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Asymmetric Synthesis of the Dibenzocyclooctadiene Lignans Interiotherin A and Gomisin R†

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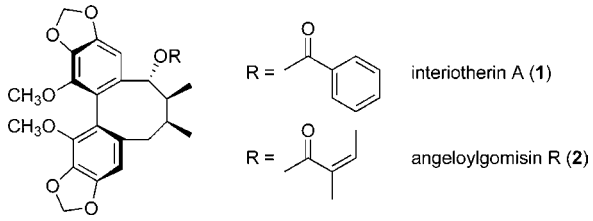
ABSTRACT



Asymmetric total syntheses of the dibenzocyclooctadiene lignans interiotherin A and angeloylgomisin R are reported. The syntheses were based on an atropdiastereoselective, copper-promoted biaryl coupling reaction, a diastereoselective hydroboration/Suzuki–Miyaura coupling reaction sequence, and an asymmetric boron-mediated tiglylation of an aryl aldehyde precursor.

Lignans are plant-derived natural products formed by dimerization of the nine-carbon skeleton of cinnamic acid. Different families of lignans include the aryltetrahydronaphthalenes, typified by podophyllotoxin, the arylnaphthalenes, and the diverse family of dibenzocyclooctadienes.[1] A wide variety of dibenzocyclooctadiene lignans are produced by the *Schisandraceae* family of plants, including schisandrin C, gomisins, and kadsurin, many of which are biologically active.[2] Although a variety of synthetic efforts toward these natural products have been reported over the years,[3] there has been a resurgence of interest in this area. Efforts by Molander and co-workers have been notable.[4]

A recent report described the isolation of interiotherins A (**1**) and B from the stems of *Kadsura interior*,[5] 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.[6] The interiotherins inhibit the replication of HIV at μg/mL levels. Interiotherin A is closely related to angeloylgomisin R (**2**).[7]

As part of a research program focused on the chemistry and biology of dibenzocyclooctadiene lignans, we report the first asymmetric total syntheses of interiotherin A and angeloylgomisin R. The basis of our synthetic approach to these natural products (Scheme 1) was fourfold, where each bond-forming event introduces a key stereogenic element of the target molecules: (1) installation of the C6 ester side-chains of the natural products by a Mitsunobu reaction,

† Dedicated to the memory of Professor Herbert C. Brown, whose contributions to science made this and countless other syntheses feasible.

(1) Ayres, D. C.; Loike, J. D. *Lignans. Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, UK, 1990.

(2) Charlton, J. L. *J. Nat. Prod.* **1998**, *61*, 1447.

(3) (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) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090. (g) Ishiguro, T.; Mizuguchi, H.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 609. (h) Tomioka, K.; Mizuguchi, H.; Koga, K. *Tetrahedron Lett.* **1979**, *16*, 1409. (i) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267.

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(5) 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.

(6) 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.

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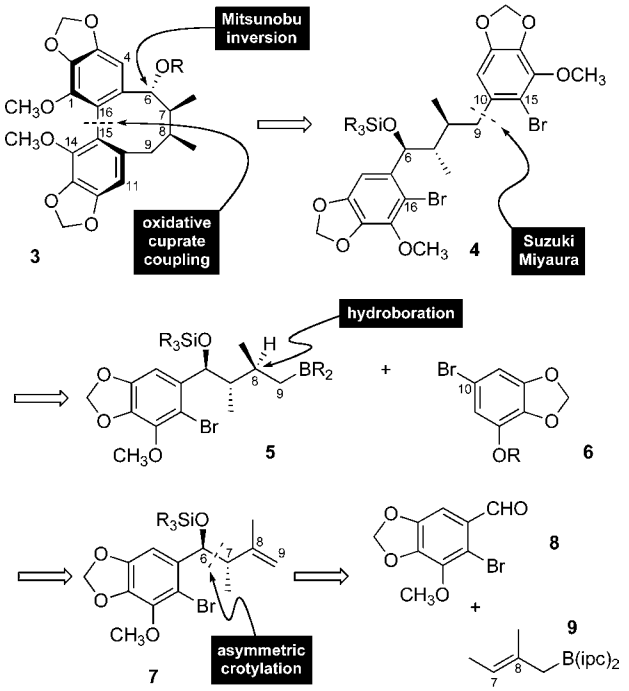
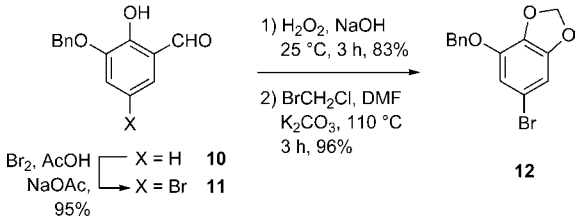
Scheme 1



concurrently setting the stereochemistry at C6; (2) intramolecular, atropdiastereoselective Lipshutz biarylcuprate coupling between C15 and C16 of **4** to afford the parent dibenzocyclooctadiene ring system in **3**; (3) diastereoselective hydroboration of the C8−C9 alkene of **7** followed by in situ Suzuki−Miyaura coupling of the resulting C9 alkylborane **5** with aryl bromide **6**; (4) asymmetric crotylation of aldehyde **8** with the Brown borane **9**, prepared from tiglyl bromide, to afford **7**.

Selective alkylation[8] of the less acidic phenol of 2,3-dihydroxybenzaldehyde with benzyl bromide provided starting aldehyde **10** (Scheme 2). Bromination of **10** under

Scheme 2



standard conditions provided aryl bromide **11**[9] (95%). Dakin oxidation[10] afforded the corresponding catechol, which was transformed into the methylenedioxy system **12** in 80% yield for the two-step sequence.

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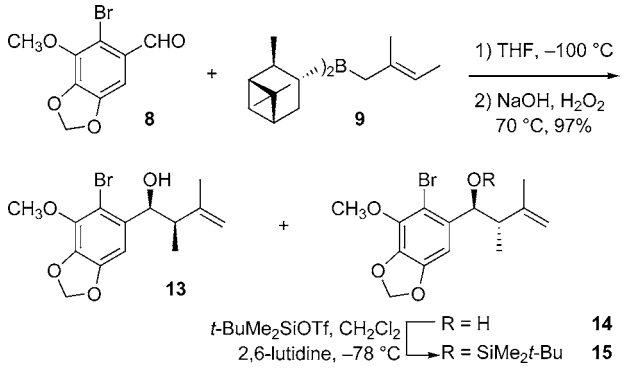
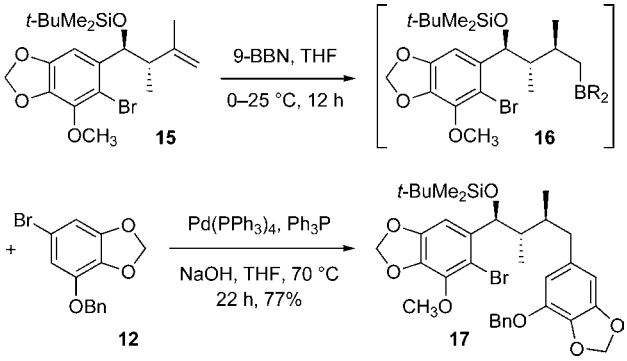
Scheme 3



Aldehyde **8** (Scheme 3) was prepared following our route used in the synthesis of eupomatilones **4** and **6**.[11] Borane **9** was prepared from (*E*)-1-bromo-2-methyl-2-butene (tiglyl bromide) via the intermediate Grignard reagent by reaction with (−)-*B*-chlorodiisopinocampheylborane [(−)-DIP−Cl].[12] The Grignard reagent equilibrates,[13] so both (*Z*)- and (*E*)-isomers of the methylcrotylborane **9** were formed and a 4:3 mixture of separable syn and anti adducts **13** and **14**,[14] respectively, was produced in 97% combined yield. The anti isomer was produced in >95:5 enantiomeric ratio and protected as the *tert*-butyldimethylsilyl ether to afford **15**.

Hydroboration of the alkene of **15** with 9-BBN afforded the intermediate trialkylborane **16** (Scheme 4), which was

Scheme 4



used directly in a subsequent Suzuki−Miyaura coupling reaction[15] with aryl bromide **12**. The product of this reaction,

(11) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025.

(12) Brown, H. C.; Jadhav, P. *J. Am. Chem. Soc.* **1983**, *105*, 2092. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(13) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701. Schlosser, M.; Hartman, J.; David, V. *Helv. Chim. Acta* **1974**, *57*, 1567. Schlosser, M.; Hartman, J. *J. Am. Chem. Soc.* **1976**, *98*, 4674. Fuzita, K.; Schlosser, M. *Helv. Chim. Acta* **1982**, *65*, 1258.

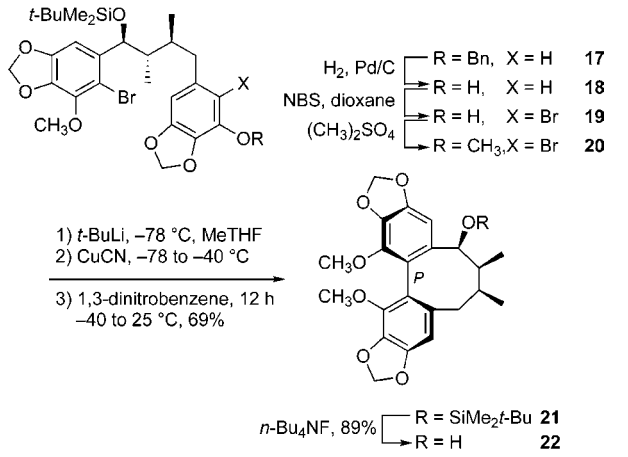
(14) Enantiomeric ratio of the diastereomerically pure anti adduct **14** was measured by chiral HPLC (OD column).

(15) (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.

1,4-diarylbutane **17** was produced in 77% isolated yield for the two-step protocol as a 97:3 diastereomeric ratio of isomers. Diastereofacial selectivity can be explained using a standard A[1,3] strain argument, which has precedent in our work[11] and in the work of others.[16] At the stage of **17**, the key issue remaining is formation of the biaryl bond and the accompanying question of atropdiastereoselection.

Installation of the aryl bromide for biaryl coupling was accomplished in 84% overall yield for the three-step reaction sequence: (1) hydrogenolysis of the benzyl ether of **17** (EtOAc, 6 h, 25 °C, 98%) afforded phenol **18**; (2) selective bromination ortho to the phenolic hydroxyl group of **18** (15 °C, 12 h, 90%) provided bromide **19**; (3) alkylation of the phenolic hydroxyl group (K_2CO_3, acetone, 95%) afforded methyl ether **20** (Scheme 5). It is well established that bromination can be selectively achieved ortho to a phenolic hydroxyl group.[17]

Scheme 5



Implementation of the Lipshutz methodology for biaryl coupling,[18] which involves oxidation of a mixed biarylcuprate species to effect formation the carbon−carbon biaryl bond, proved ideal in this system. This reaction is insensitive to steric or electronic features of aromatic systems, and we have successfully used it with other sterically crowded, electron-rich aromatic systems.[11,19]

In the present case (Scheme 5), halogen−lithium exchange of **20** with *tert*-butyllithium afforded an intermediate bis-lithiated system, which was reacted directly with 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,[20] and dibenzocyclooctadiene **21** was isolated in 69% yield as the sole diastereomer present. Removal of the silyl ether of **21** (THF, 55 °C, 12 h) afforded the corresponding alcohol **22**.

Assignment of absolute configuration about the biaryl axis of **21** was obtained by correlation of key ^{1}H NMR chemical shifts with those of the related system **23**,[21] whose relative configuration was determined by single-crystal X-ray crystallographic analysis (Figure 1). In the structure of **23**, the P_{axial} configuration about the stereogenic biaryl bond correlates with the 6*S*,7*S*,8*S* configuration at the stereogenic centers of the four-carbon bridge.

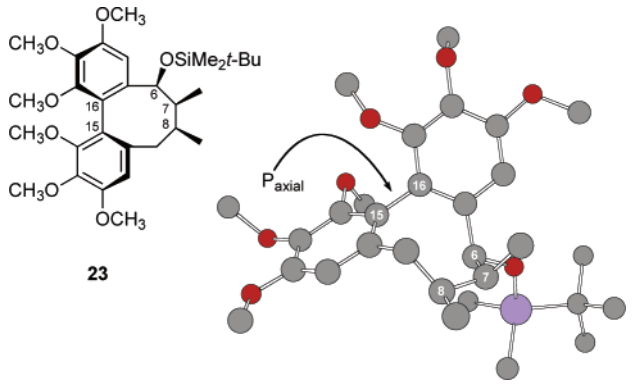


Figure 1. X-ray Structure of dibenzocyclooctadiene (*P*)-**23**.

These C6, C7, and C8 stereogenic centers of precursor **20** therefore control the sense of axial chirality during the formation of the biaryl bond, such that this stereogenic axis is introduced with a high degree of selectivity. We observed that oxidative cuprate coupling of the corresponding 1,2-syn/2,3-anti diastereomer of 1,4-diarylbutane **20** afforded a 3:2 mixture of configurationally undefined stereoisomers.

Alcohol **22** underwent a Mitsunobu reaction/inversion with benzoic acid (Scheme 6) to afford interiotherin A (**1**). In a similar manner, reaction of alcohol **22** 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.

As it turned out, our concerns about the regioselectivity of bromination (Scheme 5) were unwarranted. Suzuki−Miyaura coupling of borane **16** with the methoxy-substituted aryl bromide **24**[22] occurred smoothly to afford 1,4-diarylbu-

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(18) (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.

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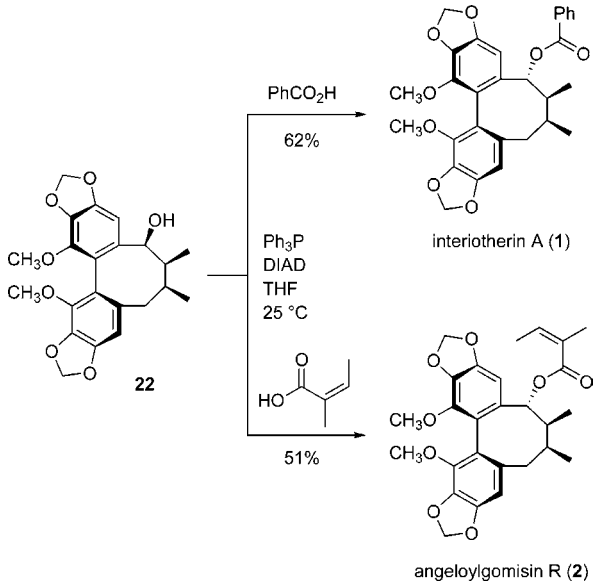
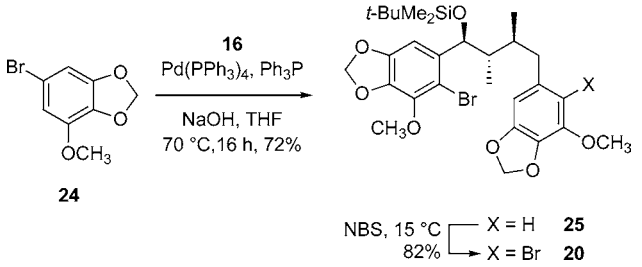
(21) Characteristic chemical shifts for (*P*)-**23**: C4−H/C10−H δ 7.02/6.50; C6−H δ 4.42; C7−CH_3/C8−CH_3 δ 1.03/0.66. For (*M*)-**23**: C4−H/C10−H δ 6.47/6.36; C6−H δ 4.73; C7−CH_3/C8−CH_3 δ 1.17/0.97. For compound **21**: C4−H/C10−H δ 6.87/6.43; C6−H δ 4.37; C7−CH_3/C8−CH_3 δ 0.98/0.65.

Scheme 6



Scheme 7



tane **25** (Scheme 7). Bromination under mild conditions (27 h, $CHCl_3$) occurred with complete regioselectivity to afford the ortho-brominated product **20**, identical with that previously prepared. This effectively transformed the cumbersome three-step conversion of **17** → **18** → **19** → **20** (Scheme 5) into the one-step transformation of **25** → **20** (Scheme 7).

The synthetic strategy developed for the asymmetric total synthesis of interiotherin A and angeloylgomisin R provides a potentially general route to the dibenzocyclooctadiene family of lignans. While the asymmetric crotylation reaction (**8** + **9**) occurs with little diastereoselection as a result of the inability to form crotylborane in geometrically pure form, this problem is under active investigation, and a successful solution to this problem will be described in a subsequent report. Overall, starting from known aryl bromides **8** and **24**, the syntheses of interiotherin A and angeloylgomisin R were achieved in just seven steps.

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Supporting Information Available: Experimental procedures and spectral characterization of intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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