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Synthetic Studies on Dolabellane Diterpenoids. Synthesis of 10-epi-Clavudiol A, an Epimer of a Marine Dolabellanoid

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In the line of our synthetic studies on the medium-ring containing higher terpenoids, we have applied our strategy, which is featured by obtaining a diterpenic skeleton from two monoterpene units, to the synthesis of the dolabellane family having a fused 5-11 bicyclic skeleton. From functionalized iridoid and geranyl synthons, 10-epi-clavudiol A, an epimer of marine dolabellane clavudol A, has been totally synthesized. Noteworthy steps include a feasible isomerization of the more substituted double bond to the less substituted one via the reduction of the allylic chloride mediated by Cr(II)Cl2 in the presence of alcoholic proton source and an intramolecular pinacol coupling to form the eleven-membered ring.

Introduction

Dolabellanes are widely distributed naturally occurring diterpenoids which are characterized by the bicyclo[9.3.0]tetradecane nucleus.1) Many dolabellanes exhibit antimicrobial activity, and some possess antitumor activity.2) Those are also speculated to be precursors of families of tricyclic diterpenoids such as dolastanes3) and fusicocccanes4) having fused 5-7-6 and 5-8-5 ring systems, respectively.

Therefore, synthetic studies of this class of compounds have attracted much attention, and a few syntheses of naturally occurring dolabellanes have recently been reported; δ-araneosene (1) by Borschberg et al.,5) dolabellatrienone (2)6) by Corey et al.,7) and floerkein B (3a)8) and barbilycopodin (3b)9) by us.10) Our previous total syntheses of 3a and 3b were featured by the stereocontrolled Cope rearrangement to adjust the stereochemistry of the unique quaternary carbon (C-1) in the skeleton. As described herein, we have tried to employ the similar strategy for the rapid construction of clavudol A (4), a marine dolabellanoid, isolated from the soft coral Clavularia viridis.11)

Results and Discussion

The initial several steps of the synthesis were the same with those of our previous work.10)

Scheme 1. [Reagents (yields)]. a: CrCl2·LiAlH4 / THF-DMF (84%); 7 : 8 = 3 : 1, b: Ac2O / pyridine (100%), c: MOMCl·i-Pr2NEt / CH2Cl2 (83%), d: LiAlH4 / THF (100%), e: TMSCl / pyridine (96%).
Thus, the CrCl₂ mediated coupling reaction of (3R)-8-hydroxyind-1-en-7-al (5) and 10-((tert-butyldimethylsilyloxy)geranyl chloride (6) afforded mainly two condensates, 7 and 8, in a ratio of 3:1. Selective acetylation of the secondary hydroxy group of the major condensate 7 gave 9 whose tertiary hydroxy group was protected as a methoxymethyl (MOM) ether to afford 10. Reductive deprotection and re-protection as a trimethylsilyl (TMS) ether of the secondary hydroxy group of 10 gave rise to 12 through 11.

As has been already reported, thermally-induced Cope rearrangement of 12 cleanly proceeded to provide a single product 13 having a correct absolute stereochemistry on a newly formed quaternary carbon (C-1). The nuclear Overhauser effects (NOE) observed in 13 revealed E-configuration of the enol silyl ether moiety and Z-configuration of the newly formed trisubstituted double bond. These stereocchemical outcomes were diagnostic to conclude that the rearrangement proceeded on the less-crowded \( \beta \)-face of the cyclopentene ring through a chair-like transition state. The unsaturation in the five-membered ring of the target compound, C-11-C-12 double bond, was conveniently introduced during a conversion of 13 to an unsaturated aldehyde 14 by the photooxgenation and subsequent reductive work-up on the enol silyl ether moiety. The aldehyde was reduced and the tert-butyldimethylsilyl (TBS) group was deprotected to produce a diol 16.

We set our next goal, which is a crucial step in this synthetic studies, to the isomerization of C-3-C-4 double bond to the less substituted C-4-C-16 double bond. To this end, we envisaged applying our reductive dehalogenation reaction of allylic halides to less substituted olefins mediated by Cr(II) salts and alcoholic proton sources. Firstly, two primary hydroxy groups of 16 were protected with the trimethylsilyl (TMS) ether of the secondary hydroxy group of 10 gave rise to 12 through 11.

**Scheme 2.** [Reagents (yields)].
- a: 200°C/ xylene (100%), b: \( \text{Ph}_3\text{P} / \text{acetone} (57\%)\), c: \( \text{LiAIH}_4 / \text{THF} (91\%)\), d: \( \text{Bu}_4\text{NF} / \text{THF} (98\%)\).

**Scheme 3.** [Reagents (yields)].
- a: trimethylacetyl (Piv) chloride / pyridine (100%), b: \( \text{Ca(OCl)}_2 / \text{KHSO}_4 / \text{CH}_2\text{Cl}_2 / \text{H}_2\text{O} (98\%)\), c: \( \text{CrCl}_3 / \text{LiAIH}_4 / \text{PrOH} / \text{THF-DMF} (83\%)\), d: \( \text{LiAIH}_4 / \text{THF} (100\%)\).

We set our next goal, which is a crucial step in this synthetic studies, to the isomerization of C-3-C-4...
The molecular structure of 22 clearly suggested that there are large differences in the circumstances of the two secondary hydroxy groups. While the 9-hydroxy group (O1 in Figure 1) is located in a convex face of the molecule, the 10-hydroxy group (O2 in Figure 1) is located in a sterically crowded environment. Taking advantage of this fact, the 9-hydroxy group of the triol 23, which was derived from 22 by deprotection of the 18-MOM group, was selectively acetylated to give 24. The dissolving metal reduction of 24 successfully eliminated the allylic acetate to furnish the synthesis of 10-epi-clavudiol (25). It should be noted that the deprotection of the 18-MOM group was necessary prior to this reductive elimination reaction; otherwise over-reduction products formed in some extent.

![Scheme 5](image)

Scheme 5. [Reagents (yields)]. a: AcOH / THF-H2O (89%), b: Ac2O / pyridine (90%), c: Ca / liq. NH3 (25, 50%; 23, 25%).

Unfortunately, extensive investigations on the epimerization of the 10-hydroxy group of 25 leading to clavudiol A (4) have been unsuccessful. The oxidation-reduction process re-produced 25 and Mitsunobu-type reactions did not proceed probably due to the severe steric hindrance of the reaction site. Although we had to terminate the synthetic studies of clavudiol A (4) with this line, the following result was encouraging. In the intramolecular pinacol coupling reaction, the substrate 26 (exists as an equilibrated mixture with 26'), in which the 18-hydroxy group was deprotected, afforded 27, having a requisite C-10 stereochemistry, together with 23. Further studies utilizing this finding for the synthesis of clavudiol A (4) are in due course.

![Condensation](image)

Condensation of (3R)-8-hydroxyirid-1-en-7-al (5) and 10-(t-butyldimethylsilyloxy)geranyl chloride (6) into (3R,7S)-7-{[(3R)-8-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]irid-1-ene-7,8-diol (7) and (3R,7S)-7-{[(3S)-8-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]irid-1-ene-7,8-diol (8). To a suspension of CrCl3 (5.90 g, 37.3 mmol) in anhydrous THF (30 cm3) was added LiAlH4 (710 mg, 60.1 mmol) at 0 °C and the mixture was stirred for 1 h. THF was removed from the mixture in vacuo, and the residue was dissolved in an anhydrous DMF (60 cm3). After 30 min of vigorous stirring, the mixture was cooled to 0 °C, to which 6 (4.33 g, 14.3 mmol) dissolved in anhydrous DMF (30 cm3) and 5 (2.88 g, 17.1 mmol) dissolved in anhydrous DMF (30 cm3) were introduced consecutively. Stirring was continued at ambient temperature for 15 h. The reaction was quenched with water and the mixture was extracted with ether. The combined organic layers were washed with brine, dried, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel gave a 3:1 mixture of 7 and 8 (5.26 g, 12.0 mmol, 84%) as a colorless oil. The above mixture of 7 and 8 was subjected again to chromatography on a Lobar column to give pure 7 and 8, both as a colorless oil.

Experimental

Melting points were measured with a Yanagimoto Micro Melting Point Apparatus. Elemental analyses were performed by the Institute of Central Analysis and the Institute of Advanced Material Study, Kyushu University. The NMR spectra were recorded on JEOL GSX 270H, LA 400 and/or LA 600 in CDCl3 unless otherwise noted. The mass spectra were measured with a JEOL 01SG-2 or JMS-70 spectrometer at the Institute of Advanced Material Study, Kyushu University; among the data, only the molecular ion peak or the nearest peak as the alternative, and the base peak are recorded. The IR spectra were measured as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds, using JASCO IR-A 102 spectrometer. Optical rotations were measured with a Union PM-101 apparatus. All solvents were pre-dried by standard methods unless otherwise stated. All reaction involving nonaqueous solutions were performed under an inert atmosphere. The stationary phase for column chromatography was Wakogel C-300 and the eluent was a mixture of hexane and ethyl acetate. The organic extracts were dried over anhydrous magnesium sulfate unless otherwise stated.
(1H, br d, J=9.2 Hz), 3.98 (2H, br s), 4.31 (1H, br s), 5.04 (1H, dd, J=17.6, 1.5 Hz), 5.18 (1H, dd, J=11.0, 1.5 Hz), 5.35 (1H, br t, J=6.6 Hz), and 5.99 (1H, dd, J=17.6, 11.0 Hz); 13C NMR: δ −5.2 (2C), 13.4, 15.4, 17.9, 18.4, 22.3, 23.4, 26.0 (3C), 27.3, 30.5, 37.0, 38.5, 46.4, 58.3, 68.7, 74.0, 74.4, 114.3, 125.2, 134.0, 134.8, 142.1, and 145.4.

8: 1H NMR: δ 0.06 (6H, s), 0.91 (9H, s), 1.04 (3H, s), 1.11 (3H, s), 1.23−1.41 (2H, m), 1.30 (3H, s), 1.52 (1H, m), 1.57 (3H, br s), 1.74 (3H, d, J=0.7 Hz), 1.85−2.00 (3H, m), 2.09 (1H, m), 2.29 (1H, m), 2.93 (1H, br d, J=9 Hz), 3.99 (2H, br s), 4.29 (1H, s), 5.00 (1H, dd, J=17.6, 1.5 Hz), 5.08 (1H, dd, J=11.0, 1.5 Hz), 5.34 (1H, br td, J=7.1 Hz), and 5.86 (1H, dd, J=17.6, 11.0 Hz); 13C NMR: δ −5.2 (2C), 13.4, 15.5, 18.4, 20.6, 22.4, 23.1, 26.0 (3C), 27.2, 30.8, 37.0, 37.6, 46.3, 58.7, 68.7, 74.3, 74.8, 113.5, 125.3, 134.0, 135.2, 141.7, and 144.7.

Acetylation of a secondary hydroxy group of 7. Formation of (3R,7S)-7-acetoxy-[(3R)-8-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]-8-(methoxymethoxy)-irid-1-ene (11). To a CH2Cl2 solution (5 cm3) of 9 (161 mg, 0.369 mmol) were added diisopropylethylamine (0.4 cm3) and chloromethyl methyl ether (0.2 cm3) at 0°C. The mixture was then diluted with aqueous NaHCO3 and extracted with ether. The organic extract was washed successively with water and brine, dried, and evaporated in vacuo. The residue was chromatographed on a silica gel to afford 11 (1.060 g, 2.28 mmol) as a colorless oil.

11: Found: C 70.18, H 10.88%; Calcd for C28H32O4Si: C 70.35, H 10.75%. MS: m/z 269 (M+−211) and 151 (base peak); 1R (NaCl): v 2930, 2854, 1468, 1370, 1253, 1148, 1129, 1066, 822, 836, and 775 cm−1; 1H NMR: δ 0.06 (6H, s), 0.86 (3H, s), 0.90 (9H, s), 1.08 (3H, s), 1.32 (3H, s), 1.41 (1H, m), 1.58 (3H, br s), 1.74 (3H, br s), 1.84−2.04 (3H, m), 2.07 (1H, m), 3.06 (1H, br d, J=10 Hz), 3.39 (3H, s), 3.98 (2H, br s), 4.27 (1H, d, J=7.7 Hz), 4.76 (1H, d, J=7.7 Hz), 4.80 (1H, d, J=7.7 Hz), 4.93 (1H, dd, J=17.6, 1.5 Hz), 5.04 (1H, dd, J=11.0, 1.5 Hz), 5.36 (1H, br t, J=1.5 Hz), 5.57 (1H, d, J=8.4 Hz), and 6.01 (1H, dd, J=17.6, 11.0 Hz); 13C NMR: δ −5.2 (2C), 13.4, 15.6, 18.4, 18.5, 20.3, 22.3, 25.6, 26.0 (3C), 27.0, 37.0, 38.2, 46.2, 55.6, 57.2, 68.8, 74.5, 81.8, 90.4, 112.2, 125.5, 133.8, 135.9, 141.4, and 145.1.

Protection of the secondary hydroxy group of 11 as a TMS ether. Formation of (3R,7S)-7-[(3R)-8-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]-8-(methoxymethoxy)-7-trimethylsilyloxy-irid-1-ene (12). To a CH2Cl2 solution (5 cm3) of 11 (883 mg, 1.84 mmol) was added pyridine (1.5 cm3) and TMSCI (0.7 cm3) and the mixture was stirred for 15 h at ambient temperature. The reaction mixture was treated with aqueous NaHCO3, and extracted with ether. The combined organic layers were washed with water and brine, dried, and concentrated in vacuo. The residue was chromatographed on a silica gel to give 12 (974 mg, 1.76 mmol, 96%) as a colorless oil.

12: Found: C 67.25, H 11.04%; Calcd for

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C_{13}H_{20}O_{4}Si_{2}: C 67.33, H 10.94%; [α]_{D}^{23} +30.3 (c 1.78, CHCl_{3}); MS: m/z 318 (M^{+}→234) and 223 (base peak); IR (NaCl): ν 2930, 2856, 1465, 1366, 1251, 1136, 1066, 876, 837, and 775 cm⁻¹; 1H NMR: δ 0.04 (6H, s), 0.09 (9H, s), 0.82 (3H, s), 0.90 (9H, s), 1.08 (3H, s), 1.17 (1H, m), 1.48 (3H, s), 1.55 (3H, br s), 1.74 (3H, br s), 2.15 (1H, m), 2.36 (1H, m), 3.19 (1H, br d, J=8.8 Hz), 3.98 (3H, s), 3.98 (2H, s), 4.35 (1H, s), 4.65 (1H, d, J=7.0 Hz), 4.71 (1H, d, J=7.0 Hz), 4.93 (1H, dd, J=17.6, 1.5 Hz), 5.09 (1H, dd, J=11.0, 1.5 Hz), 5.32 (1H, td, J=7.0, 1.5 Hz), and 6.09 (1H, dd, J=18.0, 11.0 Hz); 13C NMR: δ -5.2 (2C), 0.6 (3C), 13.4, 15.7, 17.9, 18.4, 22.2, 23.0, 25.9 (3C), 26.4, 26.6, 37.4, 39.3, 45.2, 55.0, 55.2, 68.6, 76.3, 80.8, 90.9, 112.8, 125.0, 134.0, 136.4, 142.9, and 145.0.

Cope rearrangement of 12. Formation of (1S,12R)-(9-(butyldimethylsilyloxy)-18-methoxy-10-tri­methylsilyloxy-9,10-seco-dolabella-3(Z),7(E),10(E)-triene (13). An anhydrous xylene solution (8 cm³) of 12 (964 mg, 1.74 mmol) was heated in a degassed sealed tube containing 500 mg of MS 4A at 200 °C for 24 h. After cooling, the reaction mixture was concentrated in vacuo and chromatographed briefly on silica gel to give 13 (964 mg, 1.74 mmol, 100%) a colorless oil.

Reduction of the aldehyde of 14. Formation of (1S)-(9-(butyldimethylsilyloxy)-18-methoxy-9,10-seco­dolabella-3(Z),7(E),11-trien-10-ol (15). An anhydrous THF (5 cm³) solution of 14 (99 mg, 0.207 mmol) was treated with LiAlH₄ (8 mg, 1 eq.) at 0 °C and the at ambient temperature for 2 h. The reaction was quenched by an addition of aqueous NH₄Cl solution and extracted with ether, washed with water and brine, and dried over Na₂SO₄. After the evaporation of solvents, the residue was chromatographed on silica gel provided 15 (91 mg, 0.189 mmol, 91%) as a colorless oil.

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13: Found: C 67.45, H 10.80%; Calculated for C_{13}H_{20}O_{4}Si_{2}: C 67.33, H 10.94%; [α]_{D}^{23} +42.6 (c 1.22, CHCl₃); MS: m/z 358 (M^{+}→14) and 226 (base peak); IR (NaCl): ν 2930, 2856, 1465, 1366, 1251, 1136, 1066, 876, 837, and 775 cm⁻¹; 1H NMR: δ 0.07 (6H, s), 0.91 (9H, s), 1.11 (3H, s), 1.21 (3H, s), 1.31 (3H, s), 1.48–1.68 (3H, m), 1.61 (3H, br s), 1.71 (3H, d, J=1.1 Hz), 1.89 (1H, m), 2.02–2.14 (6H, m), 2.91 (1H, m), 3.36 (3H, s), 4.01 (2H, br s), 4.70 (1H, d, J=7.2 Hz), 4.74 (1H, d, J=7.2 Hz), 5.19 (1H, td, J=6.2, 1.1 Hz), 5.40 (1H, br t, J=1.5 Hz), and 6.16 (1H, d, J=2.2 Hz); 13C NMR: δ -5.3 (2C), δ 0.4 (3C), 13.4, 18.4, 23.7, 25.5, 26.0 (3C), 26.1, 26.3, 27.0, 28.1, 31.8, 38.2, 42.2, 44.4, 51.5, 55.1, 68.7, 80.3, 90.9, 123.1, 124.4, 131.9, 134.4, and 135.9.

Photosynthesis of 13. Formation of (1S)-(9-(butyldimethylsilyloxy)-18-methoxy-9,10-seco­dolabella-3(Z),7(E),11-trien-10-ol (14). Into an acetone (2 cm³) solution of 13 (227 mg, 0.410 mmol) were added small amounts of pyridine and Rose Bengal and the mixture was irradiated with W-lamp at -78 °C for 13 min under oxygen atmosphere. Then Ph₃P (220 mg, 2 eq.) was added into the reaction mixture and stirred for 2 h at ambient temperature. After an evaporation of solvents, the residue was partitioned between ether and 0.5 N HCl and stirred for 1.5 h, diluted with aqueous NaHCO₃, extracted with ether, washed with water, aqueous KHSO₄, aqueous NaHCO₃, and brine, dried, and concentrated in vacuo. The residue was chromatographed on a silica gel to give 14 (112 mg, 0.234 mmol, 57%) as a colorless oil.

14: [α]_{D}^{23} +11.5 (c 1.22, CHCl₃); MS: m/z 478 (M^{+}→165) and 165 (base peak); IR (NaCl): ν 2930, 2856, 1668, 1461, 1383, 1364, 1252, 1147, 1069, 1033, 922, 837, and 776 cm⁻¹; 1H NMR: δ 0.07 (6H, s), 0.91 (9H, s), 1.22 (3H, s), 1.48 (6H, s), 1.61 (3H, br s), 1.67 (3H, b, J=1.1 Hz), 1.81 (1H, m), 2.22 (1H, m), 2.46–2.37 (3H, m), 3.36 (3H, s), 4.00 (2H, br s), 4.68 (1H, d, J=7.3 Hz), 4.70 (1H, d, J=7.3 Hz), 5.01 (1H, br t, J=6.8 Hz), 5.38 (1H, m), and 10.47 (1H, s); 13C NMR: δ -5.2 (2C), 13.4, 18.4, 23.7, 26.0 (3C), 26.1 (2C), 28.4, 28.5, 31.7, 34.1, 35.2, 37.2, 51.1, 55.7, 68.7, 78.2, 92.1, 122.1, 124.5, 134.5, 136.6, 143.7, 165.0, and 192.8.

Reduction of the aldehyde of 14. Formation of (1R)-(9-(butyldimethylsilyloxy)-18-methoxy-9,10-seco­dolabella-3(Z),7(E),11-trien-10-ol (15). A colorless oil.
65.6, 68.8, 78.3, 91.8, 122.3, 125.5, 135.1, 136.0, 142.5, and 143.2.

Protection of the primary hydroxy groups of 16 as pivaloates. Formation of (1S)-18-methoxymethoxy-9,10-di(trimethylacetoxy)-9,10-seco-dolabella-3(Z),7(E),11-tetraene (17). An anhydrous pyridine (5 cm$^3$) solution of 16 (298 mg, 0.814 mmol) was treated with trimethylacetyl chloride (1 cm$^3$) at ambient temperature for 18 h. The reaction was quenched by an addition of aqueous NaHCO$_3$ solution and extracted with ether, washed with water and brine, and dried over Na$_2$SO$_4$. After the evaporation of solvents, the residue was chromatographed on silica gel to give 17 (435 mg, 0.814 mmol, 100%) as a colorless oil.

17: Found C 71.78, H, 10.20%; Calc for C$_{32}$H$_{54}$O$_6$: C 71.87, H 10.18%; [a]$_D$ = 18.7 (c 2.30, CHCl$_3$); MS: m/z 473 (M$^+$-61) and 236 (base peak); IR (NaCl): ν 2970, 1729, 1480, 1460, 1397, 1365, 1281, 1153, 1085, 1035, and 920 cm$^{-1}$; 1H NMR: δ 1.04 (3H, s), 1.18 (9H, s), 1.21 (9H, s), 1.39 (6H, s), 1.49 (1H, m), 1.64 (3H, d, J = 11 Hz), 1.69 (3H, br s), 1.75 (1H, m), 1.95–2.15 (6H, m), 2.27–2.33 (2H, m), 3.35 (3H, s), 4.44 (2H, br s), 4.64 (2H, s), 4.71 (1H, d, J = 17 Hz), 4.78 (1H, d, J = 17 Hz), 5.11 (1H, tm, J = 6.6 Hz), and 5.43 (1H, m); 13C NMR: δ 13.7, 23.6, 25.9, 26.1, 27.2 (6C), 28.2, 28.3, 31.4, 32.7, 35.1, 37.5, 38.6, 38.8, 51.3, 55.3, 58.3, 69.9, 76.5, 77.5, 92.3, 122.3, 128.5, 130.5, 135.9, 138.0, 147.2, 178.3, and 178.4.

Allylic chlorination of 17. Formation of (1S)-3-chloro-18-methoxymethoxy-9,10-di(trimethylacetoxy)-9,10-seco-dolabella-4(16),7(E),11-tetraene (18). Into a CH$_2$Cl$_2$ (20 cm$^3$) of 17 (441 mg, 0.824 mmol) were added water (2 cm$^3$), calcium hypochlorite (120 mg), and NaHCO$_3$ (440 mg). Into this suspension, an aqueous (5 cm$^3$) solution of KHSO$_4$ (650 mg) was added dropwise under vigorous stirring at 0°C. After 1 h stirring, the reaction mixture was diluted with water and extracted with ether. The organic layer was washed successively with an aqueous solution of Na$_2$SO$_4$, water, and brine. After drying over MgSO$_4$, the solvents were evaporated to give 18 (464 mg, 0.817 mmol, 98%) as a colorless oil.

18: Found C 71.91, H, 10.20%; Calc for C$_{32}$H$_{54}$O$_6$: C 71.87, H 10.18%; MS: m/z 473 (M$^+$-61) and 233 (base peak); 1H NMR: δ 1.05 (3H, s), 1.18 (9H, s), 1.21 (9H, s), 1.39 (6H, s), 1.64 (3H, br s), 1.42–1.65 (3H, m), 1.78 (1H, m), 1.84–2.10 (4H, m), 2.10–2.20 (2H, m), 2.11–2.20 (2H, m), 3.35 (3H, s), 4.44 (2H, br s), 4.65 (2H, s), 4.70 (1H, br s), 4.71 (1H, d, J = 11.7 Hz), 4.72 (1H, br s), 4.78 (1H, d, J = 11.7 Hz), and 5.43 (1H, br td, J = 7, 1.1 Hz); 13C NMR: δ 13.8, 25.9, 26.0, 27.2 (6C), 28.2, 28.3, 31.3, 32.8, 35.1, 35.8, 38.3, 38.7, 38.9, 50.9, 55.4, 58.3, 69.8, 77.5, 92.4, 108.8, 128.3, 130.5, 138.2, 147.1, 149.6, 178.3, and 178.4.

Reductive deprotection of pivaloyl groups in 19. Formation of (1S)-18-methoxymethoxy-9,10-seco-dolabella-4(16),7(E),11-tetraene-9,10-diol (20). An anhydrous THF (5 cm$^3$) solution of 19 (167 mg, 0.312 mmol) was treated with LiAlH$_4$ (30 mg) at 0°C and the at ambient temperature for 1 h. The reaction was quenched by an addition of aqueous NH$_4$Cl solution and extracted with ether, washed with water and brine, and dried over Na$_2$SO$_4$. After the evaporation of solvents, the residue was chromatographed on silica gel provided 20 (114 mg, 0.312 mmol, 100%) as a colorless oil.

20: MS: m/z 304 (M$^+$-62) and 273 (base peak); 1H NMR: δ 1.06 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.42–2.01 (6H, m), 1.67 (3H, br s), 2.01–2.11 (2H, m), 2.11–2.23 (2H, m), 2.23–2.33 (2H, m), 3.34 (3H, s), 3.99 (2H, br s), 4.07 (2H, br s), 4.71 (1H, br s), 4.73 (1H, br s), 4.78 (2H, s), and 5.41 (1H, br td, J = 6.8, 1.5 Hz); 13C NMR: δ 13.7, 26.0, 26.2, 27.2, 27.4, 31.5, 32.6, 34.7, 35.7, 38.4, 51.3, 55.7, 56.5, 68.8, 78.4, 91.8, 108.8, 125.7, 135.0, 142.3, 143.0, and 150.1.

Oxidation of two allylic hydroxy groups of 20. Formation of (1S)-18-methoxymethoxy-9,10-seco-dolabella-4(16),7(E),11-tetraene-9,10-dial (21). Into a solution of 20 (129 mg, 0.352 mmol) in anhydrous CH$_2$Cl$_2$ (6 cm$^3$) were added MS-4A (600 mg) and BaMnO$_4$ (1.85 g). The reaction mixture was stirred at ambient temperature for 48 h. The mixture was then passed through a pad of celite and concentrated in vacuo. The residue was chromatographed briefly on silica gel to afford 21 (91 mg, 0.251 mmol, 71%) as a colorless oil.

21: 1H NMR: δ 1.22 (3H, s), 1.49 (3H, s), 1.50 (3H, s), 1.51–1.68 (2H, m), 1.75 (3H, br s), 1.91 (1H, m), 2.12–2.23 (2H, m), 2.38–2.55 (3H, m), 3.37 (3H, s), 4.71 (2H, s), 4.71 (1H, br s), 4.78 (1H, br s), 6.48 (1H, br t, J = 7 Hz), 9.39 (1H, s), and 10.50 (1H, s).

Intramolecular reductive coupling reaction to form 11-membered ring from 21. Formation of (1S,9S,10R)-18-methoxymethoxydolabella-4(16),7(E),11-tetraene-9,10-
diol (22). Into a suspension of TiCl₄, prepared from TiCl₄ (4 cm³) and Zn dust (600 mg) in cold anhydrous THF (80 cm³), a solution of 21 (91 mg, 0.211 mmol) in THF (18 cm³) was added slowly using a micro-feeder during a period of 8 h at −30 °C. The stirring was continued at this temperature for 7 h and then at ambient temperature for 4 h. The reaction mixture was treated with an aqueous K₂CO₃ solution and then extracted with ether, which was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel to give 22 (45 mg, 0.123 mmol, 58%) as colorless prisms.

22: mp 88–89 °C; Found: C 72.46, H 9.92%; Calcld for C₂₂H₃₄O₄: C 72.89, H 9.45%; [α]D -58.0 (c 0.40, CHCl₃); MS: m/z 302 (M⁺-62) and 149 (base peak); IR (KBr): v 3418, 2934, 2854, 1448, 1258, 1116, 1085, 1030, 902, and 887 cm⁻¹; ¹H NMR: δ 1.30 (3H, s), 1.47 (3H, s), 1.77 (IH, m), 1.87 (3H, br s), 2.09 (3H, s), 2.10-2.41 (2H, m), 4.60 (IH, br d, J=2.5 Hz), 4.74 (IH, d, J=1 Hz), 5.40 (1H, s), 5.80 (1H, d, J=5 Hz), 5.83 (1H, br t, J=7 Hz), 5.85 (1H, d, J=2 Hz); ¹³C NMR: δ 14.2, 21.5, 28.7, 30.8, 30.9, 32.2, 32.7, 33.9, 36.0, 37.1, 39.5, 52.9, 73.5, 76.8, 84.6, 110.7, 131.7, 131.7, 133.8, 144.7, 152.4, and 170.6.

Dissolving metal reduction of 24. Formation of 10-epi-clavudiol (25). Calcium metal was dissolved into liq. NH₃ (5 cm³) at −78 °C. Into the resultant blue-colored solution, THF (3 cm³) and a solution of 24 (2.9 mg, 0.008 mmol) in THF (3 cm³) were added successively and stirred at −78 °C for 1 h. After destroying an excess Ca metal by an addition of PhCOONa, liq. NH₃ was evaporated off at room temperature. The residue was diluted with aqueous NH₄Cl solution and extracted with ether, which was washed with water and brine, dried, and evaporated. The residue was chromatographed on a silica gel to give 25 (1.3 mg, 0.004 mmol, 50%) as colorless needles and 23 (0.8 mg, 0.002 mmol, 25%).

25: mp 137–138 °C; HRFABMS: m/z 327.2301 (M+Na⁺); Calcld for C₂₀H₃₂O₂·Na: 327.2300; [α]D -72 (c 0.25, CHCl₃); MS: m/z 286 (M⁺-18) and 107 (base peak); IR (KBr): v 3308, 2972, 2946, 2846, 1453, 1375, 1162, 1099, 1000, 974, and 886 cm⁻¹; ¹H NMR: δ 1.32 (3H, s), 1.45 (3H, s), 1.54 (3H, s), 1.63 (3H, br s), 1.95–2.13 (2H, m), 2.13–2.40 (7H, m), 2.55 (1H, br m), 2.55 (1H, br d, J=9.9 Hz), 4.64 (1H, br s), 4.72 (1H, br s), 5.29 (1H, m), and 5.59 (1H, d, J=9.9, 6.6 Hz); ¹³C NMR: δ 18.1, 28.7, 30.6, 30.7, 31.5, 32.4, 33.4, 38.3, 39.1, 41.7, 42.1, 51.9, 66.1, 72.9, 71.0, 110.6, 124.0, 132.5, 142.9, 148.3, and 152.5.

Crystallographic structure determination of 22. The single crystal of 22 was obtained as a colorless prism by recrystallization of the compound from a mixture of hexane and ethyl acetate.

Table 1. Crystallographic Data for 22.

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The measurement was made on an Enraf-Nonius FR590
diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54184 Å). The data were collected at a temperature 23 ± 2 °C using ω-2θ scan technique to a maximum 2θ value of 129.8°. The structure was solved by direct method (SIR92) and was refined using full-matrix least squares (SHELXL93) based on F² of all independent reflections measured. All H atoms were located at ideal positions and were included in refinement, but restrained to ride on the atom to which they are bonded. Isotropic thermal factors of H atoms were held fixed to 1.2 times or 1.5 times (for methyl groups) Ueq of the riding atoms. The crystallographic data are listed in Table 1.

References


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