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Enantioselective Total Synthesis of Isishippuric Acid B via Intramolecular Michael Reaction

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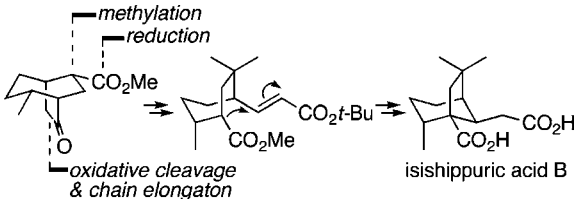
ABSTRACT



The first enantioselective total synthesis of isishippuric acid B bearing a novel 4,5-seco-6-norquadrane skeleton was accomplished from (*R*)-citronellal with use of a Diels–Alder cycloaddition and an intramolecular Michael addition as the ring-forming steps. Comparison of the optical rotation of the synthetic material with that of the natural product confirmed the absolute configuration of isishippuric acid B to be 1*R*, 2*R*, 8*R*, and 11*R*.

In the course of screening for cytotoxic substances from the gorgonian coral *Isis hippuris*, Sheu and co-workers isolated two novel sesquiterpenoids, isishippuric acids B and A, and determined their structures as **1** and **2**, respectively, on the basis of spectroscopic analyses, albeit without assignment of their absolute configurations.[1] Although the biological activity of the keto carboxylic acid **2** was not mentioned in their report, the dicarboxylic acid **1** was found to exhibit potent cytotoxicity (ED_{50} < 0.1 μg/mL) toward P-388 (mouse lymphocytic leukemia), A549 (human lung adenocarcinoma), and HT-29 (human colon adenocarcinoma) cancer cell lines, which suggested that further biological studies on **1** were warranted as an anticancer drug. In addition to the intriguing biological activity of **1**, the totally new carbon skeleton (4,5-seco-6-norquadrane, which has never been found in natural products so far) and the undefined absolute stereochemistry prompted us to embark on the enantioselecive total synthesis of **1**. We adopted the (1*R*,2*R*,8*R*,11*R*)-enantiomer of isishippuric acid (**1** in Figure 1) as our target molecule, since two synthetic studies on optically active quadranoids, Isoe's synthesis of (−)-terrecyclic acid A from (+)-fenchone[2] and Smith's synthesis of (+)- and (−)-quadrones through optical resolution,[3] had established the absolute configurations of natural terrecyclic acid A and quadrone as **3** and **4**, respectively. Unexpectedly, our literature search revealed that

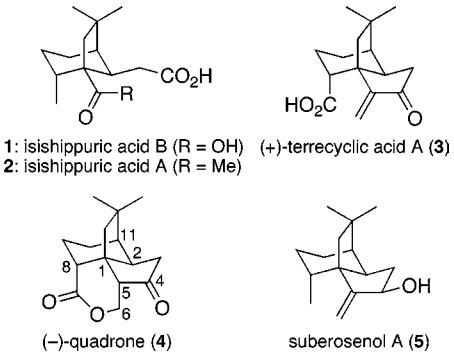


Figure 1. Isishippuric acid B (**1**) and related quadranoids.

(1) Sheu, J.-H.; Chao, C.-H.; Wang, G.-H.; Hung, K.-C.; Duh, C.-Y.; Chiang, M. Y.; Wu, Y.-C.; Wu. C.-C. *Tetrahedron Lett.* **2004**, *45*, 6413−6416.

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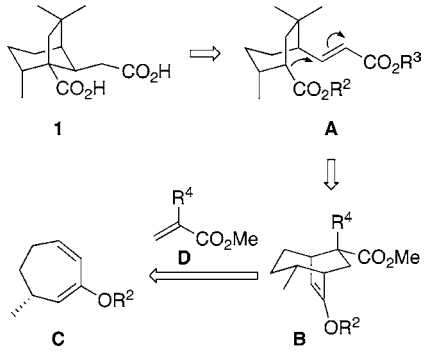
most of the synthetic efforts toward quadranoids had only been focused on the synthesis of racemic quadrone,[4] and no report on the synthesis of optically active forms of quadranoids had been published except for the two syntheses mentioned above.[5] These circumstances also encouraged us to develop a new enantioselective synthetic route to **1**, which could also lead to related quadranoids such as suberosenol A (**5**), a potent cytotoxin with an ED_{50} value of $<5 \times 10^{-6}$ μg/mL toward P-388 and HT-29,[6,7] via, for example, acyloin-type ring formation between the C4 and C5 positions of an appropriate derivative of **1**.

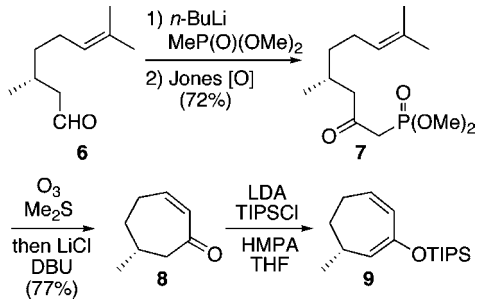
Scheme 1. Retrosynthetic Analysis of Isishippuric Acid B



Scheme 1 shows our basic synthetic plan for **1**, which features the intramolecular Michael addition reaction of monocyclic intermediate **A** to form the bicyclo[3.2.1]octane system incorporated in **1**. The seven-membered monoene diester **A** was considered obtainable from **B** through oxidative cleavage of the double bond of **B** and subsequent two-carbon elongation of the resulting aldehyde intermediate. As for the intermediate **B**, we envisaged its construction by the Diels−Alder reaction of cycloheptadiene derivative **C** with acrylate **D**. The first task for the enantioselective total synthesis of **1** was, therefore, the preparation of an appropriately protected cycloheptadiene derivative **C** in its *R*-form.

Our preparation of **9**, the TIPS-protected form of **C**, began with the nucleophilic addition of the lithium anion generated from dimethyl methylphosphonate to (*R*)-citronellal (**6**) followed by oxidation of the resulting alcohol intermediate to furnish **7** in 72% for the two steps (Scheme 2). Exposure

Scheme 2. Synthesis of Diels−Alder Precursor **9**

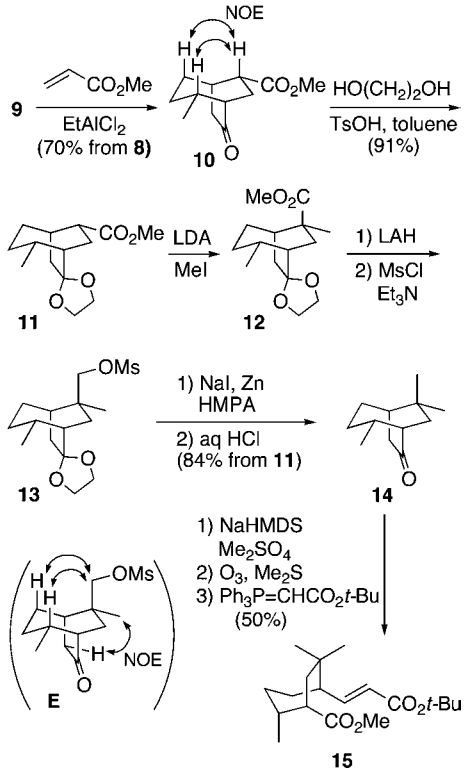


of the olefin **7** to ozonolysis conditions and subsequent in situ treatment of the product with DBU/LiCl afforded conjugated cycloheptenone **8**.[8] This enone **8** was converted into the corresponding silyl enol ether **9** by treatment with LDA/THF at −78 °C followed by trapping of the resulting lithium enolate with TIPSCl in HMPA/THF.[9] When the silylation was conducted without the addition of HMPA, no silylation product was obtained, resulting only in the recovery of **8**. The transformation of **8** into the corresponding methyl enol ether was also attempted (LDA, THF, 0 °C; then Me_2SO_4, HMPA, 0 to 20 °C), but the product was an intractable mixture of two dienol ethers with high volatility and susceptibility to silica gel column chromatography.

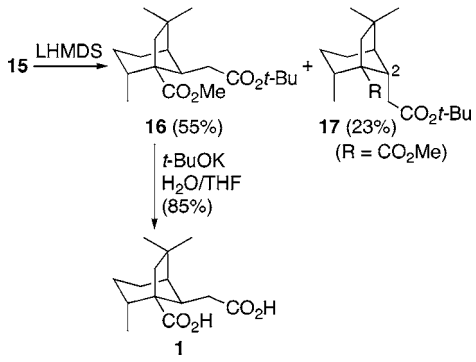
To obtain a bicyclic intermediate corresponding to **B** in Scheme 1, the Diels−Alder reaction of **9** with methyl methacrylate or methyl acrylate was examined (Scheme 3). Although the cycloaddition reaction of **9** with the former was unsuccessful (resulting in the formation of a mixture of unidentified products),[10] the reaction of **9** with the latter proceeded smoothly at −78 °C in the presence of $EtAlCl_2$ to give desilylated bicyclic keto ester **10** in 70% overall yield from **8**. The stereochemistry of **10** was assigned on the basis of the NOE correlations as shown in Scheme 3; this means that the dienophile approached the diene **9** in an *endo* manner from the less hindered face of the diene system opposite the methyl substituent. Protection of the ketone functionality of **10** and subsequent installation of a methyl group at the α-position of the resulting ester **11** afforded **12** as a single diastereomer, albeit without assignment of the stereochemistry at this stage. After reduction of the ester, the alcohol product was mesylated to deliver **13**. The stereochemistry

(2) Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739−3742.
(3) (a) Smith, A. B., III; Konopelski, J. P. *J. Org. Chem.* **1984**, *49*, 4094−4095. (b) Smith, A. B., III; Konopelski, J. P.; Wexler, B. A.; Sprengeler, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 3533−3542. (c) Stephens, P. J.; McCann, D. M.; Devlin F. J.; Smith, A. B., III. *J. Nat. Prod.* **2006**, *69*, 1055−1064.
(4) (a) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262−4263. (b) Pirrung, M. C.; Morehead, A. T., Jr.; Young, B. G. In *The Total Synthesis of Natural Products*; Goldsmith, D., Ed.; Wiley & Sons: New York, 2000; Vol. 11, pp 394−406.
(5) For a concise construction of the quadranoid skeleton by a tandem radical cyclization−rearrangement sequence and its application to the syntehsis of (±)-suberosenone, see: Lee, H.-Y.; Lim, B. G. *Org. Lett.* **2000**, *2*, 1951−1953.
(6) Sheu, J.-H.; Hung, K.-C.; Wang, G.-H.; Duh, C.-Y. *J. Nat. Prod.* **2000**, *63*, 1603−1607.
(7) For structures and biological activities of related quadranoids, see: (a) Bokesch, H. R.; McKee, T. C.; Cardellina, J. H., II; Boyd, M. R. *Tetrahedron Lett.* **1996**, *37*, 3259−3262. (b) Wijeratne, E. M. K.; Turbyville, T. J.; Zhang, Z.; Bigelow, D.; Pierson, L. S., III; VanEtten, H. D.; Whitesell, L.; Canfield, L. M.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2003**, *66*, 1567−1573. (c) Qi, S.-H.; Zhang, S.; Li, X.; Li, Q.-X. *J. Nat. Prod.* **2005**, *68*, 1288−1289.
(8) Our three-step synthetic route to **8** from commercially available (*R*)-citronellal (**6**) is operationally easy, low in cost, and therefore suitable for its large-scale production. For other methods to prepare **8** or its enantiomer, see: (a) McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378−8379. (b) Weinmann, H.; Winterfeldt, E. *Synthesis* **1995**, 1097−1101. (c) Jagt, R. B. C.; Imbos, R.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *Isr. J. Chem.* **2002**, *41*, 221−229.
(9) Upon exposure of **8** to TIPSOTf/(*i*-Pr)$_2$NEt/CH_2Cl_2 at −78 °C, two silyl enol ethers [**9** and its isomer, (*R*)-6-methyl-1-(triisopropylsilyl)oxy-1,3-cycloheptadiene] were obtained in a ratio of 1:1.
(10) The Diels−Alder reaction of **9** with methacrolein under Lewis acid-promoted conditions ($EtAlCl_2$ or BF_3·OEt_2) was also unsuccessful.

Scheme 3. Preparation of Michael Cyclization Precursor **15**



Scheme 4. Completion of the Synthesis of Isishippuric Acid B



of **13** was determined as depicted in Scheme 3 by observing some diagnostic NOE correlations in ketone **E** prepared by acidic hydrolysis of **13** (aq HCl, acetone), which also enabled us to establish the stereochemistry of the methylation of **11** to **12**. Reductive removal of the mesyloxy group of **13** followed by acidic hydrolysis of the acetal protecting group yielded bicyclic ketone **14** in 84% overall yield from **11**. Treatment of **14** with NaHMDS/Me_2SO_4 proceeded cleanly to give the corresponding methyl enol ether, the double bond of which was then oxidatively cleaved with ozone. The resulting formyl ester was exposed to Horner−Emmons olefination conditions to furnish **15**, which set the stage for the Michael cyclization step, the key process in our synthetic strategy.[11]

The intramolecular Michael addition of **15** to form bicyclic diester **16** was tried with use of various basic conditions including LDA/HMPA/THF, LDA/TMSCl/HMPA/THF, NaOMe/MeOH/toluene, *t*-BuOK/18-crown-6/THF, LHMDS/THF, and LHMDS/HMPA/THF (Scheme 4). Among those conditions, the only successful result was obtained when **15** was treated with LHMDS in THF in the presence of HMPA at 0 °C, giving a 2.3:1 mixture of **16** and its C2-epimer (**17**) in 81% combined yield.[12] After purification of the desired stereoisomer **16** by repeated silica gel column chromatography (55% isolated yield), the diester was hydrolyzed with *t*-BuOK in THF containing a small amount of water[13] to afford isishippuric acid B (**1**) in 85% yield. The ^{1}H and ^{13}C NMR spectra of the synthetic material were identical with those of natural isishippuric acid B. The optical rotation value of synthetic **1** ($[\alpha]^{22}_D$ −104) was in good agreement with that of natural **1** ($[\alpha]^{25}_D$ −115),[1] which enabled us to confirm the absolute configuration of isishippuric acid B as 1*R*, 2*R*, 8*R*, and 11*R*.

In conclusion, the first enantioselective total synthesis of isishippuric acid B (**1**), featuring the intramolecular Michael addition reaction of seven-membered monocyclic diester **15** to form the substituted bicyclo[3.2.1]octane system incorporated in **1**, was accomplished in 16 steps from (*R*)-citronellal (6.9% overall yield). Attempts to improve the stereoselectivity in the Michael cyclization step and the synthesis of related quadranoids are currently in progress.

Acknowledgment. We are grateful to Prof. Sheu (National Sun Yat-Sen University, Taiwan) for providing the NMR spectra of natural isishippuric acid B. This work was financially supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 16380075). We also thank Ms. Yamada (Tohoku University) for measuring the NMR and mass spectra.

Supporting Information Available: Experimental procedures and copies of NMR spectra for compounds **7**, **8**, **10**, **11**, **14**, **15**, **16**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Structure **15** is drawn as a conformer preferred for the Michael cyclization in the next step, and does not mean the real conformation of **15**.

(12) Interestingly, exposure of the (*Z*)-isomer of **15** [prepared by using $(PhO)_2P(O)CH_2CO_2t$-Bu/NaH/THF instead of $Ph_3P{=}CHCO_2t$Bu for **15**] to the same conditions afforded the undesired epimer **17** as a single stereoisomer in 65% yield; the stereochemistry of **17** was confirmed by NOE correlations observed between the C8 axial methyl protons and the two protons on the carbon α to the carbonyl. This exclusive formation of **17** would be explicable by considering severe steric repulsion between the CO_2t-Bu moiety and a geminal methyl group in the transition state leading from the (*Z*)-isomer to **16**.

(13) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.