JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Total Synthesis of Rubriflordilactone A

Jian Li,† Peng Yang,† Ming Yao, Jun Deng, and Ang Li*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: The first and asymmetric total synthesis of rubriflordilactone A, a bisnortriterpenoid isolated from *Schisandra rubriflora*, has been accomplished in a convergent manner. Two enantioenriched fragments were forged together to give a functionalized *cis*-triene. A 6π-electrocyclization/aromatization sequence assembled the penta-substituted arene, and a formal vinylogous Mukaiyama aldol reaction introduced the butenolide side chain.

In the past two decades, *Schisandraceae* triterpenoids have attracted increasing attention because of their intriguing structures and diverse biological activities.[1] Considerable efforts have been made toward the chemical synthesis of these molecules. Recently, Yang et al. disclosed a groundbreaking total synthesis of schindilactone A,[2] which, to our knowledge, represents the only example of the synthesis of a *Schisandraceae* triterpenoid among over 100 members.[3,4] In 2006, Sun et al. reported the isolation of rubriflordilactones A and B (**1** and **2**, Figure 1) from *Schisandra rubriflora* that has been widely used

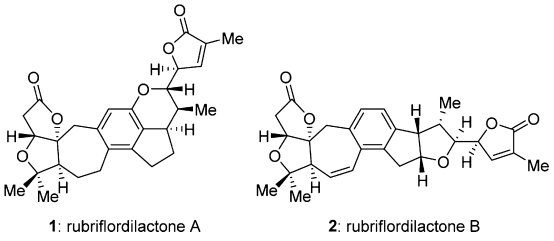
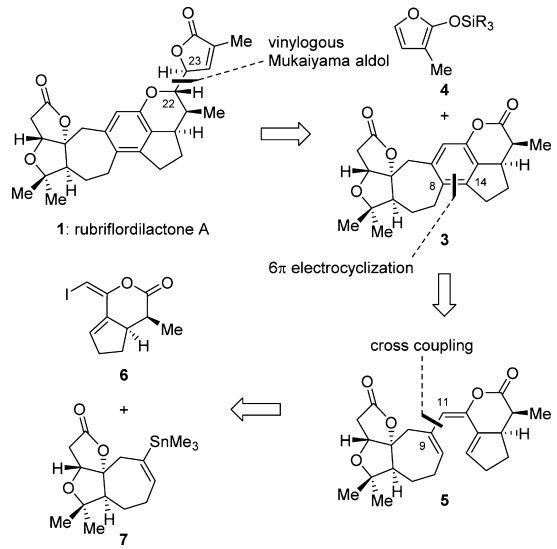


Figure 1. Rubriflordilactones A and B (**1** and **2**).

in Chinese herbal medicine.[5] It is noteworthy that the latter compound exhibits promising anti-HIV activity.[5] Distinct from the rest of the *Schisandraceae* triterpenoids, **1** and **2** possess a multisubstituted arene motif in their heptacyclic framework, which is of particular interest for us as well as others.[4a−f] Recently, we have applied a 6π-electrocyclization/aromatization strategy in the syntheses of arene-containing polycyclic natural products.[6−9] Herein, we report the first total synthesis of rubriflordilactone A (**1**) with such a strategy.

As illustrated in Scheme 1, we undertook a retrosynthetic analysis of **1**. First, the butenolide side chain is cleaved at the C22−C23 bond, giving a key intermediate, hexacyclic dilactone **3**; a vinylogous Mukaiyama aldol reaction with furan derivative **4**[10] is envisioned to install the side chain in a forward manner. The penta-substituted arene of **3** is then disassembled to afford

Scheme 1. Retrosynthetic Analysis of 1



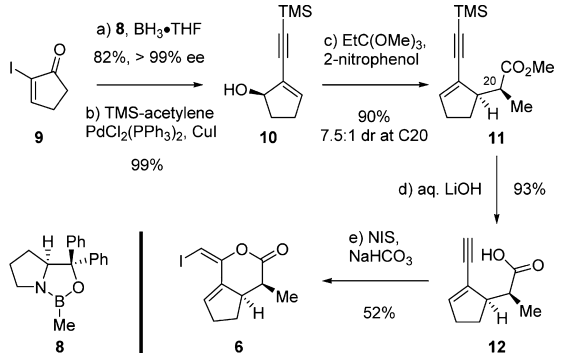
triene **5** as the precursor of a 6π-electrocyclization/aromatization sequence. Further disconnection at the C9−C11 bond provides two fragments **6** and **7**, which could be forged together by a Pd-catalyzed cross coupling reaction. This disconnection eases the segment coupling step and leaves the challenge of forming the sterically more demanding C8−C14 to the electrocyclization step. Notably, the both fragments need to be prepared in the enantioenriched forms to avoid the generation of diastereomerically mismatched coupling products. The geometry of alkenyl iodide **6**, as well as the retention of this geometry through Pd-catalyzed cross coupling, needs to be secured. The preparation of **7** would take advantage of Yang's synthesis of the racemic 5,7-bicyclic system.[2]

The synthesis commenced with preparing the right-hand segment **6** (Scheme 2). Corey−Bakshi−Shibata reduction[11] [oxazaborolidine **8** (5 mol %), BH_3·THF] of 2-iodo-2-cyclopentenone **9** afforded the corresponding alcohol (>99% ee), which underwent Sonogashira coupling with TMS-acetylene to give compound **10** with good overall efficiency.[12] This alcohol was subjected to the conditions for Johnson−Claisen rearrangement [2-nitrophenol (2 mol %), $EtC(OMe)_3$, 100 °C][13] to furnish methyl ester **11** [90%, 7.5:1 dr at C20 (the numbering system of **1**)]. Upon treatment with aq LiOH, saponification along with desilylation occurred to provide acid

Received: September 8, 2014
Published: October 31, 2014

   dx.doi.org/10.1021/ja5092563 | J. Am. Chem. Soc. 2014, 136, 16477−16480

Scheme 2. Synthesis of the Right-Hand Segment[a]



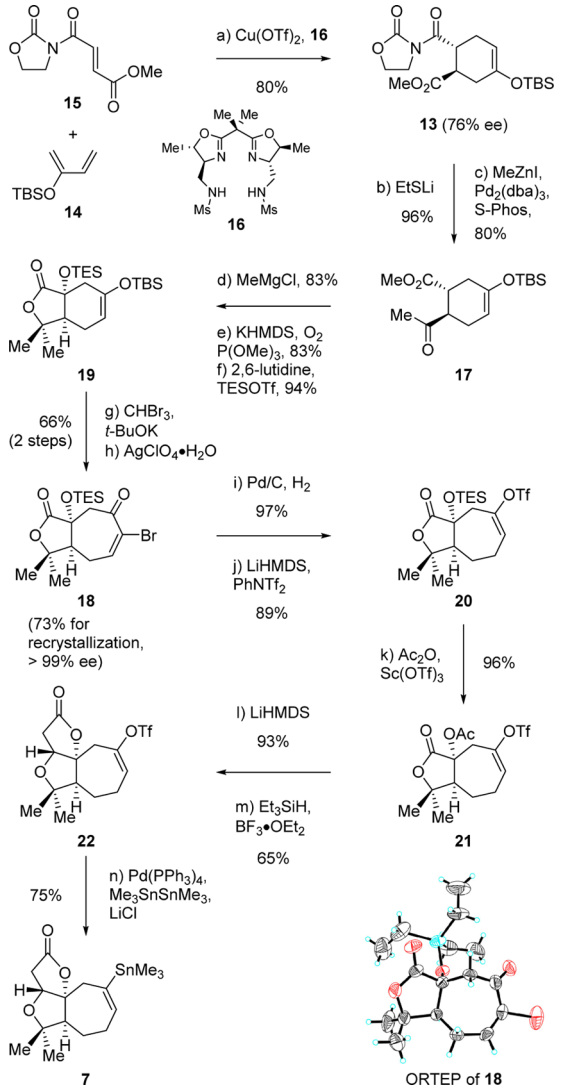
[a]Reagents and conditions: (a) **8** (5 mol %), BH_3·THF (0.67 equiv), THF, 0 °C, 30 min, 82%, > 99% ee; (b) $Pd(PPh_3)_2Cl_2$ (0.5 mol %), CuI (1 mol %), TMS-acetylene (3.0 equiv), toluene, 50 °C, 2 h, 99%; (c) 2-nitrophenol (2 mol %), $EtC(OMe)_3$ (1.7 equiv), 100 °C, 48 h, 90%, 7.5:1 dr at C20; (d) aq LiOH (1.0 M)/THF (1:1), 60 °C, 4 h, 93%; (e) NIS (1.0 equiv), $NaHCO_3$ (2.0 equiv), acetonitrile, 22 °C, 1.5 h, 52%.

12 in 93% yield. Exposure of this compound to NIS/$NaHCO_3$ resulted in a stereospecific iodolactonization,[14] giving *E*-alkene **6** in 52% yield. It is noteworthy that **6** is of poor stability and needs to be prepared freshly before use.

In Scheme 3 was depicted the construction of the left-hand segment **7**. We employed the Cu-catalyzed asymmetric Diels–Alder reaction developed by Ishihara et al.[15] to prepare the optically active building block **13** from the known diene **14** and dienophile **15**. In the presence of $Cu(OTf)_2$ and bis-oxazoline ligand **16**, the cycloaddition occurred smoothly to afford compound **13** in 80% yield, albeit with moderate ee (76%). Replacement of the oxazolidinone moiety with EtSLi, followed by Pd-catalyzed methyl coupling with the resultant thioester [$Pd_2(dba)_3$, S-Phos, MeZnI],[16] gave ketone **17** with good overall efficiency. **17** was subjected to a five-step sequence developed by Yang et al. for their elegant synthesis of racemic schindilactone A to reach bromoenone **18**,[2] via the intermediacy of lactone **19**. Fortunately, we were able to recrystallize this bromide, and the crystals so obtained turned out to be an essentially racemic mixture. Thus, the product from the mother liquid reached an excellent level of enantiopurity (>99% ee, 73% yield). The absolute configuration of the enantioenriched **18** was determined by X-ray crystallographic analysis (Scheme 3). Hydrogenation (Pd/C, H_2) saturated the enone olefin and also reduced the resulting bromide, to give the desired cycloheptanone in one pot (97% yield), which was then converted to triflate **20** (LiHMDS, $PhNTf_2$) in 89% yield in a regioselective fashion. The excellent selectivity may be attributable to the steric difference between the α and α' positions of the carbonyl. Swapping TES with Ac [Ac_2O, $Sc(OTf)_3$] furnished acetate **21** (96% yield). Intramolecular Dieckmann condensation (LiHMDS) provided a hemiketal intermediate (93% yield),[2] and the subsequent cationic deoxygenation (Et_3SiH, BF_3·OEt_2)[17] provided tricycle **22** in 65% yield along with 29% of the recovered starting material. Stannylation [$Pd(PPh_3)_4$, $Me_3SnSnMe_3$, LiCl][18] of **22** afforded the left-hand segment **7** (75% yield), setting the stage for the cross coupling with the right-hand segment **6**.

With both fragments in hand, we entered the final stage of the synthesis, as shown in Scheme 4. A variety of conditions for Stille–Migita reaction were examined, and the Pd(0)/CuTC

Scheme 3. Synthesis of the Right-Hand Side Segment[a]

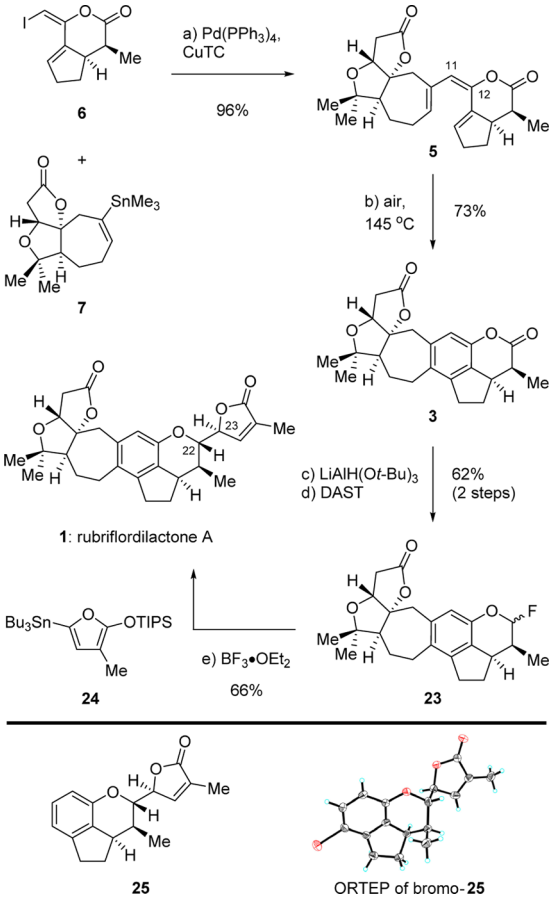


[a]Reagents and conditions: (a) $Cu(OTf)_2$ (5 mol %), **16** (5.5 mol %), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 2 d, 80%, 76% ee; (b) EtSH (3.0 equiv), BuLi (2.5 equiv), THF, 0 °C, 30 min, 96%; (c) $Pd_2(dba)_3$ (1 mmol %), *S*-Phos (5 mmol %), MeZnI (5.0 equiv), NMP/THF (1.5:1), 65 °C, 1.5 h, 80%; (d) MeMgCl (1.1 equiv), THF, −40 °C, 1 h, then −20 °C, 45 min, 83%; (e) KHMDS (1.1 equiv), THF, −78 °C, 30 min; then $P(OMe)_3$ (1.5 equiv), O_2, −78 °C, 20 min, 83%; (f) TESOTf (1.5 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0 °C, 30 min, 94%; (g) $CHBr_3$ (3.0 equiv), *t*-BuOK (3.0 equiv), petroleum ether, −20 °C, 1 h; (h) $AgClO_4$·H_2O (2.0 equiv), $CaCO_3$ (5.0 equiv), acetone, 30 °C, 10 h, 66% (2 steps); compound **18** was recrystallized with EtOAc/petroleum ether (1:6) to give the enantioenriched form (73%, > 99% ee) after removal of the essentially racemic crystals; (i) Pd/C (4 mol %), H_2 (1 atm), MeOH/EtOAc (1:1), 22 °C, 1.5 h, 97%; (j) LiHMDS (2.5 equiv), $PhNTf_2$ (1.8 equiv), THF, −25 °C, 2 h, 89%; (k) $Sc(OTf)_3$ (10 mol %), Ac_2O (5.0 equiv), acetonitrile, 10 min, 96%; (l) LiHMDS (1.6 equiv), THF, 0 °C, 5 min, 93%; (m) Et_3SiH (25.0 equiv), BF_3·OEt_2 (20.0 equiv), 35 °C, 3 h, 65% (29% for the recovered starting material); (n) $Pd(PPh_3)_4$ (10 mol %), $Me_3SnSnMe_3$ (1.5 equiv), LiCl (1.5 equiv), THF, 60 °C, 15 min, 75%.

catalytic systems[19] promoted the coupling between **6** and **7** efficiently to afford triene **5** in 96% yield. The *E*-geometry of the C11=C12 bond was strictly retained through this mild and rapid coupling, which is crucial to the following cyclization. It

dx.doi.org/10.1021/ja5092563 | J. Am. Chem. Soc. 2014, 136, 16477–16480

Scheme 4. Completion of the Synthesis of 1[a]



[a]Reagents and conditions: (a) **6** (1.23 equiv), **7** (1.0 equiv), $Pd(PPh_3)_4$ (10 mol %), CuTC (1.5 equiv), NMP, 10 min, 96%; (b) O_2, DMSO, 145 °C, 45 min, 73%; (c) $LiAlH(Ot\text{-}Bu)_3$ (1.1 equiv), THF, 5 °C, 10 min; (d) DAST (2.0 equiv), CH_2Cl_2, 22 °C, 10 min, 62% (2 steps); (e) **24** (3.8 equiv), $BF_3{\cdot}OEt_2$ (3.2 equiv), CH_2Cl_2, 22 °C, 5 min, 66%.

should be noted that the electrocyclization of multisubstituted triene containing an enol ester moiety lacked precedents to our knowledge; its thermal stability could be a problem. To our delight, heating **5** in DMSO at 145 °C under an air atmosphere effected the 6π-electrocyclization and aromatization in one pot, giving arene **3** in 73% yield. Treatment of **3** with bulky $LiAlH(Ot\text{-}Bu)_3$[20] successfully differentiated the two lactone carbonyls to furnish a mixture of the six-membered lactol and its ring-opened aldehyde form after aqueous workup. The attempts to directly react the mixture with siloxy furan **4** resulted in the formation of an open-chain secondary alcohol, and the standard acetylation conditions opened the lactol completely and generated the corresponding phenyl acetate. This ring-opening tendency may be attributable to the internal strain of the 6,5,6-tricyclic system and the good leaving ability of the phenoxide. We then exposed the lactol/aldehyde mixture to DAST and obtained fluoride **23**[21] (62% overall yield from **3**) as an activated "donor" for the next *C*-glycosylation-type reaction. However, **23** turned out to be unreactive against siloxy furan nucleophiles; only allyltrimethylsilane can attack it upon the activation of $BF_3{\cdot}OEt_2$. Thus, we made recourse to a potentially more powerful "donor" **24**.[22−24] This stannane reacted with **23** smoothly in the presence of $BF_3{\cdot}OEt_2$, to provide **1** in 66% yield as a single detectable diastereomer. A model compound **25** was synthesized through a similar protocol to confirm the stereochemical outcome of the last step: the structure of bromo-**25** was determined by X-ray crystallographic analysis (Scheme 4).[25] The spectra and physical properties of the synthetic sample are identical with those reported for the natural product, which also verifies the absolute configuration of **1**.

In summary, we have accomplished the first and asymmetric total synthesis of **1**. The two segments were prepared in essentially enantiopure forms and assembled through Stille−Migita coupling; the geometry of the triene was secured. A one-pot 6π-electrocyclization/oxidative aromatization served as the key step of the synthesis, and a formal vinylogous Mukaiyama aldol reaction installed the butenolide side chain at the final stage. The work may facilitate the biological studies on *Schisandraceae* triterpenoids.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization (cif, pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ali@sioc.ac.cn

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Prof. Zhen Yang. We thank Profs. Handong Sun, Jianxin Pu, and Weilie Xiao, and Dr. Tianwen Sun for helpful discussions. Financial support was provided by Ministry of Science & Technology (2013CB836900), National Natural Science Foundation of China (21290180, 21172235, and 21222202), and China Postdoctoral Science Foundation (2014M561537, M.Y.).

■ REFERENCES

(1) Selected reviews of *Schisandraceae* triterpenoids: (a) Zhao, J.; Shen, B.; Yuan, Q.; Jin, Z.; Li, L. *Tianran Chanwu Yanjiu Yu Kaifa* **2000**, *12*, 101. (b) Chen, Y.; Qin, G.; Xie, Y. *Huaxue Yanjiu Yu Yingyong* **2001**, *13*, 363. (c) Xiao, W.-L.; Li, R.-T.; Huang, S.-X.; Pu, J.-X.; Sun, H.-D. *Nat. Prod. Rep.* **2008**, *25*, 871. (d) Xia, Y.-G.; Yang, B.-Y.; Kuang, H.-X. *Phytochem. Rev.* **2014**, DOI: 10.1007/s11101-014-9343-7.

(2) (a) Xiao, Q.; Ren, W.-W.; Chen, Z.-X.; Sun, T.-W.; Li, Y.; Ye, Q.-D.; Gong, J.-X.; Meng, F.-K.; You, L.; Liu, Y.-F.; Zhao, M.-Z.; Xu, L.-M.; Shan, Z.-H.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 7373. (b) Sun, T.-W.; Ren, W.-W.; Xiao, Q.; Tang, Y.-F.; Zhang, Y.-D.; Li, Y.; Meng, F.-K.; Liu, Y.-F.; Zhao, M.-Z.; Xu, L.-M.; Chen, J.-H.; Yang, Z. *Chem.—Asian J.* **2012**, *7*, 2321. (c) Li, Y.; Chen, Z.-X.; Xiao, Q.; Ye, Q.-D.; Sun, T.-W.; Meng, F.-K.; Ren, W.-W.; You, L.; Xu, L.-M.; Wang, Y.-F.; Chen, J.-H.; Yang, Z. *Chem.—Asian J.* **2012**, *7*, 2334. (d) Ren, W.-W.; Chen, Z.-X.; Xiao, Q.; Li, Y.; Sun, T.-W.; Zhang, Z.-Y.; Ye, Q.-D.; Meng, F.-K.; Yon, L.; Zhao, M.-Z.; Xu, L.-M.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Chem.—Asian J.* **2012**, *7*, 2341.

(3) Related studies by Yang et al.: (a) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593. (b) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 885. (c) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 1657. (d) Zhang, Y.-D.; Tang, Y.-F.; Luo,

T.-P.; Shen, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2006**, *8*, 107. (e) Zhang, Y.-D.; Ren, W.-W.; Lan, Y.; Xiao, Q.; Wang, K.; Xu, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2008**, *10*, 665. (f) Li, Z.; Cao, Y.; Jiao, Z.; Wu, N.; Wang, D. Z.; Yang, Z. *Org. Lett.* **2008**, *10*, 5163.

(4) Synthetic studies on *Schisandraceae* triterpenoids from other groups: (a) Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323. (b) Cordonnier, M. C. A.; Kan, S. B. J.; Anderson, E. A. *Chem. Commun.* **2008**, 5818. (c) Anderson, E. A. *Org. Biomol. Chem.* **2011**, *9*, 3997. (d) Goh, S. S.; Baars, H.; Gockel, B.; Anderson, E. A. *Org. Lett.* **2012**, *14*, 6278. (e) Wang, Q.; Chen, C. *Org. Lett.* **2008**, *10*, 1223. (f) Gockel, B.; Goh, S. S.; Puttock, E. J.; Baars, H.; Chaubet, G.; Anderson, E. A. *Org. Lett.* **2014**, *16*, 4480. (g) Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 2111. (h) Lai, K. W.; Paquette, L. A. *Org. Lett.* **2008**, *10*, 2115. (i) Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 3781. (j) Chenoweth, D. M.; Chenoweth, K.; Goddard, W. A. *J. Org. Chem.* **2008**, *73*, 6853. (k) Mehta, G.; Bhat, B. A. *Tetrahedron Lett.* **2009**, *50*, 2474. (l) Mehta, G.; Bhat, B. A.; Kumara, T. H. S. *Tetrahedron Lett.* **2009**, *50*, 6597. (m) Maity, S.; Matcha, K.; Ghosh, S. *J. Org. Chem.* **2010**, *75*, 4192. (n) Bartoli, A.; Chouraqui, G.; Parrain, J. L. *Org. Lett.* **2012**, *14*, 122.

(5) Xiao, W.-L.; Yang, L.-M.; Gong, N.-B.; Wu, L.; Wang, R.-R.; Pu, J.-X.; Li, X.-L.; Huang, S.-X.; Zheng, Y.-T.; Li, R.-T.; Lu, Y.; Zheng, Q.-T.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 991.

(6) (a) Bian, M.; Wang, Z.; Xiong, X. C.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078. (b) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679. (c) Meng, Z.; Yu, H.; Li L.; Tao, W.; Chen, H.; Wan, M.; Edmonds, D. J.; Zhong, J.; Li, A. Manuscript submitted.

(7) Selected examples of 6π-electrocyclization/aromatization in natural product synthesis: (a) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998. (b) Ohmori, K.; Mori, K.; Ishikawa, Y.; Tsuruta, H.; Kuwahara, S.; Harada, N.; Suzuki, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 3167. (c) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem., Int. Ed.* **2005**, *44*, 1221. (d) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620. (e) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946. (f) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643. (g) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403. (h) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775. (i) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; Lalonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (j) Suzuki, T.; Hamura, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2248. (k) Sloman, D. L.; Mitasev, B.; Scully, S. S.; Beutler, J. A.; Porco, J. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 2511. (l) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. *Org. Lett.* **2012**, *14*, 5388.

(8) Other recent examples of 6π-electrocyclization in natural product synthesis: (a) Lumb, J.-P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Münzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Biol.* **2008**, *4*, 535. (b) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179. (c) Sloman, D. L.; Bacon, J. W.; Porco, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 9952. (d) Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47*, 10605. (e) Drew, S. L.; Lawrence, A. L.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 4221. (f) Lim, H. N.; Parker, K. A. *Org. Lett.* **2013**, *15*, 398. (g) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484. (h) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095. (i) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-l.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (j) Hayashi, R.; Ma, Z.-X.; Hsung, R. P. *Org. Lett.* **2012**, *13*, 252.

(9) An elegant review of biosynthetic and biomimetic electrocyclizations: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(10) Selected reviews for vinylogous Mukaiyama aldol reactions: (a) Rassu, G.; Zanardi, F.; Battistinib, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. (b) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929. (c) Casiraghi, G.; Zanardia, F.; Battistinia, L.; Rassuba, G. *Synlett* **2009**, 1525. (d) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

(11) A comprehensive review for CBS reduction: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(12) Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskoković, M. R. *J. Org. Chem.* **1996**, *61*, 118.

(13) (a) Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687. Selected reviews for Johnson−Claisen Rearrangement: (b) Hiersemann, M.; Nubbemeyer, U. Claisen−Johnson Orthoester Rearrangement. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007. (c) Fernandes, R. A.; Chowdhury, A. K.; Kattanguru, P. *Eur. J. Org. Chem.* **2014**, 2833.

(14) Sofia, M. J.; Katzenellenbogen, J. A. *J. Org. Chem.* **1985**, *50*, 2331.

(15) (a) Sakakura, A.; Kondo, R.; Matsumura, Y.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 17762. An elegant application: (b) Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14710.

(16) (a) Tokuyama, H.; Yokoshima, S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(17) (a) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417. (b) Lewis, M. D.; Cha, K. C.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(18) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 277.

(19) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765. (c) Fürstner, A.; Funel, J. A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873. (d) Lim, H. N.; Parker, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 20149.

(20) (a) Parham, W. E.; Huestis, L. D. *J. Am. Chem. Soc.* **1962**, *84*, 813. (b) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, 5294.

(21) (a) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5. A comprehensive review: (b) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15.

(22) The preparation of **24**: Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918.

(23) Applications of alkenyl stannanes in the *C*-glycosylation-type reactions: Elmore, S. W.; Coghlan, M. J.; Anderson, D. D.; Pratt, J. K.; Green, B. E.; Wang, A. X.; Stashko, M. A.; Lin, C. W.; Tyree, C. M.; Miner, J. N.; Jacobson, P. B.; Wilcox, D. M.; Lane, B. C. *J. Med. Chem.* **2001**, *44*, 4481.

(24) Mechanistically similar Boron-directing cationic reactions: (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583. (b) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438. (c) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42. (d) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940. (e) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994.

(25) The formal vinylogous Mukaiyama aldol reaction could indeed be a Friedel−Crafts/acidic desilylation sequence. The C22 stereochemistry may be controlled by the pseudoaxial methyl group on the rigid 6,6,5-tricyclic framework, and further computational studies are underway to rationalize the good C23 diastereoselectivity.