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Asymmetric Total Synthesis of Dibenzocyclooctadiene Lignan Natural Products

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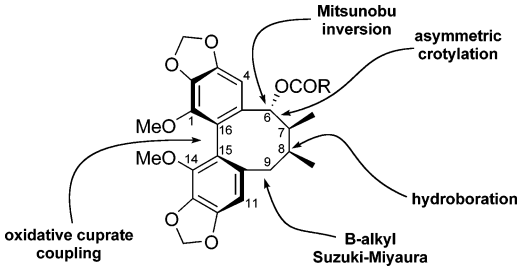

Full details of the asymmetric total syntheses of the dibenzocyclooctadiene lignans interiotherin A, angeloylgomisin R, gomisin O, and gomisin E (epigomisin O) are presented. The syntheses were based on a unified synthetic strategy involving a novel crotylation using the Leighton auxiliary that occurred with excellent asymmetric induction (>98:2 enantiomeric ratio), a diastereoselective hydroboration/Suzuki−Miyaura coupling reaction sequence, and an atropdiastereoselective biaryl-cuprate coupling, both of which occurred with total (>20:1) stereocontrol. The syntheses were achieved in six to eight steps from simple aromatic precursors.

Introduction

Lignans are a class of naturally occurring plant phenols that formally arise biosynthetically from two cinnamic acid (phenylpropanoid) residues,[1] as defined originally by Howarth in 1936.[2] Typically, the aromatic rings are highly oxygenated and often fused to additional carbocyclic or oxygen heterocyclic rings. Lignans are found in all parts of producing plants, including the roots, stems, leaves, fruit, and seeds, and they exhibit a wide range of biological activities. These natural products have been used medicinally for thousands of years. In many cases, the active principle of lignan-based traditional medicines is not known, and a detailed study of the active principles may provide useful leads in the development of new pharmaceutical agents.

A typical lignan carbon framework is formed by the β,β-union of two cinnamic acids (Figure 1). Further modification by biaryl bond formation gives the dibenzocyclooctadiene framework by a free-radical process first proposed by Erdtmann in 1933.[3] The biosynthetic pathways are well established[1] and give rise to a remarkably diverse set of structures. Many highly modified systems are known. Lignans of the dibenzocyclooctadiene family are widely occurring, and the first examples were isolated from the seeds of *Schizandra chinensis* in 1961.[4] This and a related species, *Kadsura coccinea*, produce a variety of biologically active dibenzocyclooctadienes such as schizandrol. Both of these plants are used in traditional

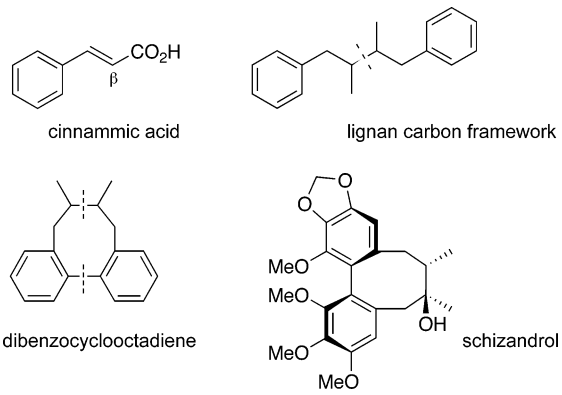

FIGURE 1. Biosynthetic considerations in the lignan family of plant natural products.

(1) *Lignans: Chemical, Biological and Clinical Properties*; Ayers, D. C., Loike, J. D., Ed.; University Press: Cambridge, 1990.
(2) Howarth, R. D. *Ann. Rep. Prog. Chem.* **1936**, *33*, 266.
(3) Erdtmann, H. *Leibigs Ann. Chem.* **1933**, *503*, 283.
(4) Kochetkov, N. K.; Khorlin, A.; Chizhov, O. S.; Sheichenko, V. I. *Tetrahedron Lett.* **1961**, *2*, 730.

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Chinese medicine and are listed in the Pharmacopoeia of the Peoples Republic of China. Dibenzocyclooctadiene lignans exhibit a wide variety of interesting biological activities,[5] including antiviral,[6] anticancer,[7] antiinflammatory,[8] and hepatoprotective effects.[9]

The best-studied lignan is podophylotoxin, and many of its derivatives exhibit strong antiviral activity against herpes simplex virus (nM MIC values).[10] Gomisin J and derived dibenzocyclooctadiene lignans are reported to have effective anti-HIV activity at sub-micromolar levels via inhibition of reverse transcriptase,[11] and schisantherin D and kadsuranin showed similarly effective anti-HIV activity.[12] Etoposide and teniposide are semisynthetic derivatives of podophylotoxin that are used for the treatment of small-cell lung cancer, testicular cancer, lymphoma, and lymphocytic leukemia. These compounds are good examples of the value of exploring traditional medicines for lead compounds and of the successful development of effective anticancer agents from plant natural products.

The first total syntheses of the dibenzocyclooctadienes steganone and steganacin were reported almost 30 years ago by Kende[13] and Raphael,[14] respectively, and Koga and co-workers more recently reported the asymmetric total synthesis of steganacin[15] and reported on structure−cytotoxicity relationships for this natural product.[16,17] An important step in the construction of the dibenzocyclooctadiene ring system is installation of the stereogenic axis. In Meyers' synthesis of (−)-schizandrin,[18] the stereogenic axis was set with 6.2:1 diastereoselection using their oxazoline/Grignard strategy, an auxiliary-based diastereoselective reaction. The absolute configuration of the axis was subsequently used to control introduction of the remaining stereogenic centers. In a report by Motherwell and co-workers on the synthesis of steganone-like systems,[19] substrate control was used with side-chain stereogenic centers controlling the sense of induction in the stereogenic axis. The level of diastereoinduction was not reported, but the correct stereoisomer was isolated in low yield. In a contribution to this area on the synthesis of (−)-steganone by Molander and co-workers,[20] diastereoselective Suzuki coupling of an arylboronic acid and Uemura's bromoaryl chromium tricarbonyl complex initially afforded the wrong atropdiastereomer, which epimerized during the reaction to the correct atropisomer, but a late-stage epimerization of the side-chain stereogenic center re-epimerized the stereogenic axis. In a more recent contribution by this group,[21] (+)-isoschizandrin was constructed in 12 steps using a diastereoselective SmI_2-promoted 8-endo closure of the cyclooctadiene ring; the stereogenic biaryl axis was introduced using the kinetic resolution method of Bringmann.[22]

A recent report described the isolation of interiotherin A from the stems of *Kadsura interior*,[23] a vine of the *Schisandraceae* family native to southern China. This group subsequently reported the isolation of the more highly modified lignans interiotherins C and D.[24] The interiotherins inhibit the replication of HIV at μg/mL levels. Interiotherin A is closely related to angeloylgomisin R (**2**).[25] Gomisin O, a prototypical dibenzocyclooctadiene lignan, was isolated from *Schizandra chinensis* along with a number of congeners, including the epimeric gomisin E (epigomisin O).[26] Herein, we report full details of the total synthesis of the dibenzocyclooctadiene lignans interiotherin A (**1**) and angeloylgomisin R (**2**)[27] and the total syntheses of gomisin O (**3**) and gomisin E (epigomisin O) (**4**) (Figure 2). The three stereogenic centers present on the eight-membered ring and the stereogenic biaryl axis are introduced with complete control of absolute and relative stereochemistry.

Results and Discussion

In our retrosynthetic analysis (Scheme 1), three critical bond construction events must be developed for the

(5) Charlton, J. L. *J. Nat. Prod.* **1998**, *61*, 1447.
(6) (a) Fujihashi, T.; Hara, H.; Sakata, T.; Mori, K.; Higuchi, H.; Tanaka, A.; Kaji, H.; Kaji, A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2000. (b) Chen, D.-F.; Zhang, S.-X.; Chen, K.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *J. Nat. Prod.* **1996**, *59*, 1066. (c) Chen, D.-F.; Zhang, S.-X.; Xie, L.; Xie, J.-X.; Chen, K.; Kashiwada, Y.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, *5*, 1715. (d) Lee, K.-H. *J. Nat. Prod.* **2004**, *67*, 273.
(7) (a) Yasukawa, K.; Ikeya, Y.; Mitsuhashi, H.; Iwasaki, M.; Aburada, M.; Nakagawa, S.; Takeuchi, M.; Takido, M. *Oncology* **1992**, *49*, 68. (b) Kuo, Y.-H.; Kuo, L.-M. Y.; Chen, C.-F. *J. Org. Chem.* **1997**, *62*, 3242. (c) Kuo, Y.-H.; Huang, H.-C.; Kuo, L.-M. Y.; Chen, C.-F. *J. Org. Chem.* **1999**, *64*, 7023.
(8) Wang, J. P.; Raung, S. L.; Hsu, M. F.; Chen, C. C. *Br. J. Pharmacol.* **1994**, *113*, 945.
(9) (a) Hikino, H.; Kiso, Y.; Taguchi, H.; Ikeya, Y. *Planta Med.* **1984**, *50*, 213. (b) Kiso, Y.; Tohkin, M.; Hikino, H.; Ikeya, Y.; Taguchi, H. *Planta Med.* **1985**, *51*, 331. (c) Yamada, S.; Murawaki, Y.; Kawasaki, H. *Biochem. Pharmacol.* **1993**, *46*, 1081. (d) Ko, K. M.; Ip, S. P.; Poon, M. K. T.; Wu, S. S.; Che, C. T.; Ng, K. H.; Kong, T. C. *Planta Med.* **1995**, *61*, 134.
(10) Markkanen, T.; Makinen, M. L.; Maunuksela, E.; Himanen, P. *Drugs Exptl. Clin. Res.* **1981**, *7*, 711.
(11) Fujihashi, T.; Hara, H.; Sakata, T.; Mori, K.; Higuchi, H.; Tanaka, A.; Kaji, H.; Kaji, A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2000.
(12) Chen, D.-F.; Zhang, S.-X.; Xie, L.; Xie, J.-X.; Chen, K.; Kashiwada, Y.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, 5, 1715.
(13) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267.
(14) Hughes, L. R.; Raphael, R. A. *Tetrahedron Lett.* **1976**, *17*, 1543.
(15) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303.
(16) Tomioka, K.; Ishiguro, T.; Mizuguchi, H.; Komeshima, N.; Koga, K.; Tsukagoshi, S.; Tsuruo, T.; Tashiro, T.; Tanida, S.; Kishi, T. *J. Med. Chem.* **1991**, *34*, 54.
(17) For other work in this area, see: (a) Takeya, T.; Yamaki, S.; Itoh, T.; Hosogai, H.; Tobinaga, S. *Chem. Pharm. Bull.* **1996**, *44*, 909. (b) Tanaka, M.; Mukaiyama, C.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *J. Org. Chem.* **1995**, *60*, 4339. (c) Takeya, T.; Ohguchi, A.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 438. (d) Takeya, T.; Ohguchi, A.; Ara, Y.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 430. (e) Takeya, T.; Ohguchi, A.; Ikeya, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 677. (f) Ishiguro, T.; Mizuguchi, H.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 609. (g) Tomioka, K.; Mizuguchi, H.; Koga, K. *Tetrahedron Lett.* **1979**, *20*, 1409.
(18) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.
(19) Bradley, A.; Motherwell, W. B.; Ujjainwalla, F. *Chem. Commun.* **1999**, *10*, 917.
(20) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52.
(21) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533.
(22) (a) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615. (b) Bringmann, G.; Breuning, M.; Pfeifer, R.-M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2002**, *661*, 31. (c) Bringmann, G.; Tasler, S.; Pfeifer, R.-M.; Breuning, M. *J. Organomet. Chem.* **2002**, *661*, 49.
(23) Chen, D.-F.; Zhang, S.-X.; Chen, K.; Zhou, B.-N.; Wang, P.; Consentino, L. M.; Lee, K.-H. *J. Nat. Prod.* **1996**, *59*, 1066.
(24) Chen, D.-F.; Zhang, S.-X.; Kozuka, M.; Sun, Q.-Z.; Feng, J.; Wang, Q.; Mukainaka, T.; Nobukuni, Y.; Tokuda, H.; Nishino, H.; Wang, H.-K.; Morris-Natschke, S. L.; Lee, K.-H. *J. Nat. Prod.* **2002**, *65*, 1242.
(25) Tan, R.; Li, L. N.; Fang, Q. *Planta Med.* **1984**, *50*, 414.
(26) Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2695.
(27) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2005**, *7*, 1849.

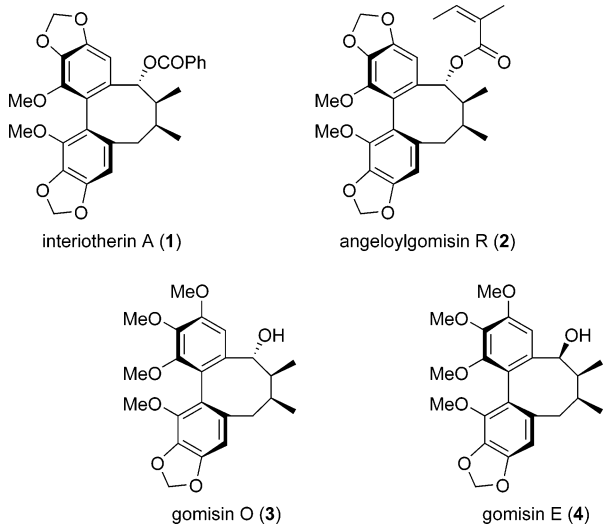
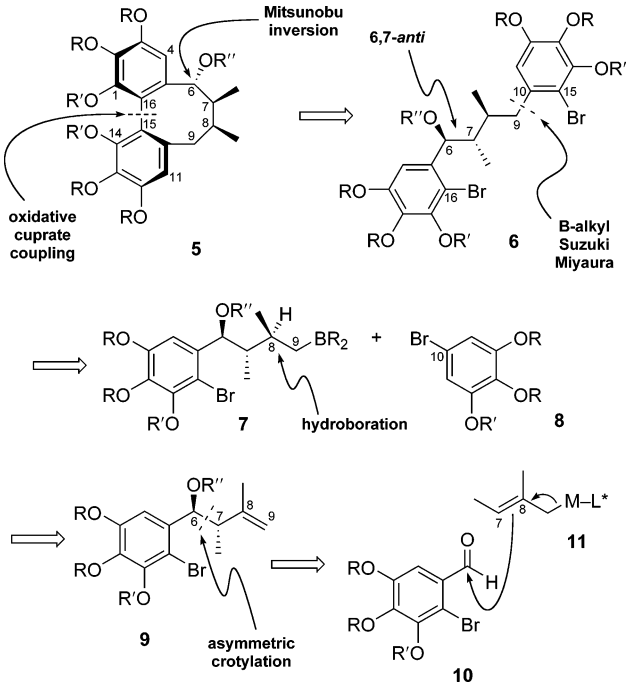


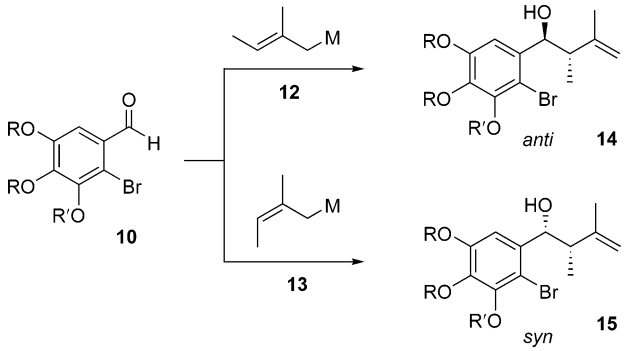
FIGURE 2. Dibenzocyclooctadiene natural product targets.

SCHEME 1



success of a stereocontrolled and synthetically efficient approach to this family of lignans. The C15/C16 stereogenic biaryl axis of prototype dibenzocyclooctadiene **5** is introduced with complete control of atropdiastereoselection using oxidative cuprate chemistry developed by Lipshutz.[28] The sense of stereoinduction in this reaction was dependent solely upon the configuration of the C6-stereogenic center of **6**, such that C6/C7-*anti* stereochemistry allows for complete stereocontrol of the newly formed axis. With respect to interiotherin A and gomisin R and O systems, typified by **5**, the relative configuration about the eight-membered ring is C6/C7-*trans*, C7/C8-*cis* and is introduced in a straightforward manner by use of the Mitsunobu inversion at C6. The C9−C10 bond of **6** is introduced concomitant with formation of the C8-stereogenic center using an $A^{1,3}$-controlled hydroboration[29] and in situ B-alkyl Suzuki−Miyaura reaction[30] sequence starting from alkene **9**, via trialkylborane **7**, which is coupled in situ with aryl bromide **8**. The key C6/C7 bond construction event is the enantioselective and diastereoselective production of alkene **9** by an asymmetric crotylation of aryl aldehyde **10** using chiral organometallic reagent **11**.

SCHEME 2



Successful implementation of this plan required solutions to three key synthetic objectives. First, methodology for asymmetric crotylation was required. There were no examples of the necessary substitution pattern of the tiglyl [(*E*)-2-methyl-2-buten-1-yl] organometallic reagent known. Second, diastereoselection in the hydroboration of the crotylated product needed to be established as this step sets the relative stereochemistry of the two methyl groups of the targets. We proposed that $A^{1,3}$ strain would control the facial selectivity of this reaction. Third, the ability to control the sense of atropisomerism about the stereogenic biaryl axis that is formed in the biaryl coupling reaction was difficult to predict *a priori*, although we had previously found that existing stereogenic centers exert a strong influence on this reaction.[31] In the end, we found solutions to all these problems, and the asymmetric synthesis of the targeted dibenzocyclooctadiene natural products was achieved with complete control of stereochemistry.

Diastereoselective Methylcrotylation of Aryl Aldehydes. The proposed asymmetric synthesis of dibenzocyclooctadiene lignans relied on the enantio- and diastereoselective crotylation of an oxygenated electron-rich aryl aldehyde (Scheme 2).[32] Given stereodefined allylic organometallic systems **12** [(*E*)-2-methyl-2-buten-1-yl (tiglyl)] and **13** [(*Z*)-2-methyl-2-buten-1-yl (angelyl)], synthesis of the *anti*-adduct **14** and *syn*-adduct **15** adduct

(28) (a) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161. (b) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276. (c) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815. (d) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567. (e) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1842.

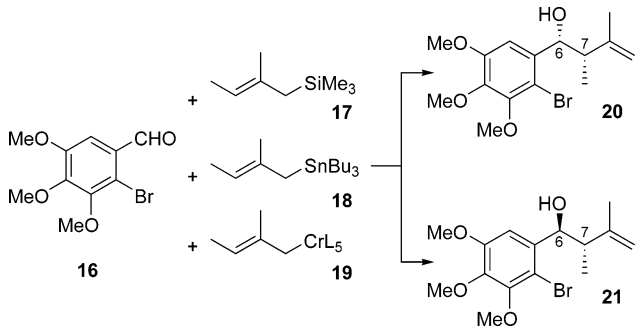
(29) (a) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629. (b) Coutts, L. D.; Cywin, C. L.; Kallmerten, J. *Synlett* **1993**, 696. (c) Bernsmann, H.; Fröhlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 4347. (d) Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983. (e) Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129.

(30) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(31) Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1994**, *116*, 8795. Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995**, *117*, 10889.

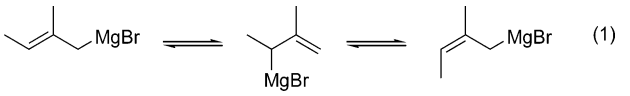
(32) Roush, W. R. Allylic Organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 1−53.

SCHEME 3



in diastereomerically and enantiomerically pure form should be possible.[33]

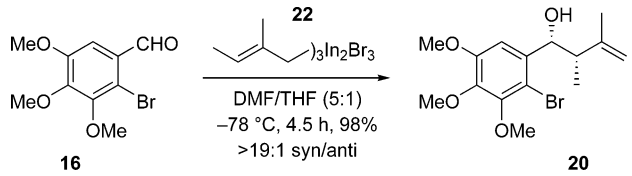
A nonobvious but precedented pitfall to this strategy is that precursor allylic organometallic reagents **12** and **13** (M = Mg, Li) undergo allylic equilibration,[34] giving rise to stereochemically scrambled crotylation reagents upon transmetalation (e.g., M = B, Sn, Si). This problem was patently obvious upon formation of the Grignard reagent **12** (M = MgBr) from the corresponding bromide (Scheme 2). This reagent failed to effect useful diastereoselection in the addition to aldehyde **10** owing to the rapidly equilibrating mixture of regioisomeric allylic isomers (eq 1).



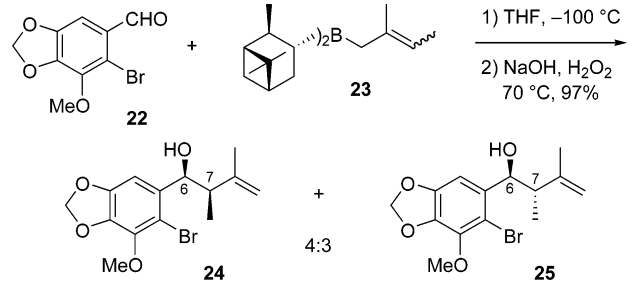
In efforts to surmount this equilibration problem, we examined silicon and tin (Scheme 3), which provide configurationally stable species.[35] Using 2-bromo-3,4,5-trimethoxybenzaldehyde (**16**),[36] Yamamoto CAB-catalyzed crotylsilylation[37] with tiglyltrimethylsilane (**17**) (CH_3CH_2CN, −10 °C, 3 h, 56%) afforded poor diastereoselectivity (1.5:1 *syn*/*anti* **20**/**21**) and the reaction of tiglyltributylstannane (**18**) in the presence of AgOTf/(*S*)-BINAP[38] (CH_2Cl_2, 25 °C, 24 h) or Ti/BINOL[39] (CH_2Cl_2, 25 °C, 18 h) failed to provide product.

The tiglylchromium reagent **19** (Scheme 3) prepared from tiglyl bromide and $CrCl_2$ in THF[40] underwent addition to aldehyde **16** (THF, −30 to +25 °C, 2 h, 69%) to afford a 13:87 ratio of *syn*/*anti* adducts **20** and **21**, respectively. Attempts to increase diastereoselectivity with lower reaction temperatures were unsuccessful because the tiglylchromium reagent was unreactive below −30 °C. Addition of stoichiometric menthol as a chiral auxiliary[41] provided no asymmetric induction and resulted in lowered yields, and this metal was not pursued.

SCHEME 4



SCHEME 5



Halogen−metal exchange of tiglyl bromide with indium in DMF afforded the tiglylindium reagent,[42] which proved highly effective in diastereoselective crotylation of aryl aldehydes (Scheme 4). At room temperature in DMF, reaction of this reagent with **16** afforded an 82% combined yield of products in a 2.5:1 ratio of *syn*- and *anti*-adducts **20** and **21**, respectively, which could be improved to 11:1 at −45 °C (85% combined yield) and to >19:1 in 5:1 DMF/THF at −78 °C (98%). The indium reagent generated in THF provided no diastereoselectivity in this addition reaction. Addition of a stoichiometric amount of (+)-cinchonidine[43] or (*S*)-BINAP (DMF/THF 5:1, −78 °C, 2 h) resulted only in decreased yield without effecting detectable asymmetric induction. Attempts at transmetalation from indium to boron using Ipc_2BX (X = Cl, OMe) were unsuccessful.

Enantioselective Methylcrotylation of Aryl Aldehydes. Starting from stereodefined tiglyl bromide, formation of the Grignard reagent and transmetalation from magnesium to boron occurred by treatment with (−)-Ipc_2-BCl to form the Brown diisopinocampheylborane reagent **23** (Scheme 5).[44] This reagent underwent quantitative addition to aldehyde **22**, although with little diastereoselectivity, to form a separable 4:3 mixture of (6*S*,7*R*)-*syn*-adduct **24** and (6*S*,7*S*)-*anti*-adduct **25** in 97% combined yield. These products were produced with good enantiomeric purity (90% ee), but with unacceptable

(33) (a) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(34) (a) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701. (b) Schlosser, M.; Hartman, J.; David, V. *Helv. Chim. Acta* **1974**, *57*, 1567. (c) Schlosser, M.; Hartman, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674. (d) Stähle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta*. **1977**, *60*, 1730. (e) Fuzita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258. (f) Hoffmann, R. W.; Polachowski, A. *Chem. Eur. J.* **1998**, *4*, 1724.

(35) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(36) (a) Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533. (b) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.

(37) (a) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561. (b) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.

(38) Yanagisawa, A.; Nakatsuka, Y.; Nakashima, H.; Yamamoto, H. *Synlett* **1997**, 933.

(39) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Hanawa, H.; Kii, S.; Maruoka, K. *Adv. Synth. Catal.* **2001**, *343*, 57. (c) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (d) Kii, S.; Maruoka, K. *Chirality* **2003**, *15*, 68.

(40) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

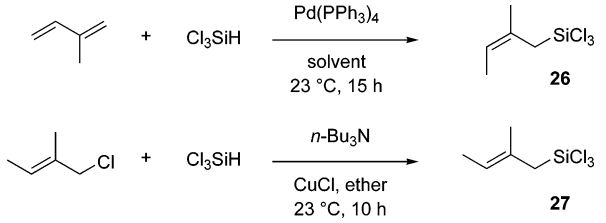
(41) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322.

(42) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.

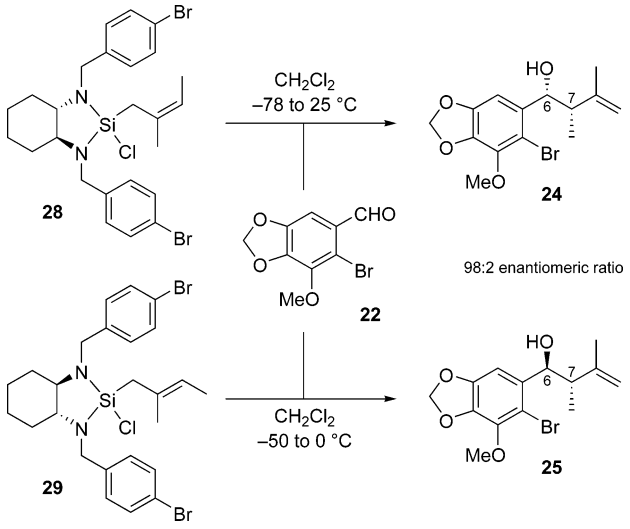
(43) (a) Loh, T.-P.; Zhou, J.-R.; Li, X.-R. *Tetrahedron Lett*. **1999**, *40*, 9333. (b) Loh, T.-P.; Zhou, J.-R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855.

(44) (a) Brown, H. C.; Jadhav, P. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (c) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (d) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (e) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23.

SCHEME 6



SCHEME 7



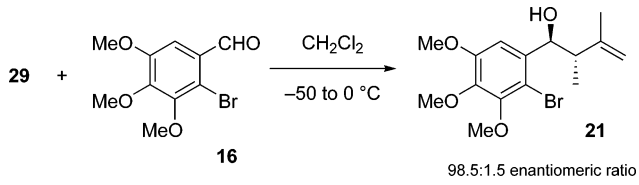
diastereoselection. Efforts to synthesize the diisopinocampheylborane reagent **23** from the configurationally stable tiglylpotassium[34] were unsuccessful.

Leighton's chiral diamine protocol[45] was successfully employed in a diastereoselective and enantioselective protocol for the formation of *syn*- and *anti*-adducts. Angelyltrichlorosilane (**26**) was formed stereoselectively by palladium-catalyzed hydrosilylation of isoprene,[46] and the complementary tiglyltrichlorosilane (**27**) was formed by base-promoted displacement of tiglyl chloride with trichlorosilane (Scheme 6).[47]

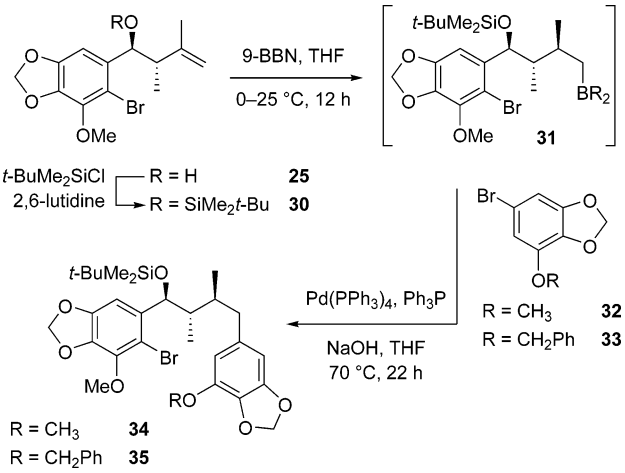
Reaction of angelyltrichlorosilane (**26**) with the (1*S*,2*S*)-1,2-diaminocyclohexane-based auxiliary (DBU, CH_2Cl_2, 25 °C, 14 h) afforded chiral angelylsilane **28** (Scheme 7). This reagent underwent addition to aldehyde **22** to afford (6*R*,7*S*)-*syn*-adduct **24** (78%) with complete diastereoselection (>50:1 *syn*/*anti*) and excellent enantioselectivity (96% ee). The reagent **28** could not be crystallized, whereas allyl and crotyl reagents are reported to be stable crystalline solids.[45] Consequently, it was critical to use a trichlorosilane/auxiliary ratio of exactly 1:1; with a 1.1:1 or 1.2:1 ratio, the resulting reagent systems afforded adduct **24** in 80% ee and 60% ee, respectively.

Reaction of tiglyltrichlorosilane (**27**) with the (1*R*,2*R*)-1,2-diaminocyclohexane-based auxiliary (DBU, CH_2Cl_2, 25 °C, 14 h) afforded chiral tiglylsilane **29** (Scheme 7),

SCHEME 8



SCHEME 9



which underwent addition to aldehyde **22** to afford (6*S*,7*S*)-*anti*-adduct **25** (78%) with complete diastereoselectivity and excellent enantioselection (96% ee).

Using this protocol, adduct (6*S*,7*S*)-*anti*-**21** was obtained from aldehyde **16** in 75% yield (97% ee) through reaction with tiglylsilane **29** (Scheme 8).

Hydroboration/Suzuki–Miyaura Coupling: 1,4-Diarylbutane Construction. Protection of the benzylic hydroxyl group of **25** as the *tert*-butyldimethylsilyl ether afforded **30** (98%). Hydroboration of the alkene of **30** with 9-borabicyclononane (9-BBN) occurred with complete diastereofacial selectivity to afford the intermediate trialkylborane **31**, which was coupled in situ with aryl bromides **32** or **33** under standard Suzuki–Miyaura coupling conditions[30] to afford 1,4-diarylbutanes **34** (72%) and **35** (77%) overall yield (Scheme 9). These compounds contain three of the four necessary stereogenic elements of interiotherin and gomisin R in the correct absolute and relative configuration, and which were introduced via two highly stereoselective transformations.

Initially, it was unclear whether bromination of the newly installed aromatic ring of **34** could be achieved regioselectively (i.e., *ortho* to the methoxy group). Consequently, the benzyloxy compound **35** was used to take advantage of the established *ortho*-directing effect of a phenolic hydroxyl group (Scheme 10).[48] Hydrogenolysis of the benzyl ether of **35** (EtOAc, 25 °C, 6 h, 98%) afforded the corresponding phenol **36**, which underwent facile bromination with complete regioselectivity (dioxane, 15 °C, 12 h, 90%) to afford **37**. Methylation of **37** (acetone, K_2CO_3, 56 °C, 2 h, 95%) provided **38**. It was subsequently established that bromination could be achieved with complete regioselectivity ($CHCl_3$, 25 °C, 6 h), ortho to the

(45) (a) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375. (b) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946.

(46) (a) Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143. (b) Takahashi, S.; Shibano, T.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1969**, 161. (c) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (d) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099.

(47) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1.

(48) (a) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576. (b) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.

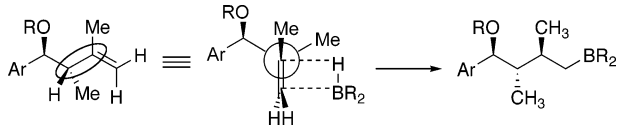
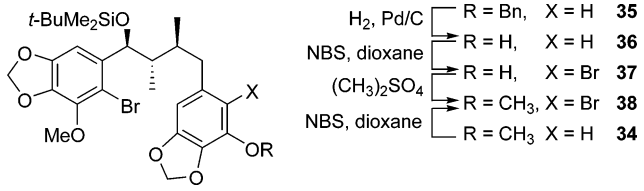
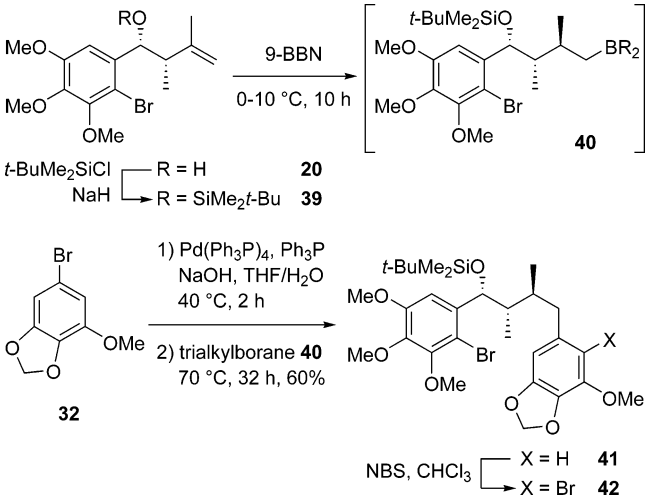


FIGURE 3. $A^{1,3}$-strain model for diastereofacial selectivity.

SCHEME 10



SCHEME 11



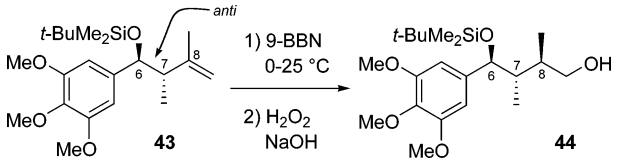
methoxy group of **34**, which significantly shortened the route to dibromide **38**.

The *syn*-stereoisomer **20** similarly provided excellent diastereoselection upon hydroboration/Suzuki−Miyaura coupling (Scheme 11). Protection as the *tert*-butyldimethylsilyl ether (95%) and hydroboration of **39** provided the intermediate trialkylborane **40**. This species was mixed with the preformed reagent obtained upon reaction of aryl bromide **32** with Pd(0). Coupling of borane **40** with aryl bromide **32** under standard Suzuki−Miyaura conditions afforded a good yield of 1,4-diarylbutane **42**. Bromination occurred selectively ortho to the methoxy group of **41** ($CHCl_3$, 22 °C, 7 h) to afford dibromide **42** (85%) in excellent yield.

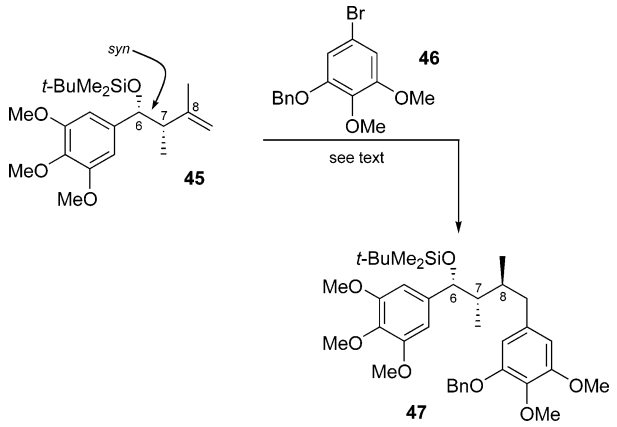
The origin of the diastereoselection in the hydroboration of **30** and **39** is explained by examination of the lowest energy conformation (MM3) about the sp^2-sp^3 bond, wherein the allylic hydrogen is eclipsed with the alkene in order to minimize $A^{1,3}$ strain (Figure 3). The least sterically congested approach by 9-BBN is from the side of the allylic methyl group, giving a new stereogenic center wherein the methyl groups are *anti*. This model has precedent in a number of related contexts.[29]

The sense of diastereoselection in the hydroboration was confirmed by single-crystal X-ray structural analysis of **44** (see the Supporting Information). Treatment of **43**[49] with 9-BBN in EtOH and subsequent oxidation with basic hydrogen peroxide afforded primary alcohol **44** (91%), as a 94:6 ratio of diastereomers (Scheme 12). Crystals of purified **44** were obtained from hexane, and the resulting structure showed that the model proposed above was determinant with respect to diastereofacial selectivity. The C7/C8 methyl groups in product **44** are *anti*.

SCHEME 12



SCHEME 13



The relative configuration of the benzylic alcohol stereocenter had no effect on the diastereofacial selectivity of the approach of the borane (Scheme 13). Hydroboration of **45**[49] followed by in situ Suzuki−Miyaura coupling (THF, $Pd(Ph_3P)_4$, aq NaOH, 70 °C, 12 h) with aryl bromide **46** afforded 1,4-diarylbutane **47** as a single stereoisomer (70%). Crystals of **47** were obtained from hexane, and the resulting X-ray structure possessed 6,7-*syn*/7,8-*anti* stereochemistry, with the key methyl groups *anti* (see the Supporting Information). Thus, it appeared that the $A^{1,3}$-based model was the controlling factor with respect to diastereofacial selectivity.

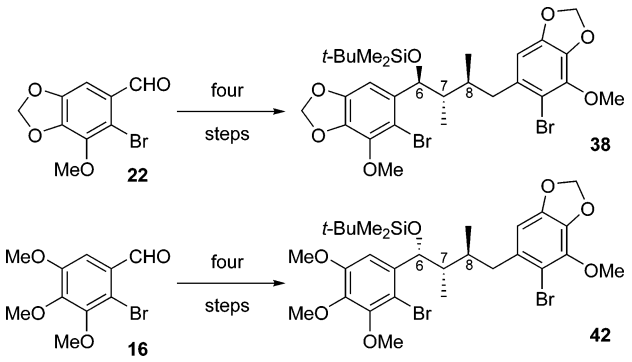
This straightforward protocol of hydroboration/Suzuki−Miyaura coupling effectively complemented the asymmetric crotylation methodology and, when coupled with the high-yielding and regioselective bromination reaction, provided for an efficient, four-step conversion of aryl aldehydes **22** and **16** to 1,4-diarylbutanes **38** (41% overall) and **42** (38% overall), respectively, with complete control of absolute and relative stereochemistry (Scheme 14). These compounds possess all necessary functionality for conversion to the target dibenzocyclooctadiene natural products.

Oxidative Cuprate Biaryl Coupling. Of particular concern in the present case was the issue of atropdiastereoselection in the key intramolecular biaryl coupling. Tobinaga and co-workers[50] have reported that oxidative aryl−aryl coupling of 1,4-diarylbutanes bearing stereogenic centers in the aliphatic tether results in significant

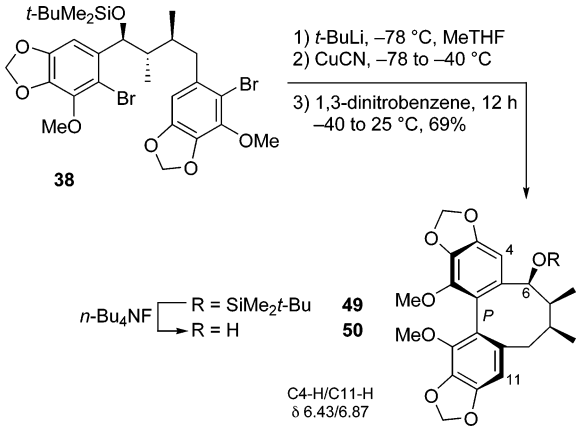
(49) Racemic **43** and **45** were obtained from addition of Grignard reagent **12** (Scheme 2, M = MgBr) to 3,4,5-trimethoxybenzaldehyde.

(50) Takeya, T.; Ohbuchi, A.; Tobinaga, S. *Chem. Pharm. Bull.* **1994**, *42*, 438−442.

SCHEME 14



SCHEME 15



diastereoselection, but in extremely low yields (5−36% with 85:15 diastereoselection). In a later study, this same group[51] reported a similar oxidation, mediated by Fe(III) salts, to proceed with 4:1 diastereoselection in 36% yield. In our own work, we observed 8:1 atropdiastereoselection in the formation of a key biaryl bond during the course of the total synthesis of calphostin A.[31,52]

In the present case the conformation about the carbon-metal−carbon bond of an intermediate biaryl cuprate will depend most importantly on the conformational biases of the four-carbon tether, and it was presumed that the relative configuration of the stereogenic center(s) in the butane tether would control the sense of stereoinduction during biaryl bond formation.

Implementation of the Lipshutz methodology[27] for biaryl coupling proved exceptionally effective in these systems. This protocol involves low temperature formation of a mixed diarylcuprate and oxidation of this species to form the carbon−carbon biaryl bond. This reaction is relatively insensitive to steric or electronic features of the aromatic systems when compared to palladium-mediated processes. We have previously used this chemistry in the total syntheses of eupomatilones 4 and 6.[53]

Remarkably, complete diastereoselectivity was observed in the Lipshutz coupling of 6,7-*anti*/7,8-*anti* diarylbutane **38** (Scheme 15). In this case, halogen-lithium exchange with *tert*-butyllithium afforded the intermediate bis-lithiated system, which was reacted directly with

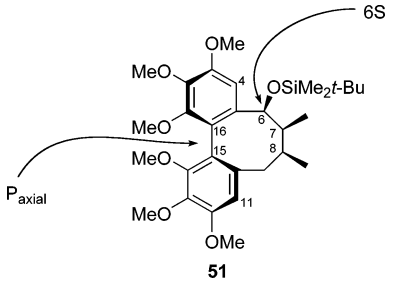


FIGURE 4. Relative configuration of biaryl coupled product **51**.

cuprous cyanide at −40 °C to form an intermediate cyclic, higher-order biarylcuprate. Oxidation occurred smoothly using oxygen, as originally described, or more effectively using 1,3-dinitrobenzene,[54] and dibenzocyclooctadiene **49** was isolated in 69% yield as the sole diastereomer present. Removal of the silyl ether of **49** (THF, 55 °C, 12 h) afforded the corresponding alcohol **50** (89%).

Assignment of configuration about the biaryl axis of **49** was obtained by correlation of key ^{1}H NMR chemical shifts with those of the related system **51**, obtained by biaryl coupling as a 15:1 mixture of separable diastereomers (Figure 4). The relative configuration of the major diastereomer **51** was determined by single-crystal X-ray analysis (see the Supporting Information). In this structure, the P_{ax} configuration about the stereogenic biaryl bond correlates with the *S* configuration at the C6 benzylic stereogenic center of the four-carbon bridge. The chemical shifts of the C4-H and C11-H protons of **51** were diagnostic of the relative configuration between the C6-stereogenic center and the stereogenic biaryl axis. When the absolute configuration of C6 is *S*, as in **51**, the C4-H and C11-H protons resonated with a chemical shift difference of $\Delta\delta = 0.52$ ppm in the P_{ax} diastereomer, whereas this difference was $\Delta\delta = 0.11$ ppm in the minor M_{ax} diastereomer. Since $\Delta\delta = 0.44$ for C4-H/C11-H of **49**, the axial configuration must be P_{ax}. Correlation of other ^{1}H NMR resonances of **49** and **51** was observed,[55] further strengthening the stereochemical assignment.

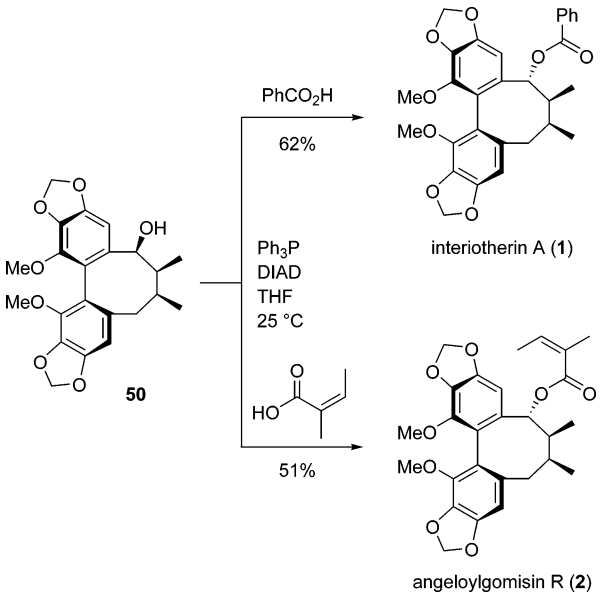
Alcohol **50** underwent a Mitsunobu inversion with benzoic acid to afford interiotherin A (**1**) (Scheme 16). In a similar manner, reaction of alcohol **50** with angelic acid under Mitsunobu reaction conditions afforded angeloylgomisin R (**2**). The ^{1}H and ^{13}C NMR data for synthetic **1** and **2** were identical with those reported for the naturally occurring compounds.

In the case of the 6,7-*syn*/7,8-*anti* stereoisomer of the diarylbutane (**42**), treatment with four equivalents of *tert*-butyllithium in 2-methyltetrahydrofuran (MeTHF) afforded the dilithio species, which was treated with copper cyanide at −40 °C to form the higher order biarylcuprate (Scheme 17). Even though exchange of the aryl ligands on copper is not possible because of the cyclic nature of the cuprate, it was important to perform the subsequent oxidation at low temperature in order to avoid protode-

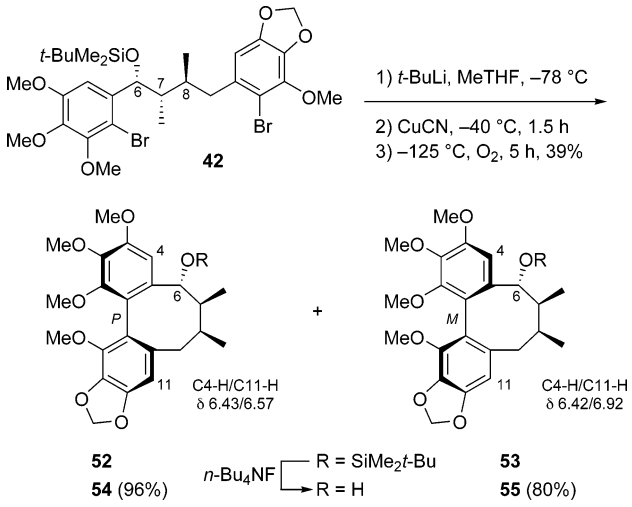
(51) Takeya, T.; Yamaki, S.; Itoh, T.; Hosogai, H.; Tobinaga, S. *Chem. Pharm. Bull.* **1996**, *44*, 909−918.
(52) Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1993**, *34*, 2225.
(53) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025.

(54) (a) Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**. *122*, 5656. (b) Reference 28b.
(55) Characteristic chemical shifts for (*P*)-**51**: C4-H/C10-H δ 7.02/6.50; C6-H δ 4.42; C7-CH_3/C8-CH_3 δ 1.03/0.66. For (*M*)-**51**: C4-H/C10-H δ 6.47/6.36; C6-H δ 4.73; C7-CH_3/C8-CH_3 δ 1.17/0.97. For compound **49**: C4-H/C10-H δ 6.87/6.43; C6-H δ 4.37; C7-CH_3/C8-CH_3 δ 0.98/0.65.

SCHEME 16



SCHEME 17

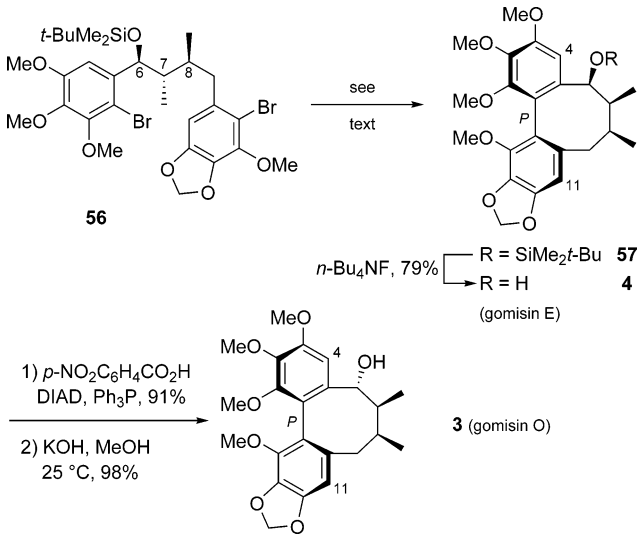


cupration after workup. Oxygen proved to be the best oxidant in this system, and a 1:2 mixture of two atropisomers **52** and **53** were isolated from the reaction in modest yield. 1,3-Dinitrobenzene was not effective in this case.

Upon deprotection of the silyl ethers of **52** and **53** (THF, 55 °C, 5 h), the minor stereoisomeric product **54** gave identical ^{1}H and ^{13}C NMR spectral data with that reported for gomisin O and thus must possess P absolute configuration about the stereogenic axis. Again, the C4-H and C11-H protons were diagnostic of the relationship between the C6-stereogenic center and the biaryl stereogenic axis. When the absolute configuration of C6 is *R*, as in **54** and **55**, the C4-H and C11-H protons resonated with chemical shifts $\Delta\delta = 0.14$ ppm in the P_{ax} diastereomer **54** and by $\Delta\delta = 0.50$ ppm in the M_{ax} diastereomer **55**, or opposite to the system with the C6 stereogenic center in the *S* configuration.

In contrast, Lipshutz coupling of the 6,7-*anti*/7,8-*anti* diarylbutane **56** provided a single atropdiastereoisomer in 35% yield (Scheme 18). Upon deprotection of the silyl ether of product **57** (THF, 55 °C, 3 h), the product **4**

SCHEME 18



provided ^{1}H NMR spectral data identical with that reported for gomisin E (epigomisin O). Mitsunobu inversion using *p*-nitrobenzoic acid[56] (THF, 0−25 °C, 12 h) with subsequent saponification of the inverted ester (25 °C, 10 h) provided gomisin O (**3**) in excellent yield for the two-step conversion. By this route, gomisin E and gomisin O were synthesized in six and eight steps, respectively, from aromatic precursors **16** and **41**.

In this key biaryl coupling, the C6-stereogenic center seemed to be the determining element in controlling the relative configuration of the incipient biaryl axis. With the 6*S* configuration, as in **38** and **56**, the emergent stereogenic axis is P and the coupling reaction occurs with complete atropdiastereoselectivity. When this center is 6*R*, as in **43**, the emergent axis is formed with essentially no diastereoselectivity and the major diastereomer possesses the M configuration (1:2 P/M). However, we have not performed biaryl coupling reactions on the complete series of diastereomeric 1,4-diarylbutanes, so more subtle effects may be evident when the other stereogenic centers are altered in relative configuration. It is assumed that this stereogenic center effects the chirality of the intermediate diarylcuprate prior to reductive elimination, but lacking detailed knowledge of the structure of this intermediate, it is difficult to provide detailed speculation about the origin of the diastereoselection at this point.

Conclusion

The total syntheses of the dibenzocyclooctadiene natural products interiotherin A, angeloylgomisin R, gomisin O, and gomisin E (epigomisin O) were achieved in a convergent and efficient fashion.[27] Starting from known aromatic systems **16**, **22**, and **32**, the natural products were produced in six to eight steps with complete control of absolute and relative stereochemistry. Key steps included a novel asymmetric crotylation reaction using the Leighton auxiliary that provided adducts with 96−97% ee, a diastereoselective hydroboration reaction coupled with an in situ Suzuki−Miyaura alkylborane coupling

(56) (a) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

that occurred with >20:1 diastereoselectivity, and an oxidative biarylcuprate coupling that occurred with complete atropdiastereoselection.

Experimental Section

(1*R*,2*S*)-1-(6-Bromo-7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2,3-dimethylbut-3-en-1-ol (24). A solution of aryl aldehyde **22** (50 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise to a solution of reagent **28** (0.125 g, 0.2 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C over 10 min. The reaction mixture was gradually allowed to warm to 0 °C and was stirred for 12 h at this temperature. The reaction mixture was acidified with 1 N hydrochloric acid (3 mL) and was stirred for 15 min. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and water (10 mL), and the organic layer was separated. The organic layer was washed with water, saturated aqueous NaCl, and water, and was dried and concentrated. The residue was purified by flash chromatography (silica, 15% EtOAc/hexane) to afford **24** (47 mg, 75%) as a colorless oil: 98:2 enantiomeric ratio.

(1*S*,2*S*)-1-(6-Bromo-7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2,3-dimethylbut-3-en-1-ol (25). Following the procedure for the preparation of **24**, a solution of aryl aldehyde **22** (0.10 g, 0.38 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of reagent **29** (0.22 g, 0.37 mmol) in CH_2Cl_2 (2 mL) at −50 °C. The reaction mixture was gradually allowed to warm to 0 °C and was stirred for 24 h at this temperature. Purification afforded **25** (95 mg, 75%) as a colorless oil: 98:2 enantiomeric ratio.

(1*S*,2*S*)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-2,3-dimethylbut-3-en-1-ol (21). Following the procedure for the preparation of **24**, a solution of aryl aldehyde **16** (72 mg, 0.31 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of reagent **29** (0.27 g, 0.46 mmol) in CH_2Cl_2 (1.5 mL) at −50 °C. The reaction mixture was gradually allowed to warm to 0 °C and was stirred for 24 h at this temperature. Purification afforded **21** (70 mg, 78%) as a colorless oil: 97:3 enantiomeric ratio.

((1*S*,2*S*,3*S*)-1-(5-Bromo-4-methoxybenzo[*d*][1,3]dioxol-6-yl)-4-(4-methoxybenzo[*d*][1,3]dioxol-6-yl)-2,3-dimethylbutoxy)(*tert*-butyl)dimethylsilane (34). Following the procedure for the preparation of 1,4-diarylbutane **35**, a solution of 9-BBN in THF (0.5 M, 0.65 mL, 0.32 mmol) was added to a solution of **30** (0.10 g, 0.22 mmol) in THF (1 mL), which was transferred to a flask containing 6-bromo-4-methoxybenzo[*d*]-[1,3]dioxole (**32**) (0.10 g, 0.44 mmol), $Pd(PPh_3)_4$ (0.016 g, 0.014 mmol), and aqueous NaOH (3 M, 0.25 mL, 0.73 mmol, NaOH dissolved in 0.2 mL water) in THF (2 mL) at 0 °C. The reaction mixture was warmed at 70 °C for 16 h to afford **34** (96 mg, 72%) as a syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (s, 1H), 6.39 (d, 1H, J = 1.1 Hz), 6.37 (app s, 1H), 5.98 (ABq, 2H, J = 1.4 Hz, $\Delta\nu$ = 16.5 Hz), 5.93 (s, 2H), 5.10 (d, 1H, J = 7.8 Hz), 4.04 (s, 3H), 3.90 (s, 3H), 2.99 (dd, 1H, J = 13.2, 3.2 Hz), 2.30−2.15 (m, 1H), 2.11 (dd, 1H, J = 13.1, 11.7 Hz), 1.80 (qd, 1H, J = 7.4, 1.7 Hz), 0.91 (s, 9H), 0.79 (d, 3H, J = 6.8 Hz), 0.73 (d, 3H, J = 7.2 Hz), 0.13 (s, 3H) −0.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.7, 148.6, 143.3, 139.4, 138.7, 136.8, 136.3, 133.0, 107.9, 107.7, 103.1, 102.8, 101.5, 101.1, 75.9, 60.1, 56.4, 46.3, 37.2, 33.9, 25.9, 18.3, 18.0, 10.5, −4.5, −4.8; IR (film) ν_{max} 2954, 2884, 2856, 1632, 1608, 1508, 1472, 1400, 1374, 1277, 1252, 1132, 1087, 1046, 960, 934, 857, 837, 776, 736, 678 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{39}BrO_7SiNa$ 617.1546, found 617.1541.

((1*S*,2*S*,3*S*)-1,4-Bis(5-bromo-4-methoxybenzo[*d*][1,3]-dioxol-6-yl)-2,3-dimethylbutoxy)(*tert*-butyl)dimethylsilane (38). A solution of **34** (90 mg, 0.15 mmol) in $CHCl_3$ (2 mL) was cooled to 15 °C, and a solution of *N*-bromosuccinimide (30 mg, 0.16 mmol) in $CHCl_3$ (6 mL) was added dropwise by syringe over 1 h at this temperature. The reaction mixture was stirred for 6 h at 25 °C and was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (1 mL). The mixture was concentrated, and the residue was dissolved in EtOAc (25 mL) and washed with saturated aqueous $Na_2S_2O_3$, water, and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (silica, 15% EtOAc/hexane) to afford **38** (83 mg, 82%) as colorless solid.

(6*S*,7*S*,8*S*,P_{ax})-Dibenzocyclooctadiene 49. A solution of **38** (0.05 g, 0.074 mmol) in MeTHF (2 mL) was treated with *t*-BuLi (2.3 M, 0.13 mL, 0.29 mmol) at −78 °C under argon. After 15 min, the pale yellow reaction mixture was transferred via cannula to a flask containing CuCN (7.0 mg, 0.074 mmol) in MeTHF (2 mL) at −78 °C under argon. The heterogeneous mixture was allowed to warm to −40 °C over 1 h and was stirred at this temperature until homogeneous (ca. 1.5 h). The reaction mixture was treated with a freshly prepared solution of 1,3-dinitrobenzene (0.5 M, 0.59 mL, 0.29 mmol) at −40 °C and was allowed to warm to 25 °C. The reaction mixture was stirred at this temperature for 10 h and was quenched by the addition of 10% NH_4OH in saturated aqueous NH_4Cl. The resulting two-phase mixture was stirred for 30 min and the phases were separated. The aqueous phase was extracted two times with EtOAc (20 mL), and the combined organic layers were washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4), concentrated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to afford **49** (26 mg, 69%) as colorless solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (s, 1H), 6.43 (s, 1H), 5.96 (app t, 2H, J = 1.2 Hz), 5.95 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 27.9 Hz), 4.37 (d, 1H, J = 1.3 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 2.12 (dd, 1H, J = 13.3, 9.2 Hz), 1.93 (d, 1H, J = 13.3 Hz), 1.90−1.80 (m, 2H), 0.97 (d, 3H, J = 6.9 Hz), 0.83 (s, 9H), 0.65 (d, 3H, J = 6.9 Hz), −0.14 (s, 3H), −0.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9, 147.8, 140.8, 140.3, 138.2, 136.2, 134.8, 134.0, 120.0, 119.5, 103.2, 102.6, 100.7, 100.6, 73.6, 59.6, 59.4, 44.4, 39.3, 34.7, 25.9, 22.0, 18.1, 7.8, −4.8, −5.2; IR (film) ν_{max} 2954, 2885, 1632, 1607, 1506, 1474, 1400, 1277, 1252, 1134, 1087, 1046, 960, 936, 857, 776, 736, 678 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{38}O_7SiNa$ 537.2285, found 537.2279.

Interiotherin A (1). A solution of **50** (12.0 mg, 0.03 mmol), Ph_3P (32.0 mg, 0.12 mmol), and benzoic acid (14.0 mg, 0.12 mmol) in THF (1 mL) was vigorously stirred at 0 °C for 10 min. Diisopropyl azodicarboxylate (24.0 μmL, 0.13 mmol) was added dropwise over a period of 5 min, and the reaction mixture was allowed to warm to 25 °C and was stirred at this temperature for 10 h. The reaction mixture was diluted with EtOAc (10 mL) and was washed with water and saturated aqueous NaCl. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (5% EtOAc/hexane) to afford interiotherin A (**1**) (9.0 mg, 62%) as a solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, 2H, J = 7.3 Hz), 7.50−7.40 (m, 1H), 7.35−7.30 (m, 2H), 6.69 (s, 1H), 6.49 (s, 1H), 5.98 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 21.8 Hz), 5.88 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 10.2 Hz), 5.86 (overlapping d, 1H, J = 6.0 Hz), 3.79 (s, 3H), 3.58 (s, 3H), 2.26 (d, 2H, J = 6.5 Hz), 2.15−2.00 (m, 2H), 1.02 (d, 3H, J = 7.0 Hz), 0.86 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3, 148.8, 141.6, 141.2, 136.8, 134.2, 132.6, 131.1, 129.7 (2C), 127.9 (2C), 122.4, 121.5, 106.3, 102.5, 101.2, 100.6, 81.4, 59.7, 59.0, 37.6, 36.6 (2C), 19.3, 14.1; IR (film) ν_{max} 2924, 2358, 1713, 1616, 1475, 1450, 1372, 1269, 1211, 1101, 1070, 1049, 936, 711 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}O_8Na$ 527.1682, found 527.1641.

Angeloylgomisin R (2). Following the procedure for the preparation of interiotherin A, diisopropyl azodicarboxylate (16 μL, 0.08 mmol), **50** (8.0 mg, 0.02 mmol), PPh_3 (21.0 mg, 0.08 mmol), and angelic acid (8.0 mg, 0.08 mmol) in THF (1 mL) afforded angeloylgomisin R (**2**) (5.0 mg, 51%) as a syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.70 (s, 1H), 6.41 (s, 1H), 5.98 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 15.0 Hz), 5.95−5.90 (m, 3H), 5.68 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H), 3.79 (s, 3H), 2.45−2.25 (m, 3H), 2.20−1.95 (m, 1H), 1.85 (dq, 3H, J = 7.2, 1.4 Hz), 1.59 (q, 3H, J = 1.4 Hz), 0.94 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 6.8 Hz); IR (film) ν_{max} 2924, 2358, 1710, 1638, 1611, 1450, 1374, 1250,

1211, 1100, 1070, 1049, 936 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}O_8Na$ 505.1838, found 505.1827.

Gomisin O (3). A solution of *n*-Bu_4NF (1.0 M, 20 μL, 0.015 mmol) in THF was added to a solution of **52** (8.0 mg, 0.015 mmol) in THF (0.80 mL) at room temperature, and the reaction mixture was warmed at 55 °C for 6 h. The volatiles were removed, and the residue was dissolved in EtOAc (5 mL) and was washed with saturated aqueous NH_4Cl (5 mL) and saturated aqueous NaCl solution (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (silica gel, 30% EtOAc/hexane) to afford **3** (6.0 mg, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.57 (s, 1H), 6.43 (s, 1H), 5.97 (ABq, 2H, J = 1.4 Hz, $\Delta\nu$ = 8.6 Hz), 4.35 (dd, 1H, J = 8.0 Hz), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.54 (s, 3H), 2.32 (dd, 1H, J = 13.0, 5.6 Hz), 2.03 (dd, 1H, J = 12.9, 9.8 Hz), 1.86 (m, 1H), 1.67 (br s, 1H), 0.94 (d, 3H, J = 7.4 Hz), 0.92 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.1, 152.0, 149.3, 141.6, 141.5, 137.0, 135.5, 134.6, 122.2, 120.6, 110.1, 102.6, 100.8, 81.4, 60.9, 60.4, 59.5, 56.0, 40.0, 37.1, 31.6, 22.7, 14.1; IR (film) ν_{max} 3482, 2937, 2361, 1723, 1617, 1474, 1327, 1105, 1050 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_7Na$ 439.1733, found 439.1740.

***epi*-Gomisin O (*M*)-55.** A solution of *n*-Bu_4NF (1.0 M, 50 μL, 0.05 mmol) in THF was added to a solution of **53** (18.0 mg, 0.034 mmol) in THF (1.0 mL) at room temperature, and the reaction mixture was warmed at 55 °C for 6 h. The volatiles were removed and the residue was dissolved in EtOAc (5 mL) and washed with saturated aqueous NH_4Cl (5 mL) and saturated aqueous NaCl solution (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and the residue was purified by flash chromatography (silica gel, 30% EtOAc/hexane) to afford **55** (12 mg, 86%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93, 6.42, 5.95 (ABq, 2H, J = 1.2 Hz, $\Delta\nu$ = 6.3 Hz), 4.32 (dd, 1H, J = 8.0, 2.4 Hz), 3.93 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H), 3.64 (s, 3H), 2.61 (dd, 1H, J = 15.6, 4.8 Hz), 2.37 (dd, 1H, J = 16.0, 10.4 Hz), 1.72 (d, 1H, J = 2.8 Hz), 1.61 (m, 2H), 1.02 (d, 3H, J = 6.8 Hz), 0.82 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 151.5, 148.3, 140.9, 140.4, 140.0, 135.1, 134.6, 120.9, 120.4, 105.1, 102.2, 100.9, 74.2, 61.0, 60.9, 59.6, 55.9, 46.9, 40.2, 33.5, 19.4, 12.3; IR (film) ν_{max} 3410, 2958, 1597, 1463, 1404, 1107, 1050 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_7Na$ 439.1733, found 439.1753.

***O-tert*-Butyldimethylsilyl 6-*epi*-Gomisin O (57).** A solution of *anti-anti* dibromosilyl ether **56** (0.052 mg, 0.075 mmol) in MeTHF (4 mL) was treated with a solution of *t*-BuLi (2.5 M, 0.12 mL, 0.30 mmol) at −78 °C under argon. After 30 min, the pale yellow mixture was transferred via cannula to a flask containing CuCN (7.0 mg, 0.075 mmol) in MeTHF (7 mL) at −78 °C under argon. The heterogeneous reaction mixture was allowed to warm to −40 °C over 1.5 h and was stirred vigorously until homogeneous at this temperature. The resulting solution was cooled to −125 °C (liquid N_2/*n*-pentane), and oxygen gas was bubbled into the reaction for 4 h using a fritted glass tube. The reaction mixture was purged with argon and kept under high vacuum for 1 min to remove dissolved oxygen. The reaction mixture was warmed to −30 °C and was quenched by the addition of 10% NH_4OH in saturated aqueous NH_4Cl (4 mL). The two-phase mixture was stirred for 30 min as it was allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organics were washed with saturated aqueous NH_4Cl (10 mL) and saturated aqueous NaCl (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (silica gel, 5% EtOAc/hexane) to afford **57** (14 mg, 35%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (s, 1H), 6.43 (s, 1H), 5.95 (ABq, 2H, J = 1.5 Hz, $\Delta\nu$ = 17.6 Hz), 4.42 (d, 1H, J = 1.4 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.57 (s, 3H), 2.12 (dd, 1H, J = 13.3, 9.1 Hz), 1.93 (d, 1H, J = 13.3 Hz), 1.88 (m, 2H), 0.99 (d, 3H, J = 7.0 Hz), 0.86 (s, 9H), 0.65 (d, 3H, J = 6.9 Hz), −0.13 (s, 3H), −0.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.6, 150.7, 148.9, 140.9, 140.5, 140.1, 137.9, 137.0, 120.6, 119.8, 107.2, 102.5, 100.7, 73.7, 60.9, 60.6, 59.9, 55.7, 44.5, 39.3, 34.7, 26.0, 25.8, 22.1, 18.1, 7.8, −4.6, −5.3; IR (film) ν_{max} 2954, 1597, 1471, 1268, 1200, 1107, 1053 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{42}O_7SiNa$ 553.2598, found 553.2574.

Gomisin E (6-*epi*-Gomisin O) (4). A solution of *n*-Bu_4NF (1.0 M, 25 μL, 0.024 mmol) in THF was added to a solution of **57** (9.0 mg, 0.02 mmol) in THF (0.80 mL) at room temperature, and the reaction mixture was warmed at 55 °C for 6 h. The volatiles were removed, and the residue was dissolved in EtOAc (5 mL) and washed with saturated aqueous NH_4Cl (5 mL) and saturated aqueous NaCl solution (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by flash chromatography (silica gel, 30% EtOAc/hexane) to afford **4** (5.5 mg, 79%) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.02 (s, 1H), 6.45 (s, 1H), 5.95 (s, 2H), 4.58 (d, 1H, J = 1.4 Hz), 3.93 (s, 3H), 3.92 (s, 1H), 3.86 (s, 1H), 3.55 (s, 3H), 2.12 (dd, 1H, J = 13.4, 9.4 Hz), 2.02 (m, 1H), 1.97 (d, 1H, J = 13.2 Hz), 1.93 (m, 1H), 1.65 (br s, 1H), 1.02 (d, 3H, J = 7.2 Hz), 0.71 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 151.1, 149.1, 140.8, 140.6, 137.9, 136.4, 134.5, 121.2, 119.4, 106.2, 102.8, 100.8, 73.4, 61.0, 60.6, 59.6, 55.9, 42.4, 39.2, 34.6, 22.0, 7.8; IR (film) ν_{max} 3437, 2934, 1618, 1463, 1402, 1269, 1203, 1106, 1050 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_7Na$ 439.1733, found 439.1753.

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Supporting Information Available: Full experimental procedures and spectral characterization of intermediates and products and CIF files for reported crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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