(pyrrolidinium chloride), 102779-91-9; **13**, 102745-78-8; **13**·$^1/_2$tartrate, 102745-79-9; **14**, 102745-80-2; **15**, 102745-81-3; **16**, 102745-82-4; **17**, 102745-83-5; **18**, 102745-86-8; **19**, 102779-92-0; **20**, 102745-87-9; **21**, 102745-88-0; **22**, 102745-89-1; **22**·2HCl, 102745-90-4; **23**, 102745-93-7; **24**·2HCl, 102745-94-8; 4-acetamidocyclohexanone, 27514-08-5; *p*-acetamidophenol, 103-90-2; *p*-acetamidocyclohexanol, 23363-88-4; 1-chloro-2,4-dinitrobenzene, 97-00-7; 3-hydroxybutanone, 513-86-0; 5-hydrazinoquinoline, 15793-79-0; 5-nitroquinoline, 607-34-1; 5-aminoquinoline, 611-34-7; amrinone, 60719-84-8.

Synthesis and Analgesic Evaluation of 4-(2-Heptyloxy)-7-[(*Z*)-(3-hydroxycyclohexyl)]indole: A Caveat on Indole–Phenol Bioisosterism

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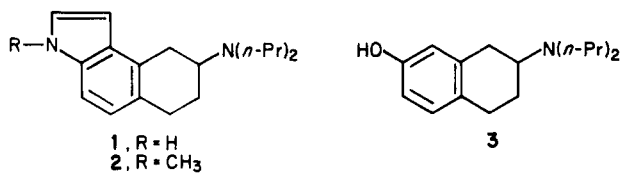
The synthesis of 4-(2-heptyloxy)-7-[(*Z*)-(3-hydroxycyclohexyl)]indole (**7**) is described. Compound **7** was tested for analgesic properties in the phenylbenzoquinone writhing test and was found to be essentially devoid of activity. In contrast, *cis*-3-[4-(2-heptyloxy)-2-hydroxyphenyl]cyclohexanol (**8**), the analogue in which the pyrrolo ring is replaced by a hydroxyl group, had an ED_{50} of 8.3 mg/kg, sc, in the same model. The absence of bioisosterism between the pyrrolo ring and the phenolic hydroxyl group, in this instance, is discussed in terms of the circumstances that control the manifestation of bioisofunctionality between a pyrrolo ring and a phenolic hydroxyl group, which functions as a hydrogen-bond donor.

We have demonstrated, in two instances,[1,2] that a phenolic hydroxyl group in a drug molecule can be replaced by a pyrrolo grouping with retention of similar biological activity. Thus, the benz[*e*]indole **1**,[1] the pyrrolo analogue of the dopaminergic agonist **3**,[3-5] was found also to be a potent dopaminergic agonist,[1] while **4**, the pyrrolo analogue of labetalol, **6**,[6] was shown also to block α- and β-adrenergic receptors.[2]



1, R = H
2, R = CH_3

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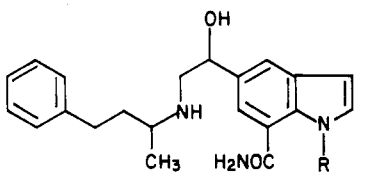
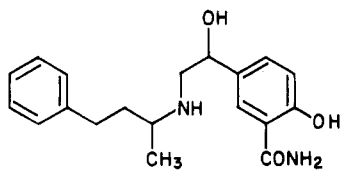


4, R = H
5, R = CH_3



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The biological activities of these pyrrolo analogues were ascribed to the capacity of the pyrrolo NH groups to function as hydrogen-bond donors to acceptor nuclei on the receptor macromolecules with which they interact, and this conclusion was supported by the lack of activity of the *N*-methylpyrroles **2** and **5** as dopaminergic agonist[1] and as adrenergic blocker,[2] respectively.

Having explored the scope of this indole–phenol equivalency in other drug molecules, we now report the synthesis and a comparison of the analgesic activities of the indole **7** with the phenol **8**.[7]

Compound **8**, an analgesic, is a member of a series of simplified cannabinoids lacking the dihydropyran ring, among which **9** (CP-47497) has been extensively studied.[8,9] Compound **8** also bears the 2-heptyloxy side chain, which has been shown to be compatible with high analgesic activity in the cannabinoid-related compound **10**,[10] and a phenolic hydroxyl group, which has been shown to be essential for activity in cannabinoid-derived analgesics. For example, phenol **11** has been shown to be up to 436 times more potent than **12** as an analgesic.[10]

These structural features of compound **8**, viz, the heptyloxy side chain and the phenolic hydroxyl group, as well as the alcohol and the aryl ring, are through to be necessary for the binding of cannabinoid-derived analgesics with their receptor.[11] Compound **8** thus provides an appropriate model for testing the scope and generality of indole–phenol bioequivalency.

Chemistry. It was anticipated that the 1,3-relationship between the hydroxyl group and the indolyl moiety in **7** could be secured by a Michael addition to cyclohexenone

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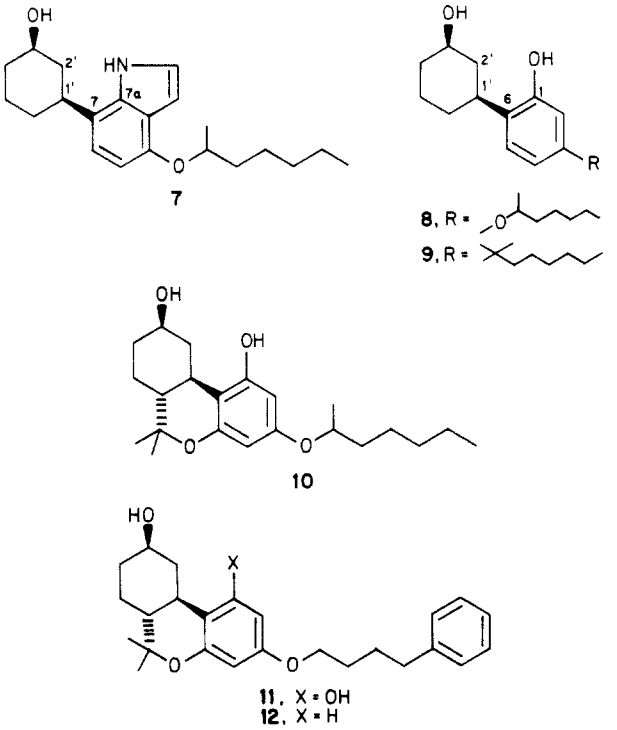

of an appropriately protected 7-metalated indole. The required indole was obtained from 5-bromosalicylaldehyde, as shown in Scheme I. 5-Bromosalicylaldehyde **13** was etherified with 2-bromoheptane in 92% yield to give **14**. Under the conditions of the Hemetsberger reaction,[12,13] aldehyde **14** was treated with 4 equiv of ethyl azidoacetate and sodium methoxide in methanol to give vinyl azide **15**, which, in refluxing xylene,[13d,e] gave ester **16** in 29% yield from **14**. Basic hydrolysis to **17**, followed by copper chromite decarboxylation in hot quinoline, furnished the key intermediate indole **18** in 66% yield. The indolic nitrogen was protected as the triisopropylsilyl derivative **19** in 77% yield. This was accomplished by quenching the corresponding indolic anion, generated with lithium bis(trimethylsilyl)amide at −78 °C, with triisopropylsilyl trifluoromethanesulfonate (TIPSTRIF).[14]

Attachment of the cyclohexyl moiety was achieved by a Michael addition to activated cyclohexenone according to the following sequences: (1) metal–halogen exchange of indole **19** with 2.2 equiv of *tert*-butyllithium in anhydrous ether at −78 °C, (2) formation at −78 °C of the cuprate derived from 1 equiv of copper iodide and 2 equiv of tri-*n*-butylphosphine,[15] (3) addition of 1.2 equiv of boron trifluoride etherate,[16] and (4) careful addition of a *precooled dilute* solution of ethereal cyclohexenone. Following this protocol, indole **20** was obtained in nearly 60% yield. Reduction of ketone **20** with sodium borohydride in methanol gave the desired cis alcohol **21** in 82% yield and trans epimer **22** in 13% yield.[17] Removal of the triisopropylsilyl group from **21** by exposure to tetra-*n*-butylammonium fluoride provided the target indole **7** as an oil in 87% yield. The cis stereochemistry of the product is suggested from examination of the proton NMR spectrum.

Scheme I

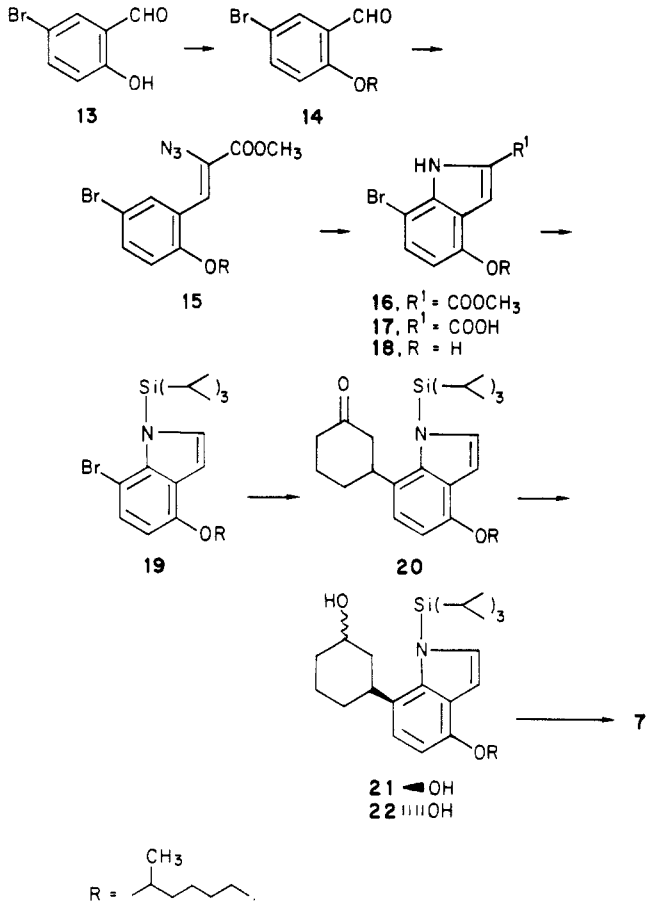

Table I. Effects of Compounds 7 and 8 in the Mouse PBQ Writhing Assay[a]

compd	dose, mg/kg	pretreatment time, min	mean writhes/ mouse	% inhibn of writhing
7	control vehicle,		21.3	
	20 sc	15	16.7	21.6
		60	27.2	0
		120	32.4	0
7	control vehicle,		27.1	
	20 ip	20	24.4	10.0
		60	29.2	0
7	control vehicle,		31.1	
	20 iv	10	24.8	20.3
		30	31.9	0
8[b]	control vehicle		33.6	
	5 sc	60	23.8	29.2
	10 sc	60	15.3	54.5
	20 sc	60	2.9	91.4

[a] N = 10 mice/group. [b] ED_{50} = 8.3 (5.2–13.6) mg/kg sc.

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(17) Assignment of isomers (**21** vs. **22**) was made by comparison (TLC mobility and ^1H NMR examination at 200 MHz) with the corresponding phenolic compounds.[9] cis-Isomer **21**, the more polar of the two, displays absorptions of the cyclohexyl methinyl proton at 3.71 ppm as a triplet of triplets with couplings of 10.2 and 4.8 Hz and of the benzylic proton at 3.15 ppm as a broad triplet of 11-Hz coupling. In trans-isomer **22**, the corresponding protons resonate as a broad singlet at 4.32 ppm and as a broad multiplet at 3.58 ppm, respectively.

The methinyl proton of the cyclohexyl carbon bearing the hydroxyl group appears at δ 3.80 ppm as a triplet of triplets and displays couplings of 10.8 and 3 Hz; the benzylic proton appears at δ 2.82 ppm as a broad triplet (J = 11 Hz), consistent with axially oriented hydrogens.[18] Compound 8 was prepared by a modification of the published procedure and was obtained as an oil as described.[7]

Results and Discussion

Compounds 7 and 8 were tested for analgesic activity in the mouse phenylbenzoquinone writhing test; the results are shown in Table I. The phenolic derivative 8 was found to possess significant analgesic activity, having an ED_{50}, with 95% confidence limits, of 8.3 (5.2–13.6) mg/kg, on sc administration. Under the same experimental condition, morphine has an ED_{50} (95% confidence limits) of 0.60 (0.48–0.78) mg/kg, sc. In contrast, the pyrrolo analogue 7 was essentially devoid of analgesic activity at 20 mg/kg when administered sc, ip, or iv.

In this instance, the pyrrolo ring and the phenolic hydroxyl group are clearly not bioisosteres. The manifestation of this type of bioisosterism will be influenced by the following general considerations:

(1) The phenolic hydroxyl group must be necessary for manifestation of the observed activity, and it must function as a hydrogen-bond donor in its interaction with the receptor.

(2) Because of free rotation about the C–O bond of the phenolic hydroxy group, when it functions as a hydrogen-bond donor, an infinite number of directional vectors can be assumed. Because of the C–O–H bond angle of ~110°, for a linear hydrogen bond, the acceptor nucleus can lie anywhere on the periphery of the base of a cone, with the donor nucleus lying at the apex. Thus, the phenolic hydroxyl group can adjust the directional vector of a hydrogen bond in which it participates so that an effective bond can be formed with a uniquely located acceptor nucleus on the receptor macromolecule. In marked contrast, the pyrrolo NH has a unique directional vector, which may be incompatible with hydrogen-bond formation with a specific receptor-based acceptor nucleus.

(3) The receptor with which the phenolic hydroxyl group interacts may be unable to accommodate the additional space requirements of the pyrrolo ring. Using a program that calculates volumes of molecules,[19] we found that while phenol occupies a volume at 56 Å^3 indole requires a volume of 73.6 Å^3.

(4) The phenolic hydroxyl group may be required to function simultaneously both as a hydrogen-bond donor *and* acceptor; while the pyrrolo analogue can function as a donor, it is incapable of acting as an acceptor.

In the present instance, an additional consideration is relevant; replacement of the phenolic hydroxyl group by a pyrrolo ring may lead to the adoption of a conformation of the heptyloxy side chain or in a torsion angle about the bond joining the aryl moiety and the cyclohexane ring, which are different than those in the corresponding phenol. In that event, the groups that are thought to be involved in binding to the receptor[11] may be unable to assume the orientation that is required for a productive interaction with the receptor. Using molecular mechanics calculations,[20] we have investigated the effect of rotation about the bond joining the cyclohexyl and aromatic rings in 7 and 8; energy minima were observed for 7 with torsion angles about $C_{7a\text{-}7\text{-}1'\text{-}2'}$ of 60° and 240°, while with 8, minima were found at 60° and 250° about $C_{1\text{-}6\text{-}1'\text{-}2'}$. At the present time, therefore, there is no basis for ascribing the inactivity of 7 to any of the factors discussed above. Any or all of them may play a contributory role.

In conclusion, despite the instances cited above[1,2] in which the bioisosterism of the phenolic hydroxyl group and the pyrrolo ring was demonstrated, the results of the present investigation serve as a caveat that this type of "bioisofunctionality" is not universal.

Experimental Section

Pharmacology. A modification of the mouse phenylbenzoquinone (PBQ) writhing test of Siegmund et al.[21] was employed. Groups of 10 male Swiss albino mice (Charles River, Kingston, NY) weighing 15–25 g were injected with 0.3 mL/20 g of body weight of a 0.02% solution of PBQ (2-phenyl-1,4-benzoquinone, Eastman Kodak, Rochester, NY). The mice were placed in individual observation boxes, and the total number of writhes in each group was counted during the following 15-min period. Compound 7 was administered sc, ip, and iv at 20 mg/kg, whereas compound 8 was administered only sc at 5, 10, and 20 mg/kg. Compound 7 was administered 15, 60, or 120 min (for sc), 20 or 60 min (for ip), or 10 or 30 min (for iv) prior to the PBQ injection. Compound 8 was tested subcutaneously 60 min prior to the PBQ. The ED_{50} (dose of drug causing 50% inhibition of writhing relative to vehicle-treated control mice) with 95% confidence limits was determined by the Litchfield–Wilcoxon technique.[22]

Stock solutions of drugs were prepared by dissolving 100 mg of compound in an emulphor/ethanol (1:1) mixture. Dilutions were made with emulphor/ethanol/saline (1:1:18). Control mice were injected with the above vehicle. Emulphor was purchased from GAF Corporation (Linden, NJ).

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Beckman Aculab 2 or on a Perkin-Elmer 291 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM360 or XL-200 instrument, using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in δ units, and coupling constants are in hertz. Mass spectra were recorded on a Hewlett-Packard 9876A spectrometer. Flash chromatography referred to the technique described by Still.[23] Thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was effected with UV light and one of the following stains: 10% phosphomolybdic acid in ethanol, ceric ammonium sulfate (100 mg/10 mL of 35% sulfuric acid), or anisaldehyde (1 mL/1 mL of sulfuric acid/18 mL of ethanol). R_f refers to the ratio of the distance of the spot from the origin to that of the solvent front. Solvents for TLC are indicated. CHN analyses were measured on a Perkin-Elmer 240 analyzer. Anhydrous solvents were distilled from the following reagents: ether and tetrahydrofuran–sodium/benzophenone; methylene chloride and dimethylformamide–calcium hydride.

2-(2-Heptyloxy)-5-bromobenzaldehyde (14). To 503 mg (2.47 mmol) of 5-bromosalicylaldehyde (13) in dry dimethylformamide was added 641 mg (4.6 mmol) of potassium carbonate. To the resulting yellow suspension was added 400 μL (1.6 mmol) of 2-bromoheptane. After heating at 100 °C overnight, another 200 μL (1.6 mmol) of 2-bromoheptane was added, and stirring was continued for another 1.5 h at 100 °C. The reaction mixture was cooled, diluted with water (100 mL), and extracted with ether (3 × 50 mL). The combined organic extracts were washed with 1 M sodium hydroxide (100 mL) and then brine. Drying ($MgSO_4$), followed by flash chromatography (2.5% ether–petroleum ether), provided the product as a colorless oil (681 mg, 92%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 10.3 (s, 1 H, O=CH), 7.9 (d, 1 H, 1.5 Hz), 7.5

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(dd, 1 H, J = 8, 1.5 Hz), 6.75 (d, 1 H, J = 8 Hz), 4.3 (septet, 1 H, OCH); IR 1690 (C=O) cm^{-1}; mass spectrum, m/e 298 (M^+). Anal. ($C_{14}H_{19}BrO_2$) C, H.

2-Carbomethoxy-4-(2-heptyloxy)-7-bromoindole (16). At 0 °C, to 235 mL of freshly prepared 1.5 M sodium methoxide (353 mmol) was added 26.19 g (87.5 mmol) of aldehyde **14** in 240 mL of tetrahydrofuran. To the solution was added 45.2 g (350 mmol) of ethyl azidoacetate in 80 mL of methanol. After stirring overnight at 0–5 °C, water (350 mL) was added, and the reaction mixture was extracted with ether (5 × 300 mL). The combined organic extracts were washed with brine (2×) and dried ($MgSO_4$). After filtration and concentration, the residue retained a considerable amount of water. The residue was diluted with methylene chloride and washed with brine. The organic phase was dried ($MgSO_4$), concentrated, and used directly in the following reaction.

Crude vinyl azide **15** (5.04 g) was passed through a pad of silica gel (10% ether–petroleum ether) and concentrated to provide 2.73 g of material. This was diluted with 200 mL of xylene and then added dropwise to 15 mL of refluxing xylene. TLC analysis of the reaction showed no vinyl azide present. The cooled reaction mixture was concentrated and the residue flash chromatographed (7% ether–petroleum ether) to provide pure indole (1.30 g) as a colorless oil. This procedure was repeated several times with varying amounts of crude vinyl azide (0.56–6 g) to provide a total of 8.04 g (29% based on recovered aldehyde) of indole **16** as a solid (mp 51–52 °C) and 3.46 g of recovered aldehyde: R_f (7% ether–petroleum ether) 0.32; ^1H NMR ($CDCl_3$, 60 MHz) δ 9.1 (br s, 1 H, NH), 7.4 (d, 1 H), 7.5 (s, 1 H), 6.5 (d, 1 H), 4.5 (m, 1 H, OCH), 4.0 (3 H, OCH_3); IR ($CHCl_3$) 3460 (NH), and 1715 (C=O) cm^{-1}; mass spectrum, m/e 367, 369 (M^+). Anal. ($C_{17}H_{22}BrNO_3$) C, H, N.

4-(2-Heptyloxy)-7-bromoindole (18). To a solution of 5.81 g (15.8 mmol) of ester **16** in dioxane was added 31.5 mL (31.5 mmol) of 1 N sodium hydroxide. The reaction was heated at 110 °C (bath temperature), and consumption of ester was monitored by TLC. The reaction mixture was cooled to room temperature, diluted with water (100 mL), and acidified with 1 N hydrochloric acid. The mixture was extracted with ether (4 × 100 mL) and concentrated to provide 6.31 g of the crude acid **17** for which the following chromatographic and spectral data were obtained: R_f (50% ether–petroleum ether–0.5% acetic acid) 0.3; ^1H NMR ($CDCl_3$, 60 MHz) δ 9 (br s, 1 H, OH), 7.8 (br s, 1 H, NH), 7.5 (d, 1 H, J = 2 Hz), 7.3 (d, 1 H, J = 8 Hz), 6.5 (d, 1 H, J = 8 Hz), 4.5 (m, 1 H, OCH); IR ($CHCl_3$) 3470 (NH), 2400–3700 (OH), 1699 (C=O) cm^{-1}.

A mixture of 3.01 g (8.50 mmol) of acid **17** in 21 mL of quinoline containing 386 mg of copper chromite (barium promoted; Aldrich 20,932-5) was heated in a preequilibrated bath at 210 °C for 1 h. The cooled reaction was filtered through a pad of florisil (ether rinses, 800 mL), and the ethereal filtrate was washed with 1 M hydrochloric acid (3 × 300 mL) followed by a brine wash. The organic layer was dried ($MgSO_4$) and flash chromatographed (6% ether–petroleum ether) with the crude product obtained from a 2.0-g run of acid to provide 2.90 g (66%) of pure indole as an oil: R_f (6% ether–petroleum ether) 0.34; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.2 (br s, 1 H, NH), 7.20 (d, 1 H, J = 8.3 Hz), 7.13 (t, 1 H, J = 2.5 Hz), 6.72 (t, 2 H, J = 2.5 Hz), 6.44 (d, 1 H, J = 8.3 Hz), 4.48 (sextet, 1 H, OCH_3), 0.88 (br t, 3 H, CH_3); IR ($CHCl_3$) 3470 (NH) cm^{-1}; mass spectrum, m/e 309 and 311 (M^+). Anal. ($C_{15}H_{20}NOBr$) C, H, N.

***N*-(Triisopropylsilyl)-4-(2-heptyloxy)-7-bromoindole (19).** At −78 °C, to 93.9 mg (0.304 mmol) of indole **18** in 4 mL of dry tetrahydrofuran was added 490 μL (0.49 mmol) of lithium bis(trimethylsilyl)amide (1 M in THF). After stirring at −78 °C for 10 min, 150 μL (0.56 mmol) of triisopropylsilyl triflate was added. The cold bath was removed, and the reaction was monitored by TLC. Upon completion, 50 mL of pH 7 buffer solution was added, and the reaction mixture was extracted with ether (75 mL). The ethereal layer was washed with 1 N hydrochloric acid (30 mL), saturated sodium bicarbonate solution (40 mL), and brine. Drying ($MgSO_4$) and flash chromatography (1% ether–petroleum ether) provided 109 mg (77%) of the protected indole as a colorless oil: R_f (1% ether–petroleum ether) 0.31; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.2–7.3 (m, 2 H), 6.77 (d, 1 H, J = 3.2 Hz), 6.42 (d, 1 H, J = 8.3 Hz), 4.44 (sextet, 1 H, OCH, J = 6 Hz), 2.06 (m, 3 H, CH_3); mass spectrum, m/e 465 and 467 (M^+).

***N*-(Triisopropylsilyl)-4-(2-heptyloxy)-7-(3-oxocyclohexyl)indole (20).** At −78 °C, to 3.44 g (7.40 mmol) of bromoindole **19** in dry ether (20 mL) was added dropwise *tert*-butyllithium (10.5 mL, 16.3 mmol, 1.55 M in pentane). During the *tert*-butyllithium addition, a white viscous slurry resulted. This slurry was diluted with another 30 mL of dry ether. After stirring at −78 °C for 45 min, metalation was complete, as judged by TLC. To the reaction mixture was added, via cannula, an ethereal solution of copper iodide, 1.69 g (8.88 mmol), and tributylphosphine (5.05 mL, 19.4 mmol), precooled to −78 °C. After 1 h at −78 °C, 1.09 mL (8.9 mmol) of boron trifluoride etherate was added to the yellow slurry, followed immediately by a very slow addition, over a 15-min period, via cannula, of cyclohexenone (1.48 mL, 14.8 mmol) in ether (20 mL), precooled to −78 °C. The resulting orange solution was stirred at −78 °C for 2 h and then quenched with pH 7 buffer. The reaction mixture was extracted with ether (3 × 300 mL), washed with brine solution, and dried ($MgSO_4$). Flash chromatography (1% ether–petroleum ether to 10% ether–petroleum ether) provided 2.08 g (58%) of the ketone as an oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24 (d, 1 H, J = 3.5 Hz), 7.03 (d, 1 H, J = 8.0 Hz), 6.75 (d, 1 H, J = 3.2 Hz), 6.57 (d, 1 H, J = 7.9 Hz), 4.47 (sextet, 1 H, OCH, J = 6.0 Hz), 3.5 (m, 1 H, benzylic CH), 1.16 (d, 18 H, isopropyl CH_3), 0.88 (br t, 3 H, CH_3); IR ($CHCl_3$) 1605 (C=O) cm^{-1}; mass spectrum, m/e 483 (M^+).

***N*-(Triisopropylsilyl)-4-(2-heptyloxy)-7-[*cis*- and *trans*-(3-hydroxycyclohexyl)]indole (21 and 22).** To 989 mg (2.05 mmol) of ketone **20** at −78 °C in tetrahydrofuran (20 mL) and methanol (5 mL) was added 193 mg (5.12 mmol) of sodium borohydride. It appeared that the reaction was incomplete by TLC, but it was found later that alcohol **22** has the same R_f as the ketone. The reaction mixture was warmed to −40 °C; 193 mg (5.12 mmol) of sodium borohydride was added, and the reaction mixture was warmed to 0 °C. The reaction mixture was recooled to −40 °C, sodium borohydride added (193 mg, 5.12 mmol), and the reaction mixture allowed to warm to 0 °C. Again by TLC, the reaction still seemed incomplete. The reaction mixture was quenched carefully with saturated aqueous sodium potassium tartrate solution (300 mL) and extracted with ether (3 × 200 mL). The combined ethereal extracts were washed with brine, dried ($MgSO_4$), and flash chromatographed (20% ether–petroleum ether and 100% ether) with crude product obtained from the reduction of 0.47 g total of ketone to provide 1.17 g (82%) of cis isomer **21** and 181 mg (13%) of trans isomer **22** as colorless oils. Cis isomer **21**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25 (d, 1 H, J = 3 Hz), 7.02 (d, 1 H, J = 8 Hz), 6.97 (d, 1 H, J = 3 Hz), 6.58 (d, 1 H, J = 8 Hz), 2.47 (sextet, 1 H, ArOCH), 3.71 (tt, 1 H, OCH, J = 4.8, 10.2 Hz), 3.15 (br t, 1 H, benzylic H, J = 11 Hz); R_f (40% ether–petroleum ether) 0.30. Trans isomer **22**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.25 (d, 1 H, J = 3 Hz), 7.10 (d, 1 H, J = 8 Hz), 6.78 (d, 1 H, J = 3 Hz), 6.58 (1 H, J = 8 Hz), 4.50 (sextet, 1 H, ArOCH), 4.32 (br s, 1 H, OCH), 3.58 (m, 1 H, benzylic H); IR ($CHCl_3$) 3610 (OH) cm^{-1}; mass spectrum, m/e 485 (M^+); R_f (40% ether–petroleum ether) 0.76.

4-(2-Heptyloxy)-7-[(*Z*)-(3-hydroxycyclohexyl)]indole (7). To a solution of 1.02 g (2.11 mmol) of alcohol **21** in 20 mL of dry tetrahydrofuran at 0 °C was added 2.53 mL (2.53 mmol) of tetra-*n*-butylammonium fluoride. After 15 min, 400 mL of water was added, and the reaction mixture was extracted with ether (3 × 175 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and flash chromatographed (80% ether–petroleum ether to 100% ether) to provide 685 mg (87%) of analytically pure product as a colorless foam: ^1H NMR ($CDCl_3$, 200 MHz) δ 8.13 (br s, 1 H, NH), 7.10 (t, 1 H, J = 2.9 Hz), 6.92 (d, 1 H, J = 8.0 Hz), 6.67 (q, 1 H, J = 1.9, 2.9 Hz), 6.47 (d, 1 H, J = 8.0 Hz), 4.48 (sextet, 1 H, ArOCH), 3.80 (tt, 1 H, OCH, J = 3, 10.8 Hz), 2.82 (br t, benzylic H), 0.88 (br t, 3 H, CH_3); IR ($CHCl_3$) 3600 (OH), 3480 (NH) cm^{-1}; mass spectrum, m/e 329 (M^+); R_f (80% ether–petroleum ether) 0.31. Anal. ($C_{21}H_{31}NO_2$) C, H, N.

Registry No. **7**, 102651-69-4; **14**, 102651-61-6; **15**, 102651-62-7; **16**, 102651-63-8; **17**, 102651-64-9; **18**, 102651-65-0; **19**, 102651-66-1; **20**, 102651-67-2; **21/22**, 102651-68-3; 2-cyclohexenone, 930-68-7; 5-bromosalicylaldehyde, 1761-61-1; 2-bromoheptane, 1974-04-5.