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TOTAL SYNTHESIS OF (+)-MAYOLIDE A: THE ABSOLUTE CONFIGURATION OF MAYOLIDE A

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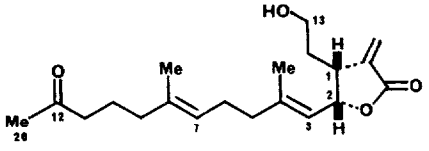
Summary: (+)-Mayolide A (1) was synthesized stereoselectively from D-mannitol via butenolide 5. This accomplishment determined the absolute configuration of mayolide A.

Mayolide A is the first secocembrane diterpene isolated from the soft coral Sinularia mayi.[1] The novel structure has been elucidated by NMR analysis except the absolute configuration. Herein, we wish to describe the total synthesis of 1, (+)-mayolide A, by an enantioselective manner. The result defined the absolute configuration of mayolide A as depicted in 2. This synthesis involves two crucial steps of stereoselective introduction of two carbon unit into β-position of the conjugated system in butenolide 5 to form C-1 asymmetric center, and repeated Claisen rearrangement to construct the side chain (C-3 to 20) in 1.



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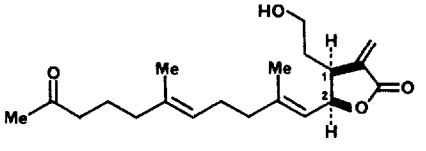


2: Mayolide A

Readily available (S)-4,5-di-O-isopropylidene-pent-2-enoate (3)[2] from D-mannitol was converted into butenolide 5 via 4[3] by two step sequence: lactonization by catalytic amount of dl-camphorsulfonic acid (CSA) in methanol at 20°C (95% yield) and protection of the hydroxyl group as tetrahydropyranyl (THP) ether (93% yield). Michael reaction of 5 with the lithium enolate of t-butyl acetate in THF at -78°C gave lactone 6[4] highly stereoselectively in 82% yield.[5,6] Selective reduction of lactone carbonyl in 6 with diisobutylaluminium hydride (DIBAL) in THF at -78°C, followed by treatment with sodium borohydride gave diol 7 with a requisite side chain (C-13, 14) at

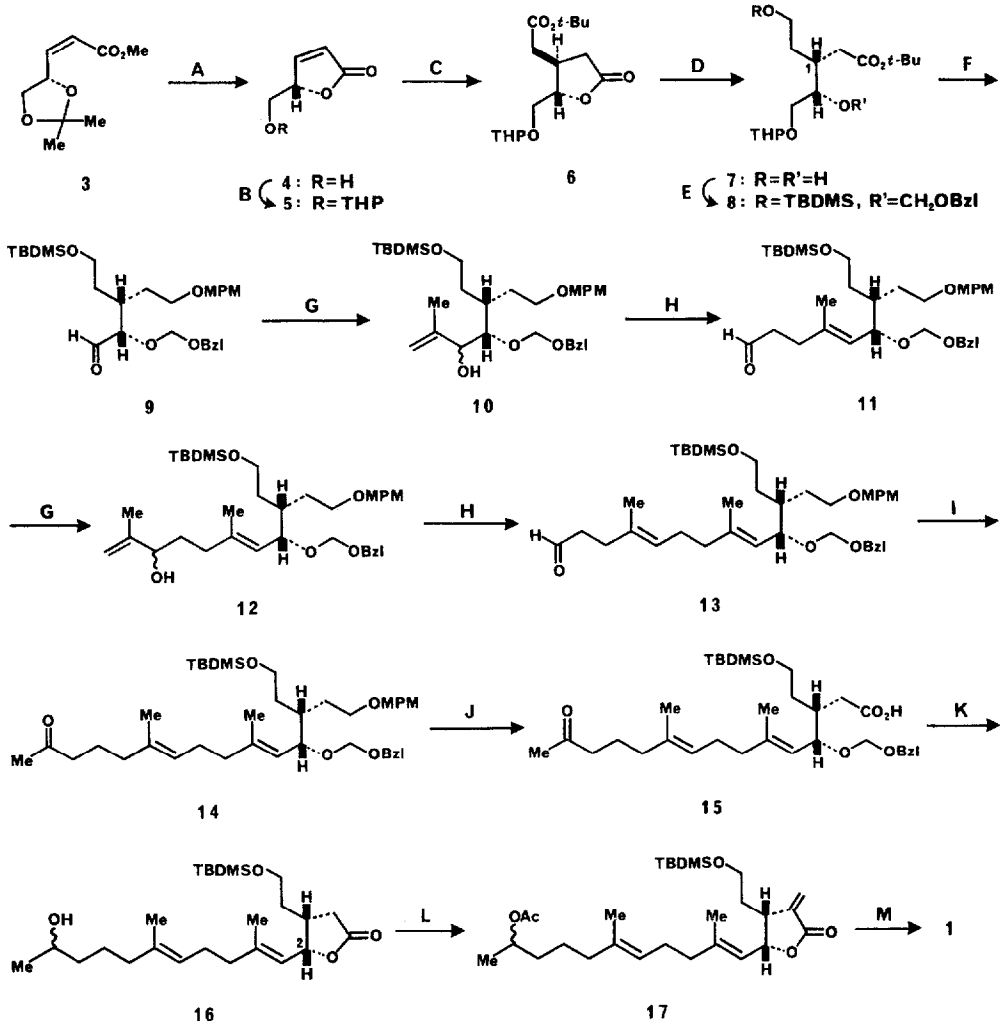
C-1 position[7] in 93% overall yield.

The resulting primary and secondary hydroxyl groups in 7 were selectively protected as t-butyldimethylsilyl ether and benzyloxymethyl ether, respectively, to give 8 (88% yield, two steps). Compound 8 was converted into aldehyde 9, $[\alpha]_D$ -5.9°(c 1.0, $CHCl_3$), in 62% overall yield by four step sequence: 1) reduction of t-butyl ester with lithium aluminium hydride; 2) protection of the primary hydroxyl group as p-methoxyphenylmethyl ether; 3) selective deprotection of THP group with magnesium bromide in ether at 20°C; 4) oxidation of the hydroxyl group by Swern's procedure. Grignard reaction of 9 with 1-methylvinylmagnesium bromide in THF at -78°C gave allylic alcohol 10 as a diastereomeric mixture (5:2) in 85% yield. Without separation of these isomers, the solution of 10 in ethyl vinyl ether was heated in the presence of mercuric acetate at 135°C for 48 h to afford (3E)-olefin 11, $[\alpha]_D$ -49.3° (c 1.4, $CHCl_3$), being accompanied with (3Z)-isomer (E:Z=5:1) in 63% yield from 10.[8] Furthermore, (3E)-olefin 11 was treated again with the same Grignard reagent to give allylic alcohol 12 (76% yield, 1:1 diastereomixture), which was then subjected to Claisen rearrangement under the similar reaction condition to that of 11 to afford dienal 13 (3E,7E), $[\alpha]_D$ -53.5° (c 0.23, $CHCl_3$), as a major isomer in 63% yield (7E:7Z=14:1).

Further extension of two carbon unit to the aldehyde 13 furnished the side chain (C-3 to 20) to give methyl ketone 14, $[\alpha]_D$ -54.0° (c 0.40, $CHCl_3$), in 90% overall yield by the following sequence: 1) reduction of aldehyde; 2) mesylation of the resulting hydroxyl group; 3) iodination with sodium iodide in acetone; 4) treatment with 1-ethoxyvinyllithium in THF at -78°C to 0°C; 5) selective hydrolysis of the resulting vinyl ether. Removal of the p-methoxyphenylmethyl group in 14 with 2,3-dichloro-5,6-dicyanobenzoquinone[9] in dichloromethane containing a small amount of water at 25°C and stepwise oxidation (pyridinium dichromate oxidation and then sodium chlorite oxidation[10]) afforded carboxylic acid 15 in 72% overall yield. Deprotection of the benzyloxymethyl group in 15 with lithium in liquid ammonia, followed by treatment with catalytic amount of CSA in ethyl acetate at 60°C gave lactone alcohol 16 without causing epimerization[11] at C-2 position in 93% yield from 13.

Introduction of exomethylene group into α-position to the lactone carbonyl in 16 giving 17 was carried out by the following reaction sequence: 1) reaction of the enolate, generated from 16 with 2.1 equiv of lithium diisopropylamide, with formaldehyde in THF at -78°C to -30°C (74% yield); 2) acetylation with acetic anhydride and pyridine in the presence of N,N-dimethyl-

Scheme I



Reagents: (A) CSA, MeOH; (B) DHP, CSA; (C) t-BuOAc, LDA, THF, -78°C; (D) i) DIBAL, ii) $NaBH_4$; (E) i) t-Bu(Me)$_2$SiCl, imidazole, ii) $PhCH_2OCH_2Cl$, i-Pr_2NEt; (F) i) $LiAlH_4$, ii) p-MeOPhCH_2Br, NaH, iii) $MgBr_2$, Et_2O, iv) DMSO, $COCl_2$ then Et_3N; (G) CH_2=C(Me)MgBr, THF; (H) CH_2=CHOEt, $Hg(OAc)_2$, 135°C; (I) i) $NaBH_4$, ii) MsCl, Et_3N, iii) NaI, Me_2CO, iv) CH_2=CHOEt, t-BuLi, THF, v) AcOH-H_2O-THF (2:1:4); (J) i) DDQ, CH_2Cl_2, H_2O, ii) PDC, 4Å molecular sieves, iii) $NaClO_2$, NaH_2PO_4, $MeCH=CMe_2$, t-BuOH-H_2O; (K) i) Li, liq.NH_3, ii) CSA; (L) i) LDA then HCHO, ii) Ac_2O, pyridine, DMAP, iii) DBU; (M) i) DIBAL, ii) PDC, 4Å molecular sieves, iii) n-Bu_4NF.

aminopyridine at 25°C and elimination of acetic acid with DBU in benzene at 50°C (95% yield, two steps). Finally, adjustment of the functional groups in 17 accomplished the synthesis of 1. Reaction of 17 with DIBAL in THF at -78°C gives the corresponding hydroxy hemiacetal (with concomitant reduction of the lactone). Oxidation of hydroxy hemiacetal with pyridinium dichromate in the presence of 4Å molecular sieves in dichloromethane at 25°C, followed by removal of the silyl group with tetra-n-butylammonium fluoride in THF furnished compound 1 (1R,2R) in 47% overall yield. ^{1}H NMR, IR, and TLC behavior were identical with those of the natural mayolide A, though the optical rotation of 1 observed as ($[\alpha]_D$ +56.4°, c 0.075, $CHCl_3$) was contrary to that of natural one ($[\alpha]_D$ -52°, c 1.76, $CHCl_3$). The synthesis of the antipodal (+)-mayolide A (1) revealed the absolute configuration of the natural mayolide A as depicted in 2 (1S,2S).

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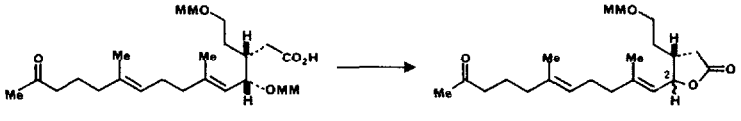
4) Structural assignments for all stable synthetic intermediates were made by ^{1}H NMR (400 MHz), IR, high resolution mass spectroscopy and/or combustion analysis.
5) Deprotection of THP group in 6 with 80% acetic acid at 40°C gave the corresponding primary alcohol as a single product. ^{1}H NMR (400 MHz) δ ppm 1.45 (9H, s), 3.72 (1H, dd, J=12.5, 4.0 Hz), 3.92 (1H, dd, J=12.5, 3.0 Hz), 4.28 (1H, ddd, J=6.0, 4.0, 3.0 Hz).
6) Similar stereoselective reactions were reported. For example: K.Tomioka, T.Ishiguro, and K.Koga, *J. Chem. Soc. Chem. Comm.*, 652 (1979); K.Tomioka, T.Ishiguro, and K.Koga, *Tetrahedron Lett.*, 21, 2973 (1980); J.P.Vigneron, R.Méric, M.Larchevêque, A.Debal, G.Kunesch, P.Zagatti, and M.Gallois, *Tetrahedron Lett.*, 25, 5051 (1982); S.Hanessian and P.J.Murray, *J. Org. Chem.*, 52, 1170 (1987).
7) Numbering of the compounds described here is in accordance with that for mayolide A.
8) In this Claisen rearrangement, the stereochemistry of the allylic hydroxyl group in 10 did not affect the E/Z ratio of the products.
9) Y.Oikawa, T.Yoshida, and O.Yonemitsu, *Tetrahedron Lett.*, 23, 885 (1982).
10) B.S.Bal, W.E.Childers, Jr., and H.W.Pinnick, *Tetrahedron*, 37, 2091 (1981).
11) Acid treatment (80% acetic acid, 60°C, 2 h) of 18, similarly synthesized, caused



18 19 (2β H) : 20 (2α H) = 1 : 2

epimerization at C-2 position to give lactone 20 (1,2-trans) as a major isomer.

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