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TOTAL SYNTHESIS OF (+)-HALIMEDATRIAL: THE ABSOLUTE CONFIGURATION OF HALIMEDATRIAL

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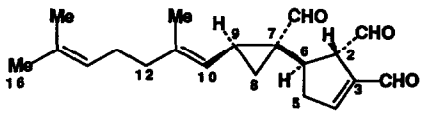
Summary: *(+)-Halimedatrial (1) was synthesized stereoselectively from (S)-4-hydroxy-2-cyclopentenone. This accomplishment determined the absolute configuration of halimedatrial as shown in 2.*

Halimedatrial, a structurally unique marine diterpene, was reported as the chemical defence adaptation in the calcareous reef-building algae *Halimeda* (Udoteaceae).[1] This diterpene shows potent antimicrobial activities toward a variety of marine microorganisms and also a highly inhibitory effect on the growth of a marine bacterium and a gray fungus. At concentration of 1 μg/ml, halimedatrial completely inhibits the first cell division of fertilized sea urchin eggs. The structure of halimedatrial has been elucidated by NMR analysis and chemical reactions, except the absolute configuration. In this paper, we describe the total synthesis of **1**, (+)-halimedatrial, by an enantioselective manner starting from (*S*)-4-hydroxy-2-cyclopentenone. As the results, the absolute configuration of halimedatrial was determined as **2**. This synthesis involves stereoselective formation of the cyclopropane ring system and construction of the diformylcyclopentene moiety as crucial steps.



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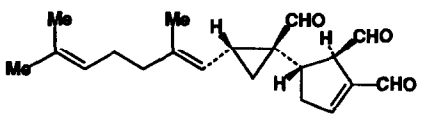


2 halimedatrial

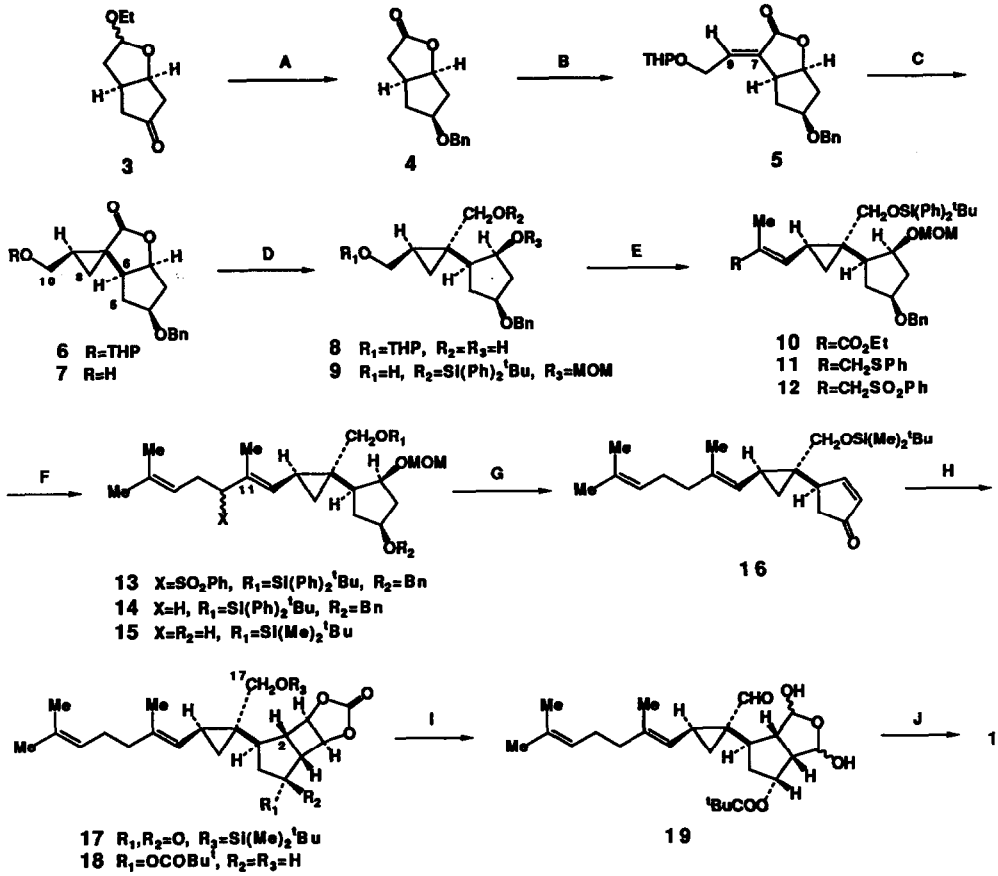
Keto acetal **3**, prepared from (*S*)-4-hydroxy-2-cyclopentenone, $[\alpha]_D^{25}$ -45.5° (*c*=1.78, $CHCl_3$),[2] was converted into lactone **4** by the following four sequential steps: (1) stereoselective reduction of the ketone with sodium borohydride, (2) protection of the secondary hydroxyl group as benzyl ether, (3) acid hydrolysis of the acetal, (4) oxidation of the resultant hemiacetal with Jones reagent to give lactone. Reaction of the lithium enolate, prepared from **4** with 1 equiv of lithium diisopropylamide, with (tetrahydro-2-pyranyloxy)acetaldehyde[3] in an 8:1 mixture of THF and

HMPA at -78°C gave β-hydroxy lactone, which was dehydrated *via* the mesylate to give (*E*)-α,β-unsaturated lactone **5** (55%) and its *Z* isomer (28%).[4] Formation of the cyclopropane ring system (C_7-C_9) was achieved by the following reactions. Stereoselective 1,3-dipolar addition reaction of **5** with diazomethane in a 2:1 mixture of ether and methylene chloride at 0°C gave a pyrazoline derivative, and irradiation of the adduct with a Hanovia 100-W high pressure lamp (Pyrex filter, -70°C) in the presence of a catalytic amount of benzophenone gave cyclopropane derivative **6** (77%) as a major product along with 9-methyl-5[5] (7*E*:7*Z*=2:1) (13%). The stereochemistry of **6** was confirmed by analysis of ^{1}H-NMR spectrum of alcohol **7**, $[\alpha]_D^{25}$ -133.5° (*c*=1.17, $CHCl_3$), obtained from **6** by treatment with acid (AcOH:H_2O=4:1, 50°C): positive NOEs were observed between the α-proton at C_5 and one of the protons at C_{10}, and between the proton at C_6 and the β-proton at C_8. Lactone **6** was then reduced with lithium aluminum hydride to give diol **8** in 83% yield. The resulting primary and secondary hydroxyl groups were selectively protected as *t*-butyldiphenylsilyl ether and methoxymethyl ether, respectively, and then the THP ether was hydrolized by mild acid treatment to give **9**, $[\alpha]_D^{25}$ +25.9° (*c*=1.78, $CHCl_3$), in 90% overall yield.

Elongation of the side chain in **9** to give **15** was accomplished as follows. Swern oxidation of **9** and subsequent treatment with ethyl diisopropylphosphonoacetate and potassium *t*-butoxide gave (*E*)-α,β-unsaturated ester **10**, $[\alpha]_D^{25}$ +20.2° (*c*=2.43, $CHCl_3$), as a single isomer in 88% overall yield. The ethoxycarbonyl group in **10** was reduced and the resulting alcohol was treated with *N*-(phenylthio)succinimide and tributylphosphine in benzene at room temperature to give phenylthioether **11**, $[\alpha]_D^{25}$ +5.2° (*c*=2.22, $CHCl_3$), which was then oxidized with potassium peroxymonosulfate (OXONE, Aldrich)[6] to give sulfone **12**, $[\alpha]_D^{25}$ +21.7° (*c*=1.58, $CHCl_3$). The carbanion, prepared from **12** with butyllithium in a 4:1 mixture of THF and HMPA at -78°C, was treated with 1-bromo-3-methyl-2-butene to give **13**. The phenylsufonyl group was reductively removed with lithium triethylborohydride in the presence of $PdCl_2$(dppp)[7] in THF at 0°C to give an inseparable mixture consisting mainly of **14** and its regio-isomers of the double bond (11-ene). The protection group of the primary hydroxyl group in the product was exchanged to *t*-butyldimethylsilyl group, and then the benzyl group was removed to give alcohol **15**, $[\alpha]_D^{25}$ +40.8° (*c*=1.68, $CHCl_3$), (73% from **12**) and a small amount of its regio-isomers (12% from **12**) (11*E*:11*Z*=2:1) after silica gel chromatography. Alcohol **15** was transformed into enone **16**, $[\alpha]_D^{25}$ +24.3° (*c*=1.30, $CHCl_3$), in 75% yield by two step sequence: (1) Swern oxidation of the hydroxyl group, (2) DBU treatment.

Construction of the diformylcyclopentene moiety was successfully carried out by stereoselective photocycloaddition of **16** with vinylene carbonate followed by oxidative cleavage of the resulting cyclobutane ring system. Irradiation of **16** in a 1:10 mixture of vinylene carbonate and acetone with a Hanovia 100-W high pressure lamp (Pyrex filter, -70°C) gave carbonate **17**, $[\alpha]_D^{25}$ +118° (*c*=1.57, $CHCl_3$), (27%), 10*Z* isomer of **17** (9%), recovered enone **16** (50%), and 10*Z* isomer of **16** (16%).[8] The above reaction was repeated by using the recovered enone **16**. The configuration of

Scheme 1



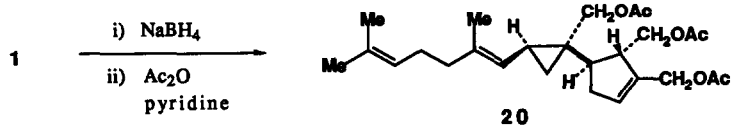
Reagents: (A) 1) $NaBH_4$, MeOH, 0°C; 2) BnBr, NaH, THF-DMF (4:1), rt; 3) 1*N* HCl-DME (2:1), rt; 4) Jones reagent, acetone, 0°C (63% from **3**); (B) 1) LDA then $THPOCH_2CHO$, THF-HMPA, -78°C, 2) MsCl, Et_3N, CH_2Cl_2, -10°C, 3) DBU, PhH, 50°C (55% from **4**); (C) 1) CH_2N_2, Et_2O-CH_2Cl_2 (2:1), 0°C, 2) hv, Ph_2CO, $PhCH_3$, -70°C, 77% of **6**, 13% of 9-methyl-**5**; (D) 1) $LiAlH_4$, Et_2O, -10°C (83%), 2) *t*-$Bu(Ph)_2SiCl$, imidazole, DMF, rt, 3) $MeOCH_2Cl$, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 50°C, 4) AcOH-H_2O-THF (4:1:2), 60°C (90% from **8**); (E) 1) Swern oxidation; 2) (*i*-PrO)$_2$P(O)CH_2CO_2Et, *t*-BuOK, THF, -78°C to rt (88% from **9**), 3) DIBAL, hexane-CH_2Cl_2 (1:1), -78°C, 4) *N*-(phenylthio)succinimide, *n*-Bu_3P, PhH, rt, 5) $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, THF-MeOH-$H_2O$ (1:1:1), rt (63% from **10**); (F) 1) *n*-BuLi, THF-HMPA (4:1), -78°C then 1-bromo-3-methyl-2-butene, 2) $LiHBEt_3$, $PdCl_2$(dppp), THF, 0°C; 3) *n*-Bu_4NF, DMF, 50°C, 4) *t*-$Bu(Me)_2Cl$, imidazole, DMF, rt, 5) Na, liq NH_3, THF, -78°C, (73% from **12**); (G) 1) Swern oxidation, 2) DBU, PhH, 80°C (75% from **15**); (H) 1) vinylene carbonate, hv, acetone, -70°C, 27% of **17**, 9% of 10Z isomer of **17**, 50% of **16**, 16% of 10Z isomer of **16**, 2) $NaBH_4$, MeOH, 0°C, 3) *t*-BuCOCl, pyridine, $ClCH_2CH_2Cl$, rt, 4) *n*-Bu_4NF, THF-AcOH (100:1), rt (83% from **17**); (I) 1) Swern oxidation; 2) K_2CO_3, MeOH, rt, 3) $NaIO_4$, 5% $NaHCO_3$, DME, rt (38% from **18**); (J) *i*-Pr_2NEt, PhH, 80°C, 83%.

C_2 in **17** was confirmed by analysis of ^{1}H-NMR spectrum: NOE was observed between the methine proton at C_2 and one of the protons at C_{17}. Ketone **17** was then converted into **18**, $[\alpha]_D^{25}$ +30.6° (*c*=0.75, $CHCl_3$), in 83% overall yield by three steps: (1) stereoselective reduction of the ketone with sodium borohydride; (2) esterification of the resulting hydroxyl group with pivaloyl chloride and pyridine; (3) deprotection of the silyl group. Swern oxidation of the primary alcohol in **18** and hydrolysis of the carbonate with potassium carbonate in methanol gave the corresponding 1,2-diol which was then oxidized with sodium metaperiodate in the presence of 5% sodium bicabonate in DME to give hemiacetal **19** in 38% overall yield. Then, **19** was treated with diisopropylethylamine in benzene at 80°C to give the final compound **1** in 83% yield. The ^{1}H-NMR and ^{13}C-NMR spectra of **1** were identical with those reported for halimedatrial, though the optical rotation of **1** observed as $[\alpha]_D^{25}$ +73.9° (*c*=0.28, $CHCl_3$) was contrary to that of the natural one, $[\alpha]_D^{25}$ -59° (*c*=0.9, $CHCl_3$).[1,9] The synthesis of the antipodal (+)-halimedatrial (**1**) revealed the absolute configuration of natural halimedatrial as shown in **2**.

ACKNOWLEDGEMENT This work was supported in part by a Grant-in-Aid for Scientific Research (No. 01571166) from the Ministry of Education, Science and Culture, Japan.

REFERENCES AND NOTES

1) V. J. Paul and W. Fenical, *Science*, **211**, 747 (1983); V. J. Paul and W. Fenical, *Tetrahedron*, **40**, 3053 (1984).
2) H. Miyaoka, H. Nagaoka, T. Okamura, and Y. Yamada, *Chem. Pharm. Bull.*, **37**, 2882 (1989).
3) I. Iwai, T. Iwashige, M. Asai, K. Tomita, T. Hiraoka,, and J. Ide, *Chem. Pharm. Bull.*, **11**, 188 (1963).
4) Chemical shift of the proton at 6.65 ppm (C_9-H, dt, J=2.6, 5.8 Hz,) in ^{1}H-NMR spectrum of the allylic alcohol, prepared from **5** by deprotection of THP group, indicates the *E* configuration, while chemical shift of the proton at 6.31 ppm (C_9-H, dt, J=2.2, 5.7 Hz,) of the allylic alcohol, prepared from the geometrical isomer of **5**, indicates the *Z* configuration.
5) Numbering of compounds used here was accorded with that for halimedatrial.
6) B. M. Trost and D. P. Curran, *Tetrahedron Lett.*, **22**, 1287 (1981).
7) M. Mohri, H. Kinoshita, K. Inomata, and H. Kotake, *Chemistry Lett.*, 451 (1985).
8) D. Helmlinger, P. de Mayo, M. Nye, L. Westfelt, and R. B. Yeats, *Tetrahedron Lett.*, 349 (1970).
9) The sign of the optical rotation of triacetate **20**, $[\alpha]_D^{25}$ -14.1° (c=0.23, $CHCl_3$), derived from **1** according to Fenical's procedure,[1] was also opposite to that reported for the triactate, $[\alpha]_D^{25}$ +13.3° (*c*=0.9, $CHCl_3$),[1] which was derived from natural halimedatrial.



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