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# Total Synthesis of (+)-Isoschizandrin Utilizing a Samarium(II) Iodide-Promoted 8-Endo Ketyl−Olefin Cyclization

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The 13-step synthesis of (+)-isoschizandrin reported herein features a samarium(II) iodide-promoted 8-endo ketyl−olefin coupling to assemble the eight-membered ring present in the target concomitantly with the required functionality and stereochemistry. In constructing (+)-isoschizandrin as a single atropisomer, the synthesis utilizes a kinetic resolution of a seven-membered lactone using a CBS-oxazaborolidine.

## Introduction

(+)-Isoschizandrin (**1**) and (+)-schizandrin (**2**) represent two of nearly forty dibenzocyclooctadiene lignans isolated from the fruit of *Schizandra chinesis*, a creeping vine native to northern China (Figure 1).[1] The extracts from this lignan-rich plant have been used in Chinese and Japanese traditional medicine as an antitussive and a tonic. Several lignans isolated from these extracts are thought to exhibit antirheumatic and antihepatotoxic activity. (+)-Isoschizandrin, a minor component of the extract, displays antiulcer activity in rats.[2] Although these lignans exhibit significant biological activity, the principal synthetic interest in this family of natural products lies within the unique dibenzocyclooctadiene structure.

To date, three research groups have communicated syntheses of isoschizandrin. The Meyers group[3] first reported the total synthesis of (−)-isoschizandrin, thereby establishing the absolute stereochemistry of the natural product. This was soon followed by a racemic synthesis of (±)-isoschizandrin from the laboratories of Tobinaga.[4]

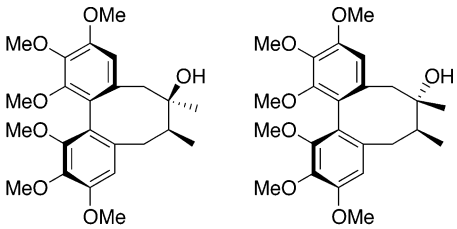


**FIGURE 1.** Cyclooctadiene lignans isoschizandrin and schizandrin.

More recently, Tanaka and co-workers[1d] reported the first asymmetric total synthesis of (+)-isoschizandrin.

In the current synthetic approach, we sought to demonstrate a samarium(II) iodide-promoted 8-endo ketyl−olefin radical cyclization as a means to provide the eight-membered ring, the required functionality, and the correct stereochemistry present in (+)-isoschizandrin in a single transformation.[5] This general approach to dibenzocyclooctadiene lignan synthesis was first demonstrated in a reported synthesis of (−)-steganone.[6] In that study, a samarium(II) iodide-promoted coupling between an aromatic aldehyde and a butenolide proceeded in good yields and with moderate selectivity.

To obtain a single atropisomer of (+)-isoschizandrin, the synthesis described herein utilizes the method of

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(1) (a) Ayres, D. C.; Loike, J. D. *Chemistry & Pharmocology of Natural Products: Lignans; Chemical, Biological, and Chemical Properties*; Cambridge University Press: Cambridge, U.K., 1990. (b) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (c) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499. (d)Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339.

(2) (a) Ikeya, Y.; Taguchi, H.; Mitsuhashi, H.; Takeda, S.; Kase, Y.; Aburada, M. *Phytochemistry* **1988**, *27*, 569. (b) Ikeya, Y.; Sugama, K.; Okada, M.; Mitsuhashi, H. *Phytochemistry* **1991**, *30*, 975.

(3) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.

(4) Takeya, T.; Ohguchi, A.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 438.

(5) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186.

(6) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52.

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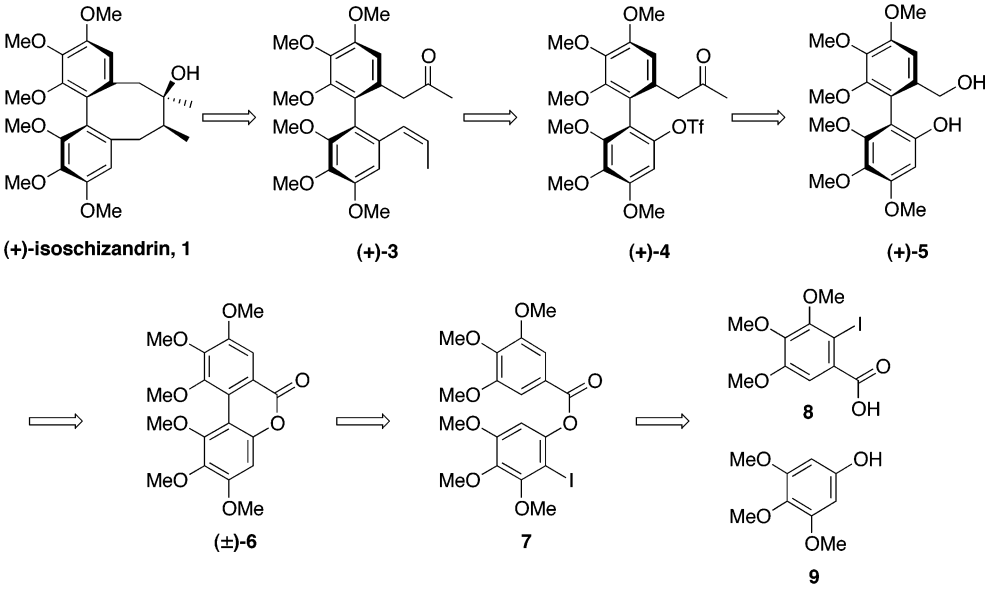
**SCHEME 1**




Bringmann[7] that allows for configurationally stable seven-membered lactones to be kinetically resolved by utilizing a chiral oxazaborolidine.[8] Applying this method provides the desired lactone intermediate with excellent enantioselectivity.

## Results and Discussion

Retrosynthetic analysis utilizing a samarium(II) iodide-promoted 8-endo ketyl−olefin coupling suggests structure (+)-**3** as a direct precursor to isoschizandrin **1** (Scheme 1). Samarium(II)-promoted 8-endo ketyl−olefin cyclizations are greatly enhanced by placing an electron-withdrawing or $\pi$-conjugating substituent directly on the olefin, thereby increasing the radical SOMO/alkene LUMO interactions in the transition state leading to the product.[5,6] In the present synthesis, the aryl group thus provides a useful structural element in facilitating this type of cyclization.

To obtain the penultimate ketoolefin (+)-**3**, we initially envisioned a Pd-mediated coupling reaction between a (*Z*)-propenyl moiety and ketotriflate (+)-**4** to install the necessary carbon functionality in the ortho position. Construction of the tetra-ortho-substituted biaryl moiety must proceed with special regard to its atropisomerism, because the 8-endo cyclization sets the remaining stereocenters relative to the biaryl geometry. Generally, three or four ortho substituents are required to make asymmetric biaryl synthesis a viable consideration. Few biaryl couplings succeed when three or four ortho substituents are present,[9] and fewer still control the resultant biaryl geometry.[10] Meyers' pioneering method, which utilizes a chiral oxazoline auxiliary to facilitate nucleophilic aromatic substitution of a methoxy group, provides yields in the 60−90% range with good to excellent levels of diastereoselection (up to 96% de) and has been used successfully in several total syntheses.[11] This protocol has the advantage of forming the biaryl and establishing the stereochemistry in a single step.

By contrast, novel methods developed by Bringmann and co-workers[7] control the formation of the biaryl juncture and atropisomerism separately, a strategy nevertheless competitive because construction and deconstruction of a chiral auxiliary are excluded from the linear sequence. Our initial interest lay in the application of dynamic kinetic resolution[7c,d] to set the biaryl stereochemistry en route to an asymmetric isoschizandrin synthesis. In principle, the key diol (+)-**5** could be generated as a single atropisomer from benzocoumarin lactone (±)-**6** via borane reduction in the presence of the CBS ligand.

The synthesis of the key benzocoumarin lactone **6** (Scheme 2) was achieved by iodination of 3,4,5-trimethoxybenzoic acid, followed by DCC coupling with 3,4,5-trimethoxyphenol (**9**), which provided phenyl halobenzoate ester **7**. Mizoroki−Heck coupling of **7** afforded lactone **6**, which was used to generate racemic diol **5** by LAH reduction. Alternatively, lactone **6** provided entry to an asymmetric synthesis of the target via dynamic kinetic resolution by analogy to Bringmann's method.[7c,d] Atropoenantioselective reduction of benzocoumarin lactone (±)-**6** with 4 equiv of $BH_3$·THF in the presence of excess (*R*)-2-methyl-CBS-oxazaborolidine (3 equiv) provided the nonracemic diol (+)-**5** in 95% yield and 95.6% ee by chiral HPLC.[12] Notably, the scale of this reaction was 10-fold higher than that reported by Bringmann, demonstrating its viability in total synthesis. Neverthe-

(7) Kinetic resolution: (a) Bringmann, G.; Hinrichs, J. *Tetrahedron: Asymmetry* **1997**, *8*, 4121. (b) Bringmann, G.; Hinrichs, J.; Pabst, T.; Henschel, P.; Peters, K.; Peters, E.-M. *Synthesis* **2001**, 155. Dynamic kinetic resolution: (c) Bringmann, G.; Hartung, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 761. (d) Bringmann, G.; Hartung, T. *Tetrahedron* **1993**, *49*, 7891.

(8) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

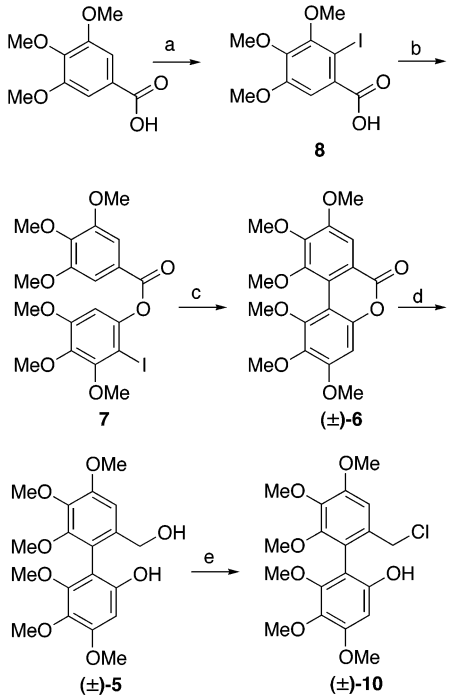
(9) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(10) (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 3161. (c) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

(11) (a) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. (b) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989. (c) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993.

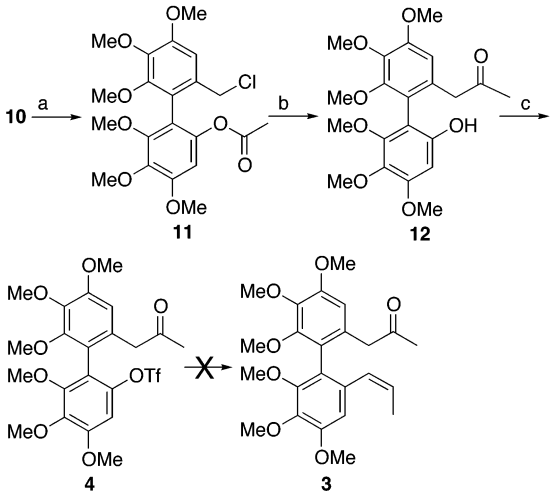
(12) Monovich, L. G. Ph.D. Thesis, University of Colorado at Boulder, 1998.

**SCHEME 2**[a]




[a] Reagents and conditions: (a) $AgO_2CCF_3$, $I_2$, $CHCl_3$, 99%; (b) **9**, DCC, DMAP, $CH_2Cl_2$, 99%; (c) $PdCl_2(PPh_3)_2$, NaOAc, DMA, 120 °C, 3 h, 87%; (d) LAH, THF, 80%; (e) $SOCl_2$, $CH_2Cl_2$, imidazole, 99%.

**SCHEME 3**[a]




[a] Reagents and conditions: (a) AcCl, $CH_2Cl_2$, pyridine, 89%; (b) $SmI_2$, $NiI_2$, THF, 81%; (c) $Tf_2O$, DMAP, $CH_2Cl_2$, triethylamine, 71%.

less, the more facile LAH reduction was employed to provide diol **5**, which was then used to explore the success of the subsequent transformations.

Utilizing racemic material, benzyl chloride (±)-**10** was prepared using $SOCl_2$ (Scheme 2). Acylation of the corresponding phenol (Scheme 3) provided a substrate capable of undergoing a samarium(II) iodide-promoted acyl-transfer reaction.[13] The use of $NiI_2$[14] as an additive

(13) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216.

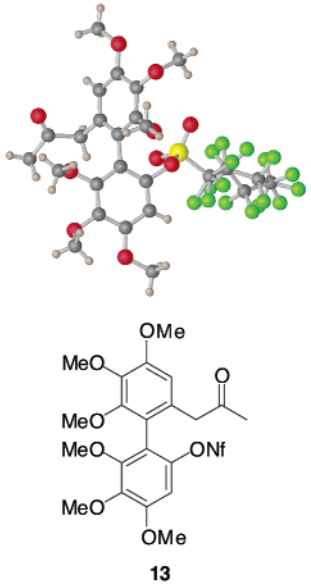



**FIGURE 2.** X-ray crystal structure of ketononaflate **13**.

in this reaction provided the desired phenolic ketone **12** but required high dilution (0.007 M). Treatment of ketophenol **12** with $Tf_2O$ afforded the desired coupling precursor **4**.

Transition-metal-catalyzed carbon−carbon bond formations are extraordinarily difficult with sterically hindered, electron-rich aryl triflates.[15] However, just such a transformation was required to install the (*Z*)-propenyl fragment necessary for the samarium-mediated cyclization. Consequently, numerous cross-coupling strategies were tested (utilizing both *cis*-propenyl and 1-propynyl organometallics) to convert **4** to **3** or a suitable precursor. After an exhaustive number of protocols were investigated, the desired product unfortunately could not be obtained reproducibly, yielding instead detriflated material as the major product. The analogous nonafluorobutanesulfonate (nonaflate) **13**, a pseudohalide generally known to be less prone to oxygen−sulfur cleavage than the triflate, also proved to be an unsuccessful coupling partner in transition-metal couplings.[16] The X-ray crystal structure of ketononaflate **13** provides evidence of the steric hindrance in this system, and this, combined with the electron-rich nature of the electrophile, explains the lack of successful coupling (Figure 2). Clearly, a new approach was needed to arrive at the desired samarium precursor **3**.

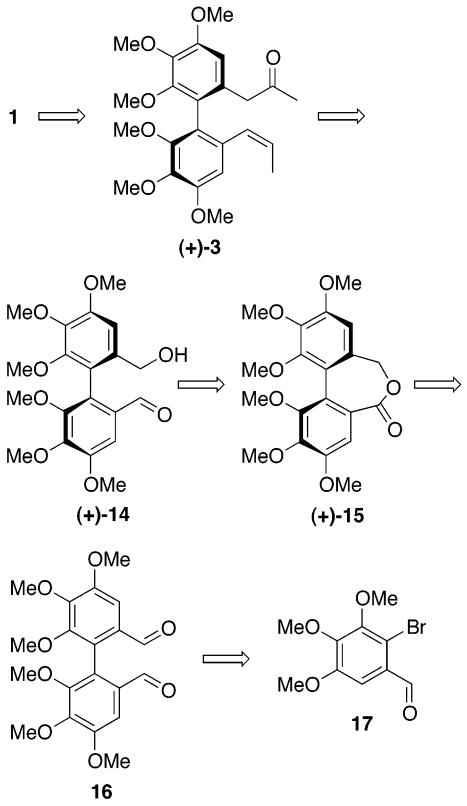
Because the atropoenantioselective reduction of benzocoumarin lactone (±)-**6** provided an excellent pathway to a single atropisomer, we sought to apply a related strategy to the synthesis of a seven-membered lactone. By altering our approach, both carbon ortho substituents would now be poised for further chemistry without the need to couple a carbon unit into a sterically hindered, electron-rich position. Bringmann and co-workers have

(14) Machrouhi, F.; Hamann, B.; Namy, J. L.; Kagan, H. *Synlett* **1996**, *7*, 633.

(15) (a) Ritter, K. *Synthesis* **1993**, 735. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(16) (a) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

**SCHEME 4**

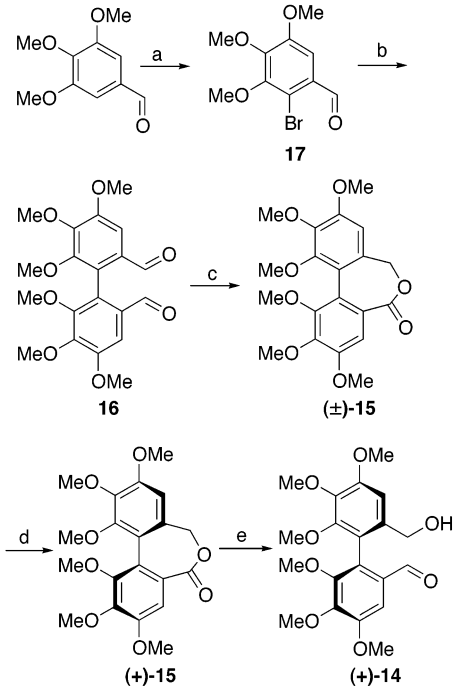



recently developed such chemistry to obtain enantiomerically enriched biaryls via the kinetic resolution of conformationally stable biaryl lactones using a chiral oxazaborolidine.[7a,b] We sought to apply this chemistry to our synthesis.

With this new approach in mind, our revised retrosynthetic analysis would utilize two different Wittig reactions to homologate the carbon side chains, providing ketoolefin (+)-**3** (Scheme 4). Further disconnection reveals hydroxy aldehyde (+)-**14** which could arise from a selective DIBALH reaction of lactone (+)-**15**. Applying Bringmann's method,[7a,b] lactone (+)-**15** would be enantiomerically enriched via a kinetic resolution of a racemic lactone mixture. Racemic lactone (±)-**15** could arise from a Cannizzaro reaction of **16** followed by DCC coupling. Finally, this dialdehyde can be accessed by an Ullmann coupling of the corresponding haloaldehyde **17**.

Our revised approach began with the bromination of 3,4,5-trimethoxybenzaldehyde (**18**) to provide the corresponding bromoaldehyde **17**[17a] (Scheme 5). Using a standard Ullmann coupling protocol, bromoaldehyde **17** was heated with activated Cu in DMF to provide the desired biaryl dialdehyde in good yields.[10a,17] Treatment of **16** with KOH in boiling ethanol[18] afforded the hydroxy acid, which was directly lactonized with DCC to produce

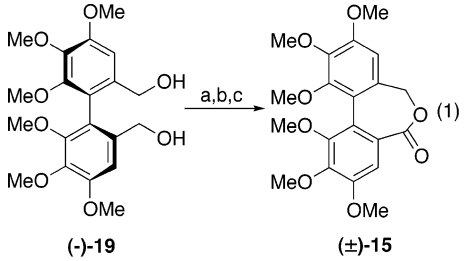
**SCHEME 5**[a]




[a] Reagents and conditions: (a) NBS, $CHCl_3$, reflux, 3 h, 96%; (b) Cu, DMF, reflux, 18 h, 74%; (c) (i) KOH, EtOH, reflux, 1.5 h; (ii) DCC, DMAP, $CH_2Cl_2$, rt, 63%; (d) (*R*)-2-methyl-CBS-oxazaborolidine, $BH_3$·THF, THF, −20 °C, 61% overall (after recycling), 98% ee; (e) DIBALH, $CH_2Cl_2$, toluene, −78 °C, 70%.

the desired racemic seven-membered lactone (±)-**15**. This lactone underwent kinetic resolution using Bringmann's method[7a,b] to provide the desired lactone (+)-**15** in a 45% yield (out of a possible 50%) with 98% ee as determined by chiral HPLC.

The undesired diol (−)-**19** was recycled by first oxidizing to the dialdehyde with Dess−Martin's reagent[19] (eq 1). After the dialdehyde was heated in acid to racemize the material, (±)-**16** was again subjected to the Cannizarro/DCC conditions, providing racemic lactone (±)-**15** in a 60% yield. Repeating this process increased the overall yield of enantiomerically enriched lactone to 61% (98% ee).




(a) Dess-Martin periodinane, $CH_2Cl_2$ (b) AcOH, reflux, 24 h (c) i. KOH, EtOH, reflux, 1.5 h. ii. DCC, DMAP, $CH_2Cl_2$, 60%

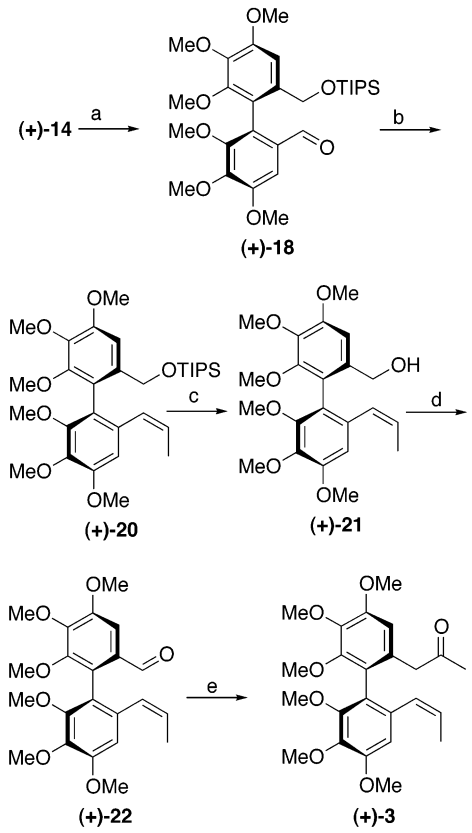
DIBALH reduction of the enantiomerically enriched lactone at −78 °C revealed aldehyde (+)-**14** (Scheme 5). Using ethyltriphenylphosphonium bromide, aldehyde (+)-**14** was then converted to the desired (*Z*)-propenyl

(17) (a) Ziegler, F. E.; Chliwner, I.; Fowler, K.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. (b) Fanta, P. E. *Synthesis* **1974**, 9. (c) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762.

(18) (a) Abbaszadeh, M. R.; Bowden, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2081. (b) Kobayashi, S.; Kihara, M.; Hashimoto, T.; Shingu, T. *Chem. Pharm. Bull.* **1976**, *24*, 716. (c) Kobayashi, S.; Mineo, S.; Kihara, M.; Tagashira, S. *Chem. Pharm. Bull.* **1976**, *24*, 2191. (d) Kobayashi, S.; Senoo, F.; Kihara, M.; Sakata, K.; Miura, A. *Chem. Pharm. Bull.* **1971**, *19*, 1262.

(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

**SCHEME 6**[a]

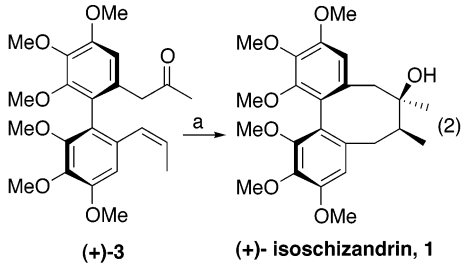



[a] Reagents and conditions: (a) TIPSCl, $CH_2Cl_2$, DMAP, imidazole, 98%; (b) ethyltriphenylphosphonium bromide, KHMDS, THF, −78 °C, 85% (4:1 *Z*/*E*); (c) TBAF, THF, 91%; (d) Dess−Martin periodinane, $CH_2Cl_2$, 90%; (e) (i) (α-methoxyethyl)triphenylphosphonium chloride, *n*-BuLi, THF; (ii) *p*-TsOH, THF, 0 °C, 54%.

fragment via a Wittig reaction in a 2:1 *Z*/*E* ratio (Scheme 6). After several protecting group strategies were tested, the TIPS ether improved the *Z*/*E* selectivity to 4:1 (85% yield), and also enabled the geometric isomer ratio to be more easily enriched to >10:1 (35% yield) via MPLC. The enriched material was then carried through to the end of the synthesis. After the TIPS group was removed using TBAF, benzyl alcohol (+)-**21** was then oxidized using Dess−Martin periodinane to provide unsaturated aldehyde (+)-**22**. Treatment of aldehyde (+)-**22** with the ylide derived from (α-methoxyethyl)triphenylphosphonium chloride[20] afforded an enol ether that was carefully hydrolyzed to alkenyl ketone (+)-**3**.

With the desired substrate in hand, ketoolefin **3** was treated with 2.2 equiv of samarium(II) iodide and HMPA[21] in THF along with 2 equiv of *t*-BuOH (eq 2). The natural product was obtained with a dr >18:1 and with no loss of ee (98%). The identity of the target compound was confirmed by comparison with reported analytical data.[1d]

There are several important factors that contribute to the high yield and selectivity of the samarium(II) iodide-promoted coupling. In terms of the yield, we have alluded previously to the favorable SOMO/LUMO interactions

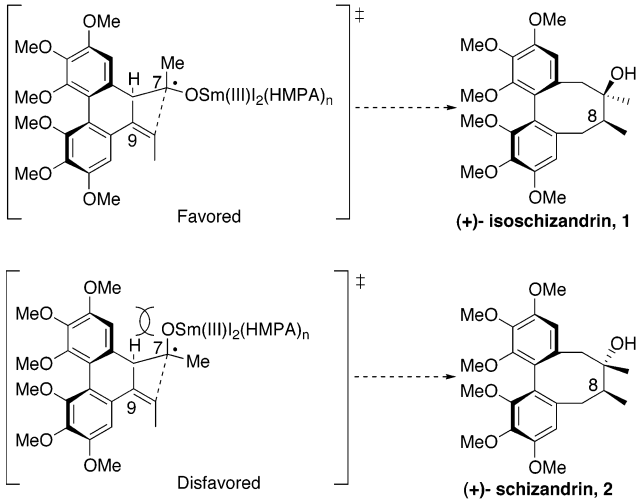



a. 2.2 equiv $SmI_2$, 2 equiv *t*-BuOH, THF/HMPA, 85%

engendered by an aryl unit on the olefin. Additionally, the biaryl motif likely enhances the rate of 8-endo cyclization by partially ordering at least four of the ring's eight carbons, thereby reducing the entropic demand on the reaction and further enhancing ring closure.

Access to the correct relative stereochemistry of isoschizandrin is realized through three separate stereochemical control elements (Scheme 7). First, the stereo-

**SCHEME 7**




chemistry at C-8 is set by the (*Z*)-olefin geometry, which was obtained via a standard Wittig reaction. Conformational restrictions placed on dibenzocyclooctadiene ring systems are generally restricted to the twist-boat-chair (TBC) and the twist-boat (TB) limiting conformations.[22] The stereodefined (*Z*)-alkene excludes the TB structure. We therefore expected carbons 6−9 to assume the chair-like transition-state geometry of the TBC conformation.

The second source of stereochemical control is a result of the alkoxysamarium moiety assuming a pseudoequatorial orientation. Scheme 7 depicts how the alkoxysamarium(III) substituent of the slightly pyramidalized[23] ketyl radical anion at C-7 may take on either a pseudoaxial or a pseudoequatorial orientation. Tight coordination of the ketyl oxygen to the Sm(III) species, adorned with up to four HMPA ligands in its coordination sphere,[24] is more sterically imposing than that of the

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(21) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (b) Otsubo, K.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1487.

(22) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(23) (a) Davies, A. G.; Neville, A. G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 163. (b) Russell, G. A.; Stevenson, G. R. *J. Am. Chem. Soc.* **1971**, *93*, 2432. (c) Bennett, J. E.; Mile, B. *J. Chem. Soc. A* **1968**, 298. (d) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1986**, *114*, 1656. (e) Novoa, J. *Can. J. Chem.* **1986**, *64*, 2359.

methyl group to the pseudoaxial hydrogen at C-9 and to the pendant aromatic ring.

Third, the diastereotopic facial selectivity between the olefin and the ketyl is determined by the biaryl stereochemistry. This stereocontrol element, set earlier via a kinetic resolution of racemic lactone (±)-**15**, provided an enantiomerically enriched atropisomer (98% ee) that was carried throughout the synthesis without loss of stereochemical integrity.

## Conclusion

The present synthesis illustrates in another format the potential for the samarium(II) iodide-promoted reductive coupling to achieve rapid and efficient access to the dibenzocyclooctadiene lignans. Specifically, a stereocontrolled 8-endo ketyl−olefin coupling produced (+)-isoschizandrin (**1**) in good yield with excellent stereo- and regioselectivity. Samarium diiodide is often featured as a mild, chemoselective reagent for simple functional group transformations employing complex substrates.[25] Therefore, the flexibility in the 8-endo cyclization introduced by varying the olefin substitution can be applied to the construction of many eight-membered ring-containing natural products, creating the rings and installing the attendant functionality stereoselectively in a single synthetic operation.

## Experimental Section

**Synthesis of (+)-Isoschizandrin.**

**2-Bromo-3,4,5-trimethoxybenzaldehyde (17).** To a solution of 3,4,5-trimethoxybenzaldehyde (50.0 g, 254 mmol) in $CHCl_3$ (500 mL) was added *N*-bromosuccinimide (54.43 g, 305.8 mmol). The solution was heated at reflux for 3 h. After the reaction was complete by TLC and cooled to rt, the solution was washed with water and extracted with $Et_2O$. The combined extracts were dried with $MgSO_4$ and concentrated. The bromoaldehyde was recrystallized in two crops from hexanes and $Et_2O$ to give 67 g (96%) of the white solid: $R_f = 0.6$ (30% EtOAc in hexanes); mp 70−71 °C (lit.[26] mp 70.5−71.5 °C); IR (film) 2940, 2844, 2750, 1688, 1586, 1481, 672 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 10.15 (s, 1H), 7.18 (s, 1H), 3.88 (s, 3H), 3.81 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.4, 152.7, 150.5, 148.4, 128.5, 115.2, 107.2, 60.9, 60.8, 55.9; HRMS *m*/*z* calcd for $(C_{10}H_{11}BrO_4 + Na)^+$ 296.9738, found 296.9769. Anal. Calcd for $C_{10}H_{11}BrO_4$: C, 43.66; H, 4.03. Found: C, 43.80, H, 4.15.

**(±)-4,4′,5,5′,6,6′-Hexamethoxy-1,1′-biphenyl-2,2′-dicarbaldehyde (16).** Bromoaldehyde **17** (17.1 g, 62.1 mmol) was dissolved in degassed DMF (50 mL) and treated with activated copper[27] (15.78 g, 248.6 mmol) under $N_2$ at 100 °C for 3 h and then heated at reflux for 18 h. After the mixture had cooled to rt, the copper was filtered off and water was added. The products were extracted with $Et_2O$, and the combined ether extracts were washed with water and then a saturated NaCl solution, dried with $Na_2SO_4$, and concentrated. The resulting solid was purified via flash chromatography (30% EtOAc in hexanes) to give 9.01 g (74%) of a white solid: $R_f = 0.3$ (30% EtOAc in hexanes); mp 124−126 °C (lit.[28] mp 128 °C); IR (film) 3080, 2976, 2943, 2868, 1694, 1578, 1471 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.57 (s, 2H), 7.38 (s, 2H), 3.96 (s, 6H), 3.96 (s, 6H), 3.08 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.0, 153.8, 151.5, 147.2, 130.4, 124.3, 105.6, 61.0, 60.6, 56.0; HRMS *m*/*z* calcd for $(C_{20}H_{22}O_8 + Na)^+$ 413.1212, found 413.1222. Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.38; H, 5.52.

**(±)-1,2,3,9,10,11-Hexamethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one [(±)-15].** A solution of dialdehyde **16** (1.00 g, 2.62 mmol) in EtOH (131 mL, 0.020 M) was treated with KOH (4.86 g, 86.7 mmol) and heated at reflux for 1.5 h. The solvent was removed in vacuo, $H_2O$ was added, and the mixture was acidified with 2 N HCl. Extraction with $CH_2Cl_2$, drying with $Na_2SO_4$, and concentrating the material afforded the corresponding hydroxy acid as a white solid, which was used without purification for the next step. The hydroxy acid was dissolved in $CH_2Cl_2$ (200 mL) together with DMAP (0.64 g, 5.2 mmol) and DCC (0.81 g, 3.9 mmol) and was stirred for 6 h at rt under $N_2$. The solution was then washed with $H_2O$ and then brine and was subsequently dried and concentrated. The residue was purified via flash chromatography (40% EtOAc in hexanes) to yield racemic lactone (0.649 g, 63%) as a yellow solid: $R_f = 0.35$ (50% EtOAc in hexanes); mp 155−157 °C; IR (film) 2942, 2837, 2251, 1716, 1593, 1487 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.14 (s, 1H), 6.74 (s, 1H), 4.94−4.76 (AB, $J$ = 11.9 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.71 (s, 3H), 3.65 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 169.7, 153.3, 153.2, 152.9, 151.3, 144.9, 142.9, 131.3, 126.6, 121.3, 120.8, 108.5, 106.9, 69.7, 61.1, 61.0, 60.8, 60.8, 56.0; HRMS *m*/*z* calcd for $(C_{20}H_{22}O_8 + Na)^+$ 413.1212, found 413.1209. Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.35; H, 5.52.

**Kinetic Resolution of *rac*-1,2,3,9,10,11-Hexamethoxy-7*H*-dibenzo[*c*,*e*]oxepin-5-one [(+)-15].** To a solution of (*R*)-2-methyl-CBS-oxazaborolidine (4.5 mL of a 1 M solution in toluene, 4.5 mmol) in THF (45 mL) at 0 °C under argon was added $BH_3$·THF (6.0 mL of a 1 M solution, 6.0 mmol). After being stirred for 30 min at rt, the solution was cooled to −20 °C and added dropwise over 5−10 min to a solution of lactone (±)-**15** (0.585 g, 1.5 mmol) in THF (40 mL) at −20 °C. After 3 h, the mixture was hydrolyzed by careful addition of $H_2O$ and acidified with 2 N HCl. After removal of the organic solvent in vacuo, the mixture was extracted with $CH_2Cl_2$. The organic phase was dried with $Na_2SO_4$, the solvent was removed in vacuo, and the residue was purified via column chromatography to afford lactone (*R*)-(+)-**15** (0.250 g, 43%, 98% ee) and diol (*S*)-(−)-**19** (0.280 g, 47%, 88% ee). The diol could be recycled by a two-step procedure involving oxidation with Dess−Martin's reagent to the dialdehyde and heating at reflux in acetic acid for 24 h. The resulting dialdehyde was then treated again in the Cannizzaro and DCC coupling conditions to provide racemic lactone (0.080 g, 46%) and diol (0.091 g, 53%). Repeating this process provided a combined total of 0.357 g (61%) of the enriched lactone: $[\alpha]^{25}_D$ +3.39 (*c* 6.44, $CHCl_3$). The physical[3] and HPLC[29] data for diol (*S*)-(−)-**19** have been reported.

**(+)-(*R*)-6′-Hydroxymethyl-4,5,6,2′,3′,4′-hexamethoxybiphenyl-2-carbaldehyde [(+)-14].** The enantio-enriched lactone (+)-**15** (0.728 g, 1.86 mmol) was dissolved in $CH_2Cl_2$ (3 mL) and toluene (9 mL) and cooled to −78 °C. A 1.36 mL sample of a 1.5 M solution of DIBALH in toluene (2.05 mmol) was then added to the solution in one swift addition. The mixture was stirred for 20 min at −78 °C, then quenched with

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MeOH (10 mL), and allowed to warm to rt. The material was filtered, concentrated and purified via chromatography (40% EtOAc in hexanes) to give 0.513 g (70%) of material: $R_f = 0.3$ (50% EtOAc in hexanes); $[\alpha]^{28}_D$ +21.9 (*c* 4.54, $CHCl_3$); IR (film) 3500, 2938, 2847, 2751, 2250, 1685, 1588, 1482 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.52 (s, 1H), 7.35 (s 1H), 6.90 (s, 1H), 4.23−4.21 (m, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.63 (s, 3H), 3.60 (s, 3H), 2.55 (bs, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.8, 153.8, 153.2, 151.5, 150.9, 147.5, 141.1, 135.8, 129.9, 127.8, 117.8, 107.7, 105.5, 63.5, 61.0, 60.9, 60.7, 60.5, 56.0, 55.8; HRMS *m/z* calcd for $(C_{20}H_{24}O_8 + Na)^+$ 415.1369, found 415.1361.

**(+)-(*R*)-4,5,6,2′,3′,4′-Hexamethoxy-6′-(triisopropylsilanyloxymethyl)biphenyl-2-carbaldehyde [(+)-18].** To a solution of hydroxy aldehyde (+)-**14** (0.504 g, 1.28 mmol) in $CH_2Cl_2$ (13 mL, 0.10 M) were added DMAP (0.023 g, 0.15 mmol), imidazole (0.130 g, 0.192 mmol), and TIPSCl (0.271 g, 1.41 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred under $N_2$ for 2 h. The reaction was quenched with $H_2O$, washed with brine, dried with $Na_2SO_4$, and concentrated. After purification via radial chromatography (20% EtOAc in hexanes), 0.609 g (98%) of the silyl ether was obtained as an oil: $R_f = 0.3$ (20% EtOAc in hexanes); $[\alpha]^{27}_D$ +16.2 (*c* 4.66, $CHCl_3$); IR (film) 2941, 2892, 2865, 2748, 2604, 1964, 1681, 1588, 1481 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.48 (s, 1H), 7.31 (s, 1H), 7.05 (s, 1H), 4.46 (d, $J = 13.5$ Hz, 1H)), 4.24 (d, $J = 13.5$ Hz, 1H), 3.90 (s, 6H), 3.87 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 0.99 (s, 18H), 0.97 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.0, 153.4, 153.0, 151.2, 151.1, 147.4, 140.1, 136.3, 129.6, 127.7, 116.1, 105.1, 104.8, 62.8, 60.7, 60.6, 60.5, 60.3, 55.8, 55.5, 17.7, 12.1, 11.7; HRMS *m/z* calcd for $(C_{29}H_{44}O_8Si + Na)^+$ 571.2703, found 571.2687.

**(+)-(*R*)-(4,5,6,2′,3′,4′-Hexamethoxy-6′-[(*Z*)-propenyl]biphenyl-2-ylmethoxy)triisopropylsilane [(+)-20].** To a suspension of ethyltriphenylphosphonium bromide (1.21 g, 3.23 mmol) in 30 mL of freshly distilled THF at 0 °C under $N_2$ was added via syringe KHMDS (6.56 mL of a 0.5 M solution in toluene, 3.23 mmol). The resulting orange solution was allowed to stir at 0 °C for 30 min. The ylide solution was then cooled to −78 °C, and a solution of the aldehyde (+)-**18** (0.600 g, 1.09 mmol) in 30 mL of THF was added dropwise. The reaction was stirred at −78 °C and then slowly warmed to rt. The reaction was then quenched with cold MeOH, extracted with EtOAc, dried with $Na_2SO_4$, and concentrated. The crude reaction provided 0.520 g (85%) of a 4:1 mixture of *Z*/*E* olefins. After column chromatography via flash MPLC, 0.327 g (54%) of a >10:1 *Z*/*E* mixture was obtained. This sample was carried through the rest of the synthesis: $R_f = 0.3$ (20% EtOAc in hexanes); $[\alpha]^{26}_D$ +39.9 (*c* 4.07, $CHCl_3$); IR (film) 2940, 2892, 2865, 2716, 1593, 1562, 1483 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.09 (s, 1H), 6.71 (s, 1H), 5.93 (d, $J = 11.6$ Hz, 1H), 5.55 (dq, $J = 11.5$, 6.9 Hz, 1H), 4.36−4.25 (AB, $J = 14.0$ Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 1.83 (d, $J = 6.6$ Hz, 3H), 1.00 (s, 18H), 0.99 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 152.7, 151.9, 151.3, 150.8, 140.9, 140.0, 135.9, 132.0, 128.8, 125.7, 122.2, 119.7, 108.4, 104.3, 62.5, 60.7, 60.6, 60.3, 60.2, 55.8, 55.5, 17.8, 14.4, 11.8; HRMS *m/z* calcd for $(C_{31}H_{48}O_7Si + Na)^+$ 583.3067, found 583.3096.

**(+)-(*R*)-(4,5,6,2′,3′,4′-Hexamethoxy-6′-[(*Z*)-propenyl]biphenyl-2-yl)methanol [(+)-21].** To a solution of the silyl ether (+)-**20** (0.117 g, 0.208 mmol) in THF (2 mL) at 0 °C was added TBAF (0.260 mL of a 1 M solution in THF, 0.260 mmol). The reaction was stirred under $N_2$ and was warmed to rt over 1−2 h. The reaction was quenched with $H_2O$ and extracted with $Et_2O$. The combined organic extracts were washed with brine, dried with $Na_2SO_4$, and concentrated. After purification via column chromatography (30% EtOAc in hexanes), 0.076 g (91%) of benzyl alcohol was obtained as an oil: $R_f = 0.2$ (40% EtOAc in hexanes); $[\alpha]^{26}_D$ +20.0 (*c* 3.92, $CHCl_3$); IR (film) 3494, 2937, 2838, 1540, 1483 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.82 (s, 1H), 6.69 (s, 1H), 5.88−5.85 (dq, $J = 11.5$, 1.69 Hz, 1H), 5.49−5.48 (dq, $J = 11.7$, 6.98 Hz, 1H), 4.10 (s, 2H), 3.83 (s, 9H), 3.79 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H), 2.57 (br s, 1H), 1.77−1.76 (d, $J = 7.08$, 1.72 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 152.8, 151.9, 151.08, 151.03, 141.0, 140.7, 135.1, 132.2, 128.8, 125.9, 122.5, 121.5, 108.6, 106.8, 63.2, 60.6, 60.49, 60.40, 60.1, 55.7, 55.5, 14.2; HRMS *m/z* calcd for $(C_{22}H_{28}O_7 + Na)^+$ 427.1733, found 427.1733.

**(+)-(*R*)-4,5,6,2′,3′,4′-Hexamethoxy-6′-[(*Z*)-propenyl]biphenyl-2-carbaldehyde [(+)-22].** To a solution of the benzyl alcohol (+)-**21** (0.1058 g, 0.261 mmol) in $CH_2Cl_2$ (3 mL) was added 0.166 g (0.391 mmol) of Dess−Martin reagent at 0 °C under $N_2$. The mixture was warmed to rt and was monitored for completion via TLC. After 2 h, the mixture was diluted with $Et_2O$ and poured into a 1:1 mixture of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ (1.5 M). The mixture was stirred until the ether layer was clear. The organic layer was then separated, washed with brine, dried with $Na_2SO_4$, and concentrated to give 0.0945 g (90%) of the desired aldehyde: $R_f = 0.3$ (EtOAc in hexanes); mp 116−119 °C; $[\alpha]^{26}_D$ +66.86 (*c* 1.895, $CHCl_3$); IR (film) 2938, 2844, 1733, 1635, 1588, 1483 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.41 (s, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 5.81−5.79 (dq, $J = 11.5$, 1.7 Hz, 1H), 5.50−5.46 (dq, $J = 11.4$, 6.99 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.59 (s, 3H), 3.57 (s, 3H), 1.70−1.69 (d, $J = 6.96$, 1.7 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.9, 152.9, 152.7, 151.8, 151.2, 147.3, 140.6, 132.9, 129.6, 129.0, 128.6, 126.8, 119.0, 108.2, 104.5, 60.69, 60.66, 60.38, 60.35, 55.78, 55.76, 14.19; HRMS *m/z* calcd for $(C_{22}H_{26}O_7 + Na)^+$ 425.1576, found 425.1583. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.44; H, 6.43.

**(+)-(*R*)-2-(2′-Oxopropyl-4,5,6-trimethoxy-2′-[(*Z*)-propenyl]-3′,4′,5′-trimethoxybiphenyl [(+)-3].** A suspension of 0.58 g (1.4 mmol) of (α-methoxyethyl)triphenylphosphonium chloride in 2.5 mL of THF was cooled to −78 °C under argon, and *n*-BuLi (0.90 mL of a 1.6 M solution in hexanes, 1.44 mmol) was added dropwise, giving a characteristic red color that persisted after 30 min of stirring at −78 °C. Aldehyde (+)-**22** (0.058 g, 0.14 mmol) in THF (2.0 mL) was then added at −78 °C to the ylide mixture, and the resulting suspension was stirred for 3 h at −78 °C. The reaction was quenched with $H_2O$ and extracted with $Et_2O$. The combined organic extracts were concentrated to give the crude enol ether. A catalytic amount of *p*-TsOH (1 crystal) was added to the crude enol ether in THF (2 mL) at 0 °C, and the mixture was stirred for 30 min. The reaction was then quenched with water and extracted with $Et_2O$. The organic extracts were dried with $Na_2SO_4$, concentrated, and purified via radial chromatography (40% EtOAc in hexanes) to give 0.033 g (54%) of ketoolefin: $R_f = 0.2$ (30% EtOAc in hexanes); IR (film) 2937, 2847, 1712, 1592, 1483 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.72 (s, 1H), 6.53 (s, 1H), 5.88 (dq, $J = 11.7$, 1.8 Hz, 1H), 5.55 (dq, $J = 11.7$, 7.1 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.67 (s, 3H), 3.62 (s, 3H), 3.28 (AB, $J = 10.3$ Hz, 2H), 1.91 (s, 3H), 1.84 (dd, $J = 7.1$, 1.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 206.7, 152.7, 152.2, 151.6, 132.4, 129.4, 128.9, 128.8, 126.6, 126.1, 123.6, 122.9, 108.5, 108.3, 60.8, 60.7, 60.6, 60.4, 55.9, 55.8, 47.9, 29.5, 14.5; HRMS *m/z* calcd for $(C_{24}H_{30}O_7 + Na)^+$ 453.1889, found 453.1875.

**(+)-Isoschizandrin (1).** A solution of samarium(II) iodide was generated by adding $CH_2I_2$ (0.084 g, 0.31 mmol) to a slurry of samarium metal (0.048 g, 0.32 mmol) in THF (3 mL). After the solution was stirred overnight, HMPA (0.500 mL) was added followed by the dropwise addition of ketoolefin (+)-**3** (0.027 g, 0.063 mmol) and *t*-BuOH (9 mg, 0.125 mmol) in THF (12 mL) via syringe pump over 2 h. Two hours after the addition was complete, the reaction was quenched with aqueous $NaHCO_3$, concentrated, and extracted with EtOAc. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated. The residue was purified via radial chromatography (40% EtOAc in hexanes) to give the natural product as

a white foam (0.023 g, 85%) contaminated with <5% of diastereomers. Purification by preparative HPLC [hexane/*i*-PrOH (97:3, 10.0 mL/min)] was used to remove the minor diastereomers. This revealed that the natural product was formed with 98% enantiomeric excess by chiral HPLC: $R_f$ = 0.2 (50% EtOAc in hexanes); $[\alpha]^{25}_D$ +112.0 (*c* 0.400, $CHCl_3$), {lit.[1d] $[\alpha]^{24}_D$ +110.5 (*c* 0.405, $CHCl_3$)}; IR (film) 3476, 2934, 1596, 1489 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.59 (s, 1H), 6.52 (s, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H), 3.53 (s, 3H), 2.81 (d, $J$ = 13 Hz, 1H), 2.54−2.47 (m, 2H), 2.31 (d, $J$ = 13 Hz, 1H), 1.88−1.86 (m, 1H), 1.53 (bs, 1H, OH), 1.17 (s, 3H), 0.87 (d, $J$ = 7.5, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 152.0, 151.79, 151.73, 151.6, 140.4, 140.3, 133.5, 123.3, 122.8, 110.5, 110.3, 74.0, 60.95, 60.92, 60.58, 60.55, 60.3, 55.9, 42.1, 40.7, 35.3, 29.2, 13.5; HRMS *m*/*z* calcd for $(C_{24}H_{32}O_7 + Na)^+$ 455.2045, found 455.2029.

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**Supporting Information Available:** Experimental details and structural data for all new compounds not described within the text, as well as X-ray structure data for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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