A METHOD FOR SYNTHESIZING THE DIFORMYLCYCLOPENTENE MOIETY OF HALIMEDATRIAL

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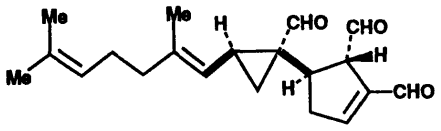
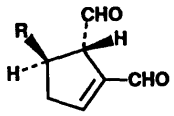
The diformylcyclopentene moiety 2 of halimedatrial was stereoselectively synthesized in an optically active form from (S)-4-hydroxy-2-cyclopentenone (3) via 4-alkyl-2-cyclopentenone 6 and cyclobutene 8.

KEYWORDS 1,5-diformylcyclopentene derivative; radical cyclization reaction; photocyclization reaction; (trimethylsilyl)acetylene; ozonolysis; halimedatrial; marine diterpene

Halimedatrial (1), a structurally unique marine diterpene, was reported as a chemical defense adaptation in the calcareous reef-building alga Halimeda.[1] This diterpene is not only toxic and a feeding-deterrent against herbivorous fishes but it also has a significant antimicrobial activity toward a variety of marine microorganisms, including the common bacteria Serratia marinorubra, Vibrio splendida, V. leiognathi, and V. harveyi. The structure of halimedatrial has been elucidated by NMR analysis and chemical reaction, except its absolute configuration.[1] Recently, the total synthesis of (±)-udoteatrial,[2] (+)-petiodial[3] and (±)-petiodial,[4] which are marine diterpenes structurally related to halimedatrial, have been reported, but the total synthesis of halimedatrial has not yet been reported. It is necessary to find an effective method for synthesizing the diformylcyclopentene moiety 2 of halimedatrial before this natural product can be synthesized. Here we describe the efficient conversion of (S)-4-hydroxy-2-cyclopentenone (3) into optically active diformylcyclopentene 2a. This synthesis involves the covnersion of 3 into 4-alkyl-2-cyclopentenone 6, the stereoselective photocycloaddition of 6 with (trimethylsilyl)acetylene, and the oxidative cleavage of the cyclobutene ring in 8.



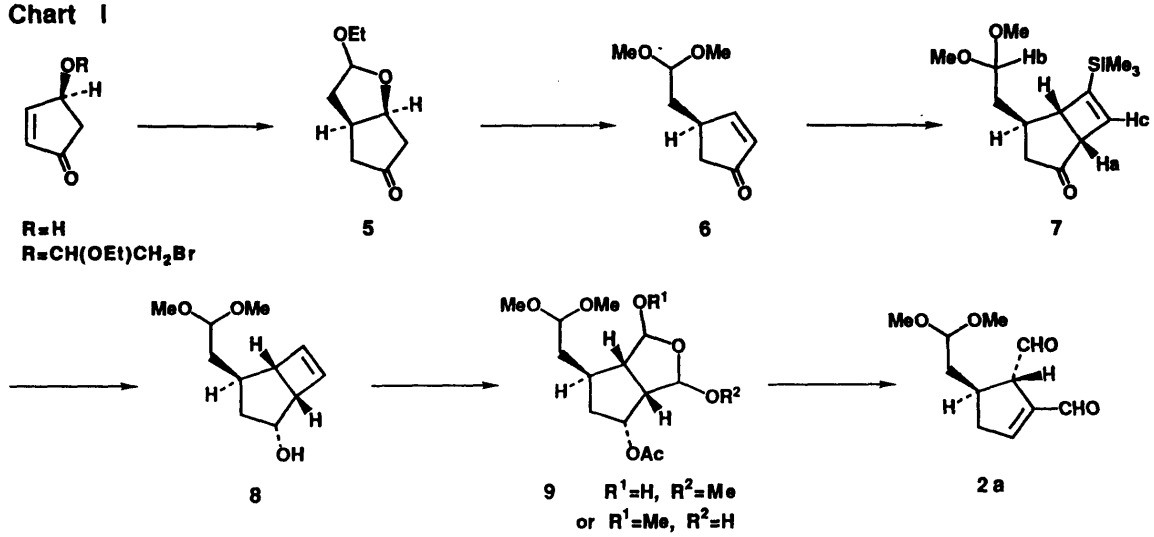
1 halimedatrial



2

Treatment of (S)-4-hydroxy-2-cyclopentenone (3), prepared in 95% e.e. from diethyl L-tartrate,[5,6] with 1.2 eq of 1,2-dibromo-1-ethoxyethane[7] and 1.5 eq of N,N-diisopropylethylamine in dichloromethane at 20°C gave bromoacetal 4 as a diastereomeric mixture in 90% yield (Chart I). The radical cyclization reaction of 4 with 1.1 eq of tributyltin hydride and a catalytic amount of AIBN in benzene at 80°C gave keto acetal 5 in 96% yield.[8] The keto acetal 5 was treated with a catalytic amount of dl-camphorsulfonic acid in methanol at 60°C to give (R)-4-(2',2'-dimethoxyethyl)-2-cyclopentenone (6),[9,10] $[\alpha]_D^{25}$ +106.7° (c=0.89, $CHCl_3$), as a single product in 77% yield. Irradiation of a mixture of 6 and (trimethylsilyl)acetylene with a Hanovia 100-W high pressure lamp (Pyrex filter, -70°C, 6 h) stereoselectively afforded cycloadduct 7,[11] $[\alpha]_D^{25}$ -174.9° (c=2.13, $CHCl_3$), in 67% yield. The regio- and stereoisomers of 7 were not detected in the reaction mixture. The trimethylsilyl group in 7 was successfully removed by a two step sequence: 1) sodium borohydride reduction of the ketone in methanol at 0°C, and 2) treatment with 1.0 equiv of sodium hydride in hexamethylphosphoric triamide at 50°C for 2 h gave 8,[12] $[\alpha]_D^{25}$ +6.6° (c=1.36, $CHCl_3$), in 73% overall yield. Use of other acetylene equivalents, such as ethyl vinyl ether and vinyl acetate, for the photocycloaddition reaction gave unsatisfactory results. Acetylation of the hydroxy group in 8 (Ac_2O,pyridine, 50°C), followed by ozonolysis in a mixture of methanol and dichloromethane (1:1) at -78°C gave hemiacetal 9 as a mixture of

Chart I



3 R=H
4 R=CH(OEt)CH_2Br

5 6 7

8

9 R^1=H, R^2=Me
or R^1=Me, R^2=H

2a

regio- and stereoisomers. Finally, treatment of 9 (without separation of the isomers) with 2 eq of N,N-diisopropyletyhylamine in benzene at 80°C gave,1,5-diformyl-4-(2',2'-dimethoxyethyl)cyclopentene (2a),[13] $[\alpha]_D^{25}$ -76.1° (c=0.56, $CHCl_3$), from 8 in 40% overall yield.

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6) The optical purity of 3 was determined by analysis of the ^{1}H-NMR (400 MHz) spectrum of (R)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester of 3.

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9) Structural assignments for the separable compounds were made by ^{1}H-NMR (400 MHz), IR, and high resolution mass spectroscopy and/or combustion analysis.

10) 6: ^{1}H-NMR ($CDCl_3$) δ: 1.71 (1H, ddd, J=14.0, 8.4, 4.9 Hz), 1.88 (1H, dt, J=14.0, 6.1 Hz), 2.09 (1H, dd, J=18.8, 2.3 Hz), 2.57 (1H, dd, J=18.8, 6.5 Hz), 3.07 (1H, m), 3.34 (3H, s), 3.35 (3H, s), 4.44 (1H, dd, J= 6.1, 4.9 Hz), 6.16 (1H, dd, J=5.7, 2.1 Hz), 7.66 (1H, dd, J=5.7, 2.7 Hz).

11) 7: ^{1}H-NMR ($CDCl_3$) δ: 0.05 (9H, s), 1.7-1.8 (2H, m), 2.1-2.3 (2H, m), 2.57 (1H, dd, J=16.1, 11.5 Hz), 3.22 (1H, brs), 3.316 (3H, s), 3.322 (3H, s), 3.45 (1H, dd, J=7.0, 2.8 Hz), 4.39 (1H, t, J=5.7 Hz), 6.80 (1H, s). Positive NOEs were observed between the protons Ha (3.22 ppm) and Hb (4.39 ppm), and between Ha (3.22 ppm) and Hc (6.80 ppm).

12) 8: ^{1}H-NMR ($CDCl_3$) δ: 1.45-1.95 (5H, m), 3.11 (1H, dd, J=6.3, 3.2 Hz), 3.21 (1H, dd, J=7.0, 3.2 Hz), 3.29 (6H, s), 4.00 (1H, dt, 10.1, 7.0 Hz), 4.36 (1H, t, J=5.8 Hz), 6.15 (2H, s).

13) 2a: ^{1}H-NMR ($CDCl_3$) δ: 1.7-1.9 (2H, m), 2.38 (1H, m), 2.8-2.95 (2H, m), 3.30 (3H, s), 3.31 (3H, s), 3.65 (1H, m), 4.38 (1H, t, J=5.6 Hz), 6.97 (1H, m), 9.75 (1H, s), 9.83 (1H, d, J=2.2 Hz). IR (neat): 1729, 1681 cm^{-1}. UV (EtOH) λ_{max} nm (ε): 242 (9400). HRMS (EI) m/z: 180.0821. Calcd for $C_{10}H_{12}O_3$ (M-CH_3OH), 180.0786.

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