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An Oxazoline Based Approach to (*S*)-Gossypol

A. I. Meyers*⁺ And Jeffrey J. Willemsen

Department Of Chemistry, Colorado State University, Fort Collins, CO 80523 U.S.A.

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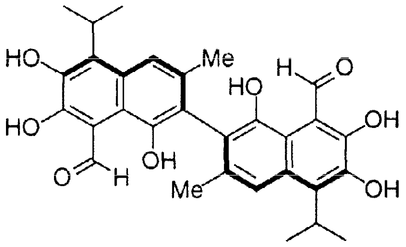
Abstract: (*S*)-Gossypol **(*S*)-1**, a yellow pigment of cottonseed, has been accessed by a total asymmetric synthesis. The sequence leading to (*S*)-gossypol **(*S*)-1** was highlighted by four oxazoline mediated reactions, including coupling of *ortho*-(methoxy)aryloxazolines with Grignard reagents, butyllithium based *ortho*-lithiation of aryloxazolines, stereocontrolled Ullmann couplings of bromonaphthyloxazolines, and ethoxyvinyllithium hexamethylphosphoric triamide complex based *ortho*-lithiation of aryloxazolines. © 1998 Elsevier Science Ltd. All rights reserved.

In 1886, J. Longmore isolated the main coloring pigment of cotton seeds.[1] Later in 1899, L. Marchlewski named this molecule gossypol[2] due not only to the fact that this constituent was isolated from the genus *Gossypium* but also because it had phenolic characteristics. Over 50 years later, R. Adams and coworkers, in a massive effort, elucidated the structure and identified much of the chemistry of this highly colored binaphthyl.[3-11] A formal synthesis of racemic gossypol **(*R,S*)-1** was reported in 1957 by J. Cashaw and J. Edwards.[12] Due to its interesting biological activity this compound has recently attracted considerable attention. Pharmacologically, (*R*)-gossypol **(*R*)-1** has been reported to be an oral antifertility agent in men and male animals,[13,14] and has shown activity for the potential treatment of HIV infections and cancer.[15] (*R*)-Gossypol **(*R*)-1** and (*S*)-gossypol **(*S*)-1** are chiral molecules due to rotational restriction about the internaphthyl 2,2' bond and are C_2 symmetric. Both stereoisomers have been isolated from natural sources but an asymmetric synthesis has yet to be reported.[14] Herein, an efficient asymmetric synthesis of (*S*)-gossypol **(*S*)-1** is described.



(*S*)-1

Important to the retrosynthetic analysis of (*S*)-gossypol **(*S*)-1** was not only the C_2 symmetry of this highly oxygenated binaphthalene, but also the fact that gossypol existed as either of two atropisomers. Initial disconnection of the 2,2'-biaryl bond gave two identical naphthyl pieces, simplifying the construction of the

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⁺ E-mail: aimeyers@lamar.colostate.edu
FAX: 970-491-2114

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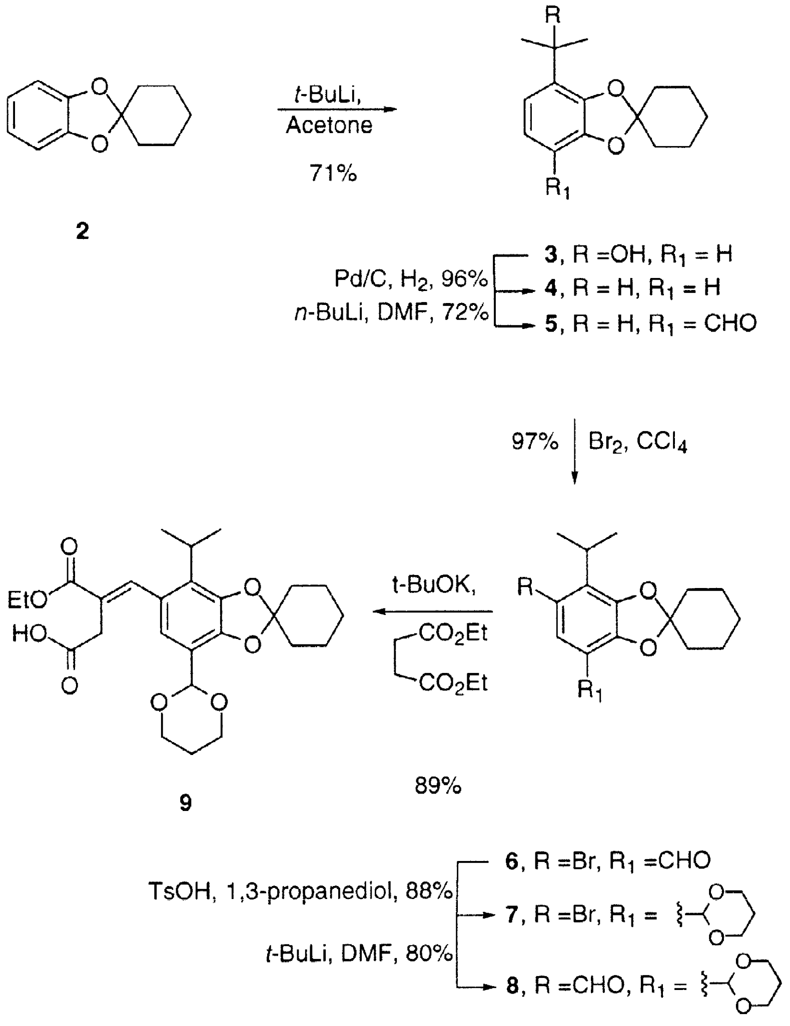
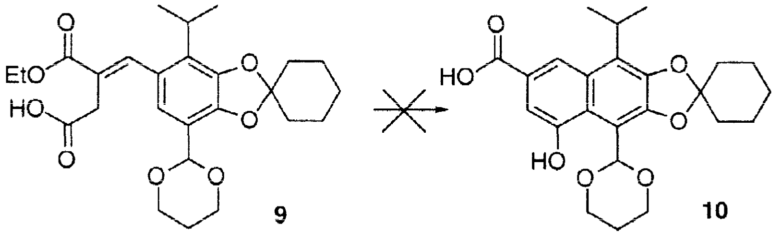
requisite carbon framework. Further, it was envisioned that the 2,2'-biaryl bond could be constructed asymmetrically *via* an Ullmann coupling[16-19] using functionalized chiral non-racemic bromonaphthyloxazolines.

Oxazoline **(*S*)-19** was chosen as the initial target for the Ullmann precursors. According to a procedure of Boeckmann,[20] treatment of catechol with cyclohexanone with azeotropic removal of H_2O in refluxing benzene provided **2**. Deprotonation of **2** with *t*-butyllithium[21-23] and subsequent treatment with isopropyl halides gave exclusively starting material. In contrast, *ortho*-lithiation[22,23,24] of **2** followed by treatment with acetone furnished carbinol **3** in 71% yield. The latter was hydrogenolyzed[25] in good yield to give the isopropyl substituted derivative **4**. The resulting isopropyl ketal **4** was treated with *n*-butyllithium[22] and *N,N*-dimethylformamide to give **5** which then was brominated[26] to afford bromobenzaldehyde **6**. Protection provided the 1,3-dioxane, **7**, which under conditions of halogen metal exchange at -90 °C gave the corresponding lithioanion.[22] The latter, in turn, was treated with *N,N*-dimethylformamide to give the substituted benzaldehyde, **8**.

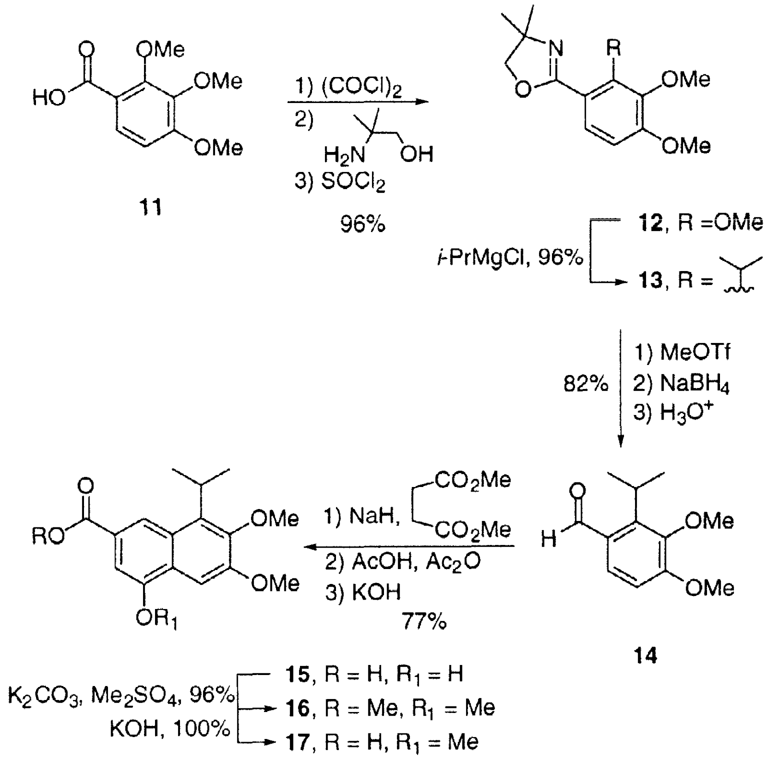


According to the procedure of Edwards[27] benzaldehyde **8** was subjected to Stobbe condensation conditions using potassium *t*-butoxide and diethyl succinate to give the benzylidine ester acid **9** in 85% yield. Subsequently ring cyclization to afford **10** according to the procedure of Mollov[28] was unsuccessful. Modification of these ring closure conditions gave starting material or large amounts of decomposition products. It was proposed that the unsuccessful conversion of **9** to **10** was due to the steric encumbrance of the dioxane ketal substituent blocking the *ortho* position to prevent cyclization from taking place.



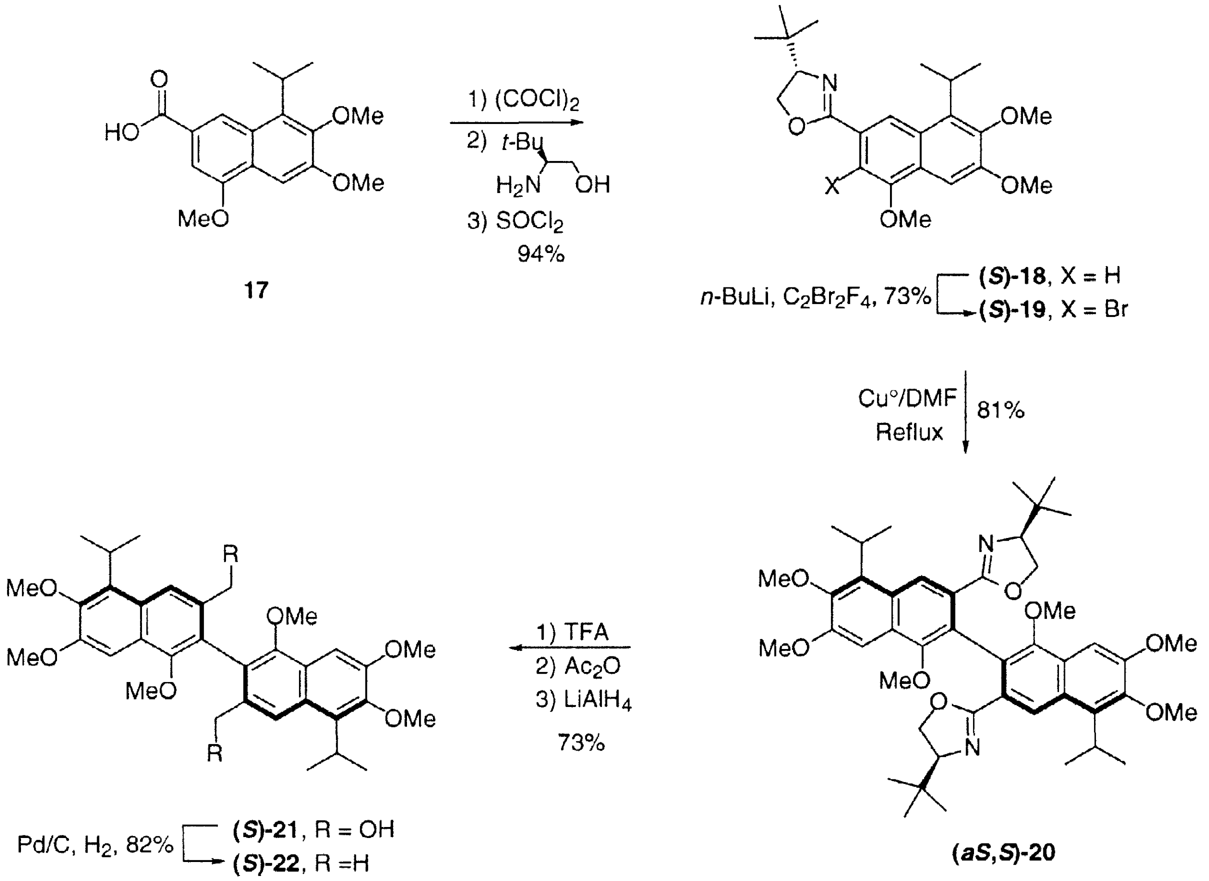
A synthetic route which would bypass the above ring cyclization problem was then examined. It was postulated that the formyl groups could be installed at a later stage in the synthesis. In particular, it was felt that recently discovered methodology utilizing EVL-HMPA[29] could be used to install the requisite formyl groups.

In accordance with the above approach, commercially available 2,3,4-trimethoxybenzoic acid **11** was treated with oxalyl chloride to furnish the corresponding acid chloride which was treated with 2-amino-2-



methyl-1-propanol under Schotten-Baumann conditions[30,31] to afford the amide alcohol. Cyclization with thionyl chloride followed by basic workup provided the oxazoline **12**.[32] Displacement of the *ortho*-methoxy group of trimethoxyoxazoline **12**, gave isopropylated oxazoline **13** when treated with 5 eq of isopropylmagnesium chloride.[32-35] The latter was then treated with methyl trifluoromethanesulfonate to provide the oxazoline *N*-methyl triflate salt which was further reduced with $NaBH_4$ and hydrolyzed with oxalic acid[33,22] to provide 2-isopropyl-3,4-dimethoxybenzaldehyde **14**. Aldehyde **14** was alkylated *via* Stobbe condensation[36] using NaH and dimethyl succinate and then cyclized efficiently according to the procedure of Mollov.[28] Saponification furnished 4-hydroxy-8-isopropyl-6,7-dimethoxy-2-naphthoic acid **15** which was then treated with dimethyl sulfate and K_2CO_3 affording the methyl ester **16**.[37] Finally the methyl ester **16** was converted to **17** upon treatment with methanolic KOH.

Naphthoic acid **17** was treated with oxalyl chloride, (*S*)-(+)-*t*-leucinol, and thionyl chloride to give oxazoline **(*S*)-18**.[32] Conversion of **(*S*)-18** to **(*S*)-19** utilizing *n*-BuLi as a base and 1,2-dibromotetrafluoroethane, occurred in 73% yield. Treatment of bromooxazoline **(*S*)-19** with Cu° in refluxing *N*,*N*-dimethylformamide[17] for 30 minutes gave a 81% yield of a mixture of **(*aS*,*S*)-20** to **(*aR*,*S*)-20** in a diastereomeric ratio of 11 : 1 as seen by integration of the *t*-butyl signals in the ^1H NMR. The bis-



17

(*S*)-18, X = H

(*S*)-19, X = Br

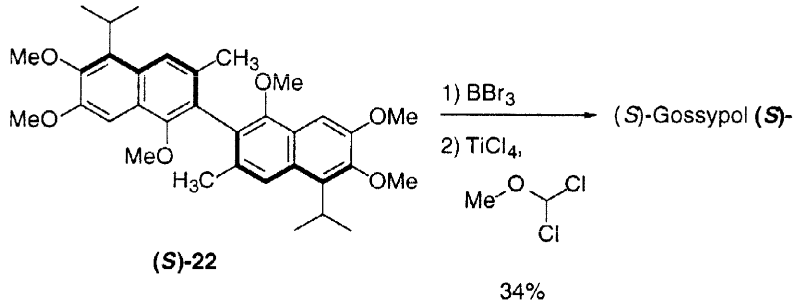
(*aS*,*S*)-20

(*S*)-21, R = OH

(*S*)-22, R =H

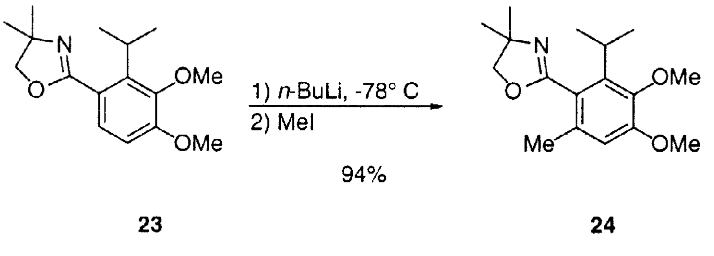
naphthyloxazoline **(*aS*,*S*)-20**, when treated with trifluoroacetic acid and Na_2SO_4 gave the corresponding bis-amino ester, which was bis-acylated using acetic anhydride and pyridine.[38] The acetylated ester amide was then reduced using $LiAlH_4$ affording the bis-carbinol **(*S*)-21**. Reduction of the chiral diol **(*S*)-21** to (*S*)-apogossypol hexamethyl ether **(*S*)-22** was accomplished with 10% Pd/C, H_2, and a catalytic amount of HCl.[39]

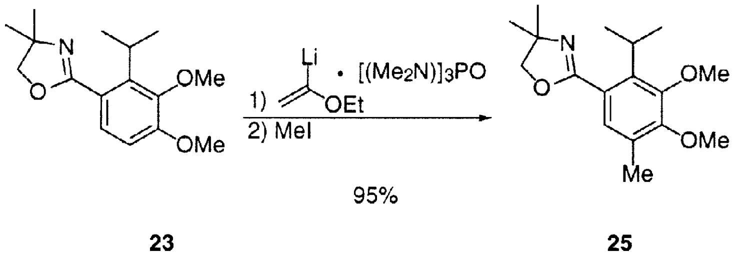
(*S*)-Apogossypol hexamethyl ether **(*S*)-22** was taken on to (*S*)-gossypol **(*S*)-1** following the procedure reported by Meltzer[40]. **(*S*)-22** was treated with boron tribromide which removed all six of the methyl protecting groups, and the crude material was treated immediately with titanium tetrachloride and α,α-dichloromethyl methyl ether to give an 34% yield of (*S*)-gossypol **(S)-1**.



Since the conversion of **(*S*)-22** to (*S*)-gossypol **(*S*)-1** proceeded in poor yield, an examination of methods to install formyl groups or their equivalents was undertaken. One of the most favorable options considered was to install the formyl equivalents using the 1-ethoxyvinyllithium (EVL)-HMPA base.[29] It was felt that a bis-*ortho*-lithiation in substrate **(*aS*,*S*)-20** could lead to regioselective bis-anion formation *ortho* to the methoxy substituents. The precedence for this work was found in the report from this laboratory in 1996.[29]

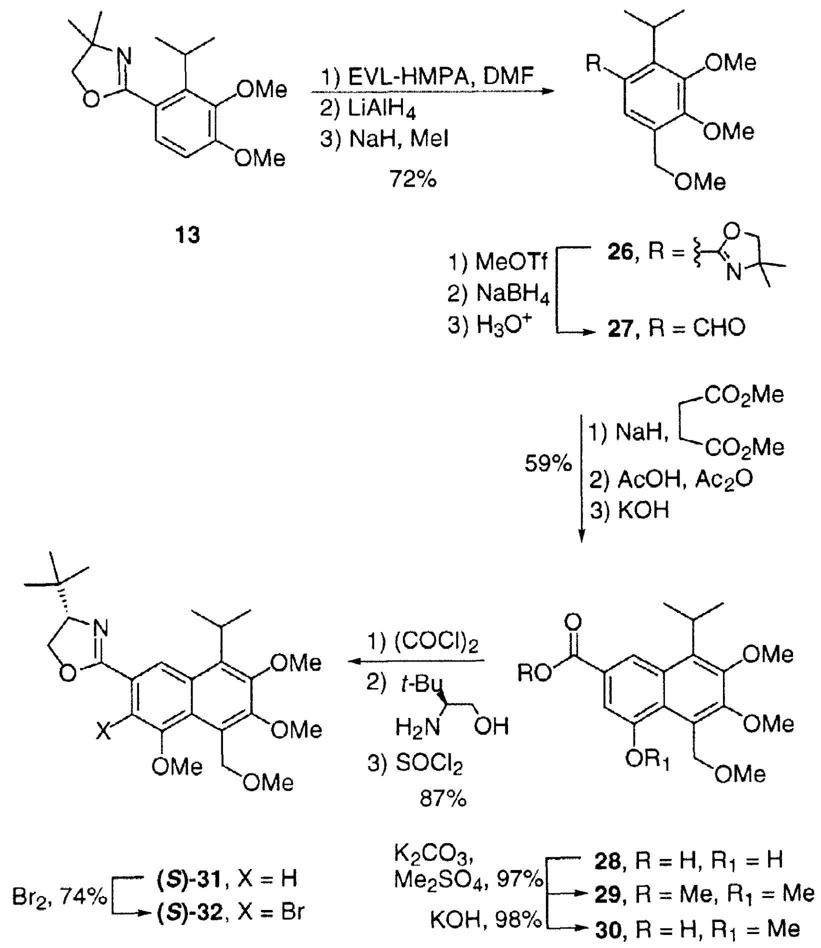
A model study was examined to test the feasibility of installing these aldehyde equivalents using EVL-HMPA. When **23** was treated with *n*-butyllithium[37] or EVL-HMPA[29] as bases, these reactions proceeded





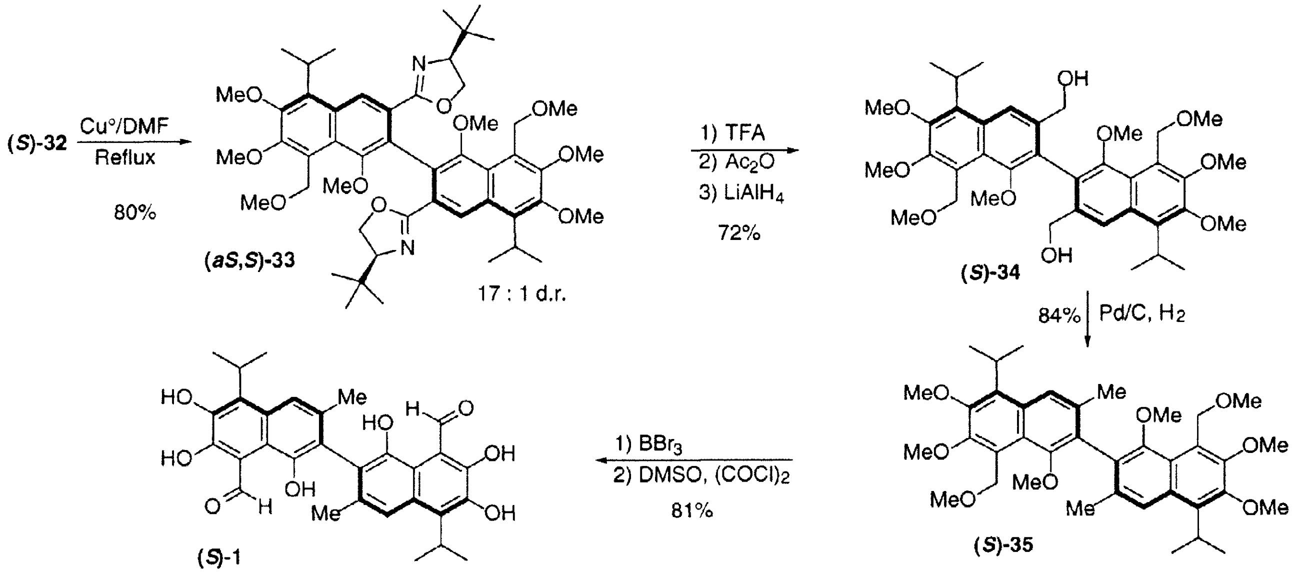
smoothly to give **24** and **25** respectively in high yields (94%, 95%). At this point attempts to alkylate either **(*aS,S*)-20** were examined. It was envisioned that if **(*aS,S*)-20** could be bis-*ortho*-lithiated to give a dianion with EVL-HMPA and subsequently alkylated, **(*aS,S*)-20** could be taken on to (*S*)-gossypol **(*S*)-1** in a more facile manner than converting (*S*)-apogossypol hexamethyl ether **(*S*)-22** on to (*S*)-gossypol **(*S*)-1**. A wide range of EVL-HMPA based*ortho*-lithiation conditions were examined for bis-oxazoline **(*aS,S*)-20**, but these reactions failed to give the desired alkylated products.

The failure of **9** to cyclize to **10**, and the failure of the EVL-HMPA base to give a satisfactory regioselective bis-alkylation of **(*aS,S*)-20**, led to a reevaluation of the synthetic approach to (*S*)-gossypol **(*S*)-1**, and the possibility of utilizing substrates which had formyl group equivalent installed at an earlier point in the synthesis. A formyl group was introduced into previously synthesized oxazoline, **13**, with the desired regiochemistry by effecting a regioselective deprotonation with EVL-HMPA[29] and subsequent treatment of the resultant lithioanion of **13** with *N,N*-dimethylformamide. The formyloxazoline was converted to oxazoline **26** by treatment with $LiAlH_4$[41,42] and subsequently with NaH and methyl iodide.[37] The oxazoline **26** was converted to **27** by reductive removal of the oxazoline to give benzaldehyde **27**. Aldehyde **27** was treated with



NaH and dimethyl succinate to effect a Stobbe condensation[36] which was followed by ring cyclization with AcOH, acetic anhydride and fused sodium acetate.[28] Hydrolysis gave naphthoic acid **28** which was converted to the naphthalene methyl ester **29** with dimethyl sulfate and K_2CO_3.[37] Ethanolic KOH effected saponifacation to efficiently convert ester **29** to naphthoic acid **30**. Sequential treatment of the acid acid **30** with oxalyl chloride, (*S*)-(+)-*t*-leucinol, and thionyl chloride gave oxazoline **(*S*)-31** in 93% yield.[32] Regioselective bromination was effected by treatment of **(*S*)-31** with bromine in AcOH to give **(*S*)-32** in 73% yield.

In a fashion similar to the conversion of bromooxazoline **(*S*)-19** to coupled product **(*aS*,*S*)-20**, **(*S*)-32** was subjected to Cu° and refluxing *N*,*N*-dimethylformamide.[17] The best results (80%) were obtained when the reaction was performed in concentrated solution (0.9 g in 2.5 mL *N*,*N*-dimethylformamide). The resultant diastereomer **(*aS*,*S*)-33** was converted to bis-carbinol **(*S*)-34** in 72% yield.[43] In an analogous conversion of **(*S*)-21** to **(*S*)-22**, the bis-naphthol **(*S*)-34** could be converted to **(*S*)-35** by treatment with Pd/C under an atmosphere of 40 PSI of H_2.[39] Removal of all eight methyl protecting groups with boron tribromide[40] followed by Swern oxidation[44,45] gave (*S*)-gossypol **(*S*)-1** in 80% yield for the last two steps.



HPLC analysis of (*S*)-gossypol **(*S*)-1** and (*R*,*S*)-gossypol **(*R*,*S*)-1** was undertaken. The initial attempts to separate the enantiomers of (*R*,*S*)-gossypol **(*R*,*S*)-1** using chiral columns were unsuccessful. However, the diastereomeric imines of (*R*,*S*)-gossypol **(*R*,*S*)-1** with (*S*)-phenylalanine methyl ester were easily separated on a C_{18} reverse phase column (5µm Hypersil®-ODS, gradient: MeCN : (Aq 0.01 M KH_2PO_4) 91 : 9 to MeCN : (Aq 0.01 m KH_2PO_4) 82 : 18) monitored at 254 nm, flowrate 0.7 ml/min).[46] These diastereomeric imines could be made in quantitative yield by treatment of (*S*)-gossypol **(*S*)-1** or (*R*,*S*)-gossypol **(*R*,*S*)-1** with (*S*)-phenylalanine methyl ester. The HPLC analysis of the imines derived from (*S*)-gossypol **(*S*)-1** synthesized from the asymmetric route gave a 99 : 1 ratio of diastereomeric phenylalanine methyl ester imines.

NMR analysis of the sample derived from the asymmetric synthesis of (*S*)-gossypol **(*S*)-1** was identical in all respects to commercially available (*R*,*S*)-gossypol ***(R, S)*-1** and to the literature values[47,48] for (*R*,*S*)-gossypol **(*R*,*S*)-1**. The rotation of **(*S*)-1**, +363.4, derived from the asymmetric synthesis of (*S*)-gossypol **(*S*)-1** was within a range of values reported in the literature, +374,[49] +376,[50] +373,[51] and +359.[52] Finally the absolute configuration for (*S*)-gossypol **(*S*)-1** has been assigned previously using x-ray crystallographic data and chiroptic methods.[53] This work has shown that the absolute configuration of (+)-gossypol is the *S* atropisomer.

EXPERIMENTAL SECTION

General: Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Fourier Transform Infrared (FTIR) spectra were recorded on a Perkin-Elmer Model 1600 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). Both low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained using a Fisons VG Autospec mass selective detector. Optical rotations were measured on a Rudolph Research Autopol III polarimeter using a one decimeter cell path length with concentrations expressed in grams per 100 mL. Optical rotations of amines taken in chloroform ($CHCl_3$) were checked over a period of two hours to insure rotation values were constant over that time frame. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz on a Bruker AM-300. Chemical shifts (δ) are reported in parts per million from tetramethylsilane relative to the residual chloroform ($CHCl_3$) resonance (δ 7.24). Multiplicity is designated as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept) and multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz on a Bruker AM-300. Chemical shifts (δ) are reported in parts per million from tetramethylsilane and were measured relative to the center resonance of the deuteriochloroform triplet (δ 77.0).

All moisture-sensitive reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Argon for inert atmosphere reactions was passed through a sulfuric acid bubbler, a drying tower of KOH and Drierite, and subsequently through a heated (200-220 °C), activated oxygen trap (BASF copper-based catalyst). Butyllithiums were purchased from the Aldrich Chemical Company and titrated in Et_2O with 2,5-dimethoxybenzyl alcohol.[54] Commercially available reagents were used as purchased unless stated otherwise. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Dichloromethane (CH_2Cl_2), was distilled from CaH_2 prior to use.

Column chromatography was performed as described by Still[55] on Davison Chemical Al_2O_3/SiO_2 mixture grade 135X. Solvent mixtures used for column chromatography are reported in V : V total. *In vacuo* refers to removal of solvent on a rotary evaporator at H_2O aspiration pressure (~16 mm Hg).

Dimethyl-(2,3-cyclohexylenedioxyphenyl)-carbinol, 3. To a cold (-78 °C) solution of **2** (1.0 g, 5.3 mmol) in dry Et_2O (20 mL) was added slowly *t*-butyllithium (2.7 mL, 5.4 mmol, 2.0 M). The reaction was stirred for 3 h at which time acetone (0.62 g, 0.78 mL, 11 mmol) was added. The solution was warmed to r.t. over the course of 1 h and then was treated with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (10 : 1 hexanes : EtOAc) to give 0.93 g (71%) of **3**, mp 50-51 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46-1.52 (m, 2H), 1.58 (s, 6H), 1.71-1.74 (m, 4H), 1.87-1.93 (m, 4H), 2.62 (s, 1H), 6.65 (d, 1H, J = 7.8 Hz), 6.74 (t, 1H, J = 7.8 Hz), 6.82 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (t), 24.8 (t), 29.8 (q), 35.3 (t), 71.9 (s), 107.6 (d), 117.4 (d), 118.6 (s), 121.0 (d), 131.0 (s), 143.4 (s), 147.6 (s); FTIR (neat) 3414, 2939, 2864, 1447, 1355, 1283, 1250, 1070 cm^{-1}; LRMS (GC-MS) calc for $C_{15}H_{20}O_3$: *m/z* 248; obsd *m/z* 248 (M^+); Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; found: C, 72.67; H, 8.11.

1,2-Cyclohexylenedioxy-3-isopropylbenzene, 4. Carbinol **3** (3.0 g, 12 mmol) was dissolved in AcOH (10 mL) and 10% Pd/C (1.0 g) was added. The mixture was stirred overnight under 50 psi of H_2. The resulting mixture was filtered, diluted with Et_2O (200 mL) and neutralized using saturated aqueous $NaHCO_3$ (900 mL). The ethereal layer was washed once with H_2O (100 mL), was dried with Na_2SO_4, and the Et_2O was removed *in vacuo*. The residue was purified by column chromatography (10 : 1 hexanes : EtOAc) to give 2.7 g (96%) of **4** as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, 6H, J = 6.9 Hz), 1.49-1.53 (m, 2H), 1.71-1.79 (m, 4H), 1.89-1.94 (m, 4H), 3.03 (sept, 1H, J = 6.9 Hz), 6.60-6.76 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3 (q), 23.4 (t), 24.9 (t), 29.0 (d), 35.4 (t), 106.2 (d), 117.8 (s), 118.8 (d), 120.8 (d), 130.1 (s), 144.8 (s), 147.1 (s); FTIR (thin film) 2938, 2867, 1456, 1356, 1282, 1250, 1068 cm^{-1}; LRMS (GC-MS) calc for $C_{15}H_{20}O_2$: *m/z* 232; obsd *m/z* 232 (M^+); Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; found: C, 77.61; H, 8.73.

2,3-Cyclohexylenedioxy-4-isopropylbenzaldehyde, 5. To a cold (-78 °C) solution of 1,2-cyclohexylenedioxy-3-isopropylbenzene **4** (1.0 g, 4.3 mmol) in dry Et_2O (50 mL) was added slowly *n*-butyllithium (2.6 mL, 5.2 mmol, 2.0 M). The reaction mixture was stirred for 12 h at this temperature and then DMF (0.60 g, 0.64 mL, 8.2 mmol) was added. The solution was warmed to r.t. over the course of 3 h and subsequently the reaction was treated with H_2O (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), dried with Na_2SO_4, and then were concentrated under reduced pressure. The residue was purified by column chromatography (10 : 1 hexanes : EtOAc) to give 0.81 g (72%) of **5**, mp 62-63 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, 6H, J = 6.9 Hz), 1.44-1.55 (m, 2H), 1.70-1.76 (m, 4H), 1.89-1.94 (m, 4H), 3.02 (sept, 1H, J = 6.9 Hz), 6.72 (d, 1H, J = 8.4 Hz), 7.17 (d, 1H, J = 8.4 Hz), 10.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8 (q), 23.4 (t), 24.7 (t), 29.3 (d), 35.4 (t), 117.6 (s), 119.4 (d), 119.9 (d), 120.9 (s), 135.9 (s), 145.9 (s), 149.7 (s), 188.0 (d); FTIR (neat) 2940, 2866, 1442, 1367, 1271, 1240, 1076 cm^{-1}; LRMS (GC-MS) calc for $C_{16}H_{20}O_3$: *m/z* 260; obsd *m/z* 260 (M^+); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74; found: C, 73.76; H, 7.75.

5-Bromo-2,3-cyclohexylenedioxy-4-isopropylbenzaldehyde, 6. To a solution of **5** (1.5 g, 5.8 mmol) in carbon tetrachloride (50 mL) was added a solution of bromine (0.93 g, 0.30 mL, 5.8 mmol) in chloroform (20 mL). The mixture was heated to reflux for 4 h and then cooled to r.t. The organic phase was washed with saturated aqueous $NaHSO_3$ (50 mL). The aqueous layer was extracted with a single portion of Et_2O (100 mL) and the combined organic layers were dried with Na_2SO_4. The solvent was removed *in vacuo* to give 1.9 g (97%) of 5-bromo-2,3-cyclohexylenedioxy-4-isopropylbenzaldehyde **6** as a light tan solid, mp 113-114 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 6H, J = 7.0 Hz) 1.38-2.00 (m, 10H), 3.35 (sept, 1H, J = 7.0 Hz), 7.39 (s, 1H), 9.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (q), 23.4 (t), 24.5 (t), 32.6 (d), 35.7 (t), 115.7 (s), 117.9 (s), 121.9 (s), 123.0 (d), 134.7 (s), 147.3 (s), 149.7 (s), 186.5 (d); FTIR (neat) 2940, 2866, 2743, 1694, 1435, 1214 cm^{-1}; LRMS (GC-MS) calc for $C_{16}H_{19}BrO_3$: *m/z* 339; obsd *m/z* 339 (M^+).

2-(5-Bromo-2,3-cyclohexylenedioxy-4-isopropylphenyl)-1,3-dioxane, 7. Bromobenzaldehyde **6** (3.0 g, 8.8 mmol), 1,3-propanediol (0.68 g, 0.65 mL, 8.9 mmol) and *para*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) were heated to reflux in toluene (50 mL) for 6 h with azeotropic removal of H_2O. The excess toluene was removed *in vacuo* and the resulting oil was passed through a plug of silica gel (1 : 1 hexanes : EtOAc) to give 3.1 g (88%) of **7** as a tan solid, mp 124-125 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 6H, J = 6.9 Hz), 1.33-2.00 (m, 10H), 2.16-2.22 (m, 2H), 3.31 (sept, 1H, J = 6.9 Hz), 3.89-3.93 (m, 2H), 4.17-4.23 (m, 2H), 5.57 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (q), 23.6 (t), 24.9 (t), 26.0 (t), 32.4 (d), 35.4 (t), 67.8 (t), 96.8 (d), 112.6 (s), 115.2 (s), 119.0 (s), 119.7 (s), 122.3 (d), 129.7 (s), 144.6 (s); FTIR (neat) 2938, 2856, 1436, 1110, 1082 cm^{-1}; Anal. Calcd for $C_{19}H_{25}BrO_4$: C, 57.44; H, 6.34; found: C, 57.40; H, 6.31.

2-(2,3-Cyclohexylenedioxy-5-formyl-4-isopropylphenyl)-1,3-dioxane, 8. To a cold (-78 °C) solution of 7 (2.0 g, 5.0 mmol) in Et_2O (20 mL) was added slowly *t*-butyllithium (5.5 mL, 11 mmol, 2.0 M). The reaction was stirred for 3 h at which time DMF (0.74 g, 0.78 mL, 10 mmol) was added. The solution was warmed to r.t. over the course of 1 h and subsequently treated with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), were dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (8 : 1 hexanes : EtOAc) to give 1.4 g (80%) of benzaldehyde **8** as a white solid, mp 137-138 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 6H, J = 7.0 Hz), 1.41-1.98 (m, 12H), 3.94-4.26 (m, 5H), 5.64 (s, 1H), 7.55 (s, 1H), 9.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (q), 23.5 (t), 24.8 (t), 25.7 (t), 26.0 (d), 35.6 (t), 67.8 (t), 96.7 (d), 118.1 (s), 120.8 (s), 128.5 (s), 128.9 (d), 132.1 (s), 146.8 (s), 149.8 (s), 192.3 (d); FTIR (neat) 2938, 2860, 1688, 1588, 1444, 1280, 1083 cm^{-1}.

Benzylidene ester acid, 9. A flame dried flask evacuated and purged three times with argon was charged with THF (30 mL), benzaldehyde **8** (0.90 g, 2.6 mmol), potassium *t*-butoxide, (0.34 g, 3.0 mmol), and diethyl succinate (0.55 g, 0.53 mL, 3.2 mmol). This solution was stirred for 4.5 h at r.t. and then was treated with H_2O (40 mL). To This mixture was added Et_2O (100 mL) and the layers were separated. The aqueous layer was acidified with 10% HCl (pH 2) and extracted with Et_2O (3 x 50 mL). The combined organic layers were subsequently combined, washed with H_2O (100 mL), dried with $MgSO_4$, and reduced *via* rotary evaporation to give 1.1 g (89%) of **9** as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.18-2.18 (m, 20H), 2.91 (sept, 1H, J = 7.1 Hz), 3.43 (s, 2H), 3.87-4.28 (m, 8H), 5.58 (s, 1H), 6.80 (s, 1H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 (q), 20.6 (d), 20.9 (q), 23.5 (t), 24.8 (t), 25.9 (t), 33.6 (t), 35.4 (t), 61.2 (t), 67.6 (t), 97.0 (d), 117.7 (s), 119.3 (d), 119.5 (s), 120.0 (s), 126.4 (s), 126.6 (s), 128.9 (s), 142.7 (d), 145.7 (s), 167.4 (s), 176.9 (s); FTIR (thin film) 3453, 2889, 1661, 1548, 1420, 1269, 1198 cm^{-1}.

4,4-Dimethyl-2-(2,3,4-trimethoxyphenyl)-2-oxazoline, 12. To a solution of 2,3,4-trimethoxybenzoic acid **11** (0.50 g, 2.4 mmol) in CH_2Cl_2 (100 mL) was added oxalyl chloride (0.50 g, 0.34 mL, 3.9 mmol) and DMF (53 mg, 0.05 mL, 0.73 mmol). The solution was stirred at r.t. for 4 h and then the solvent was removed *in vacuo*. The acid chloride was redissolved in CH_2Cl_2 and a solution of 2-amino-2-methyl-1-propanol (0.22 g, 0.24 mL, 2.5 mmol) dissolved in 10% NaOH (50 mL) was added dropwise, and the solution was stirred overnight. The layers were separated and the organic layer was concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (100 mL), and thionyl chloride (0.80 g, 0.49 mL, 6.7 mmol) was added, and the reaction was stirred overnight. H_2O (40 mL) and 10% NaOH (100 mL) were then added to the solution which was stirred for 3 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 70 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed *in vacuo*. The residue obtained was purified by column chromatography (1 : 1 hexanes : EtOAc) to give 0.60 g (96%) of phenyloxazoline **12** as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6H), 3.79-3.80 (m, 9H), 3.99 (s, 2H), 6.59 (d, 1H, J = 8.8 Hz), 7.40 (d, 1H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 56.1, 61.1, 61.6, 67.3, 78.8, 107.1, 115.7, 125.9, 142.8, 153.6, 155.9, 160.7; FTIR (thin film) 2967, 2936, 1645, 1598, 1354, 1294 cm^{-1}.

4,4-Dimethyl-2-(2-isopropyl-3,4-dimethoxyphenyl)-2-oxazoline, 13. To phenyloxazoline **12** (0.90 g, 3.4 mmol) was added isopropylmagnesium chloride ((Aldrich) 5.0 mL, 10 mmol, 2.0 M)). This solution was heated to reflux for 4 h at which time the reaction was complete by TLC. The reaction was treated slowly with H_2O (10 mL). The layers were separated and the organic phase was washed with 10% HCl (20 mL) and extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were dried with Na_2SO_4 and then were concentrated by rotary evaporation. Column chromatography (1 : 1 hexanes : EtOAc) gave 0.90 g (96%) of **13** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 12H), 3.38 (sept, 1H, J = 7.0 Hz), 3.76-3.82 (m, 8H), 6.67 (d, 1H, J = 8.5), 7.16 (d, 1H, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 28.3, 30.0, 55.6, 60.7, 67.6, 79.0, 109.5, 121.6, 125.9, 141.2, 148.3, 154.7, 163.8; FTIR (thin film) 2970, 2941, 1651, 1488, 1307, 1046 cm^{-1}; Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05; found: C, 69.39; H, 8.43; N, 4.98.

2-Isopropyl-3,4-dimethoxybenzaldehyde, 14. To a flame-dried flask containing a solution of oxazoline **13** (0.80 g, 2.9 mmol) and CH_2Cl_2 (25 mL) was added methyl trifluoromethanesulfonate (1.0 g, 0.69 mL, 6.1 mmol), and the solution was stirred for 2 h at r.t. until TLC indicated conversion of 4,4-dimethyl-2-(2-isopropyl-3,4-trimethoxyphenyl)-2-oxazoline into baseline salts. The solution was cooled to 0 °C and treated dropwise with a solution of $NaBH_4$ (0.24 g, 6.3 mmol) in THF/MeOH (4 : 1, 30 mL). After stirring for 1 h saturated aqueous NH_4Cl (30 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous NaCl (40 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated by rotary evaporation. Filtration (1 : 1 hexanes : EtOAc) through a short plug of silica was followed by reduction of the solvent *in vacuo* to give a colorless residue. The residue was taken up in a solution of THF/H_2O (4 : 1, 60 mL) and treated with oxalic acid dihydrate (1.0 g, 7.9 mmol). The solution was stirred at ambient temperature for 24 h. Et_2O (50 mL) was added and washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (40 mL). The combined extracts were dried with Na_2SO_4 and concentrated under reduced pressure. Column chromatography (10 : 1 hexanes : EtOAc) gave 0.49 g (82%) of benzaldehyde **14** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, 6H, J = 7.2 Hz), 3.81 (s, 3H), 3.90 (s, 3H), 4.02 (sept, 1H, J = 7.2 Hz), 6.85 (d, 1H, J = 8.7 Hz), 7.62 (d, 1H, J = 8.7 Hz), 10.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (q), 26.1 (d), 56.0 (q), 61.0 (q), 109.7 (d), 128.5 (s), 128.8 (d), 144.9 (s), 148.0 (s), 157.8 (s), 191.3 (d); FTIR (thin film) 2938, 2860, 1688, 1588, 1444, 1280, 1083 cm^{-1}.

4-Hydroxy-8-isopropyl-6,7-dimethoxy-2-naphthoic acid, 15. According to a modified procedure of Edwards[27] a flame dried flask was evacuated and purged three times (argon). To this flask was added THF (35 mL), benzaldehyde **14** (1.2 g, 5.8 mmol), potassium *t*-butoxide (0.73 g, 6.5 mmol), and dimethyl succinate (0.95 g, 0.85 mL, 6.5 mmol). This solution was stirred for 6 h, and then was treated with H_2O (100 mL). Et_2O (200 mL) was added, the layers were separated, the aqueous layer was acidified with 10% HCl (pH 3), and extracted with Et_2O (3 x 100 mL). The combined organic layers were extracted with saturated aqueous Na_2CO_3 (2 x 200 mL). The aqueous phase was cooled to 0 °C, acidified with 10% HCl (pH 1), and was extracted with Et_2O (4 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by rotary evaporation. To the crude product was then added AcOH (60 mL), acetic anhydride (60 mL), and fused sodium acetate (3.0 g, 37 mmol). This solution was heated at reflux for 4 h, cooled (0 °C), neutralized with saturated aqueous $NaHCO_3$ (300 mL) and extracted with Et_2O (5 x 100 mL). The organic layer was concentrated to give an oily residue which was heated to reflux in MeOH (100 mL) and 10% NaOH (100 mL) for 5 h. The MeOH was removed *via* atmospheric distillation and the resulting mixture was cooled (0 °C) and acidified with 10% aqueous HCl (pH 2). The resulting tan solid was filtered to give 4-hydroxy-8-isopropyl-6,7-dimethoxynaphthoic acid **15**. Recrystallization from benzene gave 1.3 g (77%) of a cream colored solid, mp 226-227 °C (lit.[27] 226-227 °C). ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, 6H, J = 7.0 Hz), 3.36 (s, 1H), 3.80 (s, 3H), 3.80-3.93 (m, 4H (therein 3.93 (s, 3H))), 7.35 (s, 1H), 7.47 (s, 1H), 8.27 (s, 1H), 10.31 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 (q), 26.5 (d), 55.4 (q), 60.6 (q), 100.4 (d), 106.2 (d), 117.5 (d), 125.1 (s), 126.0 (s), 127.8 (s), 135.9 (s), 147.7 (s), 152.8 (s), 152.9 (s), 168.0 (s); FTIR (KBr) 3447-2509, 1676, 1610, 1439, 1239 cm^{-1}; Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25; found: C, 66.16; H, 6.85.

Methyl 8-isopropyl-4,6,7-trimethoxynaphthalene-2-carboxylate, 16. According to a modified procedure of Edwards[27] to a stirred solution of naphthoic acid **15** (0.20 g, 0.69 mmol) in acetone (25 mL) was added K_2CO_3 (0.41 g, 3.0 mmol) and dimethyl sulfate (0.19 g, 0.14 mL, 1.5 mmol) in acetone (20 mL). After the reaction had been stirred at r.t. for 30 h, the mixture was filtered through Celite 545® and washed with CH_2Cl_2 (2 x 50 mL). The solvent was removed *in vacuo* and the resulting oil was diluted with CH_2Cl_2 (100 mL) and washed three times with H_2O (50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by rotary evaporation to give 0.21 g (96%) of **16** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (d, 6H, J = 7.1 Hz), 3.88 (s, 3H), 3.93-4.02 (m, 10H (therein 3.95 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H))), 7.33 (s, 1H), 7.52 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6 (q), 27.5 (d), 52.5 (q), 55.9 (q), 56.0 (q), 61.4 (q), 100.4 (d), 102.5 (d), 120.5 (d), 125.2 (s), 126.6 (s), 127.9 (s), 137.4 (s), 148.6 (s), 154.1 (s), 155.1 (s), 168.2 (s); FTIR (thin film) 2955, 2833, 1717, 1602, 1467, 1422, 1244 cm^{-1}.

8-Isopropyl-4,6,7-trimethoxy-2-naphthoic acid, 17. According to a modified procedure of Edwards[27] a solution of methyl ester **16** (0.42 g, 1.3 mmol) in MeOH (20 mL) was added slowly to a solution of KOH (0.25 g, 4.5 mmol) in MeOH (20 mL). The reaction was heated to reflux for 6 h and then was cooled to r.t. The MeOH was removed by rotary evaporation and the residue was taken up in H_2O (30 mL). The resulting solution was cooled (0 °C) and was acidified with dilute HCl (pH 2). The tan precipitate was filtered and dried under vacuum. The tan solid was then recrystallize from benzene twice to give 0.40 g (100%) of naphthoic acid **17** as a white solid, mp 215-217 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, 6H, J = 7.1 Hz), 3.80 (s, 3H), 3.94-4.00 (m, 7H (therein 3.94 (s, 3H), 4.00 (s, 3H))), 7.31 (s, 1H), 7.48 (s, 1H), 8.42 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 (q), 26.4 (d), 55.5 (q), 55.6 (q), 60.6 (q), 100.0 (d), 102.3 (d), 119.0 (d), 125.3 (s), 125.8 (s), 126.8 (s), 136.1 (s), 147.9 (s), 153.3 (s), 154.3 (s), 167.8 (s); FTIR (KBr) 2961, 1695, 1601, 1454, 1223 cm^{-1}; Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62; found: C, 67.15; H, 6.64.

(4*S*)-4-*t*-Butyl-2-(8-isopropyl-4,6,7-trimethoxy-2-naphthyl)-2-oxazoline, (*S*)-18. To a solution of naphthoic acid **17** (0.60 g, 2.0 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (0.37 g, 0.25 mL, 2.9 mmol) and DMF (0.10 g, 0.11 mL, 1.4 mmol). This solution was stirred for 4 h and the excess oxalyl chloride and solvent were removed by rotary evaporation. Dichloromethane (30 mL) was added and the resultant solution was cooled in an ice bath and a solution of 2-amino-3,3-dimethyl-1-butanol ((*S*)-(+)-*t*-leucinol)[56] (DeGussa, 0.34 g, 2.9 mmol) in 1 M NaOH (30 mL) was added *via* an addition funnel. After stirring for 3 h the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and reduced by rotary evaporation. After dissolving the residue in CH_2Cl_2 (30 mL) ring cyclization was effected by treatment with a solution of thionyl chloride (2.7 g, 1.7 mL, 23 mmol) in CH_2Cl_2 (30 mL). The resulting solution was stirred for 3 h and H_2O (10 mL) was added cautiously. After addition of 10% aqueous NaOH (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 35 mL). The organics were washed with saturated aqueous NaCl (25 mL) and dried with Na_2SO_4. Removal of the solvent *via* rotary evaporation was followed by column chromatography (4 : 1 hexanes : EtOAc) to afford 0.71 g (94%) of oxazoline **(*S*)-18** as a light yellow oil. $[\alpha]_D = -47$ (c = 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.52 (d, 6H, J = 7.0 Hz), 3.91 (s, 3H), 4.08 (s, 3H), 4.10-4.16 (m, 5H), 4.27-4.43 (m, 2H), 7.39 (s, 1H), 7.55 (s, 1H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0 (q), 25.7 (q), 26.9 (d), 34.0 (s), 55.3 (q), 55.6 (q), 60.9 (q), 68.5 (t), 76.0 (d), 100.0 (d), 101.8 (d), 117.6 (d), 122.7 (s), 125.0 (s), 127.6 (s), 136.5 (s), 148.4 (s), 152.9 (s), 154.4 (s), 163.8 (s); FTIR (thin film) 2963, 2935, 2831, 1646, 1600, 1466, 1237 cm^{-1}.

(4*S*)-4-*t*-Butyl-2-(3-bromo-8-isopropyl-4,6,7-trimethoxy-2-naphthyl)-2-oxazoline, (*S*)-19. To a flame dried flask was added oxazoline **(*S*)-18** (0.49 g, 1.3 mmol). The flask was purged and evacuated with argon five times, and then THF (15 mL), and NaH (0.10 g, 4.2 mmol) was added and the solution was cooled to -78 °C. *n*-Butyllithium (0.80 mL, 1.6 mmol, 2.0 M) was added slowly and after 20 min the solution was warmed to -45 °C and was stirred for 4 h. 1,2-dibromotetrafluoroethane (0.46 g, 0.21 mL, 1.8 mmol) was added dropwise and the solution was warmed to 0 °C over 2 h. H_2O (10 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried with $MgSO_4$, filtered, and reduced *in vacuo*. Column chromatography (8 : 1 hexanes : EtOAc) gave 0.43 g (73%) of bromooxazoline **(*S*)-19** as a viscous light yellow oil. $[\alpha]_D = -30$ (c = 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.42 (d, 6H, J = 7.5 Hz), 3.86 (s, 3H), 3.93 (s, 3H), 3.69 (s, 3H), 4.08-4.14 (m, 2H), 4.22-4.42 (m, 2H), 7.31 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (q), 22.3 (q), 26.2 (d), 27.2 (s), 34.2 (q), 55.8 (q), 61.0 (d), 61.2 (q), 69.1 (t), 77.0 (d), 100.1 (d), 110.9 (s), 123.7 (s), 125.5 (s), 127.4 (s), 128.3 (s), 137.1 (s), 153.3 (s), 154.4 (s), 163.5 (s); FTIR (thin film) 2957, 2870, 1655, 1606, 1464, 1418, 1247 cm^{-1}. Anal. Calcd for $C_{23}H_{30}BrNO_4$: C, 59.49; H, 6.51; N, 3.02; found: C, 60.32; H, 6.62; N, 2.92.

(4*S*)-4-*t*-Butyl-2,2'-(5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-(*S*)-2,2'-binaphthyl)-3,3'-bis-

oxazoline, (*aS,S*)-20 and (4*S*)-4-*t*-Butyl-2,2'-(5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-(*R*)-2,2'-binaphthyl)-3,3'-bis-oxazoline (*aR,S*)-20. Bromooxazoline (*S*)-**19** (0.70 g, 1.5 mmol) was added to a flame dried flask which was equipped with a flame dried condensor. Freshly distilled DMF (1.5 mL), NaH (0.10 g, 4.2 mmol) and freshly activated[57] Cu° (0.19 g, 3.0 mmol) were added. This mixture was heated at reflux for 1 h. The resulting mixture was filtered using a pad of Celite 545® and the solid was repeatedly washed with NH_4OH (3 x 30 mL), H_2O (3 x 40 mL), and Et_2O (5 x 60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 50 mL). The combined ethereal layers were washed with concentrated NH_4OH (3 x 25 mL) until no blue color persisted in the aqueous layer, washed with H_2O (3 x 100 mL), and then concentrated *in vacuo* . Subsequent azeotropic removal of pyridine and H_2O with toluene *in vacuo* gave a residue which was subjected to column chromatography (8 : 1 hexanes : EtOAc) gave 41 mg (7%) of bis-oxazoline **(*aR,S*)-20** as a light yellow oil. $[\alpha]_D = -231$ (c = 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.53 (s, 18H), 1.52-1.55 (m, 12H), 3.49 (s, 6H), 3.58 (s, 6H), 3.81-4.04 (m, 14H (therein 3.91 (s, 6H), 3.97 (s, 6H))), 7.45 (s, 2H), 8.48 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (q), 26.0 (q), 27.3 (d), 33.7 (s), 55.6 (q), 60.9 (q), 61.3 (q), 68.1 (t), 76.7 (d),100.8 (d), 121.7 (d), 125.3 (s), 126.0 (s), 127.70 (s), 127.8 (s), 136.8 (s), 148.0 (s), 152.9 (s), 153.5 (s), 163.4 (s); FTIR (thin film) 2957, 2870, 1653, 1463, 1244, 1018 cm^{-1}. Continued elution (8 : 1 hexanes : EtOAc) gave 0.47 g (81%) of bis-oxazoline **(*aS,S*)-20** as a light yellow oil. $[\alpha]_D = 249$ (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.59 (s, 18H), 1.53 (d, 12H, J = 7.1 Hz), 3.49 (s, 6H), 3.73-3.81 (m, 6H), 3.96-4.03 (m, 14H (therein 3.95 (s, 6H), 3.99 (s, 6H))), 7.42 (s, 2H), 8.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (q), 22.5 (q), 25.9 (q), 27.2 (d), 31.7 (s), 55.6 (q), 60.8 (q), 61.2 (q), 68.1 (t), 76.6 (d),100.7 (d), 121.6 (d), 125.2 (s), 126.0 (s), 127.7 (s), 127.8 (s), 136.8 (s), 147.9 (s), 152.9 (s), 153.4 (s), 163.4 (s); FTIR (thin film) 2956, 2870, 1652, 1462, 1243, 1017 cm^{-1}; LRMS (electrospray) calc for $C_{46}H_{60}N_2O_8$: m + H 769; obsd m + H 769.

5,5'-Diisopropyl-1,1',6,6',7,7'-hexamethoxy-((*S*)-2,2'-binaphthalene)-3,3'-bis-carbinol, (*S*)-21. To bis-oxazoline **(*aS,S*)-20** (2.0 g, 2.6 mmol) was added THF (20 mL), H_2O (3.0 mL), and trifluoroacetic acid (1.5 g, 1.0 mL, 13 mmol), and $Na_2SO_4 \cdot 10H_2O$ (3.0 g) and this suspension was stirred vigorously overnight at r.t. After filtration, the solvent was removed *in vacuo* and the light brown residue was dissolved in CH_2Cl_2 (25 mL). To this solution was added pyridine (1.1 g, 1.1 mL, 14 mmol) and acetic anhydride (0.82 g, 0.76 mL, 8.0 mmol) and the reaction was stirred for two d at r.t. The mixture was washed with 10% aqueous HCl (3 x 20 mL), and then H_2O (2 x 30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The solvent was removed under reduced pressure to give a brown residue which was dissolved in THF (40 mL) and added to a stirred cold (-10 °C) slurry of $LiAlH_4$ (0.21 g, 5.5 mmol) in THF (30 mL). The mixture was warmed to r.t. and stirred an additional 4 h, and $Na_2SO_4 \cdot 10H_2O$ (4.0 g) was added slowly over 20 min. Anhydrous Na_2SO_4 (5.0 g) was added and the mixture was stirred for an additional 20 min. The white slurry was filtered on a glass sintered funnel and the salts were washed with THF (2 x 30 mL). The combined filtrates were reduced *in vacuo*. The resulting residue was subjected to column chromatography (20 : 1 CH_2Cl_2 : MeOH) to give 1.1 g (73%) of bis-carbinol (*S*)-**21** as a white solid, mp 298-300 °C. $[\alpha]_D = 158$ (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, 12H, J = 7.1 Hz), 2.83 (s, 2H), 3.61 (s, 6H), 3.90-4.00 (m, 14H (therein 3.93 (s, 6H), 3.99 (s, 6H))), 4.37 (app d, 2H, J = 11.8 Hz), 4.43 (app d, 2H, J = 11.8 Hz), 7.35 (s, 2H), 8.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (q), 27.3 (d), 55.7 (q), 60.9 (q), 61.3 (q), 64.7 (t), 100.4 (d), 122.0 (d), 124.3 (s), 125.8 (s), 129.3 (s), 135.9 (s), 136.4 (s), 148.4 (s), 152.5 (s), 153.1 (s); FTIR (KBr) 3264 (br), 2952, 2922, 2872, 2832, 1957, 1456, 1240, 1029, 788 cm^{-1}; HRMS calc for $C_{34}H_{42}O_8$: *m/z* 578.2880; obsd *m/z* 578.2886.

(*S*)-Apogossypol hexamethylether, (*S*)-22. To bis-carbinol (1.1 g, 1.9 mmol) (*S*)-**21** in EtOH (15 mL) was added 10% aqueous HCl (2.0 mL) and 10% Pd/C (0.60 g) and the reaction was subjected to 40 psi of H_2. The reaction was stirred overnight at r.t. and filtered using a pad of Celite 545®. The pad was washed with EtOH (2 x 30 mL) and CH_2Cl_2 (2 x 30 mL). The combined filtrates were reduced *in vacuo* to give a residue which was taken up in Et_2O (60 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), dried with $MgSO_4$ and reduced by rotary evaporation. The colorless residue was subjected to column chromatography (8 : 1 hexanes : EtOAc) to give 0.85 g (82%) of (*S*)-apogossypol hexamethylether **(*S*)-22** as a white solid, mp 274-275 °C (lit.[40] 273-274 °C). $[\alpha]_D = 123$ (c = 3.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, 12H, J = 6.9 Hz), 2.19 (s, 6H), 3.56 (s, 6H), 3.91-3.96 (m, 14H (therein 3.92 (s, 6H), 3.97 (s, 6H))), 7.42 (s, 2H), 7.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (q), 22.4 (q), 27.2 (d), 55.6 (q), 60.7 (q), 61.3 (q), 100.8 (d), 120.6 (d), 124.9 (s), 126.6 (s), 128.9 (s), 133.0 (s), 135.3 (s), 148.0 (s), 152.1 (s), 152.9 (s); FTIR (KBr) 2958, 2933, 2875, 2833, 1598, 1456, 1245, 1036 cm^{-1}; HRMS calc for $C_{34}H_{42}O_6$: *m/z* 546.2981; obsd *m/z* 546.2982.

(*S*)-Gossypol (*S*)-1. (*S*)-gossypol **(*S*)-1** was prepared from (*S*)-apogossypol hexamethylether **(*S*)-22** according to Meltzer[40] with the following modifications. Neat boron tribromide (0.75 g, 0.28 mL, 3.0 mmol) was added to a cold (-78 °C) solution of (*S*)-apogossypol hexamethylether (0.26 g, 0.48 mmol) in $CHCl_3$. The reaction was allowed to warm to -10 °C over the course of 4 h. The crude product was passed twice in the dark through a short plug of alumina and was subsequently subjected to column chromatography in the dark (10 : 1 hexanes : EtOAc) to give 84 mg (34%) of (*S*)-gossypol **(*S*)-1** as a yellow solid, mp 186-187 °C (lit.[58] 180 °C). $[\alpha]_D = 363$ (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 12H, J = 7.0 Hz), 2.14 (s, 6H), 3.88 (sept, 2H, J = 6.9 Hz), 5.85 (s, 2H), 6.39 (s, 2H), 7.77 (s, 2H), 11.11 (s, 2H), 15.11 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 (q), 20.5 (q), 28.1 (d), 111.9 (s), 114.9 (s), 116.5 (s), 118.2 (d), 129.8 (s), 134.0 (s), 134.4 (s), 143.4 (s), 150.8 (s), 156.0 (s), 199.5 (d); FTIR (KBr) 3377 (br), 1615, 1601, 1440, 1335, 1168 cm^{-1}; HRMS calc for $C_{30}H_{30}O_8$: *m/z* 518.1941; obsd *m/z* 518.1949.

4,4-Dimethyl-2-(5-formyl-2-isopropyl-3,4-dimethoxyphenyl)-2-oxazoline, 26. To a flask containing THP (5.0 mL) was cooled to -78 °C, causing the THP to freeze. Ethyl vinyl ether (0.25 g, 0.33 mL, 3.5 mmol) was added to the flask and the mixture was warmed enough such that the THP melted and went into solution. To this solution, which was again cooled to -78 °C, was added *t*-butyllithium (1.5 mL, 3.1 mmol, 2.1 M) and the resulting bright yellow suspension was warmed to -10 °C and stirred for 30 min. The pale yellow solution was cooled to -78 °C and diluted dropwise with THF (8.0 mL). To this solution was added very slowly by syringe HMPA (0.56 g, 0.54 mL, 3.1 mmol). Oxazoline **13** (0.40 g, 1.4 mmol) in THF (6.0 mL) was added dropwise and the light yellow solution was stirred was for 24 h. DMF (0.29 g, 0.31 mL, 4.0 mmol) was then added and the solution was allowed to warm to r.t. over the course of 3 h. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was extracted with Et_2O (4 x 15 mL). The ethereal extracts were washed with H_2O (4 x 20 mL), saturated aqueous NaCl (20 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give an oily residue. The residue in THF (10 mL) was added to a cold (-10 °C) slurry of $LiAlH_4$ (60 mg, 1.6 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h and 10% aqueous NaOH (0.5 mL), H_2O (0.5 mL), and Na_2SO_4 (1.0 g) was added and the reaction was stirred for an additional 30 min. The reaction was filtered and the salts were washed with Et_2O (4 x 10 mL). The combined filtrates were dried with $MgSO_4$ and reduced *in vacuo*. The aquired residue in THF (10 mL) was added to a cold (0 °C) slurry of NaH (38 mg, 1.6 mmol) in THF (10 mL) and stirred for 1 h. Methyl iodide (0.25 g, 0.11 mL, 1.8 mmol) was added dropwise and the reaction mixture was stirred for an additional 2 h. H_2O (5 mL) was added slowly, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were dried with $MgSO_4$ and reduced by rotary evaporation. The acquired residue was subjected to column chromatography (2 : 1 hexanes : EtOAc) to give 0.33 g (72%) of oxazoline **26** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 6H, J = 6.9 Hz), 1.36 (s, 6H), 3.37-3.42 (m, 4H), 3.82 (s, 3H), 3.86 (s, 3H), 4.05 (s, 2H), 4.43 (s, 2H), 7.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 28.3, 30.0, 58.2, 60.3, 60.4, 67.7, 69.2, 79.1, 124.6, 125.9, 129.9, 141.6, 152.6, 153.2, 163.6; FTIR (thin film) 2964, 2934, 1652, 1464, 1349, 1193, 1049 cm^{-1}; LRMS calc for $C_{18}H_{27}NO_4$: *m/z* 321.4; obsd *m/z* 321.4 (M^+).

2-Isopropyl-3,4-dimethoxy-5-methoxymethylbenzaldehyde, 27. To a solution of oxazoline **26** (3.1 g, 9.6 mmol) and CH_2Cl_2 (20 mL) was added methyl trifluoromethanesulfonate (3.3 g, 2.3 mL, 20 mmol), and the solution was stirred for 2 h, cooled to 0 °C, and treated dropwise with a solution of $NaBH_4$ (0.76 g, 20 mmol) in THF/MeOH (4 : 1, 25 mL). After stirring for 1 h saturated aqueous NH_4Cl (15 mL) was added. The layers were separated and the organic layer was washed with saturated aqueous NaCl (40 mL). The combined aqueous layers were extracted (2 x 30 mL). The combined organic extracts were dried with Na_2SO_4 and reduced by rotary evaporation. Filtration (1 : 1 hexanes : EtOAc) through a short plug of silica was followed by reduction of the solvent *in vacuo* to give a colorless residue. The residue was taken up in a solution of THF/H_2O (4 : 1, 40 mL) and treated with oxalic acid dihydrate (8.0 g, 63 mmol). The solution was stirred at ambient temperature for 24 h. Et_2O (100 mL) was added and washed with saturated aqueous $NaHCO_3$ (50 mL), saturated aqueous NaCl (50 mL). The combined extracts were dried with and concentrated under reduced pressure. Column chromatography (10 : 1 hexanes : EtOAc) gave 2.2 g (89%) of **27** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, 6H, J = 7.2 Hz), 3.44 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 4.03 (sept, 1H, J = 7.2 Hz), 4.48 (s, 2H), 7.66 (s, 1H), 10.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 26.0, 58.5, 60.4, 60.5, 69.2, 127.8, 130.6, 130.7, 145.0, 152.3, 156.2, 191.3; FTIR (thin film) 2936, 2874, 1686, 1596, 1450, 1379, 1302, 1041 cm^{-1}; HRMS calc for $C_{14}H_{20}O_4$: *m/z* 252.1362; obsd *m/z* 252.1352.

4-Hydroxy-8-isopropyl-6,7-dimethoxy-5-methoxymethyl-2-naphthoic acid, 28. To an oven dried flask evacuated and purged three times (argon) was added THF (50 mL), 2-isopropyl-3,4-dimethoxy-5-methoxymethylbenzaldehyde **27** (1.4 g, 5.5 mmol), NaH (0.17 g, 7.1 mmol), and dimethyl succinate (1.0 g, 0.90 mL, 6.8 mmol). This solution was magnetically stirred for 4.5 h, and then was treated with H_2O (50 mL) and Et_2O (200 mL) was added. The layers were separated, the aqueous layer was acidified with 10% HCl (pH 2) and extracted with Et_2O (3 x 60 mL). The combined organic layers were extracted with saturated aqueous Na_2CO_3 (3 x 100 mL). The aqueous phase was cooled (0 °C), acidified with 10% HCl (pH 1), and was extracted with Et_2O (4 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by rotary evaporation. To the crude product was then added AcOH (30 mL), acetic anhydride (30 mL), and fused sodium acetate (1.0 g, 12 mmol). This solution was heated at reflux for 4 h, and then was neutralized with saturated aqueous $NaHCO_3$ (300 mL) and extracted with Et_2O (4 x 100 mL). Concentration of the combined organic extracts gave a residue which was dissolved in MeOH (80 mL). 10% NaOH (80 mL) was added slowly and the solution was heated to reflux for 5 h. The MeOH was removed *via* atmospheric distillation and the resulting mixture was cooled (0 °C), acidified with 10% aqueous HCl (pH 2), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried with $MgSO_4$, reduced *via* rotary evaporation to give an oily residue. The residue was subjected to column chromatography (1 : 1 hexanes : EtOAc) to give 1.1 g (59%) of **28** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 6H, J = 7.2 Hz), 3.58 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.03 (sept, 1H, J = 7.2 Hz), 5.06 (s, 2H), 7.62 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 27.5, 57.7, 61.0, 61.6, 66.1, 112.2, 120.3, 120.4, 121.3, 126.3, 131.6, 139.6, 150.5, 153.6, 154.8, 172.6; FTIR (thin film) 3227 (br), 2937, 1694, 1454, 1282, 1119, 1073 cm^{-1}.

Methyl 8-isopropyl-4,6,7-trimethoxy-5-methoxymethyl-naphthalene-2-carboxylate, 29. To a stirred solution of naphthoic acid **28** (0.95 g, 2.8 mmol) in acetone (15 mL) was added K_2CO_3 (0.80 g, 5.8 mmol) and dimethyl sulfate (0.90 g, 0.68 mL, 7.1 mmol) in acetone (30 mL). After the reaction had been stirred at r.t. for 24 h, the mixture was filtered through Celite 545® and washed with CH_2Cl_2 (2 x 30 mL). The solvent was removed *in vacuo* and the resulting oil was diluted with CH_2Cl_2 (3 x 20 mL) and washed with H_2O (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by rotary evaporation to give 1.0 g (97%) of methyl ester **29** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 6H, J = 6.9 Hz), 3.58 (s, 3H), 3.91 (s, 3H), 4.02-4.12 (m, 10H (therein at 4.03 (s, 3H), 4.07 (s, 3H), 4.11 (s, 3H))), 4.62 (s, 2H), 7.08 (s, 1H), 7.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 27.4, 56.1, 58.4, 61.0, 61.0, 61.8, 66.8, 104.6, 121.6, 124.9, 125.6, 126.0, 131.4, 139.0, 152.4, 153.1, 157.8, 172.5; FTIR (thin film) 2934, 1682, 1575, 1455, 1155, 1097 cm^{-1}; Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; found: C, 66.26; H, 7.17.

8-Isopropyl-4,6,7-trimethoxy-5-methoxymethyl-2-naphthoic acid, 30. To a solution of methyl ester **29** (0.90 g, 2.5 mmol) in MeOH (20 mL) was added slowly a solution of KOH (0.25 g, 4.5 mmol) in MeOH (20 mL). The reaction was heated to reflux for 8 h and then was cooled to r.t. The MeOH was removed by rotary evaporation and the residue was taken up in H_2O (25 mL). The resulting solution was cooled (0 °C) and was acidified with dilute HCl (pH 2). The aqueous solution was extracted with CH_2Cl_2 (4 x 20 mL), dried with Na_2SO_4, and reduced *via* rotary evaporation. The resultant residue was subject to column chromatography (1 : 1 hexanes : EtOAc) to give 0.85 g (98%) of naphthoic acid **30** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, 6H, J = 7.1 Hz), 3.46 (s, 3H), 3.71-4.04 (m, 10 H (therein at 3.74 (s, 3H), 3.80 (s, 3H), 4.00 (s, 3H))), 5.23 (s, 2H), 7.44 (s, 1H), 8.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 28.6, 55.7, 60.3, 64.0, 65.6, 86.4, 97.9, 101.1, 118.5, 121.5, 122.6, 123.0, 132.1, 142.6, 149.2, 150.1, 160.2; FTIR (KBr) 2955, 1718, 1449, 1221, 1042 cm^{-1}; LRMS calc for $C_{19}H_{24}O_6$: *m/z* 348.2; obsd *m/z* 348.2 (M^+).

(4*S*)-4-*t*-Butyl-2-(8-isopropyl-4,6,7-trimethoxy-5-methoxymethyl-2-naphthyl)-2-oxazoline, (*S*)-31. To a solution of naphthoic acid **30** (0.42 g, 1.2 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (0.18 g, 0.12 mL, 1.4 mmol) and DMF (0.10 g, 0.11 mL, 1.4 mmol). The solution was stirred at r.t. for 5 h at which time the solvent and the excess oxalyl chloride was removed *in vacuo*. The acid chloride was dissolved in CH_2Cl_2 (100 mL) and was added dropwise to a solution of (*S*)-(+)-*t*-leucinol[56] (DeGussa, 0.38 g, 0.32 mmol) and TEA (1.0 g, 1.4 mL, 9.9 mmol). This solution was stirred overnight and the solvent was removed by rotary evaporation. To this residue was added H_2O (35 mL), CH_2Cl_2 (50 mL), and saturated aqueous $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 30 mL), and the combined extracts were dried with Na_2SO_4. The solvent was removed *in vacuo* and the resulting oil was diluted with CH_2Cl_2 (100 mL). A solution of thionyl chloride (1.8 g, 1.1 mL, 15 mmol) in CH_2Cl_2 (50 mL) was added *via* addition funnel and this solution was stirred overnight. H_2O (35 mL) and 30% aqueous NaOH (25 mL) were then added to the solution which was stirred for 3 h. The organic layer was removed and the aqueous layer was extracted with Et_2O (4 x 50 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed by rotary evaporation. The resulting oil was purified by column chromatography (1 : 1 hexanes : EtOAc) to give 0.45 g (87%) of naphthyloxazoline **(*S*)-31** as a light yellow oil. $[\alpha]_D$ = -61 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.47 (d, 6H, J = 7.3 Hz), 3.40 (s, 3H), 3.89 (s, 3H), 3.99 (s, 3H), 4.02-4.14 (m, 5H (therein 4.07 (s, 3H))), 4.23-4.34 (m, 2H), 4.98 (s, 2H), 7.49 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8, 32.5, 34.9, 32.0, 43.0, 57.6, 62.1, 62.1, 78.4, 75.2, 85.2, 103.9, 105.0, 119.2, 124.0, 126.3, 128.4, 133.6, 143.3, 148.6, 149.8, 158.1; FTIR (thin film) 2952, 1655, 1450, 1263, 1183, 1042 cm^{-1}; HRMS calc for $C_{25}H_{35}NO_5$: *m/z* 429.2515; obsd *m/z* 429.2520.

(4*S*)-4-*t*-Butyl-2-(3-bromo-8-isopropyl-4,6,7-trimethoxy-5-methoxymethyl-2-naphthyl)-2-oxazoline, (*S*)-32. To a cold solution of naphthyloxazoline **(*S*)-31** (1.0 g, 2.3 mmol) in AcOH (24 mL) was added dropwise bromine (0.40 g, 0.13 mL, 2.5 mmol). After stirring for 2 h the solution was poured onto a saturated aqueous solution $NaHSO_3$ (7.5 g) and $NaHCO_3$ (15 g). The resultant solution was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed by rotary evaporation. Column chromatography (8 : 1 hexanes : EtOAc) gave 0.88 g (74%) of bromonaphthyloxazoline **(*S*)-32** as a viscous light yellow oil. $[\alpha]_D$ = -60 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.49 (d, 6H, J = 7.4 Hz), 3.31 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H) 4.08 (m, 5H (therein 4.03 (s, 3H))), 4.14-4.20 (m, 2H), 4.99 (s, 2H), 7.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 22.0, 26.9, 29.2 48.8, 58.0, 58.0, 63.2, 69.4, 73.1, 91.4, 114.2, 115.2, 117.2, 129.3, 134.2, 136.0, 140.9, 147.2, 151.9, 152.4, 159.6; FTIR (thin film) 2957, 1660, 1606, 1463, 1365, 1247, 1032 cm^{-1}.

(4*S*)-4-*t*-Butyl-2,2'-(5,5'-diisopropyl-1,1',6,6',7,7'-hexamethoxy-8,8'-dimethoxymethyl-(*S*)-2,2'-binaphthyl)-3,3'-bis-oxazoline, (*aS*,*S*)-33. Bromonaphthyloxazoline **(*S*)-32** (0.91 g, 2.1 mmol) was added to a flame dried which was equipped with a flame dried condensor. Freshly distilled DMF (2.5 mL), NaH (50 mg, 2.1 mmol) and freshly activated[57] Cu° (0.30 g, 4.7 mmol) were added. This mixture was heated at reflux for 1 h. The resulting mixture was filtered using a pad of Celite 545® and the pad was repeatedly washed with NH_4OH (3 x 25 mL), H_2O (3 x 40 mL), and Et_2O (5 x 70 mL). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 40 mL). The ethereal layer was washed with concentrated NH_4OH (3 x 30 mL) until no blue color persisted in the aqueous layer, and the aqueous layer was subsequently washed with H_2O (2 x 60 mL). Removal of the combined organic layers *in vacuo* and subsequent azeotropic removal of pyridine and H_2O with toluene *in vacuo* gave the crude product. Column chromatography (8 : 1 hexanes : EtOAc) gave 0.73 g (80%) of binaphthyl-bis-oxazoline **(*aS,S*)-33** as a light yellow oil. $[\alpha]_D = 228$ (c = 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 18H), 1.48 (d, 12H, J = 7.4 Hz), 3.29 (s, 6H), 3.85 (s, 6H), 3.98-4.04 (m, 16H (therein 3.98 (s, 6H), 4.03 (s, 6H))), 4.30-4.37 (m, 4H), 5.16 (s, 4H), 7.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 22.1, 24.9, 27.5, 47.3, 49.3, 52.4, 59.1, 67.1, 70.6, 81.4, 109.6, 119.2, 120.8, 123.1, 132.4, 145.2, 147.9 146.0, 150.5, 151.9, 160.1; FTIR (thin film) 2957, 1644, 1594, 1463, 1341, 1242, 1030 cm^{-1}; Anal. Calcd for $C_{50}H_{66}N_2O_{10}$: C, 70.23; H, 7.78; found: C, 70.25; H, 7.89.

5,5'-Diisopropyl-1,1',6,6',7,7'-hexamethoxy-8,8'-dimethoxymethyl-((*S*)-2,2'-binaphthalene)-3,3'-bis-carbinol, (*S*)-34. To binaphthyl-bis-oxazoline **(*aS,S*)-33** (0.70 g, 0.82 mmol) was added THF (20 mL), H_2O (1.0 mL), and trifluoroacetic acid (0.60 g, 0.41 mL, 5.3 mmol), and $Na_2SO_4 \cdot 10H_2O$ (1.0 g) and this suspension was stirred vigorously overnight at r.t. After filtration, the solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL). To this solution was added pyridine (0.31 g, 0.32 mL, 3.9 mmol) and acetic anhydride (0.23 g, 0.21 mL, 2.3 mmol) and the reaction was stirred for two d at r.t. The mixture was washed with 10% HCl (3 x 20 mL), and then H_2O (2 x 20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The solvent was removed under reduced pressure to give a residue which was dissolved in THF (12 mL) and added to a stirred cold (-10 °C) slurry of $LiAlH_4$ (40 mg, 1.1 mmol) in THF (10 mL). The mixture was warmed to r.t. and stirred an additional 8 h, and $Na_2SO_4 \cdot 10H_2O$ (1.0 g) was added slowly over 30 min. Anhydrous Na_2SO_4 (1.0 g) was added and the mixture was stirred for an additional 10 min. The white slurry was filtered on a glass sintered funnel and the salts were washed with THF (2 x 25 mL). The combined filtrates were reduced *in vacuo* and subjected to column chromatography (1 : 1 hexanes : EtOAc) to give 0.39 g (72%) of binaphthalene-bis-carbinol **(*S*)-34** as a white solid, mp 177.7-178.8 °C. $[\alpha]_D =$ 280 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (d, 12H, J = 7.3 Hz), 2.01 (s, 2H), 2.98 (s, 6H), 3.46 (s, 6H), 3.87-4.05 (m, 14H (therein 3.92 (s, 6H), 3.98 (s, 6H))), 4.24 (m, 4H), 5.07 (s, 4H), 8.30 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 34.2, 56.1, 60.7, 75.2, 75.9, 87.9, 97.3, 118.3, 120.0, 121.3, 124.6, 129.5, 130.6, 136.0, 142.3, 146.2, 147.0; FTIR (KBr) 3264 (br), 2957, 1598, 1462, 1246, 1150, 1029 cm^{-1}.

5,5'-Diisopropyl-1,1',6,6',7,7'-hexamethoxy-8,8'-dimethoxy-methyl-3,3'-dimethyl-(*S*)-2,2'-binaphthalene), (*S*)-35. To binaphthalene-bis-carbinol **(*S*)-34** (0.20 g, 0.30 mmol) in EtOH (4.0 mL) was added 10% aqueous HCl (0.25 mL) and 10% Pd/C (0.15 g) and the reaction was subjected to 40 psi of H_2. The mixture was stirred overnight at r.t. and filtered using a pad of Celite 545® followed by being washed with EtOH (2 x 30 mL) and CH_2Cl_2 (2 x 30 mL). The combined filtrates were concentrated *in vacuo* and the residue was taken up in Et_2O (60 mL) and washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), dried with $MgSO_4$ and again concentrated. The colorless oil was subjected to column chromatography (8 : 1 hexanes : EtOAc) to give 0.16 g (84%) of binaphthalene **(*S*)-35** as a colorless oil. $[\alpha]_D = 193$ (c = 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 12H, J = 7.3 Hz), 2.16 (s, 6H), 3.13 (s, 6H), 3.65 (s, 6H), 4.08 (m, 14H (therein 4.02 (s, 6H), 4.11 (s, 6H))), 5.35 (s, 4H), 7.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 24.2, 25.9, 29.1, 57.8, 62.0, 62.6, 68.4, 82.8, 103.3, 112.3, 117.2, 118.6, 120.5, 124.3, 125.9, 130.0, 134.1, 136.9; FTIR (thin film) 2957, 1654, 1602, 1459, 1290, 1246, 1034 cm^{-1}; Anal. Calcd for $C_{38}H_{50}O_8$: C, 71.90; H, 7.94; found: C, 71.95; H, 7.91.

(*S*)-Gossypol, (*S*)-1. To a cold (-78 °C) solution of binaphthalene **(*S*)-35** (75 mg, 0.12 mmol) in CH_2Cl_2 (7.0 mL) was added boron tribromide (0.28 g, 0.11 mL, 1.1 mmol). The solution was stirred for 24 h at -78 °C and poured onto a mixture of ice and 10% saturated aqueous NaOH (150 mL). The solution was acidified with 10% aqueous HCl (150 mL) and extracted into Et_2O (100 mL). The aqueous layer was further extracted with Et_2O (2 x 100 mL) and the combined organic extracts were washed with H_2O (150 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a brown residue. In a separate flask, DMSO (38 mg, 35 mL, 0.49 mmol) was added dropwise to a stirred cold (-78 °C) solution of oxalyl chloride 30 mg, 21 mL, 0.24 mmol) in CH_2Cl_2 (10 mL). After 15 min to this solution was added the crude octol dissolved in CH_2Cl_2 (20 mL) and allowed to stir 1 h. *N,N*-Diisopropylethylamine (0.39 g, 0.53 mL, 3.0 mmol) was added dropwise and the mixture was allowed to warm (1 h) to r.t., and then poured onto saturated aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was reextracted with CH_2Cl_2 (2 x 45 mL). The combined organic layers were washed with H_2O (50 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was passed through a short plug of alumina (1 : 1 hexanes : EtOAc) to give 49 mg (81%) of (*S*)-gossypol **(*S*)-1** as a yellow powder, mp 186.1-186.9 °C (lit.[58] 184 °C). $[\alpha]_D = 371$ (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 12H, J = 7.0 Hz), 2.14 (s, 6H), 3.88 (sept, 2H, J = 6.9 Hz), 5.85 (s, 2H), 6.39 (s, 2H), 7.77 (s, 2H), 11.11 (s, 2H), 15.11 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.5, 28.1, 111.9, 114.9, 116.5, 118.2, 129.8, 134.0, 134.4, 143.4, 150.8, 156.0, 199.5; FTIR (KBr) 3377 (br), 1615, 1601, 1440, 1335, 1168 cm^{-1}; HRMS calc for $C_{30}H_{30}O_8$: *m/z* 518.1941; obsd *m/z* 518.1949.

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