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Biomimetic Total Synthesis of (+)-Chabranol

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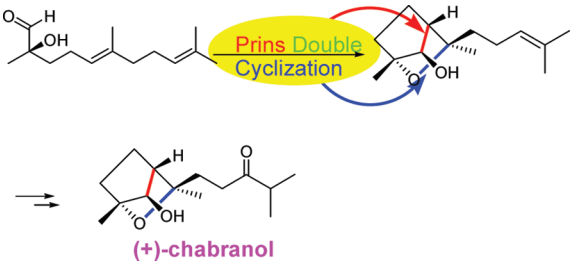


A concise, biomimetic total synthesis of the unprecedented terpenoid skeleton (+)-chabraol has been accomplished via 6 steps from the chiral epoxide **7**, involving an intramolecular Prins double cyclization to yield the bicyclo[2.2.1] core of the natural product as the key step. The absolute configuration of natural chabranol was also designated through the first asymmetric total synthesis.

Soft corals are a particularly rich source of structurally novel sesquiterpenoids with a broad range of biological functions.[1] In 2009, chabranol, possessing an unprecedented terpenoid skeleton, namely a cyclopentane ring fused to a tetrahydrofuran ring at C-3 and C-6, was isolated from the

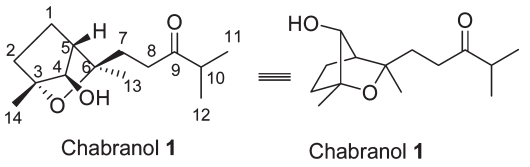
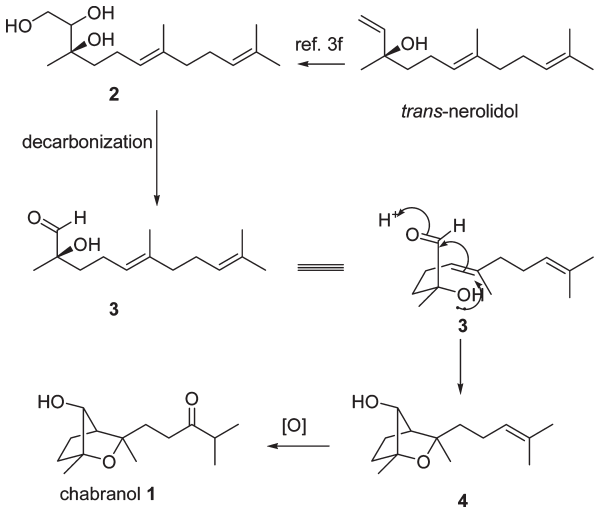


FIGURE 1. The structure of (+)-Chabraol **1**.

SCHEME 1. Proposed Biosynthesis of Chabranol 1



soft corals *Nephthea chabroli* by Duh[2] at National Sun Yat-Sen University (Figure 1). The extremely meager natural supply, novel structural features, and potent biological activities have defined chabranol as an attractive target for total synthesis. Herein, we report the first total synthesis of (+)-chabranol utilizing a biomimetic and highly stereocontrolled strategy in which the absolute configuration of chabranol was also established.

In our quest to synthesize chabranol, we decided to employ the efficient and biomimetic route to complete the target molecule. Duh thought that chabranol may derive from cyclopentane sesquiterpene by enzymatic oxidation.[2,3] On the basis of these ideas, we propose that the biosynthesis of chabranol could follow the steps depicted in Scheme 1. In this process, the protic or Lewis acids would activate aldehyde **3**, subsequently, Prins reaction could occur and the resulting carbocation might be captured by the oxygen atom to give the double cyclization product **4**,[4] which can be further oxidized to achieve chabranol **1**.

(1) (a) Blunt, J. W.; Copp, B. R.; Hu, W. P.; Munro, M. H.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2009**, *26*, 170. (b) Ahmed, A. F.; Kuo, Y. H.; Dai, C. F.; Sheu, J. H. *J. Nat. Prod.* **2005**, *68*, 1208. (c) Fraga, B. M. *Nat. Prod. Rep.* **2007**, *24*, 1350. (d) Fraga, B. M. *Nat. Prod. Rep.* **2008**, *25*, 1180. (e) Fraga, B. M. *Nat. Prod. Rep.* **2009**, *26*, 1125. (f) El-Gamal, A. A. H.; Wang, S. K.; Dai, C. F.; Duh, C. Y. *J. Nat. Prod.* **2004**, *67*, 1455. (g) Wang, S. K.; Duh, C. Y. *Chem. Pharm. Bull.* **2007**, *55*, 762. (h) Cheng, S. Y.; Wen, Z. H.; Wang, S. K.; Chiang, M. Y.; El-Gamal, A. A. H.; Dai, C.-F.; Duh, C. Y. Chem. *Chem. Biodiversity* **2009**, *6*, 86. (i) Cheng, S. Y.; Huang, Y. C.; Wen, Z. H.; Chiou, S. F.; Wang, S. K.; Hsu, C. H.; Dai, C. F.; Duh, C. Y. *Tetrahedron Lett.* **2009**, *50*, 802. (j) Anjaneyulu, A. S. R.; Gowri, P. M.; Krishna Murthy, M. V. R. *J. Nat. Prod.* **1999**, *62*, 1600. (k) Bowden, B. F.; Coll, J. C.; Mitchell, S. J. *Aust. J. Chem.* **1980**, *33*, 1833. (l) Lin, Y. C.; Abd El-Razek, M. H.; Shen, Y. C. *Helv. Chim. Acta* **2010**, *93*, 281. (m) Chang, C. H.; Wen, Z. H.; Wang, S. K.; Duh, C. Y. *J. Nat. Prod.* **2008**, *71*, 619. (n) Kamel, H. N.; Ding, Y.; Li, X. C.; Ferreira, D.; Fronczek, F. R.; Slattery, M. *J. Nat. Prod.* **2009**, *72*, 900.

(2) Cheng, S. Y.; Huang, K. J.; Wang, S. K.; Wen, Z. H; Hsu, C. H.; Dai, C. F.; Duh, C. Y. *Org. Lett.* **2009**, *11*, 4830.

(3) (a) For an excellent review on natural products and biosynthesis see: Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: New York, 2002. (b) Stefan, B.; Andreas, J.; Gerd, G.; Wilhelm, B. *Phytochemistry*. **2006**, *67*, 1661. (c) Eisenreich, W.; Bacher, A.; Arigoni, D.; Rohdich, F. *Cell. Mol. Life Sci.* **2004**, *61*, 1401. (d) Tanja, R.; Felix, R.; Juraithip, W.; Stefan, H.; Klaus, K.; Wolfgang, E; Adelbert, B.; Meinhart, H. Z.; Duilio, A. *FEBS Lett.* **2000**, *465*, 157. (e) Mitsuo, M.; Hitokazu, N.; Hiromu, K. *J. Agric. Food Chem.* **1996**, *44*, 1543. (f) Abraham, W. R. *World J. Microbiol. Biotechnol.* **1993**, *9*, 319.

(4) Jung, M. E.; Angelica, S.; D'Amico, D. *J. Org. Chem.* **1997**, *62*, 9182.

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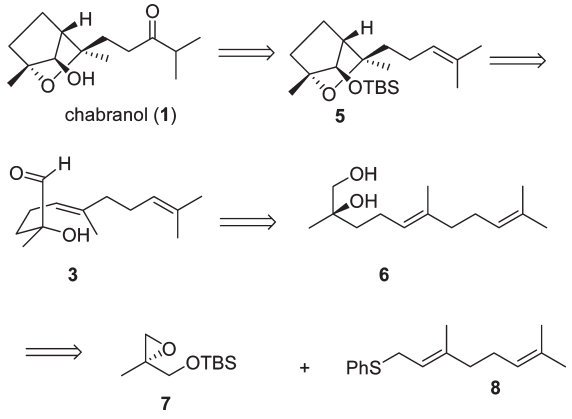
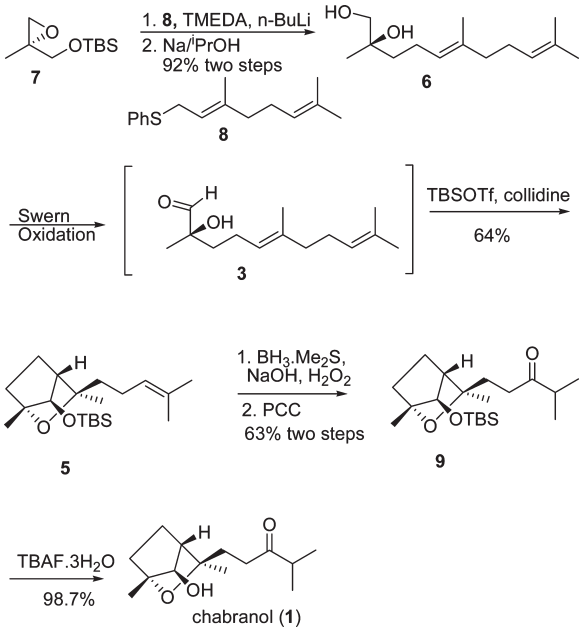
SCHEME 2. Retrosynthetic Analysis of Chabranol 1



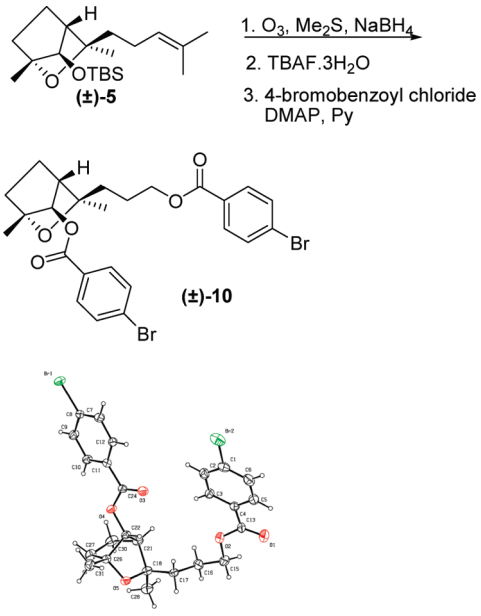
SCHEME 3. Synthesis of Chabranol 1



The retosynthetic analysis (Scheme 2) was inspired by our biosynthetic proposal. Chabranol **1** could be accessed from α-hydroxy aldehyde **3**, which could be generated by oxidation diol **6**. As for the preparation of **6**, it could in turn be obtained from epoxide **7**[5] and sulfide **8**.

The synthesis of diol **6** commenced with selective ring-opening of the known (*S*)-epoxide **7** with sulfide **8** (Scheme 3). Subsequently, phenyl sulfide and TBS were removed in one pot under Na/isopropanol condition to get the requisite intermediate diol **6** in 92% yield over two steps.[6] We next proceeded to build up the bicyclo [2.2.1] core of the target molecule. Swern oxidation[7] of diol **6** produced the desired aldehyde **3**, which was used directly in the next step without further purification. Exposure of the crude aldehyde **3** to TBSOTf and collidine in CH_2Cl_2 at 0 °C, to our delight, gave

SCHEME 4. Determination of the Relative Structure of Chabranol 1



the bicyclo [2.2.1] skeleton of the target molecule via intermolecular Prins double cyclization and afforded silyl ether **5** in 64% yield as a single diastereomer. At this stage, the three other newly generated stereogenic centers were established.[4] With **5** in hand, our next concern was the formation of the final ketone group. After hydroboration[8] and PCC oxidation, the precursor of the natural product was obtained in 63% over two steps. Finally, deprotection of TBS, the target molecule chabranol, was accomplished.

However, ^{1}H NMR and ^{13}C NMR of our synthetic chabranol displayed minor differences with those of the isolated natural product.[9] The relative configuration of our synthetic chabranol was investigated through inspection of the NOESY spectrum as well as COSY correlation. According to the NOESY and COSY spectra, the natural product and our synthetic compound are identical. To further determine the structure of our synthetic product, the corresponding derivative of chabranol (±)-diester **10** was prepared by a three-step sequence starting from the silyl ether (±)-**5**. We successfully prepared a crystal of (±)-diester **10** and its X-ray experiment unambiguously determined the relative structure of our synthetic chabranol (Scheme 4).

In summary, we have reported the first total synthesis of (+)-chabranol in 6 steps with 36.6% overall yield, the enantiomer of the natural product, and the natural product's absolute configuration was also designated as (3*S*,4*S*,5*R*,6*S*), which was further confirmed by X-ray experiment. The bicyclo [2.2.1] core of the natural product was efficiently constructed through intramolecular Prins double cyclization. This short synthesis appears to open a feasible way to design analogues for a structure−activity relationship study.

(5) (a) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790. (b) Hale, K. J.; Manaviazar, S.; Peak, S. A. *Tetrahedron Lett.* **1994**, *35*, 425.

(6) (a) Morimoto, Y.; Nishikawa, Y.; Takaishi, M. *J. Am. Chem. Soc.* **2005**, *127*, 5806. (b) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **2000**, *122*, 7124.

(7) Mancuso, A. J.; Swern, D. *Synthesis.* **1981**, 165.

(8) Brown, H. C.; Tierney, P. A. *J. Am. Chem. Soc.* **1958**, *80*, 1552.

(9) According to professor Duh, who isolated Chabranol, the small chemical shift differences arose from different spectrometers. The isolated natural product clearly contained some contaminants. Because of this, it is not easy to compare the ^{1}H NMR spectra in the 1−2 ppm region. The difference on the ^{13}C NMR may also be due to the impurity. In addition, we obtained almost the same IR spectrum in the SI.

Experimental Section

Diol 6. To a solution of the epoxide **7** (1.010 g, 5.00 mmol), sulfide **8** (1.722 g, 7.00 mmol), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (5.0 mL) dissolved in 50 mL of THF was added dropwise 3.2 mL (6.75 mmol) of *n*-butyllithium (2.1 M in hexane) under a nitrogen atmosphere at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the reaction mixture was added 20 mL of saturated NH_4Cl and the aqueous layer was extracted with ether (3 × 70 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 100:1) to afford the intermediate sulfide (2.128 g, 95% yield) as a mixture of diastereomeres.

The above sulfide (2.128 g, 4.75 mmol) was dissolved in a mixture of THF (40 mL) and 2-propanol (20 mL) under an argon atmosphere. Pieces of metallic sodium (5.373 g, 237.5 mmol) were added portionwise to the boiling solution, and the resulting mixture was stirred under reflux for 6 h. After the mixture was cooled to room temperature, 20 mL of water was added to the solution and the mixture was extracted with ether (3 × 70 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 2/1) to afford diol **6** (1.041 g, 67% ee, 97%) as a colorless oil: $[\alpha]^{20}_D$ +6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (t, J = 6.9 Hz, 1H), 5.09 (t, J = 6.3 Hz, 1H), 3.46 (dd, J = 26.3, 10.9 Hz, 2H), 2.15−2.03 (m, 4H), 2.03−1.93 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.53 (m, 2H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 131.5, 124.2, 124.1, 73.0, 69.8, 39.7, 38.4, 26.6, 25.7, 23.3, 22.3, 17.7, 16.0; IR (KBr) ν_{max} 3375, 2968, 2923, 2858, 1449, 1379, 1113, 1054 cm^{-1}; HRMS (ESIMS) caled for $C_{14}H_{27}O_2^+$ $[M + H]^+$ 227.2006, found 227.2004.

Silyl Ether 5. To a 100 mL oven-dried round-bottomed flask under argon was added 30 mL of dichloromethane dried over CaH_2. Freshly distilled oxalyl chloride (674 mg, 5.31 mmol) was added, and the solution was chilled to −78 °C. Then dimethyl sulfoxide (842 mg, 10.62 mmol) was added over 5 min dropwise in 10 mL of dry dichloromethane with stirring. The resulting clear solution was stirred for an additional 15 min, and then the diol **6** (600 mg, 2.655 mmol) in 10 mL of dry dichloromethane was added dropwise with stirring. During this time the solution acquired a white slushy appearance and stirring was continued for an additional 20 min at −78 °C. Then diisopropylethylamine (DIPEA, 2.06 g, 16.0 mmol) was added dropwise over 5 min and the reaction flask was removed from the cold bath and allowed to warm gradually to room temperature with stirring over 30 min. This was followed by the addition of 20 mL of water and stirring for another 10 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde **3** was redissolved in 40 mL of dichloromethane and flushed with argon. To this new solution were added collidine (0.98 mL, 5.31 mmol) and TBSOTf (0.915 mL, 3.98 mmol) at 0 °C. After the reaction mixture was stirred for 40 min, 20 mL of 5% Na_2CO_3 was added, and the stirring was continued for an additional 10 min. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc = 300/1) to afford TBS ether **5** (574 mg, 64%) as a colorless oil: $[\alpha]^{21}_D$ 10 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, J = 7.0 Hz, 1H), 3.96 (s, 1H), 2.08−1.81 (m, 4H), 1.65−1.76 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.52−1.45 (m, 2H), 1.45−1.36 (m, 1H), 1.18 (s, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 124.5, 84.5, 79.8, 79.5, 49. 0, 42.5, 32.5, 29.7, 25.7, 23.2, 23.2, 21.8, 18.0, 17.5, 17.3, −4.8, −4.9; IR (KBr) ν_{max} 2958, 2930, 2858, 1457, 1377, 1254, 1131 cm^{-1}; HRMS (ESIMS) caled for $C_{20}H_{39}O_2Si^+$ $[M + H]^+$ 339.2714, found 339.2716.

(+)-Chabranol 1. To a solution of ketone **9** (108 mg, 0.304 mmol) in THF (10 mL) was added TBAF·3H_2O (289 mg, 0.912 mmol) and the mixture was stirred for 5 h. The mixture was then concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc = 4/1) to provide chabranol (72 mg, 98.7%) as a colorless oil: $[\alpha]^{25}_D$ 48 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 1H), 2.69−2.55 (m, 2H), 2.36 (ddd, J = 17.3, 9.0, 5.7 Hz, 1H), 2.20 (br s, 1H), 2.00 (s, 1H), 1.98−1.86 (m, 2H), 1.86−1.77 (m, 1H), 1.74−1.64 (m, 1H), 1.59 (ddd, J = 14.2, 8.9, 5.7 Hz, 1H), 1.50−1.39 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H), 1.10 (d, J = 5.0 Hz, 3H), 1.08 (d, J = 4.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 84.7, 79.2, 78.8, 49.7, 41.0, 35.2, 34.6, 32.2, 22.9, 21.5, 18.4, 18.2, 17.0; IR (KBr) ν_{max} 3402, 2969, 2930, 1707, 1459, 1379 cm^{-1}; HRMS (ESIMS) caled for $C_{14}H_{25}O_3^+$ $[M + H]^+$ 241.1798, found 241.1802.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.