Total Synthesis of (-)-Ovatolide

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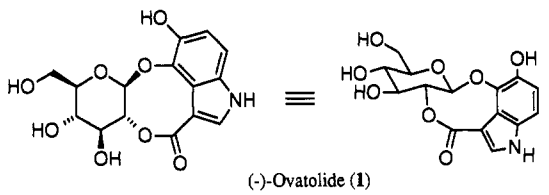
Received October 28, 1992

The total synthesis of (-)-ovatolide (1), a tetracyclic indole-containing β-glucosyl derivative with an unusual pyrano[2,3-*b*][1,4]dioxocan-6-one system, is described. The β-glucosidic linkage arose from regio- and stereocontrolled reaction of a protected 1,2-epoxyglucal derivative with 4-hydroxy-5-(benzyloxy)indole, and a lactonization reaction afforded the central dioxocanone system. An alternative strategy that afforded the tetracyclic framework as a mixture of epimers is also described.

(-)-Ovatolide (1) is an indole-containing β-glucosyl derivative isolated from the leaves of *Bridelia ovata* Decne or *Bridelia siamensis* Craib (Euphorbiaceae), a Thai medicinal plant used in folk medicine as a laxative, a febrifuge, and an astringent.[1] X-ray crystallography[2] of (-)-ovatolide shows a structure containing a β-glucoside subunit as a part of a pyrano[2,3-*b*][1,4]dioxocane system fused to the *cd* sides of a substituted indole. The singularity of the structure, together with the need for significant amounts of material for biological studies (only few milligrams of this compound can be isolated from several kilograms of dried leaves), prompted us to undertake its total synthesis.



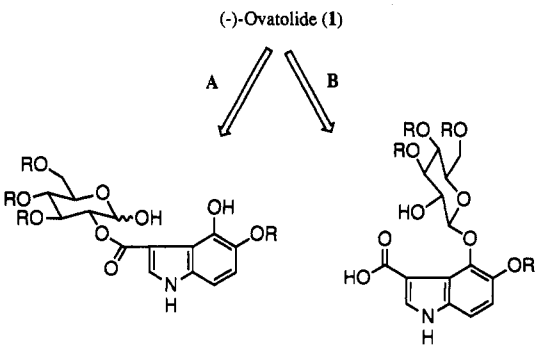
(-)-Ovatolide (1)

Results and Discussion

Retrosynthetic analysis of ovatolide led to two synthetic strategies (A and B, see Scheme I), both having as a key step the elaboration of the central 1,4-dioxocanone system from a protected glucoindole derivative. Whereas in strategy A the ester bond is formed first and the 5-oxoheptanolide system arises from a ketalization reaction, in strategy B this sequence of bond-forming reactions is reversed. In both cases, the required glucoindole precursor is formed in a convergent approach by condensation of suitably functionalized sugar and indole moieties.

In order to test the feasibility of strategy A, synthetic studies of simplified models were undertaken. Thus, condensation of easily available glucoside **5a**[3] with 4-(benzyloxy)indole-3-carboxylic acid (**3**)[4] was attempted. Although solubility problems associated with **3** precluded its condensation with **5a**, the corresponding *N*-benzyl derivative **4** afforded desired ester **6** in moderate yield (Scheme II).

Scheme I



Complete deprotection and simultaneous ketalization of **6** were first attempted. In all cases, debenzylation under acidic conditions[5] failed to afford any ketalization product, and a thermodynamic mixture of hemiketals **8** in a α/β ratio of ca. 6:4, based on NMR, was obtained instead. This mixture remained unaltered even after prolonged exposure to acidic conditions at room temperature, and total decomposition occurred upon treatment at higher temperatures. Activation of the anomeric hydroxyl group of **9** by means of the Mitsunobu reaction[6] followed by intramolecular ketalization (Scheme II) was found to be an alternative to the above approach. Thus, condensation of indole **4** with silylated sugar **5b** to give **7** and selective unmasking of the *O*-benzyl groups led to glucoindole **9**. Treatment of **9** with Ph_3P–DEAD in THF afforded an approximately 1:1 mixture (by NMR) of epimers **10** at the anomeric carbon in about 30% isolated yield. Although the pyrano[2,3-*b*][1,4]dioxocane system was obtained by this approach, the modest overall yields and the presumed difficulties associated with the separation of epimers **10** made the approach unpractical, and alternative synthetic routes were sought.

Strategy B relied on the regio- and stereocontrolled epoxide opening of 1,2-epoxyglycals.[7] We believed that treatment of 4-hydroxy-5-(benzyloxy)indole (**17**) (Scheme III) with epoxyglucal 18[3] (Scheme IV) would allow for the regio- and stereoselective formation of the β-glucoside linkage, thus overcoming one of the major drawbacks of the above strategy. Required indole **17** was synthesized by a conventional procedure, as described in Scheme III.

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(1) Smitinand, T. *Thai Plant Names (Botanical Name-Vernacular Names)*; The Forest Herbarium: Royal Forest Department Thailand, 1980; p 53.

(2) Clardy, J. et al. Unpublished results.

(3) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

(4) Marchelli, R.; Hutzinger, O.; Heacock, R. A. *Can. J. Chem.* **1969**, *47*, 4375.

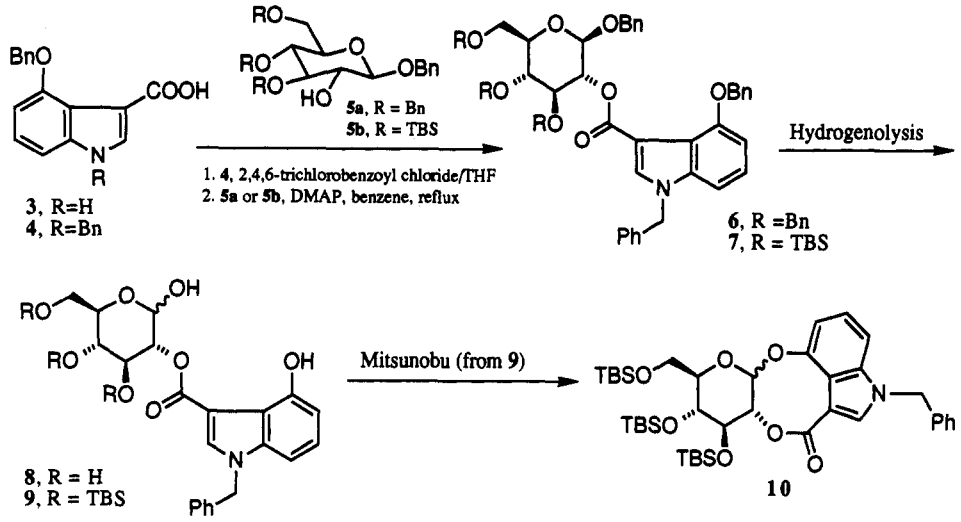
(5) Hydrogenation (10% Pd/C, EtOAc, HCl-THF) both at atmospheric and at medium pressure (50 psi), as well catalytic transfer hydrogenation (HCOOH, 10% Pd/C, EtOAc), failed to afford any ketalization product. In none of the above experiments, hydrogenolysis of the *N*-benzyl group was observed.

(6) Mitsunobu, O. *Synthesis* **1983**, 1.

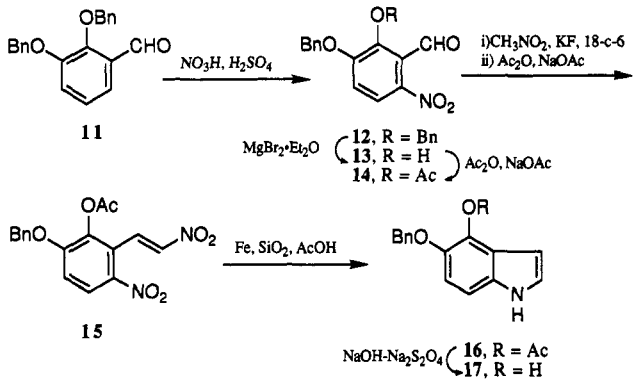
(7) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655.

0022-3263/93/1958-2862$04.00/0

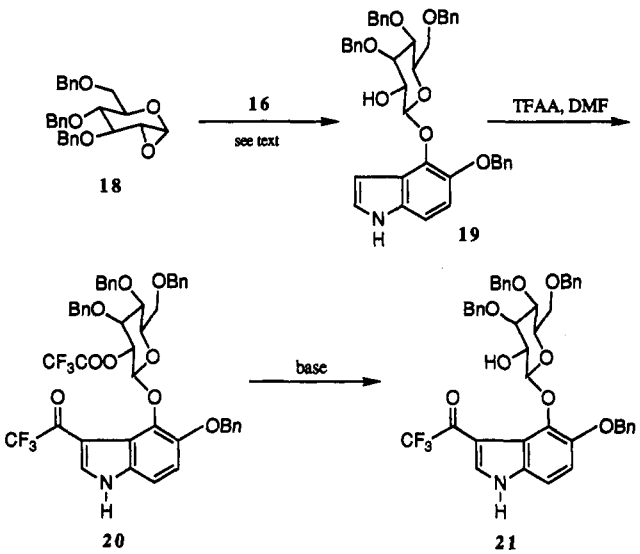
Scheme II



Scheme III



Scheme IV



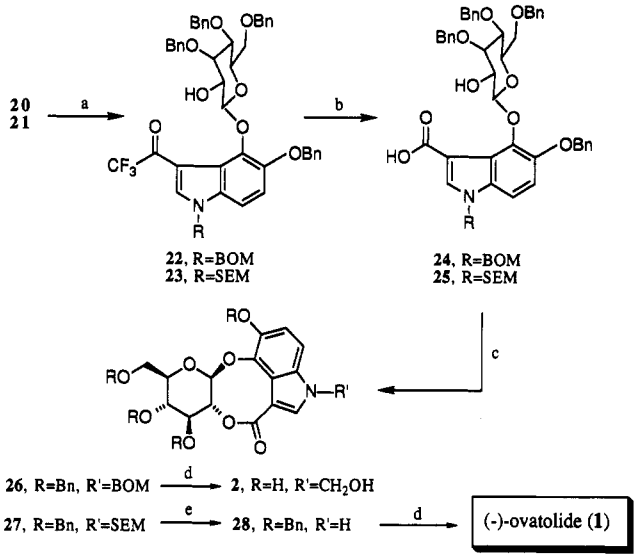
Nitration of 2,3-bis(benzyloxy)benzaldehyde (11) afforded a mixture of 5- and 6-nitro derivatives, which were separated by flash chromatography. Selective monodebenzylation[8] of 6-nitro isomer **12** gave **13**, which after acetylation, condensation with nitromethane, and further in situ dehydration,[9] afforded dinitrostyrene **15**. Finally, silica gel-assisted reductive cyclization of **15** in the presence of Fe/AcOH and subsequent hydrolysis of the resulting acetylindole **16** with NaOH–$Na_2S_2O_4$[10] afforded required hydroxyindole **17** in about 30% overall yield from **12**.

The main problem associated with the condensation of indole **17** with epoxyglucal **18** was the instability of the required indole potassium salt. It is known in the literature[10] that hydroxyindoles are very easily oxidized and that their instability is increased under basic conditions and by the presence of electron-donating groups on the ring. Optimization of the condensation reaction was carried out with 4-hydroxyindole as model compound. Treatment of **18** with 4-hydroxyindole in the presence of a stoichiometric amount of K_2CO_3[7,11] was unsuccessful; no reaction took place in refluxing acetone, whereas a complex mixture of products was obtained at 90–100 °C in DMF. The best conditions found were preformation of the indole potassium salt with a KOH–MeOH solution followed by solvent removal and overnight reaction with **18** in DMF at 60 °C in the presence of 18-crown-6. However, initial attempts to obtain the potassium salt of **17** by treatment with a KOH–MeOH solution gave instantaneous decomposition. The use of potassium *tert*-butoxide in polar aprotic solvents (DMF, DME, or THF) was also unsuccessful, since the initially formed salt decomposed prior to its reaction with epoxyglucal **18**. To our delight, the above problems could be solved by deprotection of acetylindole **16** in aqueous NaOH–$Na_2S_2O_4$ and in situ condensation with **18** in DMF–H_2O to afford glucosyl derivative **19** in about 50% isolated yield (Scheme IV).

Functionalization of the indole 3-position was carried out by treatment of **19** with TFAA. By careful choice of conditions, bis(trifluoroacetyl) derivative **20** was obtained in high yields. Trifluoroacetylation of indole is well documented in the literature.[12a,b] It is known that N- and C-substitution are competitive processes and that the final product composition is strongly dependent on the choice of experimental conditions, especially the solvent. In our case, treatment of indolylglucoside **19** with TFAA (3 equiv) in DMF at 0 °C for 1 h cleanly afforded bis(trifluoroacetyl) derivative **20** in high yield (around 80%). As expected, the trifluoroacetate ester moiety proved very sensitive toward basic conditions; some hydrolysis product **21** was occasionally obtained after prolonged treatment with

(8) Baldwin, J. E.; Haraldsson, G. *Acta Chem. Scand.* **1986**, *B40*, 400.
(9) Murphy, B. P. *J. Org. Chem.* **1985**, *50*, 5873.
(10) Beer, R. J. S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.* **1948**, 2223.
(11) Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5448.
(12) (a) Cipiciani, A.; Clementi, S.; Linda, P.; Savelli, G.; Sebastiani, G. V. *Tetrahedron* **1976**, *32*, 2595. (b) Cipiciani, A.; Clementi, S.; Giulietti, G.; Marino, G.; Savelli, G.; Linda, P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 523.

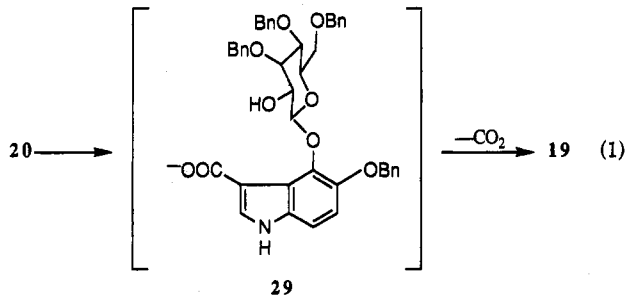
Scheme V[a]



[a] Key: (a) NaH, THF, R'Cl (1.5 equiv), 5 °C (75%); (b) NaH, DMF–H_2O, 50 °C (79%); (c) lactonization (see text) (72%); (d) $Pd(OH)_2$, EtOAc, AcOH (92%); (e) Bu_4NF, THF (85%).

aqueous $NaHCO_3$ during the workup. However, the presence of **21** was not a serious drawback since **21** could also be successfully used in the next synthetic step (Scheme V).

Although hydrolysis of 3-(trifluoroacetyl)indoles to the corresponding carboxylic acids is well precedented in the literature,[13,14] the reaction was not straightforward in our case. Treatment of **20** with an aqueous ethanolic NaOH solution at reflux temperature for 1 h afforded exclusively indolylglucoside **19**, whereas experiments at room temperature showed only hydrolysis to **21**. Formation of **19** can be explained by assuming the initial formation of carboxylate salt **29** (eq 1), arising from hydrolysis of **20**.[15]



We solved this problem elegantly by using our recently developed chemistry involving the transformation of aryl trifluoromethyl ketone hydrates into aryl carboxylic acids with NaH in DMF.[16] When the chemistry is applied to indole 3-trifluoroacetyl derivatives, protection of the indole NH is required.[17] For uniformity with the rest of protecting groups, *N*-BOM (*N*-[(benzyloxy)methyl]) protection was considered first. Protection of indolylglucoside **20** with BOMCl required a careful choice of conditions. Initial attempts in acetone with K_2CO_3 as a base failed;[18] only **21**, arising from hydrolysis of the trifluoroacetate group in **20**, was obtained. Alkylation of **20** was cleanly carried out with NaH in THF in the presence of 1.5 equiv of BOMCl at 0 °C for 10 min. Under these conditions, compound **22** was obtained in high purity and yield. However, the use of excess BOMCl, higher temperatures, or prolonged reaction times led to complex mixtures.

Treatment of **22** with NaH in 2% aqueous DMF afforded required hydroxy acid **24** in good yield and high purity. Cyclization of **24** according to the lactonization protocol initially described by Corey and Nicolaou[19] and later modified by Gerlach and Thalman[20] furnished desired 5-oxoheptanolide system **26** in 70–75% yield. However, hydrogenolysis of **26** under both neutral and acidic conditions afforded *N*-(hydroxymethyl)ovatolide **2**. Attempts to remove the hemiaminal moiety were unsuccessful since compound **2** readily decomposed even under very mild basic conditions (Triton B in THF–H_2O at 50 °C).[21] As indicated above, the instability of **2**, as well as that of (−)-ovatolide, toward basic conditions can be attributed to the hydroxyindole moiety.

In the light of the above results, we planned a stepwise deprotection strategy that incorporated an indole N-protecting group removable late in the synthesis under mild and selective conditions. The [(trimethylsilyl)ethoxy]-methyl group (SEM)[22] was chosen for this purpose. A reaction sequence identical to that described above for the BOM series led to differentially O- and N-protected (−)-ovatolide derivative **27** (Scheme V). Removal of the SEM group (1.0 M Bu_4NF in THF in the presence of ethylendiamine[23] and molecular sieves[24]) followed by hydrogenolysis ($Pd(OH)_2$, EtOAc, AcOH drops) afforded (−)-ovatolide (**1**) in 73% combined yield from **27**. Both synthetic and natural compounds exhibited identical physical properties, thus establishing the absolute configuration of (−)-ovatolide to be the one related to (−)-glucose.

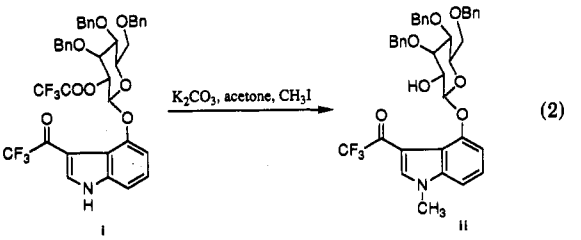
Biological studies are currently being undertaken in order to evaluate the pharmacological profile of this previously unreported natural product.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification.

(13) Katner, A. S. *Org. Prep. Proced.* **1970**, *2*, 297.
(14) Mackie, R. K.; Mhatre, S.; Tedder, J. M. *J. Fluorine Chem.* **1977**, *10*, 437.
(15) Decarboxylation of indole-3-carboxylates at high temperatures is also well precedented in the literature (see, for example: Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970).
(16) Delgado, A.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 2789.
(17) Although reported for trifluoroacetophenone derivatives, this transformation is also suitable for indole derivatives, provided that the NH group is masked; otherwise, no neat transformation is observed because of the reaction between NaH and the acidic indole NH.

(18) These conditions proved effective in the alkylation of model compound **i** with MeI to give **ii**.



The failure observed for **20** can be explained in terms of the lower acidity of the indole NH due to the presence of the *p*-benzyloxy group.
(19) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
(20) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.
(21) Anderson, H. J.; Groves, J. K. *Tetrahedron Lett.* **1971**, 3165–3166.
(22) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley Interscience: New York, 1991; p 393.
(23) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203.
(24) Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417.

Solvents were purified by standard techniques.[25] The normal processing of organic extracts consisted of washing the extract with brine, drying over Na_2SO_4, filtering, and concentrating with a rotary evaporator. Melting points are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent. Flash chromatography refers to the procedure of Still, Kahn, and Mitra.[26] Chemical shifts in NMR spectra are reported in δ-scale (ppm) relative to TMS. IR data are given in cm^{-1}.

2,3-Bis(benzyloxy)-6-nitrobenzaldehyde (12). A solution of 2,3-bis(benzyloxy)benzaldehyde (11)[27] (20 g, 62.9 mmol) in glacial AcOH (400 mL) was cooled to 5 °C and treated with fuming HNO_3 (95 mL). After being stirred at room temperature for 3 h, the mixture was poured over ice and kept cold until an abundant yellow precipitate formed. Filtration and H_2O washings (4 × 150 mL) afforded 15 g (65%) of a mixture of 5- and 6-nitro derivatives. Purification by flash chromatography (CCl_4/EtOAc, 95:5 to 70:30, ratio mixture of isomers/silica gel 1/120) afforded 8.6 g (37%) of the 5-nitro derivative and 6.2 g (26%) of 6-nitro isomer 12. Compound 12: IR ($CHCl_3$) 3050, 1705, 1525, 1275; ^1H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1 H), 7.95–7.12 (AB, 2 H, J_{AB} = 9.3 Hz), 7.48–7.37 (m, 5 H), 7.31 (m, 5 H); mp 137–139 °C. Anal. Calcd for $C_{21}H_{17}NO_5$: C, 69.40; H, 4.71; N, 3.85. Found: C, 69.30; H, 4.58; N, 3.67.

3-(Benzyloxy)-2-hydroxy-6-nitrobenzaldehyde (13). 6-Nitro derivative 12 (4.3 g, 11.8 mmol) was dissolved in benzene (210 mL) and ether (33 mL) under argon and was heated to 75 °C. To this solution was added the $MgBr_2$–Et_2O complex (3.3 g, 13 mmol) portionwise. After being stirred at reflux temperature for 12 h, the mixture was cooled, poured over 2 N HCl–ice, and diluted with ether. The organic extracts were concentrated, taken up in CH_2Cl_2 (300 mL), washed with water until the color discharged, and treated in the usual way to afford 2.26 g (70%) of 13 as a yellow solid, which was used without further purification: IR ($CHCl_3$) 3200, 3050, 1660, 1525, 1450, 1270; ^1H NMR (300 MHz, $CDCl_3$) δ 10.4 (br s, 1 H), 8.3 (br s, 1 H), 7.65–7.05 (AB, 2 H, J_{AB} = 9.6 Hz), 7.47–7.32 (m, 5 H), 5.22 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 154.1, 152.6, 142.9, 135.2, 128.8, 128.5, 127.3, 117.4, 116.1, 113.4, 71.6. Anal. Calcd for $C_{14}H_{11}NO_5$: C, 61.53; H, 4.06; N, 5.12. Found: C, 61.69; H, 4.22; N, 5.18.

2-Acetoxy-3-(benzyloxy)-6-nitrobenzaldehyde (14). Compound 13 (2.2 g, 8.3 mmol) was stirred at 60 °C in acetic anhydride (15 mL) with sodium acetate (150 mg) for 45 min. The reaction mixture was poured onto ice and stirred until a powdery solid formed. The dispersion was filtered, and the solid was washed with cold H_2O and dried to yield 14 (2.5 g, 95%): IR (CCl_4) 1775, 1705, 1575, 1570; ^1H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1 H), 8.05–7.06 (AB, 2 H, J_{AB} = 9.6 Hz), 7.37–7.25 (m, 5 H), 5.15 (s, 2 H), 2.1 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 1679, 156.2, 140.1, 137.9, 134.7, 129.1, 128.7, 128.5, 127.0, 123.7, 114.2, 71.5, 19.9; mp 119–121 °C. Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.15; N, 4.44. Found: C, 60.85; H, 4.07; N, 4.39.

2-Acetoxy-3-(benzyloxy)-6,β-dinitrostyrene (15). Compound 14 (2.5 g, 7.93 mmol) was stirred for 12 h under argon at 10 °C with *N*-methylmorpholine (40 mL), KF (200 mg), 18-crown-6 (70 mg), and CH_3NO_2 (2.4 g, 40 mmol). The mixture was then poured into acetic anhydride (20 mL) containing sodium acetate (450 mg) and warmed to 60 °C. After 1 h, the reaction was poured over ice and stirred until a fine powder resulted. The solid was filtered and then taken up in EtOAc (100 mL), and the organic extracts were treated in the usual way to afford a red solid. Purification by flash chromatography (CCl_4/EtOAc (90:10)) afforded 1.8 g (65%) of 15: IR ($CHCl_3$) 1770, 1700, 1580; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23–8.13 (m, 2 H), 7.42–7.31 (m, 5 H), 7.25–7.11 (AB, 2 H, J_{AB} = 9.6 Hz), 5.20 (s, 2 H), 2.25 (s, 3 H); mp 144–147 °C. Anal. Calcd for $C_{17}H_{14}N_2O_7$: C, 56.98; H, 3.93; N, 7.82. Found: C, 57.10; H, 3.86; N, 7.31.

4-Acetoxy-5-(benzyloxy)indole (16). A mixture of dinitrostyrene 15 (325 mg, 0.91 mmol), silica gel (70–230 mesh, 2.3 g), reduced iron powder (870 mg), glacial AcOH (5 mL), and toluene (10 mL) was heated to 90 °C under argon with efficient mechanical stirring. After 10 min, the mixture was filtered, and the solids were washed with EtOAc (3 × 50 mL). The combined organic extracts were treated in the usual way to give a dark oil. Purification by flash chromatography (CCl_4/EtOAc (90:10)) afforded 163 mg (64%) of indole 16: IR (CCl_4) 3490, 3010, 1775, 1540; ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (br s, 1 H), 7.40–7.20 (m, 5 H), 7.07 (m, 2 H), 6.91 (B of an AB, 1 H, J_{AB} = 9.0 Hz), 6.32 (m, 1 H), 5.05 (s, 2 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 143.7, 137.9, 133.2, 128.4, 127.7, 127.5, 125.6, 122.9, 112.8, 108.8, 99.1, 73.5, 20.5. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.84; H, 5.39; N, 4.99. Found: C, 73.12; H, 5.52; N, 5.23.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)oxy]indole (19). A solution of indole 16 (700 mg, 2.49 mmol) in DMF (12 mL) at 5 °C under Ar was treated with 6 mL of a NaOH–$Na_2S_2O_4$ aqueous solution (prepared by adding 3 mL of 1.15 M $Na_2S_2O_4$ to 3 mL of 1.25 N NaOH). After the solution was stirred at 5 °C for 15 min, neat 15-crown-5 (550 mg, 2.5 mmol) and then a solution of epoxysugar 18[3] (3.24 g, 7.5 mmol) in DMF (25 mL) were added. After overnight stirring at room temperature, the mixtue was poured over crushed ice and extracted with ether (3 × 50 mL). Normal workup followed by flash chromatography (CCl_4/EtOAc (85:15)) afforded 717 mg of 19 (43% yield based on starting indole): $[\alpha]^{25}_D$ −21.3° (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$) 3480, 1505, 1220; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1 H), 7.55–7.20 (m, 20 H), 7.12–6.90 (m, 4 H), 5.20 (AB, 2 H, J_{AB} = 15.0, 10.5 Hz), 5.12–4.58 (m, 6 H), 4.76 (d, 1 H, *J* = 7.9 Hz), 4.12 (br s, 1 H), 3.96 (t, 1 H, *J* = 7.5 Hz), 3.91–3.55 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.4, 139.1, 138.6, 137.3, 133.8, 128.6, 128.3, 128.1, 127.9, 127.7, 127.6, 127.1, 124.9, 123.3, 113.2, 107.5, 106.1, 101.3, 84.7, 75.7, 74.9, 74.8, 74.4, 73.6, 69.6; FAB MS *m/z* 672, 564, 420, 330, 239. Anal. Calcd for $C_{42}H_{41}NO_7$: C, 75.17; H, 6.16; N, 2.09. Found: C, 74.80; H, 6.12; N, 2.16; mp 121–123 °C.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-2-*O*-(trifluoroacetyl)-β-D-glucopyranosyl)oxy]-3-(trifluoroacetyl)indole (20). Glucoside 19 (350 mg, 0.52 mmol) was dissolved in DMF (7 mL) under argon, and the resulting solution was cooled at 5 °C. Neat trifluoroacetic anhydride (220 μL, 1.56 mmol) was added dropwise, and the solution was stirred in an ice–water bath for 1 h. The reaction mixture was quenched by pouring it over ice. Ether extractions (3 × 30 mL), normal workup, and flash chromatography of the residue (CCl_4/EtOAc (80:20)) gave 370 mg (83%) of 20: $[\alpha]^{25}_D$ −34.1° (*c* 1.8, CH_2Cl_2); IR (CCl_4) 3100, 2900, 1760, 1650, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (br s, 1 H), 7.65–7.13 (m, 20 H), 6.95 (m, 2 H), 6.82 (s, 2 H), 5.75 (t, 1 H, *J* = 9 Hz), 5.45 (d, 1 H, *J* = 7.6 Hz), 5.12–5.02 (AB, 2 H, J_{AB} = 13.2, 7.2 Hz), 4.85–4.65 (m, 5 H), 4.45 (A of an AB, 1 H, J_{AB} = 11.8 Hz), 4.15–4.02 (AB, 2 H, J_{AB} = 12.1 Hz), 3.82–3.68 (m, 2 H), 3.55–3.35 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.46 ($^2J_{C-F}$ = 34.2 Hz), 156.45 ($^2J_{C-F}$ = 43.3 Hz), 146.9, 137.8, 137.6, 137.2, 136.7, 133.3, 128.6, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 121.5, 120.4 (q, J_{C-F} = 287 Hz), 114.9 (q, J_{C-F} = 275 Hz), 114.7, 110.6, 108.9, 99.5, 82.3, 78.2, 77.6, 75.9, 75.2, 74.9, 73.3, 72.8, 68.7; HRMS (FAB) calcd for $C_{46}H_{38}F_6NO_9$ $(M - H)^+$ 862.2447, found 862.2449.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)oxy]-*N*-[(benzyloxy)methyl]-3-(trifluoroacetyl)indole (22). According to the method described for 23 (see below), 20 (62.5 mg, 0.072 mmol) was treated with NaH (8.7 mg, 0.36 mmol) and BOMCl (22.5 mg, 0.145 mmol) in THF (2 mL) to afford 50 mg (78%) of 22 after flash chromatography (hexanes/EtOAc (80:20)): $[\alpha]^{25}_D$ −2.0° (*c* 2.5, CH_2Cl_2); IR (CCl_4) 3490, 3050, 2900, 1675, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (br s, 1 H), 7.42–6.95 (m, 27 H), 5.31 (AB, 2 H, J_{AB} = 12.0 Hz), 5.12–4.92 (m, 4 H), 4.72 (AB, 2 H, J_{AB} = 11.4 Hz), 4.38 (B of an AB, 1 H, J_{AB} = 12.0 Hz), 4.28 (s, 2 H), 4.23–4.07 (AB, 2 H, J_{AB} = 12.1 Hz), 3.95 (t, 1 H, *J* = 5.4 Hz), 3.82 (br s, 1 H), 3.55–3.42 (m, 2 H), 3.40–3.25 (m, 2 H), 3.18 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (q, $^2J_{C-F}$ = 33.9 Hz), 147.2, 140.4, 139.2, 138.5, 137.9, 137.2, 135.8, 133.7, 128.5–127.1 (aromatic), 121.8, 117.3 (q, J_{C-F} = 296.5 Hz), 115.9, 110.9, 106.6, 103.7, 84.6, 77.6, 75.9, 75.6, 75.4, 75.1, 74.7, 74.6, 73.9, 73.4, 73.2, 70.6, 70.3, 69.2; HRMS (FAB) calcd for $C_{52}H_{48}F_3NO_9$ $(M)^+$ 887.327, found 887.325.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)oxy]-3-(trifluoroacetyl)-*N*-[[2-(trimethylsilyl)ethoxy]-methyl]indole (23). A solution of compound 20 (110 mg, 0.13 mmol) in 5 mL of THF was added dropwise to a suspension of NaH (25 mg, 1.04 mmol) in THF (1 mL) under argon at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, 390 μL

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of 0.5 N solution of SEMCl in THF (0.195 mmol) was added. The reaction mixture was stirred at 5 °C for an additional 30 min, poured over ice, and extracted with 3 × 20 mL of EtOAc. Normal workup of the organic extracts gave a residue, which, after purification by flash chromatography (CCl_4/EtOAc (80:20)), afforded 87 mg (75%) of **23**: $[\alpha]^{25}_D$ −3.6° (*c* 1.5, CH_2Cl_2); IR (CCl_4) 3400, 2950, 2780, 1680, 1520; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.52–7.05 (m, 22 H), 5.45 (br s, 2 H), 5.25–5.05 (m, 3 H), 4.85 (m, 2 H), 4.65–4.35 (m, 2 H), 4.35–4.25 (AB, 2 H, J_{AB} = 12.1 Hz), 4.15 (t, 1 H, *J* = 7.2 Hz), 3.95 (br s, 1 H), 3.82–3.38 (m, 6 H), 3.32 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (q, $^2J_{C-F}$ = 34.2 Hz), 146.9, 140.4, 139.1, 138.4, 138.1, 137.1, 133.7, 128.4–127.1 (aromatic), 121.5, 118.2 (q, J_{C-F} = 293 Hz), 115.8, 110.5, 106.6, 103.8, 84.4, 77.4, 76.7, 75.8, 75.1, 74.8, 74.7, 73.2, 73.1, 68.9, 66.7, 17.4, −1.6; HRMS (FAB) calcd for $C_{50}H_{54}F_3NO_9Si$ $(M)^+$ 897.3520, found 897.3524.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)oxy]-*N*-[(benzyloxy)methyl]indole-3-carboxylic Acid (24). According to the method described below for the synthesis of **25**, compound **22** (252 mg, 0.28 mmol) afforded 185 mg (79%) of acid **24**: $[\alpha]^{25}_D$ −8.1° (*c* 1.2, CH_2Cl_2); IR (CCl_4) 3480, 3050, 2980, 1740, 1570; ^1H NMR (300 MHz, $CDCl_3$) δ 7.9 (s, 1 H), 7.48–7.03 (m, 27 H), 5.40 (s, 2 H), 5.24 (d, 1 H, *J* = 8.2 Hz), 5.18 (AB, 2 H, J_{AB} = 7.2 Hz), 4.83 (AB, 2 H, J_{AB} = 10.7 Hz), 4.82–4.50 (AB, 2 H, J_{AB} = 10.8 Hz), 4.41–4.21 (AB, 2 H, J_{AB} = 12.5 Hz), 4.32 (s, 2 H), 3.87 (t, 1 H, *J* = 10.7 Hz), 3.52 (m, 4 H), 3.35 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 145.5, 138.7, 138.5, 138.3, 137.8, 137.4, 136.6, 136.2, 133.8, 128.6, 128.5, 128.2–127.1 (aromatic), 120.9, 113.8, 108.3, 104.5, 84.7, 75.9, 74.9, 74.8, 74.7, 73.5, 73.3, 70.4, 69.0, 29.5; HRMS (FAB) calcd for $C_{51}H_{49}NO_{10}$ $(M)^+$ 835.334, found 835.332.

5-(Benzyloxy)-4-[(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)oxy]-*N*-[[2-(trimethylsilyl)ethoxy]methyl]indole-3-carboxylic Acid (25). A suspension of NaH (30 mg, 1.3 mmol) in DMF (0.8 mL) was treated with a solution of **23** (195 mg, 0.22 mmol) in wet DMF (5 mL containing 1.5% v/v of H_2O). After being stirred at 70 °C for 15 min, the mixture was poured over ice and extracted with ether (3 × 20 mL). The organic extracts were treated in the usual way to afford 148 mg (79%) of acid **25**, which was used without further purification. A sample was purified by flash chromatography ($CHCl_3$/acetone (98:2)): $[\alpha]^{25}_D$ −13.3° (*c* 2.8, CH_2Cl_2); IR (CCl_4) 3300, 3050, 2950, 1740 (br), 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1 H), 7.78–7.32 (m, 22 H), 5.57 (s, 2 H), 5.56 (d, 1 H, *J* = 10.8 Hz), 5.51–5.38 (AB, 2 H, J_{AB} = 12.2 Hz), 5.22 (A of an AB, 1 H, J_{AB} = 12.3 Hz), 5.07 (m, 2 H), 4.69–4.51 (AB, 2 H, J_{AB} = 12.5 Hz), 4.17 (t, 1 H, *J* = 10.2 Hz), 3.92–3.75 (m, 5 H), 3.68 (t, 1 H, *J* = 9.0 Hz), 3.65 (m, 1 H), 1.10 (t, 1 H, *J* = 9.0 Hz), 0.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 145.2, 138.6, 138.2, 137.9, 137.8, 136.4, 133.5, 128.4–127.0 (aromatic), 120.5, 113.4, 108.1, 104.2, 84.4, 77.0, 76.3, 74.8, 74.7, 74.5, 73.3, 72.9, 68.7, 66.3, 17.4, −1.7; HRMS (FAB) calcd for $C_{49}H_{55}NO_{10}Si$ $(M)^+$ 845.3595, found 845.3604.

(−)-Tetra-*O*-benzyl-*N*-[(benzyloxy)methyl]ovatolide (26). According to the method described below for the synthesis of **27**, hydroxy acid **24** (185 mg, 0.22 mmol) afforded 129 mg (72%) of lactone **26**: $[\alpha]^{25}_D$ −71.2° (*c* 1.61, CH_2Cl_2); IR ($CHCl_3$) 3025, 1705, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.51–7.05 (m, 26 H), 6.95 (B of an AB, 1 H, J_{AB} = 11.4 Hz), 5.48 (br s, 2 H), 5.32 (A of an AB, 1 H, J_{AB} = 9.0 Hz), 5.18 (s, 2 H), 5.06 (A of an AB, 1 H, J_{AB} = 10.8 Hz), 4.85–4.72 (m, 3 H), 4.48 (s, 2 H), 4.40 (AB, 2 H, J_{AB} = 11.5 Hz), 3.91 (t, 1 H, *J* = 9.0 Hz), 3.78–3.61 (m, 4 H), 3.55 (t, 1 H, *J* = 10.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 149.4, 148.7, 138.3, 138.2, 138.1, 136.9, 136.2, 135.3, 132.5, 128.4–127.2 (aromatic), 123.0, 116.1, 108.0, 100.0, 83.0, 77.9, 76.4, 76.0, 75.3, 74.8, 73.7, 73.5, 70.7, 68.6; HRMS (FAB) calcd for $C_{51}H_{48}NO_9$ $(M + H)^+$ 818.331, found 818.334.

(−)-Tetra-*O*-benzyl-*N*-[[2-(trimethylsilyl)ethoxy]methyl]ovatolide (27). Dipyridyl disulfide (70 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (4 mL) and added to a solution of triphenylphosphine (82 mg, 0.31 mmol) in CH_2Cl_2 (4 mL) under argon. After being stirred for 30 min at room temperature, the yellow reaction mixture was concentrated, taken up in benzene (10 mL), and added over a period of 45 min to $AgClO_4$ (65 mg, 0.31 mmol) in refluxing benzene (50 mL) under argon. After an additional 1 h, the reaction was concentrated and flash chromatographed (CCl_4/EtOAc (82:8)) to yield **27** (126 mg, 72%): $[\alpha]^{25}_D$ −79.6° (*c* 2.9, CH_2Cl_2); IR (CCl_4) 3050, 2900, 1745, 1510; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.48 (m, 1 H), 7.41–7.05 (m, 20 H), 6.95 (d, 1 H, *J* = 10.8 Hz), 5.48–5.35 (AB, 2 H, J_{AB} = 11.8 Hz), 5.32 (A of an AB, 1 H, J_{AB} = 9.6 Hz), 5.17 (s, 2 H), 5.07–4.48 (AB, 2 H, J_{AB} = 12.1 Hz), 4.85–4.72 (m, 3 H), 4.47–4.31 (AB, 2 H, J_{AB} = 12.3 Hz), 3.92 (t, 1 H, *J* = 10.2 Hz), 3.79–3.62 (m, 4 H), 3.50 (t, 1 H, *J* = 8.4 Hz), 3.49 (m, 1 H), 0.90 (t, 1 H, *J* = 8.4 Hz), −0.6 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 148.2, 137.8, 137.7, 137.5, 136.0, 132.0, 127.8–122.5 (aromatic), 122.5, 115.3, 107.7, 99.6, 82.5, 77.5–73.1 (cycloaliphatic), 68.0, 66.2, 17.2, −1.9; HRMS (FAB) calcd for $C_{49}H_{54}NO_9Si$ $(M + H)^+$ 828.3568, found 828.3586.

(−)-Tetra-*O*-benzylovatolide (28). A solution of lactone **27** (98 mg, 0.12 mmol), in THF (9 mL) containing ethylenediamine (13 μL, 0.19 mmol) and 4-Å molecular sieves under argon was treated with a 1 M solution of Bu_4NF in THF (1.2 mL). After being stirred for 3 h at 60 °C, the reaction mixture was poured over ice and extracted with EtOAc (3 × 25 mL). The organic extracts were treated in the usual way to give an oil, which was purified by flash chromatography (hexanes/EtOAc (60:40)) to yield 71 mg (85%) of tetrabenzylovatolide: $[\alpha]^{25}_D$ −110.5° (*c* 1.3, CH_2Cl_2); IR (CCl_4) 3250, 2950, 2850, 1745, 1550; ^1H NMR (300 MHz, $CDCl_3$) δ 9.35 (br s, 1 H), 7.68 (d, 1 H, *J* = 4.2 Hz), 7.48 (m, 1 H), 7.40–7.06 (m, 19 H), 6.98–6.91 (AB, 2 H, J_{AB} = 9.0 Hz), 5.35 (A of an AB, 1 H, J_{AB} = 10.8 Hz), 5.15 (s, 2 H), 5.07 (A of an AB, 1 H, J_{AB} = 11.9 Hz), 4.87–4.73 (m, 3 H), 4.51 (B of an AB, 1 H, J_{AB} = 12.0 Hz), 4.60–4.32 (AB, 2 H, J_{AB} = 12.0 Hz), 3.95 (t, 1 H, *J* = 9.0 Hz), 3.80–3.65 (m, 3 H), 3.55 (t, 1 H, *J* = 10.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 147.9, 138.0, 137.9, 134.8, 133.9, 132.1, 128.3–127.4 (aromatic), 121.8, 115.5, 109.1, 105.6, 99.9, 83.0, 78.0, 77.2, 76.3, 75.6, 74.9, 73.6, 68.5; HRMS (FAB) calcd for $C_{43}H_{40}NO_8$ $(M + H)^+$ 698.2720, found 698.2737.

(−)-Ovatolide (1). A mixture of tetrabenzylovatolide (49.4 mg, 0.071 mmol) and $Pd(OH)_2$ (15 mg) in EtOAc (5 mL) containing AcOH (0.25 mL) was stirred under an atmosphere of H_2. After 2 h, the mixture was filtered through a pad of Celite; the remaining solids were washed with refluxing MeOH (2 × 15 mL), and the methanolic extracts were filtered and combined with the first filtrate. The combined organic phases were evaporated to give a solid, which, after purification by flash chromatography ($CHCl_3$/MeOH (80:20)), yielded (−)-ovatolide in 92% yield: $[\alpha]^{25}_D$ −35.1° (*c* 0.355, DMSO); natural $[\alpha]^{25}_D$ −36.9° (*c* 0.385, DMSO); IR (KBr) 3350, 1680, 1510, 1420; ^1H NMR (300 MHz, CD_3COCD_3) δ 7.86 (s, 1 H), 7.15–6.82 (AB, 2 H, J_{AB} = 10.8 Hz), 5.27 (d, 1 H, *J* = 9.0 Hz), 4.45 (t, 1 H, *J* = 7.2 Hz), 3.86 (d, 1 H, *J* = 11.4 Hz), 3.66 (t, 1 H, *J* = 6.4 Hz), 3.58–3.42 (m, 2 H), 3.02 (t, 1 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 145.9, 135.3, 131.4, 131.0, 121.9, 115.2, 110.9, 104.4, 99.9, 78.8, 78.5, 74.5, 71.1, 61.8; FAB MS *m/z* 338 $(M + H)^+$, 263, 242. Anal. Calcd for $C_{15}H_{15}NO_8$: C, 53.45; H, 4.48; N, 4.15. Found: C, 53.47; H, 4.48; N, 3.77.

Acknowledgment. A.D. is grateful to Consejo Superior de Investigaciones Científicas (C.S.I.C., Spain) for a postdoctoral fellowship and to Universidad de Barcelona for a leave of absence. The experimental contributions of Dr. Craig Forsyth and Miss Janete Lee during the preliminary stages are also acknowledged.

Supplementary Material Available: Preparation and characterization of *N*-benzyl-4-(benzyloxy)-3-(trifluoroacetyl)-indole, 4-(benzyloxy)-3-(trifluoroacetyl)indole, and compounds **4–10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.