, 4 H), 1.29–1.20 (m, 1 H). – ^{13}C NMR ($CDCl_3$): δ = 148.4 (s), 147.4 (s), 135.8 (s), 131.3 (d), 127.1 (d), 118.6 (d), 109.9 (d), 101.5 (t), 87.1 (s), 58.1 (t), 46.7 (t), 36.5 (t), 33.1 (d), 29.0 (t), 25.2 (t), 21.3 (t). – MS (70 eV); *m/z* (%): 385 (6) [$M^{+\bullet}$], 342 (2), 290 (3), 277 (3), 261 (100), 258 (19), 164 (14), 150 (7), 135 (22), 124 (9), 95 (12), 76 (12). – $C_{16}H_{20}INO_2$ (385.24): calcd. C 49.88, H 5.23, N 3.64; found C 50.07, H 5.17, N 3.55.

Reduction of Imine 13 with $NaBH(OAc)_3$: To a solution of aldehyde **5** (248 mg, 2.00 mmol) in dry CH_2Cl_2 (2 mL) were successively added amine **9** (609 mg, 2.20 mmol) and in small portions $NaBH(OAc)_3$ (636 mg, 3.00 mmol). After stirring for 12 h at room temperature, the solution was hydrolyzed with an aqueous 2.5 M NaOH solution (5 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue

was purified by flash column chromatography on silica gel (eluting with a gradient of 10−30% of EtOAc/cyclohexane) to afford 323 mg (42%) of dialkylated amine **14** and 237 mg (25%) of trialkylated amine **14a** both as yellow oils.

***N*,*N*-Bis[2-(cyclohex-2-enyl)ethyl]-6-iodo-1,3-benzodioxole-5-methanamine (14a):** IR (neat): $\tilde{\nu}$ = 1500, 1470, 1230, 935, 720 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.22 (s, 1 H), 7.07 (s, 1 H), 5.96 (s, 2 H), 5.70−5.61 (m, 2 H), 5.58−5.49 (m, 2 H), 3.51−3.47 (m, 2 H), 2.51 (t, *J* = 7.1 Hz, 4 H), 2.17−2.04 (m, 2 H), 2.01−1.91 (m, 4 H), 1.79−1.63 (m, 4 H), 1.60−1.34 (m, 6 H), 1.29−1.13 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 148.3 (s), 147.1 (s), 135.7 (s), 131.8 (d), 126.8 (d), 118.1 (d), 110.2 (d), 101.4 (t), 87.0 (s), 62.9 (t), 51.5 (t), 33.5 (t), 33.2 (d), 29.1 (t), 25.3 (t), 21.4 (t). − MS (70 eV); *m*/*z* (%): 493 (9) [$M^{+\bullet}$], 398 (4), 384 (3), 304 (21), 261 (100), 231 (2), 203 (2), 149 (2), 135 (22), 105 (2). − $C_{24}H_{32}INO_2$: calcd. 493.1478; found 493.1459 (MS).

***N*-Chloro-*N*-[2-(cyclohex-2-enyl)ethyl]-6-iodo-1,3-benzodioxole-5-methanamine (15):** To a solution of amine **14** (4.80 g, 12.4 mmol) in dry ether (70 mL) was added anhydrous $NaHCO_3$ (200 mg, 2.50 mmol). The suspension was cooled to 0 °C and *t*BuOCl (1.42 g, 13.1 mmol) was added dropwise. After stirring for 1 h, the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to give 5.12 g (98%) of *N*-chloroamine **15** as a yellow oil. − IR (neat): $\tilde{\nu}$ = 1500, 1480, 1410, 1230, 1105, 930, 860 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.26 (s, 1 H), 6.99 (s, 1 H), 5.98 (s, 2 H), 5.73−5.65 (m, 1 H), 5.57 (dd, *J* = 2 and 9.9 Hz, 1 H), 4.08 (s, 2 H), 3.11 (t, *J* = 7 Hz, 2 H), 2.30−2.17 (m, 1 H), 2.01−1.92 (m, 2 H), 1.83−1.62 (m, 4 H), 1.60−1.44 (m, 1 H), 1.30−1.16 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 148.3 (s), 147.9 (s), 132.8 (s), 131.3 (d), 127.3 (d), 118.5 (d), 110.7 (d), 101.7 (t), 88.0 (s), 71.5 (t), 61.1 (t), 34.1 (t), 32.6 (d), 28.9 (t), 25.2 (t), 21.3 (t).

7-Chloro-1-[(6-iodo-1,3-benzodioxol-5-yl)methyl]octahydro-1*H*-indole (16): To a solution of *N*-chloroamine **15** (5.11 g, 12.2 mmol) in THF (240 mL) at −10 °C was added dropwise a solution of CuCl (245 mg, 2.40 mmol) and $CuCl_2$ (1.86 g, 12.2 mmol) in distilled water (60 mL) and acetic acid (60 mL). The solution was stirred at room temperature for 5 h and cooled to 0 °C. The pH of the solution was adjusted to 11 with NaOH pellets. The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0−7% of EtOAc/cyclohexane) to give 3.83 g (75%) of cyclization products as an inseparable diastereoisomeric mixture of **16a** and **16b** in a 3:2 ratio. − Spectral data for **16b**: IR (neat): $\tilde{\nu}$ = 1500, 1470, 1400, 1365, 1230, 1100, 935, 830, 740 cm^{-1}. − ^1H NMR (C_6D_6): δ = 7.40 (s, 1 H), 7.21 (s, 1 H), 5.23 (d, *J* = 1.5 Hz, 1 H), 5.20 (d, *J* = 1.5 Hz, 1 H), 4.57 (d, *J* = 15.2 Hz, 1 H), 3.83 (td, *J* = 3.4 and 10.4 Hz, 1 H), 3.69 (d, *J* = 15.2 Hz, 1 H), 1.99−1.86 (m, 1 H), 1.79−0.80 (series of m, 8 H). − ^{13}C NMR (C_6D_6): δ = 149.1 (s), 147.7 (s), 137 (s), 118.5 (d), 110.5 (s), 101.3 (t), 86.5 (s), 66.5 (d), 65.7 (t), 63.3 (d), 53.4 (t), 40.6 (d), 30.9(t), 30.1 (t), 26.3 (t), 23.4 (t). − MS (70 eV); *m*/*z* (%): 421 (27) [$M^{+\bullet}$], 419 (8) [$M^{+\bullet}$], 384 (6), 342 (40), 261 (100), 256 (7), 254 (6), 135 (17), 76 (10). − $C_{16}H_{19}ClINO_2$: calcd.419.0149; found 419.0143 (MS). − Spectral data for **16a** (always mixed with **16b**): ^1H NMR (C_6D_6): δ = 7.19 (s, 1 H), 7.05 (s, 1 H), 5.21 (s, 2 H), 4.00−3.93 (m, 1 H), 3.67 (d, *J* = 14.2 Hz, 1 H), 3.40 (d, *J* = 14.2 Hz, 1 H), 2.94−2.83 (m, 1 H), 2.76−2.71 (m, 1 H), 2.19−2.06 (m, 1 H), 2.03 (td, *J* = 5.1 and 9.9 Hz, 1 H), 1.90−1.80 (m, 1 H), 1.79−0.80 (series of m, 7 H). − ^{13}C NMR (C_6D_6): δ = 149.1 (s), 147.8 (s), 136.0 (s), 118.8 (s), 110.3 (s), 101.4 (t), 86.9 (s), 69.5 (d), 64.3 (t), 60.3 (d), 52.7 (t), 36.1 (d), 30.3 (t), 29.3 (t), 27.7 (t), 19.7 (t). − MS (70 eV); *m*/*z* (%): 421 (5) [$M^{+\bullet}$], 419 (13) [$M^{+\bullet}$], 384 (3), 342 (27), 261 (100), 256 (3), 203 (3), 135 (21), 105 (4), 76 (11).

7-Iodo-1-[(6-iodo-1,3-benzodioxol-5-yl)methyl]octahydro-1*H*-indole (17): A solution of chloride **12** (3.6 g, 8.6 mmol) and NaI (12.9 g, 86.0 mmol) in dry acetone (86 mL) was refluxed for 50 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). The organic layer was washed with an aqueous 2.5 N NaOH solution (2 × 10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The brown residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of EtOAc/cyclohexane) to afford 3.2 g of an inseparable mixture of iodide **17** and chloride **16b** in a 7:3 ratio. − IR of the mixture (neat): $\tilde{\nu}$ = 1680, 1500, 1475, 1405, 1230, 1100, 1040, 935, 870, 830 cm^{-1}. − Spectral data for **17** (always mixed with **16b**): ^1H NMR (C_6D_6): δ = 7.20 (s, 1 H), 7.10 (s, 1 H), 5.22 (s, 2 H,), 4.28−4.20 (m, 1 H), 3.68 (d, *J* = 14.5 Hz, 1 H), 3.71 (d, *J* = 14.5 Hz, 1 H), 3.00−2.87 (m, 2 H), 2.25−2.13 (m, 1 H), 2.02 (td, *J* = 5.2 and 9.9 Hz, 1 H), 1.90−1.00 (series of m, 8 H). − ^{13}C NMR (C_6D_6): δ = 149.0 (s), 136.0 (s), 118.6 (d), 110.4 (d), 101.4 (t), 71.2 (d), 64.4 (t), 53.0 (t), 36.7 (d), 36.4 (d), 32.4 (t), 28.9 (t), 27.9 (t), 22.7(t). − MS (70 eV); *m*/*z* (%): 511 (23) [$M^{+\bullet}$], 384 (8), 342 (21), 261 (100), 256 (10), 135 (18), 76 (10). − $C_{16}H_{19}I_2NO_2$: calcd.510.9505; found 510.9534 (MS).

1-[(6-Iodo-1,3-benzodioxol-5-yl)methyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indole (18): A solution of chloride **16b** and iodide **17** (3.2 g) and DBU (3.50 mL, 23.5 mmol) in benzene (24 mL) was refluxed for 24 h. After cooling to room temperature, the organic layer was washed with an aqueous 2.5 N NaOH solution (10 mL), dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (eluting with a gradient of 5−15% of EtOAc/cyclohexane) to yield 1.67 g (50% from **16**) of unsaturated product **18** and 803 mg (25% from **16**) of compound **16b** both as yellow oils. − Spectral data for **18**: IR (neat): $\tilde{\nu}$ = 1500, 1470, 1230, 1040, 940, 900, 830 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.23 (s, 1 H), 7.07 (s, 1 H), 5.95 (s, 2 H), 5.96−5.87 (m, 1 H), 5.83−5.76 (m, 1 H), 3.86 (d, *J* = 14 Hz, 1 H), 3.39 (d, *J* = 14 Hz, 1 H), 2.95 (td, *J* = 2.5 and 8.7 Hz, 1 H), 2.88−2.82 (m, 1 H), 2.29−2.15 (m, 2 H), 2.13−1.91 (m, 3 H), 1.71−1.42 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 148.3 (s), 147.1 (s), 135.6 (s), 130.2 (d), 125.9 (d), 118.1 (d), 110.2 (d), 101.4 (t), 86.9 (s), 61.9 (t), 61.2 (d), 52.8 (t), 35.9 (d), 29.3 (t), 27.0 (t), 24.4 (t). − MS (70 eV); *m*/*z* (%): 383 (21) [$M^{+\bullet}$], 277 (6), 261 (100), 256 (64), 254 (34), 135 (30), 122 (16), 105 (8), 77 (12), 76 (12). − $C_{16}H_{18}INO_2$ (383.22): calcd. C 50.15, H 4.73, N 3.65; found C 50.31, H 4.73, N 3.55.

1-[(1,3-Benzodioxol-5-yl)methyl]-2,3-dihydro-1*H*-indole (19): A solution of unsaturated compound **18** (100 mg, 0.26 mmol), $Pd(OAc)_2$ (6.00 mg, 0.03 mmol), PPh_3 (15.0 mg, 0.06 mmol) and triethylamine (70 μL, 0.6 mmol) in acetonitrile (2 mL) was refluxed for 14 h. After cooling to room temperature, the solution was filtered through a Celite pad. The filtrate was concentrated in vacuo and the oily residue was purified by flash column chromatography on silica gel (eluting with a gradient of 5−30% of EtOAc/cyclohexane) to give 6.6 mg (10%) of indole **19** as a orange oil. − ^1H NMR ($CDCl_3$): δ = 7.13−7.02 (m, 2 H), 6.89 (d, *J* = 1.1 Hz, 1 H), 6.85−6.81 (m, 1 H), 6.78 (d, *J* = 7.7 Hz, 1 H), 6.71−6.64 (m, 1 H), 6.52 (d, *J* = 7.7 Hz, 1 H), 5.96 (s, 2 H), 4.15 (s, 2 H), 3.34−3.26 (m, 2 H), 3.34−3.26 (m, 2 H), 3.01−2.94 (m, 2 H). − MS (70 eV); *m*/*z* (%): 253 (34) [$M^{+\bullet}$], 135 (100), 105 (4), 91(2), 77 (12), 51 (5).

Radical Cyclization with *n*Bu_3SnH in the Presence of AIBN: A solution of **18** (180 mg, 0.47 mmol) and AIBN (7.70 mg, 0.05 mmol) in benzene (25 mL) was refluxed. A solution of *n*Bu_3SnH (215 μL,

0.80 mmol) in benzene (5 mL) was added over 4 h by syringe pump. After the addition was completed, reflux was maintained for an additional hour. After cooling to room temperature, the mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with saturated aqueous KF (10 mL). The organic layer was then dried with $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography on silica gel ($CHCl_3$/EtOAc/MeOH, 80:15:5) to furnish 35 mg (30%) of (±)-γ-lycorane **20** and 30 mg (25%) of dehalogenated compound **21** both as colorless oils.

1,2,3,3a,4,5,12b,12c-Octahydro-7*H*-1,3-benzodioxolo[5,6-*c*]-pyrrolo[3,2,1-*ij*]quinoline (20): IR (neat): $\tilde{\nu}$ = 1503, 1484, 1465, 1446, 1376, 1319, 1244, 1039, 937 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 6.62 (s, 1 H), 6.50 (s, 1 H), 5.90 (d, *J* = 1.4 Hz, 1 H), 5.89 (d, 1 H, *J* = 1.4 Hz), 4.02 (d, 1 H, *J* = 14.3 Hz), 3.39 (td, *J* = 9.2 and 3.7 Hz, 1 H), 3.22 (d, *J* = 14.3 Hz, 1 H), 2.79−2.68 (m, 1 H), 2.38 (t, *J* = 4.7 Hz, 1 H), 2.24−2.10 (m, 2 H), 2.09−1.96 (m, 1 H), 1.80−1.20 (series of m, 7 H). − ^{13}C NMR ($CDCl_3$): δ = 146.0 (s), 145.6 (s), 133.2 (s), 127.3 (s), 108.3 (d), 106.2 (d), 100.6 (t), 62.9 (d), 57.1 (t), 53.7 (t), 39.5 (d), 37.4 (d), 31.7 (t), 30.4 (t), 29.3 (t), 25.2 (t). − MS (70 eV); *m*/*z* (%): 257 (30) [$M^{+\bullet}$], 256 (100), 254 (4), 162 (4), 135 (2), 115 (2), 77 (2).

6-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indole (21): ^1H NMR ($CDCl_3$): δ = 6.91−6.87 (m, 1 H), 6.82−6.72 (m, 2 H), 5.98−5.88 (m, 1 H), 5.94 (s, 2 H), 5.83−5.75 (m, 1 H), 3.92 (d, *J* = 12.9 Hz, 1 H), 3.34 (d, *J* = 12.9 Hz, 1 H), 2.92 (td, *J* = 8.8 and 2.9 Hz, 1 H), 2.81−2.71 (m, 1 H), 2.30−1.20 (series of m, 8 H). − ^{13}C NMR ($CDCl_3$): δ = 147.5 (s), 146.4 (s), 132.8 (s), 130.7 (d), 125.5 (d), 122.0 (d), 109.6 (d), 107.8 (d), 100.8 (t), 60.7 (d), 57.6 (t), 52.5 (t), 35.8 (d), 30.1 (t), 26.9 (t), 26.6 (t). − MS (70 eV); *m*/*z* (%): 257 (13) [$M^{+\bullet}$], 256 (14), 229 (4), 151 (4), 135 (100), 122 (30), 105 (8), 79 (5), 77 (14), 51 (4).

6-Iodohex-5-yn-1-ol (23): To a solution of hexynol **22** (3.3 mL, 30.0 mmol) in THF (50 mL) at −78 °C was added dropwise a 2.5 M solution of *n*BuLi in hexane (25.2 mL, 63.0 mmol). After 20 min at −78 °C, a solution of iodine (8.38 g, 33.0 mmol) in THF (50 mL) was added. The resulting mixture was stirred at room temperature for 90 min. The solution was then diluted with ether (100 mL) and hydrolyzed with brine (30 mL). The ethereal layer was washed with saturated aqueous $Na_2S_2O_3$ (10 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 3:7) to yield 6.32 g (94%) of iodohexynol **23** as an orange oil. − IR (neat): $\tilde{\nu}$ = 3600−3100, 1450, 1430, 1060 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 3.62 (t, *J* = 6 Hz, 2 H), 2.39 (t, *J* = 6.4 Hz, 2 H), 2.25 (br. s, 1 H), 1.71−1.52 (m, 4 H). − ^{13}C NMR ($CDCl_3$): δ = 94.2 (s), 62.0 (t), 31.5 (t), 24.7 (t), 20.5 (t), −6.6 (s). − MS (70 eV); *m*/*z* (%): 224 (0.5) [$M^{+\bullet}$], 196 (70), 180 (71), 178 (65), 165 (55), 127 (12), 97 (32), 79 (49), 77 (100).

(*Z*)-6-Iodohex-5-en-1-ol (24): To a suspension of iodoalkyne **23** (5.6 g, 25 mmol) and dipotassium azodicarboxylate (10.2 g, 52.5 mmol) in methanol (45 mL) and pyridine (15 mL) was added acetic acid (6.00 mL, 105 mmol) at 0 °C over 15 h by syringe pump. The resulting suspension was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (20 mL) and $nBuNH_2$ (2 mL) was added. After 12 h, the organic layer was washed successively with an aqueous 1.2 N HCl solution (2 × 20 mL) and brine (20 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. The remaining residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane, 1:9) to give 2.72 g (48%) of iodoalkene **24** as a yellow oil. − IR (neat): $\tilde{\nu}$ = 3600−3100, 1610, 1460, 1300, 1280, 700 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 6.22−6.11 (m, 2 H), 3.62 (t, *J* = 6.2 Hz, 2 H), 2.33 (br. s, 1 H), 2.20−2.12 (m, 2 H), 1.64−1.43 (m, 4 H). − ^{13}C NMR ($CDCl_3$): δ = 140.6 (d), 82.6 (d), 62.3 (t), 34.3 (t), 31.9 (t), 24.0 (t). − MS (70 eV); *m*/*z* (%): 226 (0.2) [$M^{+\bullet}$], 180 (64), 167 (15), 99 (17), 81 (100), 79 (23), 57 (17), 53 (20).

(*Z*)-6-Iodohex-5-enal (25): To a suspension of PCC (1.66 g, 7.70 mmol) in CH_2Cl_2 (105 mL) was added dropwise at room temperature a solution of **24** (1.58 g, 7.00 mmol) in CH_2Cl_2 (10 mL). After stirring for 90 min, the mixture was diluted in ether (105 mL) and the resulting solution was filtered through a silica pad. The filtrate was concentrated in vacuo and the remaining residue was purified by flash column chromatography on silica gel (eluting with a gradient of 5−10% of EtOAc/cyclohexane) to yield 1.05 g (67%) of aldehyde **25** as a yellow oil. − IR (neat): $\tilde{\nu}$ = 2722, 1722, 1644, 1285 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 9.81 (t, *J* = 1.5 Hz, 1 H), 6.29 (dt, *J* = 7.4 and 1.0 Hz, 1 H), 6.17 (dt, *J* = 7.1 and 7.1 Hz,), 2.51 (td, *J* = 7.5 and 1.5 Hz, 2 H), 2.27−2.16 (m, 2 H), 1.88−1.72 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 201.9 (d), 139.9 (d), 83.5 (d), 42.9 (t), 33.8 (t), 20.2 (t). − MS (70 eV); *m*/*z* (%): 224 (0.2) [$M^{+\bullet}$], 180 (100), 167 (16), 127 (4), 97 (26), 76 (11), 69 (21), 55(8), 53 (18).

(+)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 2-(Diethoxyphosphoryl)acetate (+)-(29): A solution of (+)-8-phenylmenthyl chloroacetate (734 mg, 2.37 mmol) in triethyl phosphite (1.22 mL, 7.13 mmol) was refluxed for 8 h. The mixture was cooled to room temperature and the excess of $P(OEt)_3$ was distilled off under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with a gradient of 20−50% of EtOAc/cyclohexane) to furnish 923 mg (95%) of phosphonate (+)-**29** as a yellow oil. − $[\alpha]_D^{25}$ = +29.2 (*c* = 5.57, MeOH). − IR (neat): $\tilde{\nu}$ = 1728, 1600, 1444, 1390, 1272, 972, 767, 702 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.30−7.22 (m, 4 H), 7.16−7.08 (m, 1 H), 4.83 (td, *J* = 4.5 and 10.7 Hz, 1 H), 4.20−3.93 (m, 4 H), 2.37 (dd, *J* = 21 and 14.3 Hz, 1 H), 2.07 (dd, *J* = 21 and 14.3 Hz, 1 H), 2.09−1.98 (m, 1 H), 1.97−1.76 (m, 2 H), 1.71−1.58 (m, 1 H), 1.54−1.40 (m, 1 H), 1.39−1.24 (m, 6 H), 1.29 (s, 3 H), 1.20 (s, 3 H), 1.22−1.06 (m, 1 H), 1.03−0.80 (m, 2 H), 0.87 (d, *J* = 6.7 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 165.0 (d, *J* = 6.2 Hz), 151.7 (s), 127.9 (d), 125.3 (d), 125.0 (d), 75.1 (d), 62.3 (td, *J* = 6.1 Hz), 50.2 (d), 41.3 (t), 39.4 (s), 34.5 (t), 33.8 (td, *J* = 132 Hz), 31.2 (d), 29.1 (q), 26.2 (t), 23.2 (q), 21.7 (q), 16.2 (qd, *J* = 6.1 Hz). − MS (70 eV); *m*/*z* (%): 410 (0.1) [$M^{+\bullet}$], 214 (10), 197 (100), 179 (34), 169 (7), 151 (12), 122 (10), 119 (20), 118 (22),109 (4), 105 (7).

(+)-(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl 8-Iodoocta-2,7-dienoate (+)-(26): To a suspension of NaH (13.0 mg, 0.55 mmol) in dry THF (1 mL) at 0 °C was added a solution of phosphonate (+)-**29** (230 mg, 0.56 mmol) in THF (2 mL). After stirring for 5 min, a solution of aldehyde **25** (112 mg, 0.50 mmol) in THF (2 mL) was added. The resulting mixture was stirred for 3 h at room temperature. After dilution with ether (5 mL), the solution was hydrolyzed with a saturated aqueous NH_4Cl solution (3 mL). The aqueous layer was then extracted with ether (2 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of EtOAc/cyclohexane) to afford 213 mg (89%) of coupling product (+)-**26** as a pale yellow oil. − $[\alpha]_D^{25}$ = +1.89 (*c* = 2.16, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 1710, 1653, 1600, 1495, 1456, 1443, 1268, 1181, 1091, 979, 733, 700 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 7.29−7.18 (m, 4 H), 7.15−7.06 (m,1 H), 6.49 (td, *J* = 15.7 and 6.7 Hz, 1 H), 6.27−6.09 (m, 2 H), 5.27 (dd, *J* = 15.7 and 1.7 Hz,

1 H), 4.81 (td, J = 10.8 and 4.3 Hz, 1 H), 2.20−1.96 (m, 5 H), 1.94−1.83 (m, 1 H), 1.72−1.40 (m, 4 H), 1.29 (s, 3 H), 1.27−1.15 (m, 1 H), 1.19 (s, 3 H), 1.13−0.81 (m, 3 H), 0.83 (d, J = 6.5 Hz, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 165.7 (s), 151.6 (s), 147.6 (d), 140.4 (d), 127.9 (d), 125.4 (d), 124.8 (d), 122 (d), 83.1 (d), 74.1 (d), 50.5 (d), 41.7 (t), 39.6 (s), 34.6 (t), 34.1 (t), 31.3 (t), 31.2 (d), 27.7 (q), 26.6 (t), 26.2 (t), 25.2 (q), 21.8 (q). − MS (70 eV); *m/z* (%): 480 (0.1) [$M^{+\bullet}$], 361 (7), 214 (16), 119 (100), 105 (6), 95 (5), 91 (21), 79 (6), 55 (6).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*R*)-2-(Cyclohex-2-ene)acetate (27a) and (1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (1*S*)-2-(Cyclohex-2-ene)acetate (27b): To a solution of iodoalkene (+)-**26** (150 mg, 0.31 mmol), nBu$_3$SnH (124 μL, 0.46 mmol) in anhydrous toluene (2.5 mL) at −20 °C under dry air were successively added a 0.4 M solution of MAD in toluene (0.80 mL, 0.31 mmol) and a 1 M solution of BEt_3 in cyclohexane (0.33 mL, 0.33 mmol). The resulting mixture was stirred for 30 min and additional BEt_3 (0.33 mL, 0.33 mmol) was added. After stirring for 30 min, the solution was treated with an aqueous 1.2 M HCl solution (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel (eluting with a gradient of 0−2% of EtOAc/cyclohexane) to give 90 mg (81%) of cyclization products as an inseparable diastereoisomeric mixture of **27a** and **27b** in a 92:8 ratio. − IR (neat): $\tilde{\nu}$ = 1726, 1654, 1600, 1496, 1457, 1364, 1164, 764, 700 cm^{-1}. − Spectral data for **27a**: ^{1}H NMR ($CDCl_3$): δ = 7.31−7.20 (m, 4 H), 7.17−7.07 (m, 1 H), 5.70−5.59 (m, 1 H), 5.45−5.35 (m, 1 H), 4.81 (td, J = 10.8 and 6.6 Hz, 1 H), 2.32−2.19 (m, 1 H), 2.09−1.80 (m, 3 H), 1.76−1.57 (m, 4 H), 1.54−1.41 (m, 3 H), 1.37−1.01 (series of m, 3 H), 1.30 (s, 3 H), 1.20 (s, 3 H), 0.99−0.78 (m, 6 H). − ^{13}C NMR ($CDCl_3$): δ = 172.0 (s), 151.7 (s), 130.3 (d), 127.9 (d), 127.7 (d), 125.3 (d), 124.9 (d), 74.0 (d), 50.3 (d), 41.7 (t), 40.7 (t), 39.6 (s), 34.6 (t), 31.8 (d), 31.3 (d), 28.7 (t), 28.3 (q), 26.5 (t), 25.0 (t), 24.6 (s), 21.8 (q), 21.0 (t). − MS (70 eV); *m/z* (%): 354 (0.02) [$M^{+\bullet}$], 235 (3), 215 (14), 199 (5), 132 (3), 123 (4), 119 (100), 105 (30), 91 (21), 81 (22), 67 (3), 55 (5). − Spectral data for **27b**: ^{1}H NMR ($CDCl_3$): δ = 7.31−7.20 (m, 4 H), 7.17−7.07 (m,1 H), 5.83−5.72 (m, 1 H), 5.31−5.22 (m, 1 H), 5.02−4.95 (m, 1 H), 2.32−2.19 (m, 1 H), 2.09−1.80 (m, 3 H), 1.76−1.57 (m, 4 H), 1.54−1.41 (m, 3 H), 1.37−1.01 (series of m, 9 H), 0.99−0.78 (m, 6 H). − MS (70 eV); *m/z* (%): 235 (3) [$M^{+\bullet}$ − $PhC(CH_3)_2^{\bullet}$], 214 (15), 199 (6), 132 (4), 119 (100), 105 (29), 95 (11), 91 (22), 81 (13), 67 (3), 55 (5).

(−)-(1*R*)-(Cyclohex-2-ene)acetaldehyde (28): To a solution of ester **27** (88.0 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added dropwise at −78 °C a 1 M solution of DIBAL-H in hexane (0.27 mL, 0.27 mmol). After 1 h at −78 °C, the mixture was hydrolyzed with a pH = 7 phosphate buffer solution (1 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (eluting with a gradient of 0−5% of Et_2O/pentane) to give 21 mg (72%) of aldehyde (−)-**28** as a colorless oil. − $[\alpha]_D^{25}$ = −18.3 (c = 2.67, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 2720, 1724, 1446, 1149 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 9.75 (t, J = 2.2 Hz, 1 H), 5.75−5.65 (m, 1 H), 5.53−5.46 (m, 1 H), 2.74−2.59 (m, 1 H), 2.41−2.35 (m, 2 H), 2.03−1.89 (m, 2 H), 1.88−1.45 (m, 3 H), 1.33−1.21 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 202.3 (d), 129.7 (d), 128.3 (d), 49.9 (t), 29.9 (d), 28.8 (t), 24.8 (t), 20.9 (t). − MS (70 eV); *m/z* (%): 124 (29) [$M^{+\bullet}$], 109 (9), 96 (18), 95 (57), 91 (17), 80 (100), 67 (56), 65 (12), 55 (22).

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