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Catalyzed Cyclizations Leading to Enrichment of Functionality and Chirality. A General Approach to Dibenzocyclooctadiene Lignans from α,ω-Diynes

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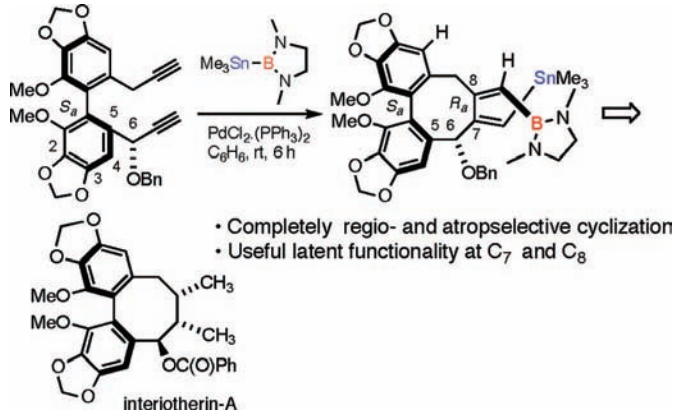
ABSTRACT



The [B−Sn]-mediated cyclization of α,ω-diynes results in not only an increase in the functionalizable groups (incorporated as highly versatile vinyl−B and vinyl−Sn groups) but also an increase in new serviceable stereochemical elements. The alkylidene functionalities at C_7 and C_8 offer unprecedented opportunities for the synthesis of highly functionalized dibenzocyclooctadienes. Examples of interiotherins and gomisins are provided.

We recently described several Pd-catalyzed, $R_3Si-SnR_3$-mediated cyclization reactions of α,ω-diynes, alleneynes, and allene-aldehydes in which relatively simple starting materials are converted into highly functionalized carbocyclic and heterocyclic products.[1,2] The Si and Sn groups in the resulting products are incorporated as vinyl or allyl moieties ready for further elaboration of the carbon frame via reactions involving metal−halogen exchange or cross-coupling chemistry.[3] In the case of diynes (eq 1), the reactions give 1,2-bisalkylidenecycloalkanes (**2**) in which the vinyl derivatives are formed with exquisite (*ZZ*)-stereoselectivity, resulting in uncommon axially chiral products, with a low activation barrier ($\Delta G^{\#} < 60$ kJ/mol at ~ 25 °C) for helical isomerization even when the substituents on silicon and tin are large.

The novel stereochemical features and the dense latent functionality in the product notwithstanding, a number of limitations remain in applying this method to natural product

(1) (a) Gréau, S.; Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2000**, *122*, 8579. (b) Shin, S.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416. (c) Warren, S.; Chow, A.; Fraenkel, G.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 15402. (d) Kumareswaran, R.; Gallucci, J.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 9151. (e) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157.

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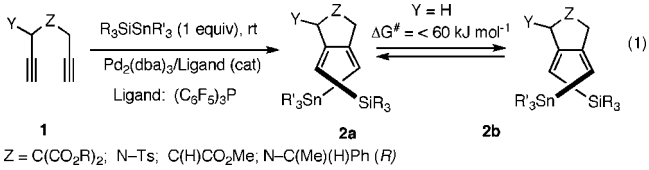
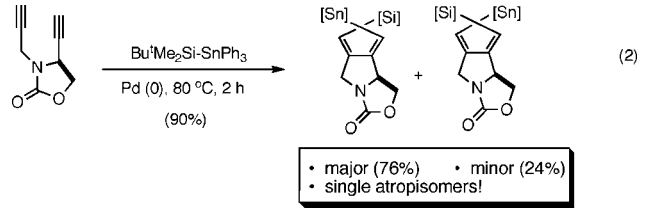


synthesis. For example, poor regioselectivity in the reactions of unsymmetrical substrates (Y ≠ H, eq 1) precludes effective use of the complementary reactivity patterns of the otherwise versatile vinyl Sn and Si moieties, even when the helical isomerization is frozen as in the bicyclic diene shown in eq 2.[3b] Yet another limitation became apparent as we sought application of the [Si−Sn]-mediated cyclization for a general synthesis of dibenzocyclooctadienes (DBCOD)[4] (Figure 1), an important class of compounds with wide-ranging biological activities including inhibition of HIV replication at microgram/milliliter levels.[5]



We reasoned that [Si−Sn]-mediated cyclization of 2,2′-propargylbiphenyl derivatives (Scheme 1) would produce

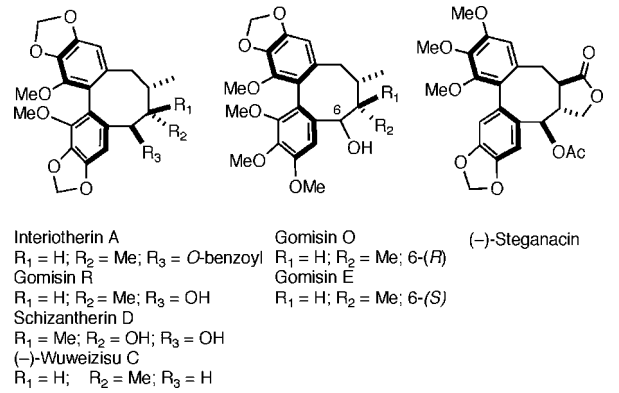
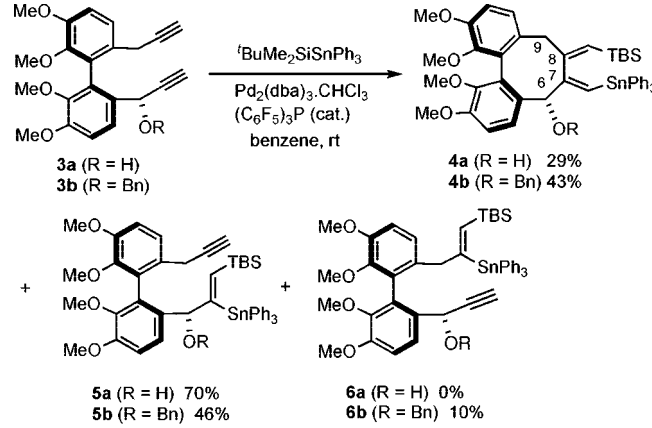


Figure 1. Biologically active dibenzocyclooctadienes.

DBCOD derivatives with dense functionality around the C_7∼C_8 carbons, providing unprecedented opportunities for the synthesis of a wide variety of these compounds, including the more oxidized members such as the antileukemic agent steganacin.

Exploratory studies of the Pd-catalyzed silyl−stannylation cyclization of the model diynes **3** (R = H, Ac, Bz, Bn, OCH_2OBn) under a variety of conditions gave only low to moderate yields of the expected product(s) **4**. Even though **4** is formed as a single stereoisomer, the reaction is complicated by significant contamination from acyclic adducts **5** and **6**.[6] The protecting group on the C_6−OH group has an effect on the regioselectivity of these reactions.[6] While screening other similar [X−Y]-reagents, we found that the diyne **3b** undergoes highly regio- and stereoselective (atropselective) cyclization upon reaction with Me_3Sn−B-[−N(Me)CH_2CH_2N(Me)][7] in the presence of $PdCl_2$·$(PPh_3)_2$ to give a single product **8** (Scheme 2). The moisture-sensitive bisazaborolidine was converted in situ into air-stable vinylboronate **9** by treatment with pinacol in the presence of catalytic amounts of a strong acid.[8] Structures of the (*ZZ*)-1,2-bisalkylidene dibenzocyclooctadienes **8** and **9** were

Scheme 1. Silyl−Stannylation Cyclization of a 2,2′-Propargylbiphenyl Derivative



(2) For recent reviews of multicomponent cyclizations, see: (a) Itoh, K.; Matsuda, I.; Yamamoto, K. J. *Synth. Org. Chem., Jpn.* **1999**, *57*, 912. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. For other representative examples involving acetylenes, see: (c) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (d) Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc.* **1993**, *115*, 11614. (e) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187. (f) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690. (g) Madine, J. W.; Xiang Wang, X.; Widenhoefer, R. A. *Org. Lett.* **2001**, *3*, 385. (h) Doung, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (i) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094. (j) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180. (k) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (l) Denmark, S. E.; Liu, H.-C. *J. Am. Chem. Soc.* **2007**, *129*, 3737.

(3) (a) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053. (b) Shin, Ph. D. Thesis, The Ohio State University, 2004.

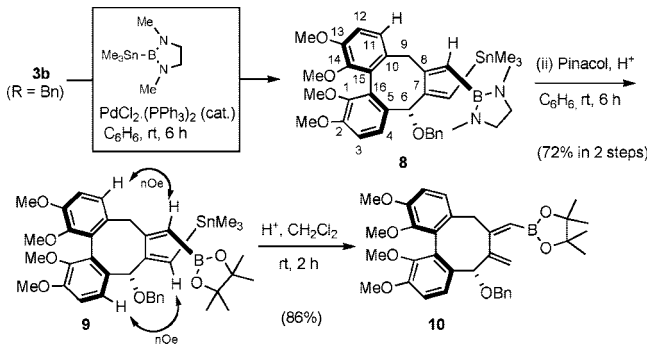
(4) (a) Ayers, D. D.; Loike, J. D. *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, U. K., 1990. (b) Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581. (c) Sefkow, M. *Top. Curr. Chem.* **2005**, *243*, 185. (d) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75. and previous biannual reports in this series.

(5) Representative references to the isolation and biological activities of these classes of compounds: (a) Li, H.; Wang, L.; Yang, Z.; Kitanaka, S. *J. Nat. Prod.* **2007**, *70*, 1999. (b) 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. (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) Kuo, Y.-H.; Wu, M.-D.; Hung, C.-C.; Huang, R.-L.; Kuo, L.-M. Y.; Shen, Y.-C.; Ong, C.-W. *Bioorg. Med. Chem.* **2005**, *13*, 1555. (e) 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. (f) Tan, R.; Li, L. N.; Fang, Q. *Planta Med.* **1984**, *50*, 414. (g) Ikeya, Y.; Taguchi, H.; Yosioka, I. *Chem. Pharm. Bull.* **1982**, *30*, 3207. (h) Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2695.

(6) See Supporting Information for details of the synthesis of axially chiral diyne(s) **3** and a summary of the cyclization studies.

(7) (a) Onozawa, S.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389. Preparation of the [B−Sn]-reagent: Niedenzu, K.; Rothgery, E. F. *Synth. Inorg. Met. Org. Chem.* **1972**, *2*, 1.

Scheme 2. [B−Sn]-Mediated Regio- and Stereoselective Cyclization of an Axially Chiral Diyne



determined by extensive NMR studies and further confirmed by X-ray crystallography of the destannylated compound **10** (Figure 2).[9] In this paper, we report the first prototypical

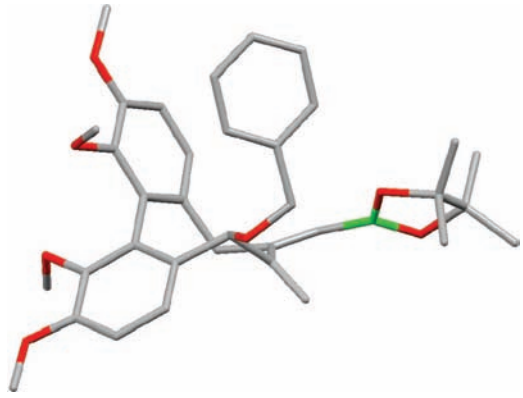


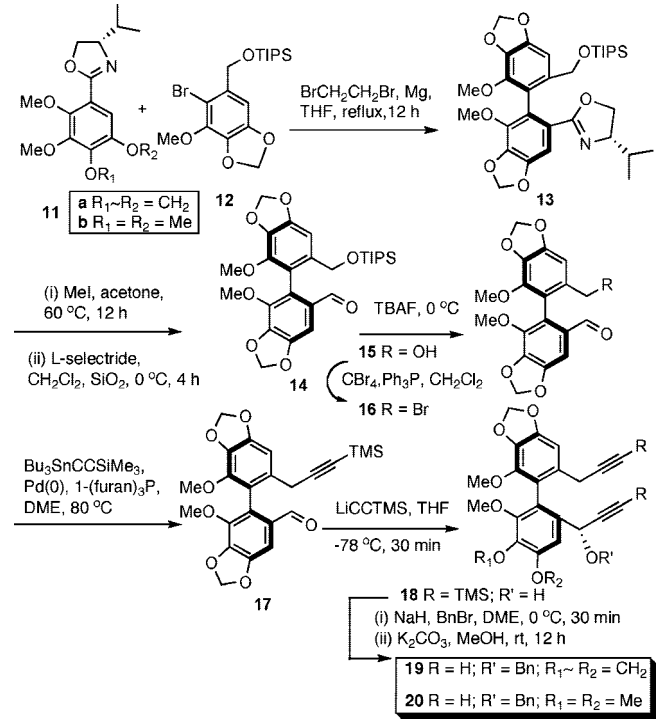
Figure 2. Solid state structure of **10**. Hydrogens omitted for clarity.

applications of the highly regioselective [B−Sn]-mediated cyclization reactions for a general synthesis of DBCOD lignans starting from enantiopure biaryl propargyl derivatives.

Several dibenzocyclooctadienes including cytotoxic agents such as gomisins, schisantherins, interiotherins, and their more oxidized congeners (Figure 2) have been isolated from *Kadura interior* A. C. Smith (Schizadraceae).[4] Gomisins[5b,g,h] E, O, and R and interiotherin A[5c] were selected for initial studies to examine how the resident axial chirality of the starting diyne affects the atropselectivity of the diyne cyclization and how such selectivity can be used to install the other chiral centers around the dibenzocyclooctadiene moiety.

The axially chiral diyne **19** was synthesized in a sequence of reactions that began with the formation of the Grignard reagent from bromoarene **12**,[10] by the entrainment method, followed by addition of aryloxazoline (*S*)-**11a** (Scheme 3).[11]

Scheme 3. Stereoselective Synthesis of 2,2′-Dipropargyl-1,1′-biphenyls



The reaction gave the axially diastereomeric biphenyls (S_aS)-**13** and (R_aS)-**13** as a 92:8 mixture in 82% yield.[12] After N-methylation of **13**, reduction and exposure to silica gel[13] provided the corresponding aldehyde **14**. Desilylation of the benzyl alcohol and its conversion to a benzyl bromide **16** followed by Stille coupling[14] with tri-*n*-butylstannyltrimethylsilylacetylene[15] yielded **17** without affecting the aldehyde functional group. Substrate controlled, stereoselective addition of lithium trimethylsilylacetylide to the *si* face of aldehyde **17** exclusively gave a single benzylic alcohol **18**, which was protected as its benzyl ether. The configuration of the benzylic carbon (C_6) in **18** was initially assigned on the basis of its relation to the solid state structure of analogous compound **10** (Scheme 2) but was eventually confirmed by its elaboration into the known compounds **30a** and **30b**. Benzyl protection followed by desilylation of **18**

(8) (a) Biffar, W.; Nöth, H.; Schwerthoffer, R. *Liebigs Ann. Chem.* **1981**, 2067. (b) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380.

(9) See Supporting Information for the details of NMR studies on **9** and X-ray analysis of **10**.

(10) For a related compound, see: Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025.

(11) (a) Lai, Y. *Synthesis* **1981**, 585. (b) Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. (c) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459.

(12) Diastereoselectivity of the reaction was determined by relative intensities of relevant proton signals in the ^{1}H NMR spectra of the reaction mixture.

(13) Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, *10*, 17.

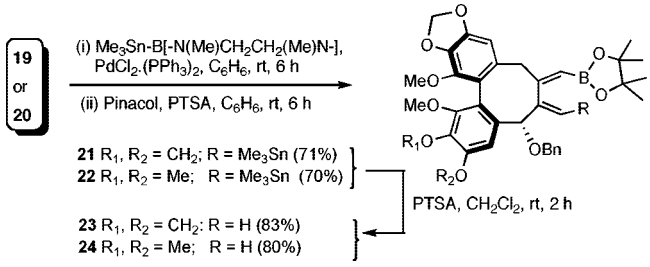
(14) Monovich, L. G.; Huérou, Y. L.; Rönn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 52.

(15) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

using catalytic K_2CO_3 in MeOH yielded the axially chiral diyne **19**. Using the same sequence of reaction conditions as shown in Scheme 3, axially chiral diyne **20** was synthesized starting from (*S*)-2,3,4,5-tetramethoxyphenyloxazoline (**11b**)[11b] instead of the aryloxazoline (*S*)-**11a**.

With the goal of exploring the scope and applications of the new transformations for the synthesis of various dibenzocyclooctadiene lignans carrying the most common aryl substitution patterns, the enantiopure diynes **19** and **20** were subjected to the cyclization reactions to form the (*ZZ*)-1,2-bisalkylidenes **21** and **22**, respectively (Scheme 4).

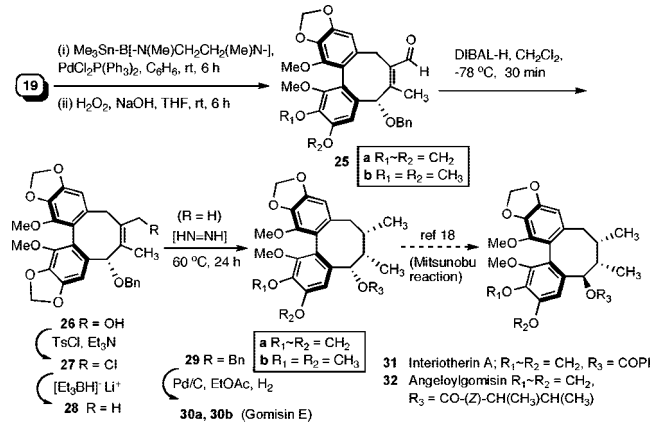
Scheme 4. Stereoselective Borostannylation−Cyclization of Axially Chiral Diynes



The exceptionally high stereoselectivity in the acetylide addition [**17** −> **18**, Scheme 3] and the equally high regioselectivity of the B/Sn incorporation in the cyclization event set the stage for a myriad of ways of functionalizing the C_7 and C_8 carbons of the octadienes **23** or **24**. Application to the synthesis of three prototypical dibenzocyclooctadiene lignans Gomisin E (**30b**), interiotherin A (**31**), and angeloylgomisin R (**32**) are shown in Scheme 5. Borostannylation−cyclization of axially chiral diyne **19** followed by in situ oxidation of air-sensitive alkenylborane by basic H_2O_2 gave a thermodynamically stable enal **25a**. Enal **25a** can also be obtained by basic H_2O_2 oxidation of isolated alkenylborane **23** (Scheme 4). Reduction of enal **25a** with DIBAL-H followed by treatment with tosyl chloride gave the allyl chloride **27**, which was reduced with lithium triethylborohydride, providing the alkene **28**. Subsequent substrate-controlled, stereoselective reduction of the olefin with diimide generated from dipotassium azodicarboxylate[16] yielded the compound **29a** (dr = 88:12), which was also obtained with a dr of 85:15 by Ir-catalyzed directed hydrogenation.[17]

(16) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91.

Scheme 5. Stereoselective Synthesis of Dibenzocyclooctadiene Lignans



After debenzylation, the major product **30a** was separated from the minor compound by column chromatography. Compound **30a** has previously been transformed into interiotherin A (**31**) and angeloylgomisin R (**32**) via Mitsunobu reaction with the appropriate acid.[18] Using a similar route starting with the diyne **20** (Scheme 3), gomisin E (**30b**) and gomisin O (6-*epi*-gomisin E)[5h] (Figure 1) can also be prepared. Further manipulations such as introduction of an −OH moiety at C_8, oxidation or deoxygenation of the C_6−OH derivatives, and adjustment of oxidation levels of C_6 and C_7 substituents would lead to a number of other more complex dibenzocyclooctadienes. Such studies are in progress.

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Supporting Information Available: Details of cyclization studies on diynes of **3**, **19**, and **20** including spectroscopic and chromatographic data for key compounds and a crystallographic information file for X-ray analysis of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) The minor product arises via hydrogenation from the opposite face of the alkene.

(18) Coleman, R. S.; Gurrala, S. R.; Mitra, S.; Raao, A. *J. Org. Chem.* **2005**, *70*, 8932.