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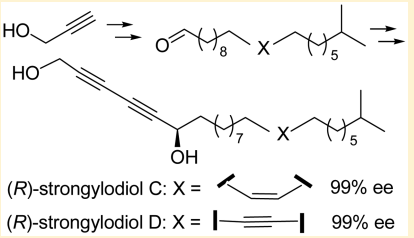
Total Syntheses of (*R*)-Strongylodiols C and D

Feipeng Liu, Jiangchun Zhong, Shuoning Li, Minyan Li, Lin Wu, Qian Wang, Jianyou Mao, Shikuo Liu, Bing Zheng, Min Wang, and Qinghua Bian*

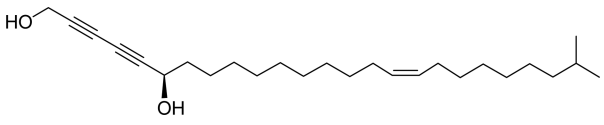
Department of Applied Chemistry, China Agricultural University, 2 West Yuanmingyuan Road, Beijing 100193, People's Republic of China

Supporting Information

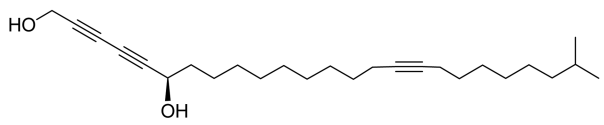
ABSTRACT: The first total syntheses of two marine natural products, (*R*)-strongylodiols C and D, with 99% ee were achieved. The key steps of the strategy include the zipper reaction of an alkyne, the asymmetric alkynylation of an unsaturated aliphatic aldehyde catalyzed with Trost's ProPhenol ligand, and the Cadiot−Chodkiewicz cross-coupling reaction of a chiral propargylic alcohol with a bromoalkyne.



Long-chain acetylenic alcohols are important marine natural products,[1] which have been found to show many biological activities such as antibacterial,[2] antitumor,[3] and neuritogenic effects.[4] Strongylodiols C and D were both isolated from an Okinawan marine sponge of the genus *Strongylophora*, and their structures were elucidated based on spectroscopic analysis.[3,5] They were found to exist as enantiomeric mixtures (*R*/*S* ratio 84:16 for strongylodiol C and 95:5 for strongylodiol D) through application of the modified Mosher's method.[3,5] Recently Ojika and co-workers reported that these compounds induced nerve growth factor (NGF)-like neuronal differentiation of PC12 cells[6] and showed an inhibitory effect on platelet-derived growth factor (PDGF)-induced DNA synthesis.[7] In addition, strongylodiol C was found to exhibit cytotoxic activity against human T lymphocyte leukemia (MOLT-4) tumor cells.[3]



(*R*)-strongylodiol C (**1**)



(*R*)-strongylodiol D (**2**)

Strongylodiols A and B, two analogues of strongylodiols C and D, were also isolated from an Okinawan marine sponge of the genus *Strongylophora*.[3] A number of enantioselective syntheses of these two acetylenic alcohols have been reported, and the main asymmetric synthetic methods involved the addition of 1,3-diynes to aldehydes by Trost,[8] Carreira,[8b] and our group[8c] or the reduction of ynones.[8d] However, these strategies tended to use lengthy sequences or 1,3-diynes that required prior preparation or gave the target product with low enantioselectivity. Therefore, it remains a challenge to search for more efficient and convenient asymmetric syntheses of these acetylenic alcohols. The enantioselective addition of commercial terminal alkynes to aldehydes is the most convenient protocol to obtain chiral propargyl alcohols.[9a,b] Furthermore, no examples of the syntheses of strongylodiols C and D have been reported. Herein, we disclose the first total syntheses of (*R*)-strongylodiols C (**1**) and D (**2**) with 99% ee and demonstrate that the asymmetric enantioselective addition of terminal alkynes to aldehydes can construct the chiral propargylic alcohol unit of long-chain acetylenic alcohols.

The retrosynthetic analysis of (*R*)-strongylodiol C (**1**) is outlined in Figure 1. The target long-chain acetylenic alcohol **1** can be formed via the Cadiot−Chodkiewicz cross-coupling reaction of chiral propargylic alcohol **19** with 3-bromoprop-2-yn-1-ol. The enantioselective addition of trimethylsilylacetylene to olefinic aldehyde **16** was envisioned to yield the key chiral intermediate **19**. Olefinic aldehyde **16** can be obtained by partial reduction and oxidation of acetylenic alcohol **14**, which would be achieved via the coupling of terminal alkyne **12** with alkyl iodide **9**. Terminal alkyne **12** would be derived from the zipper reaction of alkynol **11**. Due to the structural similarity with (*R*)-strongylodiol C (**1**), (*R*)-strongylodiol D (**2**) can be prepared through a similar approach.

Our synthesis began with the preparation of alkyl iodide **9** (Scheme 1), which served as the key building block for both (*R*)-strongylodiols C and D. Simply heating α,ω-diol **3** and concentrated hydrobromic acid in toluene at reflux gave monobromo alcohol **4** in 86% yield. 7-Bromoheptanoic acid **5** was obtained smoothly via the oxidation of **4** with concentrated HNO_3. Subsequent esterification of **5** with MeOH furnished ω-bromo ester **6** in 91% yield. 8-Bromo-2-methyloctan-2-ol (**7**) was formed from the addition of CH_3MgBr to the ester **6** in 92% yield. After dehydration with

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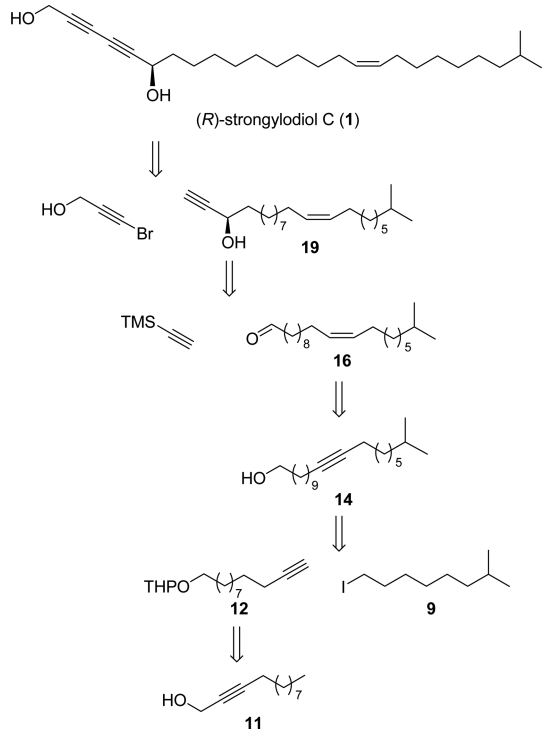
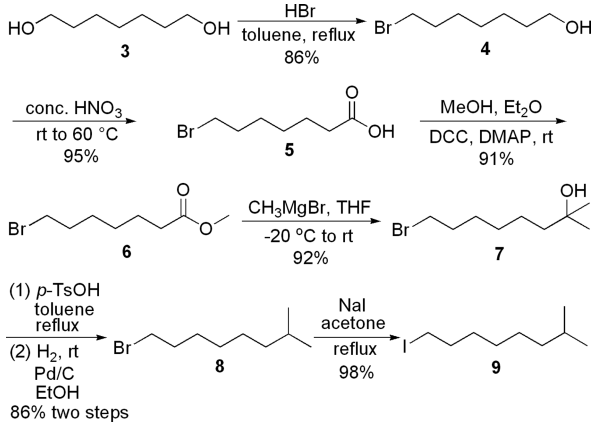


Figure 1. Retrosynthetic analysis of (*R*)-strongylodiol C (**1**).

Scheme 1. Synthesis of Alkyl Iodide 9

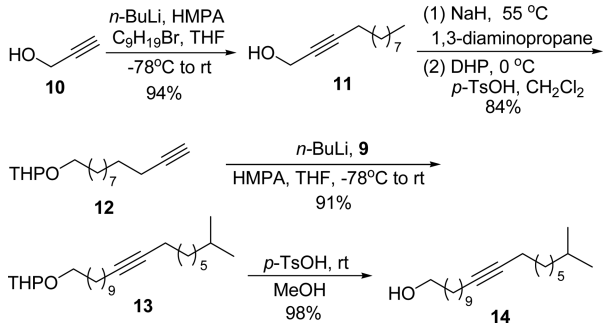


p-toluenesulfonic acid and reduction with H_2 over Pd/C, the *ω*-bromo alcohol **7** was converted to 1-bromo-7-methyloctane (**8**) in 86% yield over the two steps. Finally, alkyl bromide **8** was subjected to NaI in acetone to afford 1-iodo-7-methyloctane (**9**) in 98% yield via a Finkelstein reaction.[10]

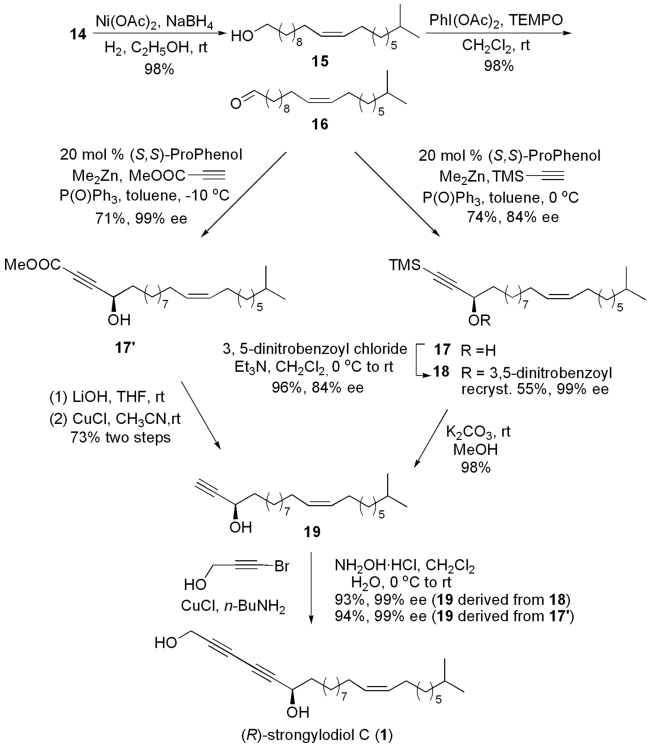
With the main intermediate **9** in hand, we next focused on the synthesis of another important fragment, alkynol **14** (Scheme 2). The alkylation of propargyl alcohol **10** with 1-bromononane in the presence of *n*-BuLi and HMPA gave dodec-2-yn-1-ol (**11**) in 94% yield. The zipper reaction of alkynol **11** with NaH[11] and the protection of the resulting alcohol with dihydropyran proceeded efficiently to furnish the desired terminal alkyne **12** in 84% yield. The alkylation of terminal alkyne **12** with alkyl iodide **9** generated the THP ether **13** in 91% yield. The final deprotection with *p*-toluenesulfonic acid afforded the corresponding alkynol **14** in 98% yield.

Having accessed building block **14**, the asymmetric synthesis of (*R*)-strongylodiol C (**1**) was studied (Scheme 3). The partial

Scheme 2. Synthesis of Alkynol 14



Scheme 3. Synthesis of (*R*)-Strongylodiol C (1)



reduction of alkynol **14** was achieved and afforded (*Z*)-19-methylicos-11-en-1-ol (**15**) as a single product in 98% yield with Brown's P2−Ni catalyst, followed by the oxidation to olefinic aldehyde **16** almost quantitatively (98% yield) with iodobenzene diacetate and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[12] Initial studies showed that aldehyde **16** was a good substrate in the enantioseletive addition with trimethylsilylacetylene using 20 mol % of the (*S,S*)-ProPhenol ligand and Me_2Zn, which provided (*R,Z*)-21-methyl-1-(trimethylsilyl)-docos-13-en-1-yn-3-ol (**17**) in 74% yield and 84% ee.[13] The enantiomeric purity of enynic alcohol **17** was determined by HPLC analysis of its 3,5-dinitrobenzoate **18**. Furthermore, slow recrystallization of **18** from *n*-hexane−diethyl ether (5:1) could improve the optical purity to 99% ee.[14] The final in situ desilylation and methanolysis of **18** with potassium carbonate and MeOH afforded enynic alcohol **19** in 98% yield, which was engaged in a Cadiot−Chodkiewicz cross-coupling reaction with 3-bromoprop-2-yn-1-ol to give the target (*R*)-strongylodiol C (**1**) in 93% yield and 99% ee.[15] The optical purity of **1** was also measured on chiral-phase HPLC analysis of its bis(4-bromobenzoate).[16] The NMR spectroscopic data and specific

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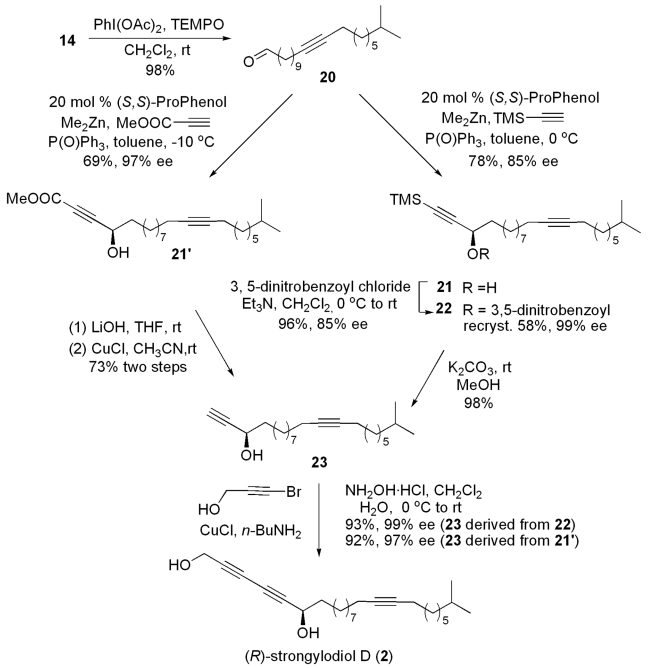
rotation of synthetic chiral acetylenic alcohol **1** ($[\alpha]^{20}_{D}$ −7.3 (*c* 1.0, $CHCl_3$)) were consistent with those of the natural (*R*)-strongylodiol C ($[\alpha]^{22}_{D}$ −7.5 (*c* 0.093, $CHCl_3$)).[3] To search for a more concise synthesis, we tried the asymmetric addition of methyl propiolate to olefinic aldehyde **16** with the (*S,S*)-ProPhenol ligand and Me_2Zn.[17] Fortunately, 99% ee enynic ester **17′** was obtained. Decarboxylation involving saponification with LiOH and treatment with CuCl gave enynic alcohol **19** in 73% yield. The final Cadiot−Chodkiewicz cross-coupling with 3-bromoprop-2-yn-1-ol also afforded almost optically pure (*R*)-strongylodiol C (94% yield, 99% ee).[15]

As depicted in Scheme 4, the synthesis of (*R*)-strongylodiol D commenced with alkynol **14**, which was oxidized to

Scheme 4. Synthesis of (*R*)-Strongylodiol D (2)



acetylenic aldehyde **20** in 98% yield with iodobenzene diacetate and TEMPO.[12] An initial attempt was the Zn-(*S,S*)-ProPhenol asymmetric addition of trimethylsilylacetylene to aldehyde **20**, which delivered (*R*)-21-methyl-1-(trimethylsilyl)docosa-1,13-diyn-3-ol (**21**) in 78% yield and 85% ee.[13] The optical purity of **21** was measured and improved to 99% ee via its 3,5-dinitrobenzoate **22**.[14] Removal of the trimethylsilyl and 3,5-dinitrobenzoyl groups from **22** proceeded smoothly with potassium carbonate and MeOH to obtain chiral propargylic alcohol **23**. Final Cadiot−Chodkiewicz cross-coupling of **23** with 3-bromoprop-2-yn-1-ol gave almost optically pure (99% ee) (*R*)-strongylodiol D (**2**) in 93% yield.[15,16] Furthermore, the specific rotation measured for **2** ($[\alpha]^{20}_{D}$ −7.0 (*c* 1.3, $CHCl_3$)) was in agreement with the value of natural (*R*)-strongylodiol D ($[\alpha]^{25}_{D}$ −8.0 (*c* 0.56, $CHCl_3$, *R/S* ratio 95:5)).[5] The synthetic route to (*R*)-strongylodiol D (**2**) was optimized as for the synthesis of (*R*)-strongylodiol C (**1**). Acetylenic ester **21′** was obtained in 97% ee via Zn-(*S,S*)-ProPhenol asymmetric addition of methyl propiolate to aldehyde **20**.[17] Subsequent decarboxylation furnished chiral propargylic alcohol **23** in 73% yield, which was coupled with 3-bromoprop-2-yn-1-ol to give (*R*)-strongylodiol D (92% yield, 97% ee).[15]

In summary, we have accomplished the total syntheses of marine natural products (*R*)-strongylodiols C (**1**) and D (**2**) with high optical purity (99% ee) for the first time. Central to our approach were a zipper reaction of an alkyne to prepare the terminal alkyne, the asymmetric alkynylation of an aliphatic aldehyde catalyzed with Trost's ProPhenol ligand to construct the chiral propargylic alcohol, and the Cadiot−Chodkiewicz cross-coupling reaction of a chiral propargylic alcohol with a bromoalkyne to obtain the long-chain acetylenic alcohols. These enantioselective syntheses further confirmed the structures of these two natural products.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were obtained on a Stuart-SMP3Melt-Temp apparatus without correction. Optical rotations were measured on a Perkin Elmer 341 polarimeter. NMR spectra were collected on a Bruker DP-X300 MHz spectrometer. Chemical shifts were reported in ppm relative to internal tetramethylsilane (TMS) for ^{1}H NMR (TMS δ = 0.00 ppm) and to $CDCl_3$ for ^{13}C NMR ($CDCl_3$ δ = 77.00 ppm). High-resolution mass spectra (HRMS) were recorded on an Agilent instrument using the TOF MS technique. Enantiomeric excesses (ee) were determined on an Agilent 1200 HPLC system using an R&C OD chiral-phase column and elution with *n*-hexane and 2-propanol. All reactions were carried out under a dry argon atmosphere. Solvents were dried according to standard procedures and distilled before use. Unless otherwise stated, all chemicals were commercially available and used without further purification.

Synthesis of (*R,Z*)-24-Methylpentacosa-16-en-2,4-diyne-1,6-diol ((*R*)-Strongylodiol C, 1) (CAS 320717-32-6). To a stirred solution of *n*-$BuNH_2$ (0.5 mL) and distilled H_2O (1 mL) was added copper(I) chloride (10 mg, 0.10 mml, 0.2 equiv) at 0 °C under argon, which resulted in a deep blue solution. A few crystals of NH_2OH·HCl were added to discharge the blue color, and a solution of enynic alcohol **19** (167 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added via syringe at the same temperature. Then 3-bromoprop-2-yn-1-ol (74 mg, 0.55 mmol, 1.1 equiv) was added slowly. The reaction mixture was warmed to room temperature and stirred for 30 min. A few crystals of NH_2OH·HCl were added occasionally to prevent the solution from turning green or blue throughout the reaction. Upon completion, the reaction solution was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane−ethyl acetate, 5:1) to furnish (*R*)-strongylodiol C (**1**) (180 mg, 93% yield, 99% ee, measured on chiral-phase HPLC analysis of its bis(4-bromobenzoate)) as a colorless oil: $[\alpha]^{20}_{D}$ −7.3 (*c* 1.0, $CHCl_3$), lit.[3] $[\alpha]^{22}_{D}$ −7.5 (*c* 0.093, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.37−5.33 (m, 2H), 4.46−4.40 (dd, *J* = 12.1, 6.2 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 2H), 2.11 (d, *J* = 5.2 Hz, 1H) 2.02−1.98 (m, 5H), 1.76−1.68 (m, 2H), 1.56−1.39 (m, 3H), 1.28−1.14 (m, 22H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 129.88, 129.81, 80.5, 77.6, 69.7, 68.8, 62.7, 51.2, 39.0, 37.4, 29.77, 29.73, 29.72, 29.51, 29.50, 29.48, 29.29, 29.27, 29.2, 27.9, 27.3, 27.2, 25.0, 22.6; HRMS (APCI-TOF) *m/z* 371.3326 $[MH^+ - H_2O]^+$ (calcd for $C_{26}H_{43}O$, 371.3314).

Synthesis of (*R*)-24-Methylpentacosa-2,4,16-triyne-1,6-diol ((*R*)-Strongylodiol D, 2) (CAS 334973-93-2). According to a similar procedure to that described above for (*R*)-strongylodiol C (**1**), the cross-coupling of chiral propargyl alcohol **23** (166 mg, 0.50 mmol) with 3-bromoprop-2-yn-1-ol (74 mg, 0.55 mmol) afforded (*R*)-strongylodiol D (**2**) (179 mg, 93% yield, 99% ee, measured on chiral-phase HPLC analysis of its bis(4-bromobenzoate)) as a white solid: mp 43−44 °C; $[\alpha]^{20}_{D}$ −7.0 (*c* 1.3, $CHCl_3$), lit.[5] $[\alpha]^{25}_{D}$ −8.0 (*c* 0.56, $CHCl_3$, *R/S* ratio 95:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.43 (dd, *J* = 12.3, 6.5 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 2.16−2.10 (m, 5H), 2.05−1.99 (m, 1H), 1.76−1.68 (m, 2H), 1.54−1.24 (m, 23H), 1.19−1.15 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 80.5, 80.3, 80.2, 77.5, 69.8, 68.8, 62.8, 51.4, 39.0, 37.4, 29.4, 29.2, 29.1,

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28.9, 28.8, 27.9, 27.3, 25.0, 22.6, 18.7; HRMS (APCI-TOF) m/z 369.3174 $[MH^+ - H_2O]^+$ (calcd for $C_{26}H_{41}O$, 369.3157).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b00713.

Experimental procedures and characterization data for the bis-bromobenzoates of **1** and **2**, **4**−**9**, and **11**−**23**; copies of ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, and the bis-bromobenzoates of **1** and **2**, **4**−**9**, and **11**−**23**; HPLC chromatography of the bis-bromobenzoates of **1** and **2**, **17′**, **18**, **21′**, and **22** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bianqinghua@cau.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhou, Z.-F.; Menna, M.; Cai, Y.-S.; Guo, Y.-W. *Chem. Rev.* **2015**, *115*, 1543−1596.
(2) Ankisetty, S.; Slattery, M. *Mar. Drugs* **2012**, *10*, 1037−1043.
(3) Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *Tetrahedron Lett.* **2000**, *41*, 9271−9276.
(4) Aoki, S.; Matsui, K.; Wei, H.; Murakami, N.; Kobayashi, M. *Tetrahedron* **2002**, *58*, 5417−5422.
(5) Watanabe, K.; Tsuda, Y.; Hamada, M.; Omori, M.; Mori, G.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *J. Nat. Prod.* **2005**, *68*, 1001−1005.
(6) Horikawa, K.; Yagyu, T.; Yoshioka, Y.; Fujiwara, T.; Kanamoto, A.; Okamoto, T.; Ojika, M. *Tetrahedron* **2013**, *69*, 101−106.
(7) Choi, B.-K.; Cha, B.-Y.; Yagyu, T.; Woo, J.-T.; Ojika, M. *Bioorg. Med. Chem.* **2013**, *21*, 1804−1810.
(8) Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5186−5192. (b) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813−6817. (c) Zheng, B.; Li, S.-N.; Mao, J.-Y.; Wang, B.; Bian, Q.-H.; Liu, S.-Z.; Zhong, J.-C.; Guo, H.-C.; Wang, M. *Chem. - Eur. J.* **2012**, *18*, 9208−9211. (d) Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron Lett.* **2004**, *45*, 5645−5647.
(9) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807. (b) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688−701.
(10) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528−1532.
(11) Santandrea, J.; Bédard, A.-C.; Collins, S. K. *Org. Lett.* **2014**, *16*, 3892−3895.
(12) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977.
(13) Trost, B. M.; Quintard, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6704−6708.
(14) Yang, Y.-Q.; Li, S.-N.; Zhong, J.-C.; Zhou, Y.; Zeng, H.-Z.; Duan, H.-J.; Bian, Q.-H.; Wang, M. *Tetrahedron: Asymmetry* **2015**, *26*, 361−366.
(15) Chodkiewicz, W.; Cadiot, P. *Compt. Rend.* **1955**, *241*, 1055−1057.
(16) The bis-bromobenzoates of **1** and **2** were prepared for the determination of the enantiomeric excess, as the ester derivatives are more readily separable by chiral-phase HPLC.
(17) Trost, B. M.; Quintard, A. *Org. Lett.* **2012**, *14*, 4698−4700.

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J. Nat. Prod. XXXX, XXX, XXX−XXX