Enantioselective Synthesis of (+)-Isobretonin A

Guy Solladié,* Marc Adamy, and Françoise Colobert

Laboratoire de Stéréochimie associé au CNRS, Ecole Européenne de Chimie, Polymères et Matériaux (ECPM), Université Louis Pasteur, 1 rue Blaise Pascal, 67008 Strasbourg, France

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An enantioselective synthesis of (+)-isobretonin A is described. The chiral glycerol moiety was enantioselectively prepared by reduction of an optically active β-keto sulfoxide. The all-trans trienic part of the molecule was stereoselectively synthesized *via* reductive elimination of a 1,6-dibenzoate 2,4-diene with sodium amalgam.

(+)-Isobretonin A is a unique chiral glycerol derivative. The chirality is due to the presence of two different substituents on the primary hydroxylic groups: an *all-E* 4,6,8-dodecatrienic ether and a 4-hydroxybenzoate.

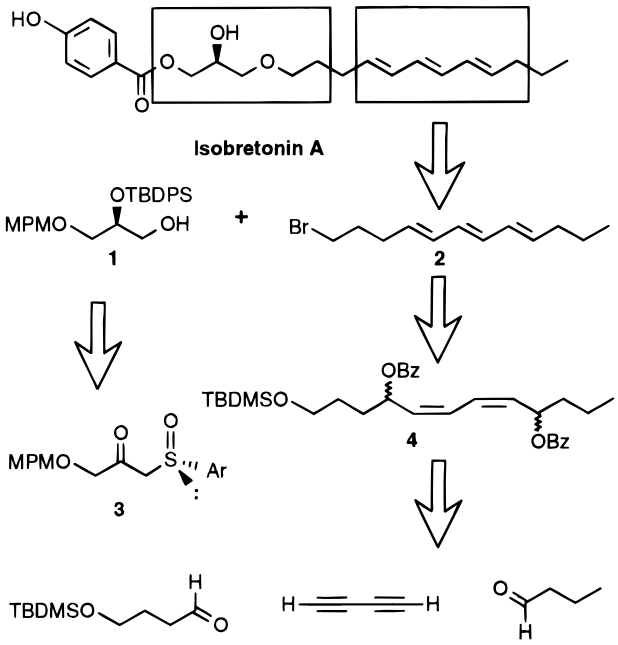
This molecule was isolated from an unidentified sponge belonging to the class Demospongiae of Brittany waters.[1] The basic structure was elucidated in 1987 and its absolute configuration, (*S*)-(+), was recently determined by total synthesis[2] of a mixture of the *all-E* and *E,Z,E* isomers.

We report in this paper the first enantio- and stereoselective synthesis of (+)-isobretonin A. As shown in the retrosynthetic Scheme 1, this approach is based on the asymmetric reduction of β-keto sulfoxide **3** to prepare the enantiomerically pure glycerol derivative **1** and on the reductive elimination of 1,6 dibenzoate 2,4-diene **4** to obtain *all-E* trienic bromide **2**.

β-Keto sulfoxide (−)-(*S*)-**3** was prepared by condensation of the *p*-methoxybenzyl ether of methyl glycolate **5,** readily available from bromoacetic acid in 85% yield, and the carbanion of (−)-(*S*)-methyl *p*-tolyl sulfoxide.[3] Following our previous results,[4] the reduction of β-keto sulfoxide **3** with DIBAL yielded [2*R*,S(*S*)]-β-hydroxy sulfoxide **6** in 61% overall yield from ester **5** (Scheme 2). The *R* configuration of the hydroxylic carbon was expected from the reaction mechanism already published[4d] and also from the numerous examples we already published.[5] The large nonequivalence ($\Delta\nu$ = 66 Hz) of the two diastereotopic protons α to the sulfoxide group in ^{1}H NMR is characteristic of the relative 2(*R*),S(*S*) configuration.[4a,b] The final comparison with natural isobretonin will indeed confirm the absolute configuration assignment. The diastereoselectivity for the reduction was higher than 98%; only one diastereoisomer was observed in the ^{1}H and ^{13}C NMR spectra of the crude reduction mixture.

After the hydroxylic group was protected with *tert*-butyldiphenylsilyl chloride, the resulting TBDPS ether

Scheme 1



7 was submitted to a Pummerer rearrangement with acetic anhydride−sodium acetate and the intermediate **8** reduced with lithium aluminum hydride in ether, affording in high yield glycerol derivative (+)-(*S*)-**1**.

The synthesis of the trienic part is based on our previous work:[6] we have shown that 1,6-dibenzoate 2,4-dienes could be very efficiently transformed into all-trans triene *via* a reductive elimination reaction induced by sodium amalgam. Condensation of the Grignard derivative of diacetylene on butyraldehyde gave **9** in 72% yield (Scheme 3). The compound **9** was lithiated with *n*-BuLi and added to protected hydroxybutyraldehyde (made from butanediol *via* monoprotection and oxidation) giving the diacetylenic diol **10** in 89%, as a mixture of diastereoisomers. The triple bonds in diol **10** were reduced with activated Zn−Cu in MeOH/H_2O,[7] affording the corresponding (*Z,Z*)-dienic diol in 85% yield, which was converted into the corresponding dibenzoate **4** in quantitative yield. The *Z,Z* configuration of the double bonds was confirmed at this stage by ^{1}H NMR.

Application of the reductive elimination reaction with sodium amalgam to compound **4** gave the triene **11** as a

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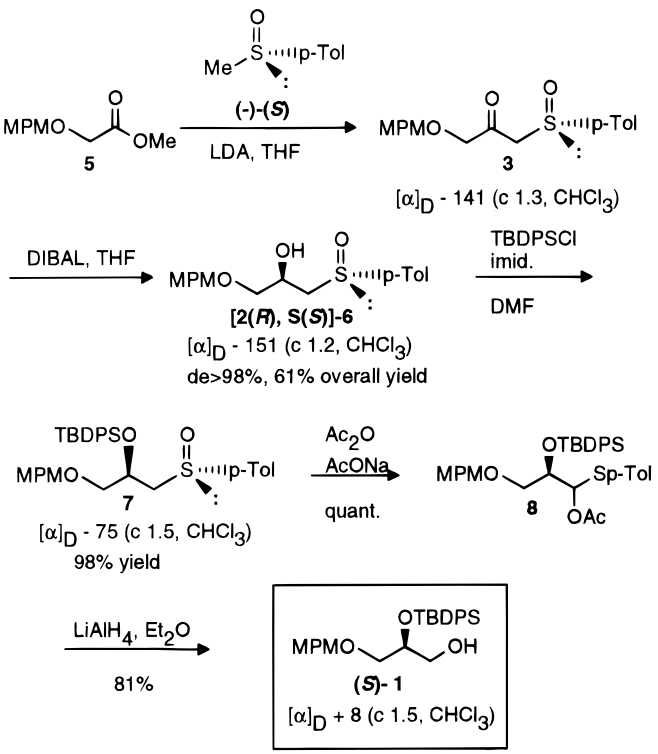
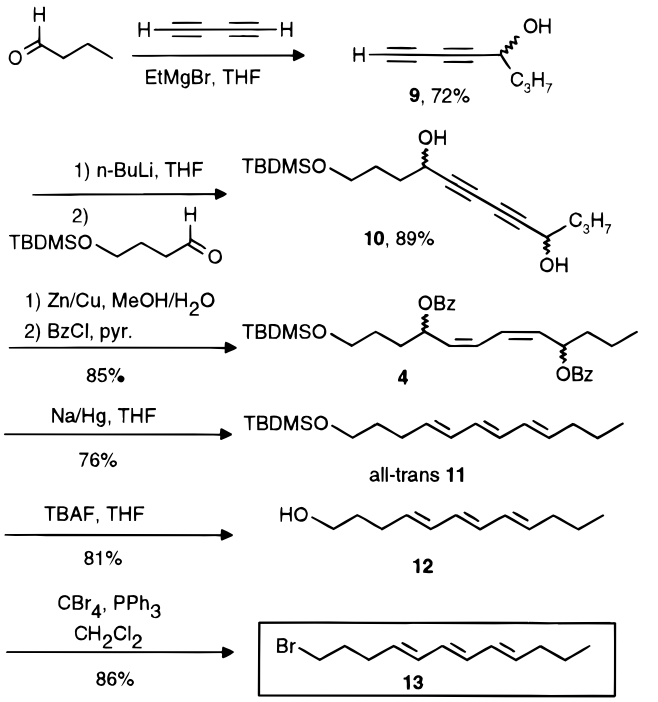
S0022-3263(96)00134-X CCC: $12.00

Scheme 2



Scheme 3



unique product in 76% yield. The *E*,*E*,*E* geometry of the double bonds of alcohol **12** was established by ^{1}H NMR in the presence of Pr(fod)$_3$. The absence of any other isomer was confirmed by ^{13}C NMR showing only one set of six vinylic carbons. Finally, the primary alcohol was transformed into bromide **13** in 86% yield.

Ether (+)-(*S*)-**14** was obtained, in 78% yield, *via* a Williamson reaction between alcohol **1** and bromide **13** (Scheme 4). After the MPM group was removed in 84% yield, esterification of the alcohol **15** with 4-hydroxybenzoic chloride followed by deprotection of the TBDPS group afforded in 83% yield (+)-isobretonin A as a colorless oil, $[\alpha]_D$ +5 (c 1.5, MeOH), identical in all respects with the natural product, $[\alpha]_D$ +5.4 (c 0.16, MeOH).[2]

In conclusion, this short and efficient synthesis of (+)-isobretonin A demonstrated the powerful combination in total synthesis of chiral sulfoxides to create the chiral centers and of the reductive elimination of dienic dibenzoates to create the polyenic parts.

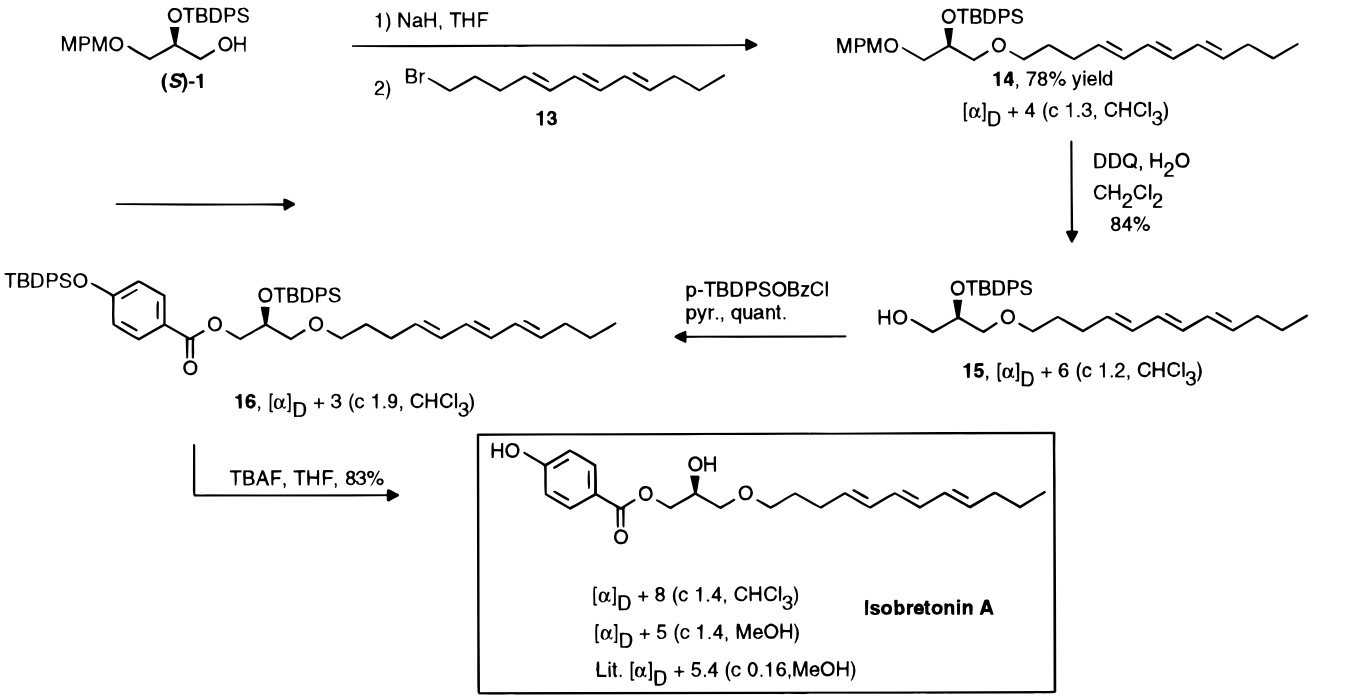
Experimental Section

Methyl (*p*-Methoxybenzyloxy)glycolate, 5. To a stirred solution of bromoacetic acid (7.25 g, 52 mmol) in anhydrous THF (150 mL) was added sodium hydride (3.13 g, 130 mmol). The solution was stirred at room temperature until the evolution of hydrogen stopped. A solution of *p*-methoxybenzyl alcohol (7.25 g, 52.5 mmol) in anhydrous THF (150 mL) was then added at 0 °C, and the resulting mixture was stirred at 25 °C until the evolution of hydrogen stopped. Tetrabutylammonium bromide (1 g, 3 mmol) was added, and the resulting mixture was heated at reflux temperature for 4 h. After the resulting mixture was cooled to 0 °C, the solution was hydrolyzed with ethanol (15 mL) and concentrated. The resulting oil was diluted with diethyl ether (50 mL), and the organic layer was extracted with aqueous $NaHCO_3$ (3 × 50 mL). The aqueous layer was acidified to pH = 1 with 10% sulfuric acid, extracted with diethyl ether (3 × 100 mL), dried ($MgSO_4$), and evaporated. The resulting oil was dissolved in methanol (200 mL) and heated at 60 °C for 4 h in the presence of *p*-toluenesulfonic acid (50 mg, 0.26 mmol). After the solution was cooled at 25 °C, the solvent was then evaporated and the crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:9) giving ester **5** as a yellow oil (9.04 g, 82%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.80 (s, 3H), 4.07 (s, 2H), 4.56 (s, 2H), 6.88−7.28 (AA′BB′, J = 10 Hz, $\Delta\nu$ = 80 Hz, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 51.5, 55.0, 66.7, 72.7, 113.7, 129.3, 126.6, 159.4, 178.7. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.64; H, 6.65.

(−)-(*S*)-3-(*p*-Methoxybenzyloxy)-1-(*p*-tolylsulfinyl)-2-propanone, 3. To a stirred solution of diisopropylamine (1.9 mL, 1.4 mmol) in THF (20 mL) under argon was added dropwise at −15 °C a 1.5 M solution of *n*-butyllithium in hexane (9.1 mL, 13.6 mmol). After 30 min of stirring, the mixture was allowed to reach 0 °C and a solution of (−)-(*S*)-methyl *p*-tolyl sulfoxide (2.0 g, 13.0 mmol) in THF (20 mL) was added. After 30 min of stirring, the resulting solution was added to a solution of ester **5** (1.28 g, 6.1 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 2 h. The reaction was finally quenched with saturated ammonium chloride (50 mL), 5% sulfuric acid was added untill pH = 2, and the solution was extracted with dichloromethane (3 × 55 mL), dried ($MgSO_4$), and evaporated. Crude product **3** was used in the next step without further purification, the excess of methyl *p*-tolyl sulfoxide being difficult to separate by chromatography. However, an analytical sample of β-keto sulfoxide **3** was obtained by crystallization in diethyl ether: $[\alpha]_D$ −141 (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.67 (s, 3H), 3.77 (s, 3H), 3.86 (AB, J_{AB} = 13.6 Hz, $\Delta\nu$ = 32.7 Hz, 2H), 3.98 (s, 2H), 4.43, (s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H): ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 55.4, 66.0, 73.3, 75.9, 114.0, 124.2, 128.9, 129.9, 130.2, 139.7, 142.3, 159.7, 199.9. Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.03; H, 6.07. Found: C, 65.00; H, 6.05.

(−)-[2(*R*),S(*S*)]-3-(*p*-Methoxybenzyloxy)-1-(*p*-tolylsulfinyl)-2-propanol, 6. To a solution of β-keto sulfoxide **3** in anhydrous THF (40 mL) under argon at −78 °C was quickly added a 1 M solution of DIBAL in toluene (7 mL, 7 mmol). After the solution was stirred for 30 min at −78 °C, the reaction was quenched with saturated ammonium chloride (30 mL) and the pH was ajusted to 4−5 with 5% H_2SO_4. The solution was extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography (EtOAc−hexane, 3:1) on silica gel to give **6** (1.24 g, 61%): $[\alpha]_D$ −151 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.74−3.03 (AB part of ABX,

Scheme 4



J_{AB} = 14 Hz, J_{AX} = 9.5 Hz, J_{BX} = 2.4 Hz, $\Delta\nu$ = 66 Hz, 2H), 3.36−3.54 (m, 2H), 3.80 (s, 3H), 4.39−4.44 (X part of ABX, 1H and m, 2H), 6.85 (d, J = 9 Hz, 2H), 7.19 (d, J = 9 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 7.51 (d, J = 8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 55.4, 59.4, 66.1, 72.9, 73.2, 113.9, 124.1, 129.5, 129.8, 130.2, 139.9, 141, 7,159.4. Anal. Calcd for $C_{18}H_{22}O_4S$: C, 65.64; H, 6.63, Found: C, 65.46; H 6.58.

(−)-[2(*R*),S(*S*)]-2-(*tert*-Butyldiphenylsiloxy)-3-(*p*-methoxybenzyloxy)-1-(*p*-tolyl sulfinyl)-propane, 7. To a solution of compound **6** (1.15 g, 3.4 mmol) in dimethylformamide (15 mL) under argon at room temperature was added imidazole (623 mg, 9 mmol). After the solution was stirred for 10 min, *tert*-butyldiphenylsilyl chloride (1.5 g, 5 mmol) was added, the solution was stirred for 12 h, the reaction was quenched with saturated ammonium chloride (30 mL), and the solution was extracted with ethyl acetate (2 × 30 mL) and dichloromethane (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:3) to give **7** (1.9 g, 98%): $[\alpha]_D$ −75 (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 9H), 2.40 (s, 3H), 2.86−3.07 (AB part of ABX, J_{AX} = 8.5 Hz, J_{BX} = 4 Hz, J_{AB} = 13 Hz, $\Delta\nu$ = 22 Hz, 2H), 3.19−3.39 (AB part of ABX, J_{AX} = 4.5 Hz, J_{BX} = 4 Hz, J_{AB} = 10 Hz, $\Delta\nu$ = 25 Hz, 2H), 3.78 (s, 3H), 4.05−4.14 (AB, J_{AB} = 11.3 Hz, $\Delta\nu$ = 31.6 Hz, 2H), 4.38−4.45 (X part of both ABX, 1H), 6.78 (d, J = 9 Hz, 2H), 7.03 (d, J = 9 Hz, 2H), 7.29−7.47 (m, 10H), 7.73−7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 21.4, 27.1, 55.2, 64.1, 67.7, 72.7 73.0, 113.4, 123.9, 127.6, 127.9, 129.3, 129.7, 130.0, 130.1, 132.7, 134.2, 135.9, 136.2, 141.1, 141.7, 159.2. Anal. Calcd for $C_{34}H_{40}O_4SSi$: C, 71.29; H, 7.05. Found: C, 71.40; H, 7.12.

(2*R*)-1-Acetoxy-2-(*tert*-butyldiphenylsilyloxy)-3-(*p*-methoxybenzyloxy)-1-(*p*-tolylthio)propane, 8. To a solution of **7** (1.45 g, 2.6 mmol) in acetic anhydride (80 mL) was added sodium acetate (2.4 g, 2.9 mmol) under argon. After the solution was heated at 130 °C for 11 h, acetic anhydride was evaporated, the residue was dissolved in diethyl ether, and the solution was filtered through Celite and concentrated. The crude product was purified by chromatography on silica gel (CH_2Cl_2−hexane, 1:1) to give **8** as a yellow oil (1.46 g, mixture of diastereomers, 94%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 and 1.09 (s, 9H), 1.78 and 1.86 (s, 3H), 2.30 (s, 3H), 3.37−3.73 (m, AB part of ABX for the two diastereomers, 2H), 3.78 and 3.80 (s, 3H), 4.01−4.3 (X part of ABX, 1H and AB, J_{AB} = 8.8 Hz, $\Delta\nu$ = 25.7 Hz, 2H), 6.18 and 6.24 (d, J = 7 Hz and 2 Hz, respectively, 1H), 6.78 and 6.82 (d, J = 6 Hz and 6 Hz, respectively, 2H), 6.98−7.09 (m, 4H), 7.20−7.42 (m, 8H), 7.60−7.72 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 21.1, 21.3, 27.1, 55.4, 71.6, 72.9, 73.8, 74.1, 81.6, 85.3, 113.8, 127.7, 128.6, 129.5, 129.8, 130.1, 130.2, 130.3, 132.9, 133.2, 133.7, 133.8, 134.0, 136.1, 136.1, 136.4, 137.8, 138.2, 159.2, 169.6. Anal. Calcd for $C_{36}H_{42}O_5SSi$: C, 70.32; H 6.89. Found: C, 70.26; H, 6.96.

(+)-(*S*)-2-(*tert*-Butyldiphenylsiloxy)-3-(*p*-methoxybenzyloxy)-1-propanol, 1. To a solution of **8** (1.0 g, 1.7 mmol) in diethyl ether (15 mL) under argon was added dropwise at −78 °C a 1 M solution of $LiAlH_4$ in diethyl ether (5.1 mL, 5.1 mmol). After the solution was stirred for 2 h at 0 °C, the reaction was quenched with saturated ammonium chloride (15 mL) and the pH of the solution adjusted to 2−3 with 5% H_2SO_4. The solution was extracted with ethyl acetate (3 × 15 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 3:1) to give **1** as a yellow oil (628 mg, 81%): $[\alpha]_D$ +6 (*c* 1.5, MeOH); +8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.5−3.6 (m, 2H), 3.63−3.76 (AB part of ABX, J_{AB} = 11.4 Hz, J_{AX} = 3.9 Hz, J_{BX} = 5.3 Hz, $\Delta\nu$ = 20 Hz, 2H), 3.80 (s, 3H), 3.85−3.93 (m, 1H), 4.60 (s, 2H), 6.89 (d, J = 9 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 7.36−7.45 (m, 6H), 7.73−7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 25.4, 55.3, 63.1, 64.6, 66.1, 76.4, 114.0, 128.0, 128.7, 130.4, 132.6, 133.4, 135.3, 159.2. Anal. Calcd for $C_{27}H_{34}O_4Si$: C, 71.96; H, 7.61. Found: C, 71.85; H, 7.53.

1,3-Octadiyn-5-ol, 9. To a solution of potassium hydroxide (51g, 0.9 mol) in a 82/18 DMSO/H_2O mixture (100 mL) was dropwise added at room temperature 1,4-dichloro-2-butyne (25 g, 0.20 mol). At the end of the addition, the mixture was heated at 95 °C for 1.5 h. Butadiyne was added to two flasks of THF (10 mL) respectively cooled at −60 and −78 °C. A total of 8.20 g of butadiyne was isolated in the THF solution. A 1 M solution of EtMgBr in diethyl ether (131.2 mL, 131.2 mmol) was added dropwise. This cloudy solution was stirred at room temperature for 1.5 h and then cooled to −78 °C. Butyraldehyde (8.91 mL, 98.4 mmol) in dry THF (20 mL) was added slowly over a period of 20 min. The reaction mixture was allowed to reach 0 °C and stirred for 50 min. Workup was carried out by quenching the reaction with saturated NH_4Cl (150 mL). The aqueous layer was then extracted three times with diethyl ether. The combined organic layers were washed with saturated NH_4Cl (150 mL) and NaCl (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by column chromatography (EtOAc−hexane, 1:5) to give **9** (22.28 g, 72%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J

= 7.5 Hz, 3H), 1.17−1.77 (m, 4H), 1.92 (d, J = 6 Hz, 1H), 2.19 (s, 1H), 4.42 (q, J = 6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.4, 31.0, 39.5, 62.5, 68.5, 68.7, 76.5. Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.26. Found: C, 78.61; H, 8.20.

1-(*tert*-Butyldimethylsiloxy)-4,9-dihydroxydodeca-5,7-diyne, 10. To a solution of **9** (1.1 g, 8.8 mmol) in anhydrous THF (60 mL) under argon at −78 °C was added dropwise a 1.5 M solution of *n*-butyllithium in hexane (11.7 mL, 17.5 mmol) producing a strong green coloration. After the solution was stirred for 1 h at 0 °C, a solution of 4-(*tert*-butyldimethylsiloxy)butyraldehyde (1.5g, 7.3 mmol) in THF (60 mL) was added at −78 °C. After the solution was stirred for 50 min at −78 °C and for 50 min at 0 °C, the reaction was quenched with saturated ammonium chloride (60 mL) and the pH was adjusted to 4−5 with 5% H_2SO_4. The solution was extracted with ethyl acetate (3 × 60 mL), dried, and evaporated. The crude product was purified by chromatography (EtOAc−hexane, 1:2) to give **10** (2.5 g, 89%, mixture of diastereomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 0.94 (t , J = 7 Hz, 3H), 1.42−1.88 (m, 10H), 3.60−3.83 (m, 2H), 4.42−4.58 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, 13.7, 18.4, 18.4, 26.0, 28.4, 34.9, 39.6, 62.2, 62.3, 63.1, 65.9, 80.5. Anal Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.95: Found: C, 66.56; H, 9.87.

(5*Z*,7*Z*)-1-(*tert*-Butyldimethylsiloxy)-4,9-dibenzoyldodecadiene, 4. (1) Preparation for activated Zn. For 1.6 g of diene (5.4 mmol), Zn (19.3 g, 0.3 mol) was stirred in water (75 mL) for 15 min under argon. A flux of argon was maintained for the entire preparation. Copper acetate (1.9 g, 10.4 mmol) was first added, and the mixture was stirred for 15 min. Then silver nitrate (1.9 g, 11.2 mmol) was added and stirring was continued for 0.5 h. The reaction mixture was then filtered and washed with water (50 mL), methanol (50 mL), acetone (50 mL), and diethyl ether (50 mL) to give activated Zn.

(2) To a solution of compound **10** (1.7 g, 5.3 mmol) in a 1/1 methanol/water mixture (75 mL) was added Zn activated by copper acetate (19.3 g, 295 mmol). After being stirred for 12 h, the solution was filtered through celite and the slurry was carefully extracted with ethyl acetate. The solution was partially evaporated, and the resulting aqueous layer was extracted with ethyl acetate (3 × 50 mL), dried, and evaporated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:2) to give the corresponding dienediol (1.5 g, 85%, mixture of diastereomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90−0.96 (s, 9H and t, J = 7 Hz overlapped, 3H), 1.17−1.66 (m, 10H), 3.6−3.75 (m, 2H), 4.56−4.68 (m, 2H), 5.43−5.57 (m, 2H), 6.28−6.37 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.3, 14.1, 18.4, 19.6, 26.0, 30.0, 35.0, 39.6, 63.4, 67.3, 67.4, 123.8, 124.3, 135.6, 135.9. Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.06. Found: C, 65.69; H, 10.99.

(3) To a solution of the preceding diol (1 g, 3 mmol) in pyridine (60 mL) under argon at room temperature was added dropwise benzoyl chloride (950 mg, 6.8 mmol). After the solution was stirred for 12 h, diethyl ether (60 mL) was added. The solution was washed successively with saturated $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was then dried, filtered, and concentrated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:5) to give dibenzoate **4** (1.63 g, quantitative yield, mixture of diastereomers): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 and 0.04 (s, 6H), 0.85 and 0.88 (s, 9H), 0.92 and 0.94 (t, J = 7.1 Hz, 3H), 1.17−2 (m, 8H), 3.62 and 3.64 (t, J = 6 Hz, 2H), 5.6 (bt, J = 8 Hz, 2H), 5.95 (bq, J = 8 Hz, 2H), 6.61 and 6.64 (bd, J = 8 Hz, 2H), 7.37−7.59 (m, 6H), 7.99−8.05 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.2, 14.0, 18.5, 26.1, 28.5, 31.4, 37.1, 65.0, 70.4, 125.9, 126.2, 126.4, 129.7, 130.61, 130.7, 131.6, 132.9, 165.9. Anal. Calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.22. Found: C, 71.53; H, 8.20.

(4*E*,6*E*,8*E*)-1-(*tert*-Butyldimethylsiloxy)dodecatriene, 11. To a solution of **4** (0.8 g, 1.5 mmol) in a 3/1 mixture of anhydrous THF/methanol (90 mL) under argon at room temperature was added Na_2HPO_4 (1.5 g, 11 mmol). The temperature was lowered to −20 °C, and a 6% Na(Hg) amalgam was added (6 g, 15.6 mmol). The mixture was stirred for 4 h. Diethyl ether (200 mL) was added, and the mixture was filtered. The organic layer was dried and evaporated. The crude product was purified by chromatography on silica gel (hexane) to give **11** (324.5 mg, 76%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H and t, J = 7.5 Hz overlapped, 3H), 1.37 (sexet., J =7.5 Hz, 2H), 1.62 (tt, J = 7.7 Hz, J = 6.4 Hz, 2H), 2.05 (q, J = 7.5 Hz, 2H), 2.13 (q, J = 7.7 Hz, 2H), 3.6 (t, J = 6.4 Hz, 2H), 5.59−5.71 (m, 2H), 6.01−6.06 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.2, 13.8, 18.4, 22.6, 26.0, 29.2, 32.5, 35.0, 62.6, 130.7, 130.8, 130.85, 131.1, 133.8, 134.4. Anal. Calcd for $C_{18}H_{34}OSi$: C, 73.40; H, 11.65. Found: C, 73.32; H, 11.60.

(4*E*,6*E*, 8*E*)-Dodecatriene-1-ol, 12. To a solution of silylated alcohol **11** (300 mg, 1 mmol) in THF (30 mL) at 0 °C under argon was added a 1 M TBAF solution in THF (1.5 mL, 1.5 mmol). The reaction mixture was allowed to reach room temperature and stirred for 12 h, the reaction was then quenched with 2 g of silica gel, and the solution was evaporated. The crude product was then dissolved in 1 mL of dichloromethane and purified by chromatography on silica gel (EtOAc−hexane, 1:4) to give alcohol **12** (149 mg, 81%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 3H), 1.39 (sextet, J = 7.5 Hz, 2H), 1.62 (tt, J = 6.5 Hz, J = 7.5 Hz, 2H), 2.05 (q, J = 7 Hz, 2H), 2.15 (q, J = 7.5 Hz, 2H), 2.44 (bs, 1H), 3.59 (t, J = 6.5 Hz, 2H), 5.55−5.75 (m, 2H), 5.09−6.15 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.6, 29.2, 32.3, 35.0, 62.2, 130.6, 130.6, 131.1, 131.3, 133.3, 134.6. Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.19 . Found: C, 79.87; H, 11.08.

(4*E*,6*E*,8*E*)-1-Bromododecatriene, 13. To a solution of alcohol **12** (140 mg, 0.8 mmol) and CBr_4 (387 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) was added over a period of 4 h a solution of PPh_3 (203.78 mg, 0.8 mmol). The mixture was then stirred for 12 h. The solution was then evaporated, and the crude product was purified by chromatography on silica gel (hexane) to give bromo derivative **13** (161 mg, 86%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, J = 7 Hz, 3H), 1.37 (sextet, J = 7 Hz, 2H), 1.83 (tt, J = 6.5 Hz, J = 7 Hz, 2H), 2.07 (q, J = 7 Hz, 2H), 2.14 (q, J = 7 Hz, 2H), 3.39 (t, J = 6.5 Hz, 2H), 5.55−5.75 (m, 2H), 5.9−6.15 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 22.4, 29.0, 32.1, 34.8, 66.4, 131.2, 131.2, 131.9, 133.8, 135.2. Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.88. Found: C, 59.15; H, 7.80.

(+)-(*S*)-(4*E*,6*E*,8*E*)- 2-(*tert*-Butyldiphenylsiloxy)-1-dodecatrienoxy-3-(*p*-methoxybenzyloxy)propane, 14. To a solution of compound **1** (172 mg, 0.4 mmol) in THF (10 mL) at 0 °C was added NaH (10 mg, 0.4 mmol). After the solution was stirred at room temperature for 1 h, a catalytic amount of tetrabutylammonium bromide (12 mg, 0.04 mmol) was added, immediately followed by the addition of a solution of bromide **13** (95 mg, 0.4 mmol) in THF (10 mL). The mixture was heated at 60 °C for 2 h, the reaction was quenched with saturated NH_4Cl (20 mL), and the solution was extracted with ethyl acetate (3 × 20 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:9) to give **14** (182 mg, 78%): $[\alpha]_D$ +3 (*c* 1.3, MeOH); +4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.14 (s, 9H), 1.40 (sextet, J = 7 Hz, 2H), 1.62 (q, J = 7 Hz, 2H), 2.05 (q, J = 7 Hz, 2H), 2.17 (q, J = 7 Hz, 2H), 3.43 (t, J = 7 Hz, 2H), 3.48−3.54 (m, 2H), 3.56−3.74 (AB part of ABX, J_{AB} = 11.4 Hz, J_{AX} = 3.7 Hz, J_{BX} = 5.6 Hz, $\Delta\nu$ = 22 Hz, 2H), 3.79 (s, 3H), 3.8−3.92 (X part of ABX, 1H), 4.58 (s, 2H), 5.55−5.75 (m, 2H), 5.82−6.12 (m, 4H), 6.87 (d, J = 9 Hz, 2H), 7.27 (d, J = 9 Hz, 2H), 7.39−7.43 (m, 6H), 7.73−7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 20.8, 22.6, 25.4, 29.2, 32.4, 34.9, 55.4, 62.5, 63.1, 65.1, 65.8, 76.2, 114.1, 127.9, 128.7, 130.3, 130.6, 130.6, 131.2, 131.4, 132.6, 133.2, 133.3, 134.7, 135.3. Anal. Calcd for $C_{39}H_{52}O_4Si$: C, 76.42; H, 8.56. Found: C, 76.37; H, 8.50.

(+)-(*R*)-2-(*tert*-Butyldiphenylsiloxy)-3-(4*E*,6*E*,8*E*-dodecatrienoxy)-propan-1-ol, 15. To a stirred CH_2Cl_2 (2 mL) solution of **14** (180 mg, 0.3 mmol) containing a small amount of water (100 μL) was added DDQ (66 mg, 0.3 mmol) at room temperature. After 1 h, saturated $NaHCO_3$ (2 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 5 mL). The extract was washed with saturated $NaHCO_3$ (10 mL) and brine and then dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed on a silica gel column

(EtOAc−hexane, 1:5) to give **15** (120 mg, 84%): $[\alpha]_D$ +4 (*c* 1.2, MeOH); +6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J = 7 Hz, 3H), 1.14 (s, 9H), 1.39 (sextet, J = 7 Hz, 2H), 1.64 (q, J = 7 Hz, 3H), 2.09 (q, J = 7 Hz, 2H), 2.13 (q, J = 7 Hz, 2H), 3.39−3.55 (m, 4H), 3.56−3.75 (AB part of ABX, J_{AB} = 11.5 Hz, J_{AX} = 3.7 Hz, J_{BX} = 5.6 Hz, $\Delta\nu$ = 21.9 Hz, 2H), 3.8−3.92 (X part of ABX, 1H), 5.57−5.76 (m, 2H), 5.94−6.15 (m, 4H), 7.39−7.46 (m, 6H), 7.74−7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 20.8, 22.6, 26.6, 29.2, 32.35, 35.0, 62.5, 63.1, 65.8, 76.2, 127.9, 130.3, 130.6, 131.2, 131.4, 132.6, 133.2, 134.7, 135.2, 135.3. Anal. Calcd for $C_{31}H_{44}O_3Si$: C, 75.56, H, 9.01. Found: C, 75.50; H, 8.92.

(+)-(*S*)-(4*E*,6*E*,8*E*)-1-((*p*-*tert*-Butyldiphenylsiloxy)-benzoyl)-2-(*tert*-butyldiphenylsiloxy)-3-dodecatrienoxypropane, 16. To a solution of **15** (116 mg, 0.2 mmol) in dry pyridine (10 mL), (*p*-*tert*-butyldiphenylsiloxy)benzoyl chloride (200 mg, 0.5 mmol) was added and the resulting mixture stirred under argon for 12 h. Workup was carried out by adding diethyl ether (10 mL) to the reaction mixture. The resulting solution was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography on silica gel (EtOAc−hexane, 1:9) to give **16** (202 mg, quantitative): $[\alpha]_D$ +2 (*c* 1.9, MeOH); +3 (*c* 1.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.15 (s, 18H), 1.41 (sextet, J = 7.3 Hz, 2H), 1.64 (q, J = 7 Hz, 2H), 2.04 (q, J = 7.3 Hz, 2H), 2.16 (q, J = 7.3 Hz, 3H), 3.41 (t, J = 6.5 Hz, 2H), 3.54 (AB part of ABX, J_{AB} = 10 Hz, J_{BX} = 6 Hz, J_{AX} = 4 Hz, $\Delta\nu$= 11 Hz, 2H), 4.13 (X part of both ABX, 1H), 4.35 (AB part of ABX, J_{AB} = 11 Hz, J_{AX} = 5 Hz, J_{BX} = 5 Hz, $\Delta\nu$ = 12 Hz, 2H), 5.52−5.70 (m, 2H), 5.94−6.02 (m, 4H), 6.87 (d, J = 9 Hz, 2H), 7.37−7.46 (m, 12H), 7.74−7.79 (m, 8H), 7.94 (d, J = 9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.81, 20.8, 22.5, 26.6, 29.2, 29.5, 34.9, 65.9, 69.1, 70.9, 71.5, 115.2, 122.0, 127.5, 128.0, 129.4, 129.9, 130.3, 130.8, 131.0, 132.1, 132.8, 134.1, 134.9, 160.2, 166.2. Anal. Calcd for $C_{54}H_{66}O_5Si_2$: C, 76.19; H, 7.82. Found: C, 76.11; H, 7.85.

(+)-Isobretonin A. To a solution of **16** (190 mg, 0.2 mmol) in THF (20 mL) at 0 °C under argon was added a 1 M solution of TBAF in THF (0.5 mL, 0.5 mmol). The reaction mixture was allowed to reach room temperature and was stirred for 12 h, the reaction was then quenched with 2 g of silica gel and the solution was evaporated. The mixture was then dissolved in 1 mL of CH_2Cl_2 and purified by column chromatography on silica gel (EtOAc−hexane, 1:3) to give isobretonin A (68.38 mg, 83%): $[\alpha]_D$ +5 (*c* 1.5, MeOH); +8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.40 (sextet, J = 7.3 Hz, 2H), 1.62 (pentet, J = 7.0 Hz, 2H), 2.04 (q, J = 7.3 Hz, 2H), 2.13 (q, J = 7.3 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 3.54 (AB part of ABX, J_{AX} = 4 Hz, J_{BX} = 6 Hz, J_{AB} = 10 Hz, $\Delta\nu$ = 13 Hz, 2H), 4.13 (X part of both ABX, 1H), 4.37 (AB part of ABX, J_{AX} = 5 Hz, J_{BX} = 5 Hz, J_{AB} = 11 Hz, 2H), 5.55−5.71 (m, 2H), 5.94−6.06 (m, 4H), 6.87 (d, J = 9 Hz, 2H), 7.94 (d, J = 9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) 13.9, 22.5, 29.2, 29.5, 34.9, 65.9, 69.1, 70.9, 71.5, 115.2, 122.0, 129.3, 130.6, 130.8, 131.4, 132.0, 132.2, 134.0, 160.2, 166.2. Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.50; H, 7.98.

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