# Highly Diastereoselective Synthesis of the 1,1′-Binaphthol Unit on a Bile Acid Template

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The use of 7-deoxycholic acid as a chiral template in the asymmetric syntheses of 1,1′-binaphthyl-2,2′-diol derivatives is reported. Intramolecular coupling of compounds **7** and **11** have been carried out with $Mn(acac)_3$ in $CH_3CN$ to afford coupled binaphthol products **8** and **12** with 65% and >99% diastereoselectivity, respectively. In both cases the predominant formation of the (*S*) isomers were predicted by computer modeling studies. This was confirmed in the case of compound **12**.

## Introduction

Chiral auxiliaries and catalysts derived from optically active 1,1′-binaphthyl-2,2′-diol (Binol) have been utilized extensively in asymmetric synthesis in recent years.[1] Intramolecular Ullman coupling[2] and alkylation of enolates[3] have been demonstrated to show high diastereoselectivity using chiral Binol as the auxiliary. Enantioselective reduction of ketones,[4] asymmetric Diels−Alder reactions,[5] Michael and nitroaldol condensations,[6] enantioselective protonation of silyl enol ethers and ketene bis(trialkylsilyl)acetals,[7] enantioselective aldol addition reactions,[8] enantioselective Mannich-type reactions,[9] enantioselective hydrophosphonylation of cyclic imides,[10] and enantioselective six-membered ring synthesis through catalytic metathesis[11] represent some of the applications of chiral Binol. Enantiomerically pure binaphthols have also been used extensively for preparing a large number of chiral synthetic receptors[12] and chiral dendrimers.[13] Central to the success of these chemistry is the availability of homochiral Binol.

A number of methods for the optical resolution of binaphthols have been reported to date.[14] Kazlauskas used pancreas acetone powder for the resolution of Binol.[15] Periasamy and co-workers have used (*S*)-proline,[16] and more recently a combination of boric acid and (*R*)-(+)-α-methylbenzylamine[17] for the resolution of 1,1′-binaphthyl-2,2′-diol. Even though a number of methods are available for the resolution, only a few attempts to synthesize Binol or its derivatives by asymmetric synthesis have been known in the literature at the time our work was initiated. A few approaches which have appeared since then do not use inexpensive source of chirality and these are also not recovered at the end of the synthesis.[18−20]

As part of a program aimed at the applications of bile acids in organic synthesis,[21] we decided to explore the possibilities of synthesizing derivatives of 1,1′-binaphthyl-2,2′-diol on a 7-dexoycholic acid template.[22] The full details of this study are described below.

## Results and Discussion

The geometrical features of 7-deoxycholic acid have been described earlier.[18] Our approach to the asymmetric

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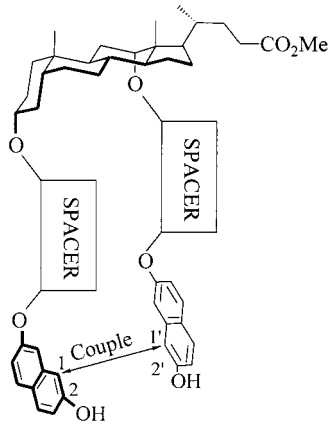
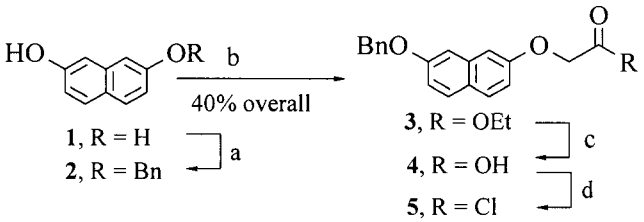



**Figure 1.** Schematic representation of the template coupling.

**Scheme 1**[a]




[a] Key: (a) BnBr, $K_2CO_3$, DMF; (b) $BrCH_2CO_2Et$, $K_2CO_3$, acetone; (c) NaOH, MeOH/$H_2O$; (d) $C_6H_6$, $(COCl)_2$, DMF (cat.).

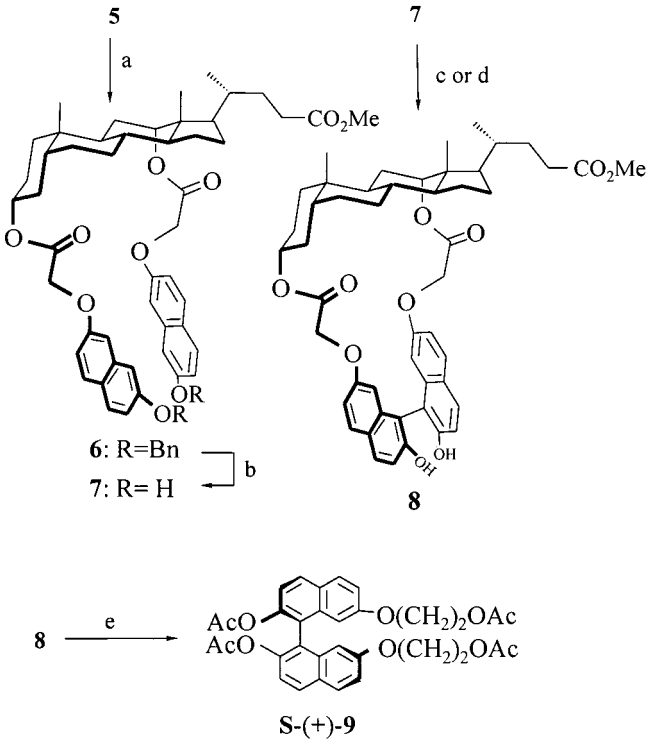
synthesis of derivatives of 1,1′-binaphthyl-2,2′-diol is schematically shown in Figure 1. We chose 2,7-dihydroxynaphthalene as the substrate so that one end of it could be easily attached to the steroid. To determine the spacers that would lead to an optimum distance between atoms 1 and 1′, detailed modeling studies were performed using PCMODEL and InsightII.[23] These studies suggested that a glycolate unit can be used as a spacer.

2,7-Dihydroxynaphthylene (**1**) was monobenzylated to **2** following a literature procedure,[12e] and the subsequent alkylation of **2** with ethyl bromoacetate afforded compound **3** in an overall yield of 40%. Ester **3** was hydrolyzed to acid **4** in 98% yield (Scheme 1).

Compound **4** was converted to the acid chloride (**5**) and then subjected to Oppenauer esterification with methyl deoxycholate to yield 85% of the diester **6** after purification (Scheme 2). Hydrogenolysis of compound **6** in the presence of 10% Pd/C in acetic acid/ethyl acetate (1:9) afforded steroidal bis(naphthol) **7** in 90% yield after purification.

Compound **7** upon reaction with $CuSO_4 \cdot 5H_2O$/pyridine complex[24] in dry methanol underwent *intramolecular* coupling to yield diastereomeric binaphthols **8** in 34% yield (Scheme 2). The diastereoisomeric excess (45%) was calculated by HPLC and NMR. Retention times for the major and the minor diastereomers were 25.3 and 34.8 min, respectively (85:15 MeOH/$H_2O$ in a 250 mm $C_{18}$

**Scheme 2**[a]




[a] Key: (a) methyl 7-deoxycholate, $CaH_2$, $BnEt_3N^+Cl^-$, $PhCH_3$, Δ, 85%; (b) 10% Pd/C, AcOH/EtOAc, 90%; (c) $Mn(acac)_3/CH_3CN$, 50%, 65%, de 65%; (d) $CuSO_4 \cdot 5H_2O$, pyridine, MeOH, 65 °C, 34%, de 45%; (e) LAH/THF then $Ac_2O$.

**Table 1: Intramolecular Binaphthol Coupling on the Steroidal Bisnaphthol 8**

| coupling reagent | temp. (°C) | de (HPLC) (%) |
|---|---|---|
| $CuCl_2$/$^t$BuNH$_2$/MeOH | 27 | 19 |
| $CuCl_2$/$^t$BuNH$_2$/MeOH | 5 | 33 |
| $CuSO_4 \cdot 5H_2O/C_5H_5N$/MeOH | 65 | 45 |
| $Mn(acac)_3$/MeCN | 50 | 65 |

column). The diastereomeric excess was also estimated from the integrations of the methyl ester signals which was in close agreement with the HPLC data.

To optimize the reaction, the coupling was subsequently carried out under various conditions, and the best result was obtained (Table 1) when a 10 mM solution of **7** was heated at 50 °C with 1.53 equiv of $Mn(acac)_3$ in MeCN[12f] for 45 h to yield 65% of **8** with a de of 65%.

The purified diastereomeric mixture obtained from the coupling reaction was removed from the steroid by $LiAlH_4$ (LAH) reduction. In situ acetylation afforded the acetylated binaphthol **9**. An authentic sample of racemic **9** was prepared from compound **3** (overall yield 37%) for the full characterization of the cleaved binaphthol (Scheme 3). This product was found to be identical (TLC, IR, NMR, UV, HPLC) to the product derived from the reduction and acetylation of **8**.

Enantiomerically enriched products **9** (obtained from a diastereomeric mixture **8** having 65% de) showed a positive specific rotation ($[\alpha]^{24}_D = +57.6°$ (*c* 1.51, $CHCl_3$)) and a CD spectrum with a positive Cotton effect with Δε +52.5 (238 nm) and −22.5 (225 nm). Compound **9** (obtained from a diastereomeric mixture **8** having 45% de) showed a positive specific rotation ($[\alpha]^{24}_D = +36.9°$ (*c* 1.22, $CHCl_3$)) and a positive Cotton effect with Δε +35.1 (239 nm) and −15.2 (226 nm).[25] The CD spectrum

(23) Modeling studies using PCMODEL and DTMM were performed in the same way as discussed in ref 21a and that suggested the feasibility of the template synthesis. This was further supported by InsightII (Biosym Technologies version 2.3.5) calculations. Both the diastereomers for **8** and **12** were constructed and minimized using the CVFF force-field. The two diastereomeric structures having (*S*) and (*R*) configuration around the biaryl bond for **8** and **12** showed a difference of 8 and 14 kcal/mol in the gas phase, respectively, suggesting the greater stability of the (*S*) isomer.

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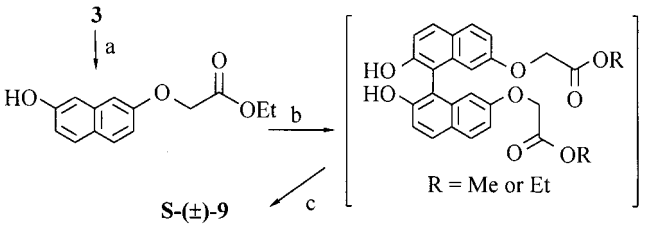
**Scheme 3**[a]




[a] Key: (a) 10% Pd/C, EtOAc/MeOH, 99%; (b) $CuCl_2$/$^t$BuNH$_2$, MeOH; (c) LAH/THF then $Ac_2O$, 37% overall.

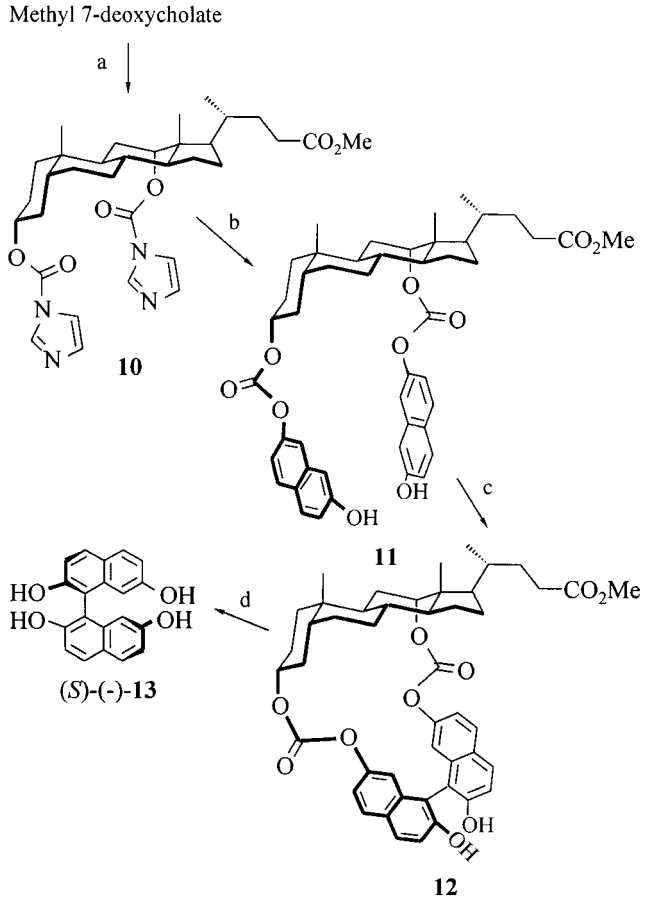
of the enantiomeric mixture was compared with the CD data reported for (*S*)-1,1′-binaphthyl-2,2′-diol.[26] Three other biaryl compounds having (*S*) configurations (including (*S*)-1,1′-binaphthyl-2,2′-diol) have also been reported to have similar CD spectral properties.[19] Additionally, (*S*)-7,7′-bis(benzyloxy)-2,2′-dihydroxy-1,1′-binaphthyl was reported to have a positive specific rotation.[12f] Therefore, on the basis of these similar spectral properties of the similar types of binaphthols, the absolute configuration of the major enantiomer was assigned to be (*S*).

To further improve the diastereoselectivity other spacer groups were examined. We felt that a carbonate linkage instead of a glycolate can bring the bond forming sites closer to the steroid and this might enhance the selectivity. Computer modeling with InsightII suggested the feasibility of the template synthesis.[21]

Bis(imidazolide) **10** was prepared from methyl deoxycholate by heating with *N*,*N*′-carbonyl diimidazole (CDI) and $CaH_2$ at 65−8 °C in 86% yield.[27] The yield of this reaction showed a marked dependence on the reaction temperature. A mixture of bis(imidazolide) **10** and 2,7-dihydroxynaphthalene was dissolved in the minimum volume of THF and heated in an oil-bath at 148−152 °C for 5 h. The desired biscarbonate **11** was isolated in 77% yield.[28]

The intramolecular coupling of **11** to produce **12**[12e] was accomplished, albeit in a moderate yield (Scheme 4). Attempts made to couple the template-bound naphthols under conditions such as $CuSO_4$·$5H_2O$/pyridine[26] in MeOH and with $CuCl_2$/$^t$BuNH$_2$[12f] in MeOH were unsuccessful and did not yield the expected product. Under the best condition, we have been able to get an isolated yield of 36% based on the recovered starting material (70% conversion). Typically a 7 mM solution of **11** in acetonitrile was heated at 65 °C with 6.85 equiv of $Mn(acac)_3$ for 62 h. Compound **12** was characterized by LRMS, $^1$H and $^{13}$C NMR, UV, and IR spectroscopies. This steroidal binaphthol **12** showed a single peak in reverse phase HPLC ($t_R$ 14.2 min, 250 mm $C_{18}$ column, MeOH/$H_2O$ 93:7), and $^1$H NMR of this material was again in agreement with the presence of *a single diastereomer* (estimated de > 99%). Compound **12** when stirred with LiOH in MeOH at room temperature under argon atmosphere for 16 h afforded binaphthol **13** in 77% isolated yield after column chromatographic purification

**Scheme 4**[a]




[a] Key: (a) $PhCH_3$, $CaH_2$, CDI, 65−68%; (b) 2,7-dihydroxynaphthalene, [THF], 148−52 °C, 77%; (c) $Mn(acac)_3$/$CH_3CN$, 65 °C, 35%; (d) LiOH, MeOH then 3 N HCl, 77%.

on neutral alumina. An authentic sample of racemic binaphthol[29] **13** was found to be identical (TLC, IR, NMR, UV) to the product derived from the template coupling.

The enantiomerically enriched product **13** showed negative specific rotation ($[\alpha]^{26}_D = -89.8°$ (*c* 0.86, $CHCl_3$)) and a CD spectrum with positive Cotton effects [$\Delta\epsilon$ +82.1 (242 nm) and −72.1 (226 nm)]. The binaphthol derivative **9** was also found to show a similar CD spectrum. Therefore, on the basis of these similar spectral properties of the similar binaphthols the absolute configuration of binaphthol **13** was initially assigned to be (*S*), which was confirmed by conversion of **12** to a binol derivative of known absolute configuration (Scheme 5).

Binaphthol **12** was methylated by reacting with MeI in the presence of $K_2CO_3$ in DMF at 50 °C for 2 days to yield **14** (87%). The methylated steroidal binaphthol was then hydrolyzed by stirring with LiOH in MeOH for 12 h to yield compound **15**[12f] in 95% yield. This compound gave a positive specific rotation ($[\alpha]^{26}_D = +48.3°$ (*c* 2.4, DMF)) which was compared to the literature value ($[\alpha]^{26}_D = +45.9°$ (*c* 1, DMF))[12f] which confirmed the stereochemistry to be (*S*) with an enantioselectivity of >99%.

## Conclusions

This work demonstrates the first application of the bile acid template for asymmetric binaphthol coupling. The

(25) These numbers are internally consistent and shows that the low yield in the conversion of **8** to **9** is not associated with the preferential loss of one diastereomer/enantiomer.

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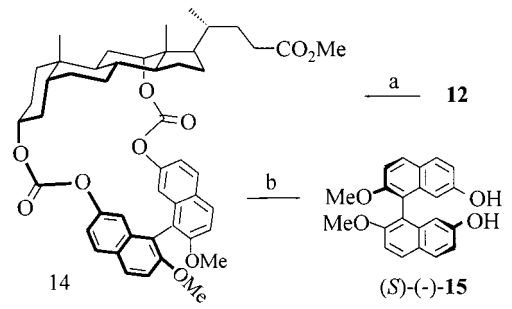
**Scheme 5**[a]




[a] Key: (a) MeI, $K_2CO_3$/DMF, 50 °C, 87%; (b) LiOH, MeOH−THF, rt, 89%.

de in the coupling reaction was increased from 65% to 99% by optimizing the spacer. We believe that further work to improve the coupling yield and to use compound **12** as a new asymmetric catalyst can lead to practical benefits. Some of these possibilities are being examined in our laboratory, and these results will be published in due course.

## Experimental Section

**General.** All reactions were carried out in oven-dried glasswares unless otherwise stated. Moisture sensitive reactions were protected with a $CaCl_2$ drying tube or were carried out under a dry nitrogen atmosphere. Solid reactants were recrystallized, checked by melting points, and used for the reaction whereas the liquids were distilled. Distilled commercial grade solvents were used for crystallization, extraction, and column chromatography. Analytical TLC were performed on homemade plates made from Acme silica gel or on precoated silica gel plates purchased from Aldrich. Visualization was done under UV (shortwave or longwave) radiation or by dipping the plates in 5% ethanolic phosphomolybdic acid or methanolic $Ac_2O/H_2SO_4$ solution or anisaldehyde/$H_2SO_4$ in acetic acid and heating on a hot plate. Columns for chromatography were made from 100−200 mesh silica gel. Toluene, benzene, tetrahydrofuran were distilled from sodium/benzophenone ketyl. Methanol, methylene chloride, and acetic anhydride were distilled from magnesium methoxide, calcium hydride, and phosphorus pentoxide, respectively. Pyridine and triethylamine were stored over KOH and distilled from $CaH_2$. Dimethyl formamide (DMF) was preliminarily dried by azeotropic distillation with benzene and then distilled from BaO under vacuum. Acetonitrile was distilled from $CaH_2$. All melting points reported are uncorrected. Optical rotations were measured at 589 nm at the specified temperatures. IR spectra were recorded on NaCl cells. NMR spectra were measured at 60, 90, 200, 270, and 400 MHz instruments in deuterated solvents as indicated; TMS or the residual solvent peaks were used as internal standards. FAB mass spectra were recorded using argon/xenon (6 KV, 10 mA) as a fab gas and using *m*-nitrobenzyl alcohol as a matrix. HPLC analysis were performed using a $C_{18}$ column (250 mm × 4.6 mm). MeOH/$H_2O$ of various proportions were used as mobile phases at a flow rate of 1 mL/min. Samples were detected at 254 nm unless otherwise mentioned. Retention times of the compounds reported typically had a standard deviation of ±0.20 min.

**Ethyl 2-(((7-Benzyloxy)naphthalene)oxy)acetate (3).** In a 10-mL round-bottom (rb) flask were mixed compound **2** (0.30 g, 1.20 mmol), $K_2CO_3$ (0.12 g, 0.85 mmol), and dry acetone (3 mL), and the mixture was refluxed for 1 h under a $N_2$ atmosphere. Ethyl bromoacetate (0.16 mL, 1.44 mmol) was added, and the mixture was refluxed for an additional 21 h. After filtration and removal of the solvent the crude product was crystallized from ethanol to get 0.39 g (96%) of the pure product: mp 100−101 °C; IR (Nujol) 1203, 1377, 1446, 1608, 1752, 2854 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 1.31 (t, $J$ = 7.1 Hz, 3H), 4.30 (q, $J$ = 7.2 Hz, 2H), 4.72 (s, 2H), 5.18 (s, 2H), 7.00 (d, $J$ = 2.2 Hz, 1H), 7.01−7.17 (m, 3H), 7.28−7.55 (m, 5H), 7.69 (d, $J$ = 8.3 Hz, 2H); $^{13}C$ NMR (22.5 MHz, $CDCl_3$) $\delta$ 14.0, 61.0, 65.0, 70.0, 107.0, 116.0, 117.0, 125.0, 127.5−129.5, 135.4, 136.9, 156.7, 157.8, 169.0; LRMS *m*/*z* 336 ($M^+$, 21); HRMS *m*/*z* 336.1359 (calcd for $C_{21}H_{20}O_4$ 336.1362). Anal. Calcd for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 74.69; H, 5.91.

**2-((7-Benzyloxy)naphthyloxy)acetic Acid (4).** Compound **3** (0.35 g, 1.02 mmol) was dissolved in MeOH/$H_2O$ mixture (9:1 v/v, 25 mL) by heating, and solid NaOH (1.62 g, 40.5 mmol) was added. The mixture was refluxed for 19 h, cooled (ice-bath), and acidified with 6 M aqueous HCl (5 mL). Methanol was removed under reduced pressure, and the residue was filtered and washed thoroughly with water and dried in vacuo. Traces of water was removed azeotropically, and the product was dried in vacuo. This crude product (0.317 g, quantitative) was pure enough for the further reactions: mp 158−61 °C; IR (Nujol) 1700, 1720, 2500−2700 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) $\delta$ 4.81 (s, 2H), 5.21 (s, 2H), 7.00−7.62 (m, 9H), 7.75 (d, $J$ = 7.7 Hz, 2H).

**Methyl 3α, 12α-Bis(2-((7-benzyloxy)naphthyloxy)acetyloxy)-5β-cholan-24-oate (6).** To a stirred suspension of compound **4** (0.268 g, 0.87 mmol) in dry benzene (2.6 mL) was added oxalyl chloride (0.16 mL, 1.83 mmol) followed by the addition of 1 drop of dry DMF. The resulting mixture was then heated to ca. 45 °C for 2.5 h. Excess oxalyl chloride and solvent were removed under vacuum, and the acid chloride (**5**) was dried in vacuo for 2 h.

The crude acid chloride (**5**) was dissolved in dry toluene (2 mL), and $CaH_2$ (0.165 g, 3.92 mmol) and methyl deoxycholate (0.161 g, 0.40 mmol) were successively added to the solution followed by the addition of benzyltriethylammonium chloride (0.01 g, 0.04 mmol). The mixture was refluxed for 18 h. The flask was cooled, the suspension was filtered to remove inorganic materials, and the residue was washed with $CHCl_3$. The combined organic layer was washed with 7% $NaHCO_3$ solution, water, and brine and finally dried over anhyd $Na_2SO_4$. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (100−200 mesh, 18.0 cm × 2.2 cm, 22 g) using 15% ethyl acetate (EA)/hexanes as the eluent. The pure product (0.327 g, 83.8%) was isolated as a foam. Several attempts for crystallization with different solvents were unsuccessful: mp 65−67 °C. $[\alpha]^{28}_D$ = +8.3° (*c* 3.14, $CHCl_3$); IR (Nujol) 1725 $cm^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.04% $CHCl_3$/EtOH v/v (*c* 1.27 × $10^{-5}$ M) 234.3 (5.34), 325.2 (3.90); $^1H$ NMR (400.1 MHz, $CDCl_3$) $\delta$ 0.649 (s, 3H), 0.731 (d, $J$ = 6.4 Hz, 3H), 0.869 (s, 3H), 1.18−2.23 (m, steroidal CH and $CH_2$), 3.619 (s, 3H), 4.657 (d, $J$ = 15.9 Hz, 1H), 4.677 (s, 2H), 4.728 (d, $J$ = 15.9 Hz, 1H), 4.883 (m, 1H), 5.099 (s, 2H), 5.114 (s, 2H), 5.170 (s, 1H), 6.95−7.21 (m, 8H), 7.30−7.51 (m, 10H), 7.598 (d, $J$ = 8.9 Hz, 1H), 7.612 (d, $J$ = 2.7 Hz, 1H), 7.634 (d, $J$ = 2.7 Hz, 1H), 7.690 (d, $J$ = 8.9 Hz, 1H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 12.18, 17.40, 22.86, 23.20, 25.49, 25,57, 26.73, 27.21, 30.57, 31.00, 32.05, 33.91, 34.17, 34.64, 35.39, 41.70, 45.04, 47.38, 48.86, 51.39, 65.37, 65.72, 69.92, 75.48, 77.31, 106.63, 106.75, 107.31, 115.47, 114.85, 116.92, 124.84, 127.40, 127.47, 127.93, 128.54, 129.19, 129.38, 129.51, 135.57, 136.84, 156.37, 157.58, 168.30, 168.47, 174.43. LRMS (FAB) *m*/*z* 986 ($M^+$, 35). Anal. Calcd for $C_{63}H_{70}O_{10}$: C, 76.64; H, 7.15. Found: C, 76.95; H, 7.27.

**Methyl 3α, 12α-bis(2-((7-Hydroxy)naphthyloxy)acetyloxy)-5β-cholan-24-oate (7).** In a 20 mL two-necked rb flask was dissolved **6** (0.100 g, 0.10 mmol) in 10% AcOH/EtOAc (1 mL), evacuated, and purged with $N_2$. Pd/C (10%, 0.080 g) was added under a $N_2$ atmosphere and flushed with $H_2$, and the reaction was stirred at room temperature under 1 atm pressure of $H_2$. Hydrogenolysis was complete after 2 days. The solution was filtered through a Celite pad and dried in vacuo to afford the crude product (0.092 g, 100%) which was purified by column chromatography on silica gel (100−200 mesh, 14.5 cm × 1.3 cm, 6 g) using 10% EA/$CHCl_3$ as the eluent. This compound (0.073 g, 90%) was characterized by $^1H$ NMR spectrum which showed the absence of the benzyl groups: $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 0.64 (s, 3H), 0.70−0.98 (m, 6H), 1.00−2.22 (m, steroidal CH and $CH_2$), 3.66 (s, 3H), 4.76 (complex,

4H), 5.20 (complex, 1H), 5.60 (complex, 1H), 6.70−7.20 (m, 8H), 7.40−7.80 (m, 4H).

**Preparation of Steroidal Binaphthol 8 Using Mn(acac)$_3$/MeCN.** To a stirred solution of compound **7** (0.067 g, 0.08 mmol) in MeCN (8.3 mL) was added Mn(acac)$_3$ (0.045 g, 0.12 mmol) under $N_2$ atmosphere, and the reaction was stirred at 50 °C for 45 h. The inorganic residue was filtered and washed with MeCN, and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel (100−200 mesh, 16.0 cm × 1.2 cm, 5 g) using 5% EA/$CHCl_3$ as the eluent. The purified product (0.044 g, 65%) was a mixture of two diastereomers. HPLC analysis of this sample showed a de of 65%. Retention times for the major and the minor diastereomers were 25.3 and 34.8 min, respectively (MeOH/$H_2O$ in a ratio of 85:15 was used as the mobile phase). For **8**: mp 170−2 °C; $[\alpha]^{25}_D$ = +144.8° (*c* 1.25, $CHCl_3$); IR (Nujol) 1720, 3200−3500 cm$^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.15% $CHCl_3$/EtOH v/v (*c* 1.22 × 10$^{-5}$ M) 234.1 (5.00), 305.9 (3.88), 328.1 (3.78); $^1$H NMR (400.1 MHz, $CDCl_3$) (resolved minor diastereomer signals are indicated in italics) $\delta$: 0.71 (s), *0.72 (s)*, 0.79 (s), 0.81 (s), *0.85 (s)*, 0.87 (s), 0.88−2.09 (m, steroidal CH and $CH_2$), 2.10−2.41 (m), 3.61 (s), *3.68 (s)*, 3.85 (d, *J* = 15.5 Hz), 4.07 (s), 4.31 (d, 15.5 Hz), 4.59 (s), 4.60 (s), 4.61 (s), 4.70−4.79 (m), *4.80−4.95 (m)*, *5.09 (br s)*, 5.13 (br s), 5.23 (br s), 5.28 (br s), 6.32 (d, *J* = 2.4 Hz), *6.64* (*d*, *J* = 2.5 Hz), 6.66 (d, *J* = 2.5 Hz), 6.85 (dd, *J* = 9.0, 2.6 Hz), *7.10 (dd*, *J* = 9.0, 2.6 Hz), 7.20 (d, *J* = 2.5 Hz), 7.22 (d, *J* = 2.5 Hz), 7.25 (d, *J* = 8.9 Hz), 7.26 (d, *J* = 8.9 Hz), 7.32 (d, *J* = 8.8 Hz), *7.81* (*d*, *J* = 9.0 Hz), 7.82 (d, *J* = 8.9 Hz), 7.89 (d, *J* = 8.9 Hz), 7.90 (d, *J* = 8.9 Hz), 8.00 (br s), 8.01 (d, *J* = 8.9 Hz); the diastereomeric excess was calculated on the basis of integrations of methyl ester signals and found to be 62.5%; $^{13}$C NMR (100.61 MHz, $CDCl_3$) (resolved minor diastereomer signals are indicated in italics) $\delta$ 12.3, *17.4*, 17.6, 22.8, *23.2*, 23.3, 25.3, *25.8*, 26.0, 26.5, 27.3, 30.7, 30.8, 31.6, *31.9*, 33.8, 33.9, *34.2*, 34.6, 35.5, *36.5*, 40.7, 41.5, *41.7*, 44.8, *44.9*, *47.0*, 47.5, 49.0, *49.8*, 51.4, 53.8, 60.8, 64.1, 65.1, *65.7*, 69.2, 71.8, 75.9, 76.7, 77.0, 77.3, 92.3, 95.4, 97.7, 98.9, 103.0, *105.2*, 108.8, *109.5*, 110.0, 110.4, 112.0, 115.6, 115.9, 116.1, 116.4, 117.2, 121.5, 125.1, 125.3, 130.0, 130.3, 131.0, 131.1, *131.4*, 135.1, 135.2, 153.2, 153.3, 156.9, 162.6, 166.8, 169.4, 174.5; the diastereomeric excess calculated from $^{13}$C NMR was 63%; FABMS *m*/*z* 804 (M$^+$, 79). Anal. Calcd for $C_{49}H_{56}O_{10}\cdot H_2O$: C, 71.51; H, 7.10. Found: C, 71.57; H, 7.17.

**Property of 8 Synthesized Using $CuSO_4\cdot 5H_2O$/Pyridine.** This product, isolated in 34% yield, showed de of 45.3% by HPLC and 42% by NMR.

**Cleavage of the Binol Unit from 8. 7,7′-Bis(2-acetoxyethoxy)-2,2′-diacetoxy-1,1′-binaphthyl (9) from the Diastereomers Obtained Using Mn(acac)$_3$.** A mixture of diastereomers **8** (0.067 g, 0.08 mmol) obtained from the Mn(acac)$_3$/$CH_3CN$ coupling was dissolved in dry THF (10 mL) and flushed with $N_2$. LAH (0.050 g, 1.32 mmol) was added, and the mixture was refluxed for 72 h. After the completion of the reaction, the flask was cooled in an ice-bath, $Ac_2O$ (0.3 mL) was added and stirring was continued for 24 h. The mixture was filtered and washed with MeOH and ethyl acetate, and the volatiles were removed in vacuo. The crude product was purified by column chromatography on silica gel (100−200 mesh, 8.0 cm × 1.2 cm, 3.0 g) using 30% EA/hexanes as the eluent. The partially purified product (0.012 g) was further purified by preparative TLC, developing with 30% EA/hexanes four times to yield 0.00452 g of the product **9**. This compound was analyzed by HPLC ($t_R$ = 8.9 min, MeOH/$H_2O$ in a ratio of 75:25 was used as the mobile phase, and the sample was detected at 230 nm). For **9**: $[\alpha]^{24}_D$ = +57.62° (*c* 1.51, $CHCl_3$); IR (neat) 1741 cm$^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.12% $CHCl_3$/MeCN v/v (*c* 1.05 × 10$^{-5}$ M) 232.1 (4.95), 328.9 (3.73); CD $\Delta\epsilon$ M$^{-1}$ cm$^{-1}$ ($\lambda_{max}$ nm) 0.12% $CHCl_3$/MeCN v/v (*c* 1.05 × 10$^{-5}$ M) +52.5 (238), −22.5 (225); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.80 (s, 6H), 2.02 (s, 6H), 3.81 (m, 2H), 3.90 (m, 2H), 4.27 (t, *J* = 4.5 Hz, 4H), 6.51 (d, *J* = 2.3 Hz, 2H), 7.14 (d, *J* = 2.4 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H).

In an analogous manner, compound **8** (0.033 g) obtained from the $CuSO_4\cdot 5H_2O$/pyridine coupling yielded **9** (0.0041 g) with the following $[\alpha]_D$ and CD data ($^1$H NMR, IR, UV identical with **9** prepared in the previous experiment): $[\alpha]^{24}_D$ = +36.9° (*c* 1.22, $CHCl_3$); CD $\Delta\epsilon$ M$^{-1}$ cm$^{-1}$ ($\lambda_{max}$ nm) 0.12% $CHCl_3$/MeCN v/v (*c* 1.02 × 10$^{-5}$ M) +35.1 (239), −15.2 (226).

**(±)-7,7′-Bis(2-acetoxyethoxy)-2,2′-diacetoxy-1,1′-binaphthyl (9).** Compound **3** (0.307 g, 0.91 mmol) was dissolved in a 1:1 mixture of EtOAc/MeOH (10 mL) and degassed. Pd/C (10%, 0.031 g) was added, and the flask was immediately flushed with $H_2$. The reaction was stirred at 27 °C for 8 h. The mixture was filtered, and the crude product (0.224 g, 99%) was used for the next step: mp 97−8 °C; IR (Nujol) 1730, 1745, 3360−3400 cm$^{-1}$; $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 1.30 (t, *J* = 6.8 Hz, 3H), 4.30 (q, *J* = 6.8 Hz, 2H), 4.70 (s, 2H), 5.00 (s, 1H), 6.83−7.19 (m, 4H), 7.68 d, *J* = 9.0 Hz, 2H); LRMS *m*/*z* 246 (M$^+$, 100); HRMS *m*/*z* 246.0914 (calcd for $C_{14}H_{14}O_4$ 246.0892).

To a stirred solution of crude product (0.204 g, 0.82 mmol) and $CuCl_2$ (0.266 g, 1.68 mmol) in degassed dry MeOH (12 mL) was added $^t$BuNH$_2$ (0.70 mL, 6.66 mmol), and the mixture was stirred at 27 °C under $N_2$ for 26 h. The ice-cold solution was acidified with dilute HCl and extracted with EtOAc. The combined organic layer was washed with water and brine and finally dried over anhydrous $Na_2SO_4$. The solvent was removed in vacuo to yield the crude product (0.197 g), which was subjected to LAH reduction without further purification.

To a solution of the crude product (0.197 g, 0.40 mmol) in dry THF (4 mL) was added LAH (0.033 g, 0.87 mmol), and the resulting mixture was refluxed for 20 h. To the cold reaction at 0 °C was added $Ac_2O$ (1 mL, 10.6 mmol), and the solution was stirred for 18 h. The solution was filtered, and the residue was washed with ethyl acetate. Solvents were removed to yield the crude product, which was purified by column chromatography on silica gel (100−200 mesh, 20.0 cm × 1.5 cm, 12 g) using 30−40% of EA/hexanes as the eluent. The pure product weighed 0.084 g (37%): HPLC of this compound was identical with the enantiomerically enriched binaphthol; IR (neat) 1740 cm$^{-1}$; $^1$H NMR (400.1 MHz, $CDCl_3$) $\delta$ 1.79 (s, 6H), 2.01 (s, 6H), 3.81 (m, 2H), 3.90 (m, 2H), 4.26 (t, *J* = 4.5 Hz, 4H), 6.51 (d, *J* = 2.3 Hz, 2H), 7.14 (d, *J* = 2.4 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.84 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (100.61 MHz, $CDCl_3$) $\delta$ 20.47, 20.69, 62.49, 65.60, 105.29, 116.93, 118.51, 119.61, 121.32, 121.83, 122.37, 127.08, 129.18, 129.47, 129.65, 134.40, 147.28, 157.07, 169.27, 170.73; EIMS *m*/*z* 574 (M$^+$, 5).

**Methyl 3α,12α-Bis(1-imidazolylcarbonyloxy)-5β-cholan-24-oate (10).** In a 20-mL rb flask were dissolved methyl deoxycholate (1.151 g, 2.83 mmol) and N,N′-carbonyldiimidazole (1.168 g, 7.20 mmol) in dry toluene (14.0 mL), and $CaH_2$ (0.270 g, 6.41 mmol) was added. The reaction mixture was stirred at 65−68 °C for 50 h. The mixture was cooled and filtered, and the residue was washed with $CHCl_3$. Volatiles were removed in vacuo, and the crude product was purified by column chromatography on silica gel (100−200 mesh, 21.5 cm × 2.2 cm, 25 g) using 30−50% EA/hexanes as the eluent. The pure bisimidazolide **10** weighed 1.440 g (86%); mp 55−6 °C; $[\alpha]^{26}_D$ = +78.0° (*c* 1.87, $CHCl_3$); IR (neat) 1750 cm$^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 3.2% $CHCl_3$/EtOH v/v (*c* 1.50 × 10$^{-5}$ M) 230.2 (4.02); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.82 (s, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.97 (s, 3H), 1.08−1.93 (m, steroidal CH and $CH_2$), 2.02−2.40 (m), 3.63 (s, 3H), 4.83 (m, 1H), 5.35 (s, 1H), 7.04 (s, 1H), 7.13 (s, 1H), 7.36 (s, 1H), 7.48 (s, 1H), 8.09 (s, 1H), 8.21 (s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 12.5, 17.6, 22.9, 23.4, 25.7, 25.9, 26.3, 26.6, 27.0, 27.2, 30.7, 31.0, 31.3, 32.0, 33.8, 34.0, 34.5, 34.7, 35.6, 41.6, 45.5, 48.3, 50.0, 51.5, 78.6, 81.2, 116.7, 117.1, 130.5, 130.9, 136.9, 137.1, 148.0, 148.2, 174.3; LRMS *m*/*z* 594 (M$^+$, 4). Anal. Calcd for $C_{33}H_{46}O_6N_4\cdot 0.5H_2O$: C, 65.63; H, 7.85; N, 9.28. Found: C, 65.94; H, 7.80; N, 8.92.

**Methyl 3α,12α-Bis((2-(7-hydroxynaphthyl)oxy)carbonyloxy)-5β-cholan-24-oate (11).** In a flask (10 mL) fitted with an 18-cm air condenser ($N_2$ atmosphere) were dissolved bisimidazolide **10** (0.250 g, 0.42 mmol) and 2,7-dihydroxynaphthalene (0.500 g, 3.12 mmol) in 1 mL of THF; the flask was flushed with $N_2$ and immersed in an oil-bath (148−52 °C) for 5 h 15 min. Traces of solvent was removed under vacuum, and the crude product was purified by column chromatography on

silica gel (100−200 mesh, 14.5 cm × 2.2 cm, 15 g) using 15−25% EA/hexanes as the eluent, to yield 0.252 g (77%) of the title compound: mp 212−4 °C; $[\alpha]^{24}_D = +73.8°$ (*c* 0.596, 1:4 $CH_3CN/CHCl_3$); IR (neat) 1710, 1730, 1760, 3410 $cm^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.16% $CHCl_3$/MeCN v/v (*c* 1.50 × $10^{-5}$ M) 228.5 (5.16), 276.4 (3.85), 327.8 (3.52); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.72 (s, 3H), 0.94 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.20−2.10 (m, steroidal CH and $CH_2$), 2.22−2.54 (m), 3.63 (s, 3H), 4.76 (m, 1H), 5.05 (s, 1H), 5.70 (br s, OH), 6.00 (br s, OH), 6.98−7.20 (m, 6H), 7.35−7.50 (m, 2H), 7.62−7.86 (m, 4H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 12.3, 12.4, 14.2, 17.7, 22.9, 23.0, 23.3, 25.4, 25.8, 25.9, 26.5, 26.8, 27.2, 30.8, 31.1, 32.0, 34.0, 34.3, 34.4, 34.7, 34.8, 35.6, 35.8, 41.8, 45.4, 47.5, 48.9, 49.1, 51.6, 60.5, 72.2, 79.5, 81.2,109.4, 116.7, 118.0, 118.2, 126.9, 129.5, 129.6, 129.7, 135.1, 149.3, 149.5, 153.1, 153.4, 154.4, 154.5, 174.8; FABMS *m*/*z* 778 ($M^+$, 7). Anal. Calcd for $C_{47}H_{54}O_{10}$: C, 72.47; H, 6.99. Found: C, 72.32; H, 7.09.

**Coupling of Compound 11 to Steroidal Binol 12.** To a 20-mL two-necked flask were added bis(carbonate) **11** (0.055 g, 0.071 mmol) and dry $CH_3CN$ (10 mL). To the almost homogeneous solution at 65 °C under $N_2$ atmosphere $Mn(acac)_3$ (0.170 g, 0.483 mmol) was added. The reaction was stirred at 65 °C for 62 h and filtered, and volatiles were removed. The crude product was purified by column chromatography on silica gel (100−200 mesh, 11.5 cm × 1.2 cm, 5 g) using 2−8% EA/hexanes as the eluent. The yield from the reaction was 41%(0.018 g), based on recovered starting material (0.011 g, 20%). Purity of this material was different for different batches of samples. However, the reaction was optimized to afford pure coupled product **12** in 35−41% yield based on the recovery of the starting material (20−30%). HPLC analysis of **12** showed a single peak at 14.2 min (MeOH/$H_2O$ in a ratio of 93:7 was used as the mobile phase): mp 180−2 °C; $[\alpha]^{23}_D = +63.5°$ (*c* 0.504, $CHCl_3$); IR (Nujol) 1760, 3100−3500 $cm^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.16% $CHCl_3$/MeCN v/v (*c* 0.973 × $10^{-5}$ M) 230.8 (5.08), 280.9 (3.96), 331.6 (3.80); $^1$H NMR (400.1 MHz, $CDCl_3$) $\delta$ 0.72 (s, 3H), 0.85 (s, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 1.00−2.30 (m, steroidal CH and $CH_2$), 3.61 (s, 3H), 4.59 (m, 1H), 4.85 (s, 1H), 5.02 (s, OH), 5.12 (s, OH), 6.785 (d, *J* = 2.2 Hz, 0.5H), 6.818 (br s, 0.5H), 7.076 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.352 (d, *J* = 8.9 Hz, 1H), 7.368 (d, *J* = 9.0 Hz, 1H), 7.894 (d, *J* = 9.0 Hz, 1H), 7.907 (d, *J* = 1.3 Hz, 3H), 7.981 (d, *J* = 9.1 Hz, 1H), 8.013 (d, *J* = 8.9 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 12.3, 17.5, 22.5, 23.3, 23.6, 25.8, 26.0, 26.6, 27.2, 30.7, 31.0, 33.3, 33.8, 34.4, 34.9, 35.5, 41.6, 45.3, 47.3, 48.9, 51.5, 79.7, 81.5, 110.3, 111.1, 113.3, 114.9, 117.2, 117.8, 117.9, 119.3, 127.1, 127.6, 129.6, 130.1, 131.4, 134.6, 134.8, 150.6, 150.9, 151.0, 151.5, 153.5, 153.6, 174.6; LRMS *m*/*z* 776 ($M^+$, 0.5). Anal. Calcd for $C_{47}H_{52}O_{10}\cdot 1.5H_2O$: C, 70.22; H, 6.90. Found: C, 70.28; H, 6.93.

**(*S*)-(−)-1,1′-Binaphthyl-2,2′,7,7′-tetrol (13).** The coupled steroidal binaphthol **12** (0.016 g, 0.021 mmol) was dissolved in degassed MeOH (1.0 mL), and LiOH (0.010 g, 0.416 mmol) was added under argon atmosphere. The reaction was stirred at room temperature for 16 h and acidified with 3 N HCl solution. Volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on neutral alumina (4.2 cm × 1.2 cm, 5 g) using 40−80% EA/hexanes as the eluent, to yield 0.005 g (77%) of **13**: mp 130−2 °C (lit.[51] 151−2 °C for racemic mixture); $[\alpha]^{26}_D = -89.8°$ (*c* 0.86, $CHCl_3$); IR (neat) 1690, 3350 $cm^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.08% $CHCl_3$/MeCN v/v (*c* 1.21 × $10^{-5}$ M) 233.7 (4.88); CD $\Delta\epsilon$ $M^{-1}$ $cm^{-1}$ ($\lambda_{max}$ nm) 0.4% $CHCl_3$/MeCN v/v (*c* 1.21 × $10^{-5}$ M) +82.1 (242), −72.1 (226); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 5.03 (s, 2H), 5.10 (s, 2H), 6.43 (d, *J* = 2.5 Hz, 2H), 6.98 (dd, *J* = 8.76, 2.5 Hz, 2H), 7.21 (d, *J* = 8.87 Hz, 2H), 7.79 (d, *J* = 8.78 Hz, 2H), 7.88 (d, *J* = 8.86 Hz, 2H).

**Conversion of Compound 12 to Compound 14.** In a 10-mL rb flask, compound **12** (0.023 g, 0.03 mmol) and $K_2CO_3$ (0.025 g, 0.18 mmol) in DMF (0.3 mL) was treated with MeI (0.3 mL, 4.8 mmol) in three 0.1 mL portions at intervals of about 10 h. The reaction mixture was stirred for 40 h at 50° C. The solvent was evaporated in vacuo, and the residue was extracted with ethyl acetate and washed with dilute HCl, water, and brine and dried over $Na_2SO_4$. The crude product obtained on evaporation of the volatiles was purified on a silica gel column (1.2 cm × 18 cm) using 4% EA/$CHCl_3$ to yield 0.021 mg (87%) of **14**: $[\alpha]^{23}_D = +33.5$ (*c* 1.13, $CHCl_3$); IR (neat) 1759 $cm^{-1}$; UV $\lambda_{max}$ (log $\epsilon$) 0.02% $CHCl_3$/MeCN v/v (*c* 1.04 × $10^{-5}$ M) 233.5 (5.07), 284.0 (3.97), 335.0 (3.82); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.72 (s, 3H), 0.86 (s, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 1.04−2.3 (m, steroidal CH and $CH_2$), 3.62 (s, 3H), 3.72 (s, H), 3.78 (s, 3H), 4.59 (m, 1H), 4.85 (s, 1H), 6.8 (dd, *J* = 6.6 and 2.4 Hz, 2H), 7.03 (dd. *J* = 8.7 and 2.7 Hz, 1H), 7.43 (dd, *J* = 9 Hz and 2.4 Hz, 2H), 7.86−8.03 (m, 5H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 12.27, 17.46, 22.43, 23.27, 23.46, 25.74, 25.87, 26.52, 27.19, 30.66, 30.88, 33.12, 33.67, 34.39, 34.81, 34.41, 41.52, 45.23, 47.23, 48.80, 51.46, 56.83, 56.87, 79.34, 81.27, 113.51, 113.93, 114.10, 115.11, 116.69, 118.34, 118.99, 119.29, 126.86, 127.35, 129.23, 129.49, 129.69, 134.43, 134.58, 149.93, 150.19, 151.07, 151.61, 155.90, 155.92, 174.53.

**(*S*)-(−)-7,7′-Dihydroxy-2,2′-dimethoxy-1,1′-binaphthyl (15).** Compound **14** (0.021 g, 0.026 mmol) was dissolved in degassed MeOH/THF (3:1) (2.0 mL), and LiOH (0.011 g, 0.46 mmol) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 16 h and acidified with 3 M HCl solution. Volatiles were removed under reduced pressure, and the crude product was purified by column chromatography on a silica gel column (21 cm × 1.2 cm) using 8−12% EA/$CHCl_3$ as the eluent to yield 0.008 g (90%) of **15**: $[\alpha]^{26}_D = +48.3°$ (*c* 2.4, DMF); lit.[12f] $[\alpha]^{26}_D = +45.9°$ (*c* 1.0, DMF) for the (*S*) isomer: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.76 (s, 6H), 4.78 (s, 2H), 6.34 (d, *J* = 2.7 Hz, 2H), 6.94 (d, *J* = 2.4 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 2H). 7.89 (d, *J* = 9.0 Hz, 2H).

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