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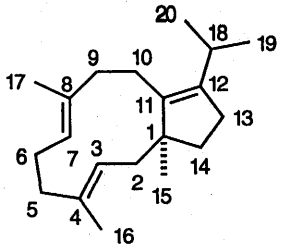
Synthetic Studies on Dolabellane Diterpenoids. Synthesis of 10-*epi*-Clavudiol A, an Epimer of a Marine Dolabellanoid

Nobuo KATO, Kohji NAKANISHI, Mineko OMOTO, Akira MORI, and Hitoshi TAKESHITA†

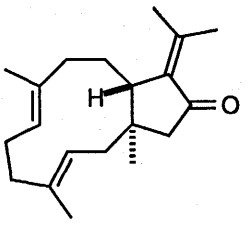
In the line of our synthetic studies on the medium-ring containing higher terpenoids, we have applied our strategy, which is featured by obtaining a diterpenic skeleton from two monoterpene units, to the synthesis of the dolabellane family having a fused 5-11 bicyclic skeleton. From functionalized iridoid and geranyl synthons, 10-*epi*-clavudiol A, an epimer of marine dolabellane clavudiol 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 $Cr(II)Cl_2$ in the presence of alcoholic proton source and an intramolecular pinacol coupling to form the eleven-membered ring.

Introduction

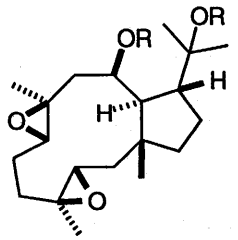
Dolabellanes are widely distributed naturally occurring diterpenoids which are characterized by the bicyclo[9.3.0]tetradecane nucleus.[1] Many dolabellanes exhibit antimicrobial activity, and some possess antitumer activity.[2] Those are also speculated to be precursors of families of tricyclic diterpenoids such as dolastanes[3] and fusicoccanes[4] having fused 5-7-6 and 5-8-5 ring systems, respectively.



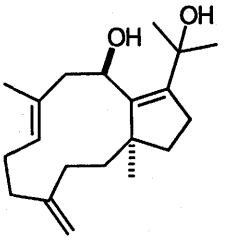
1 : δ-Araneosene



2 : Dolabellatrienone



3a : Floerkein B (R=H)
3b : Barbilycopodin (R = Ac)

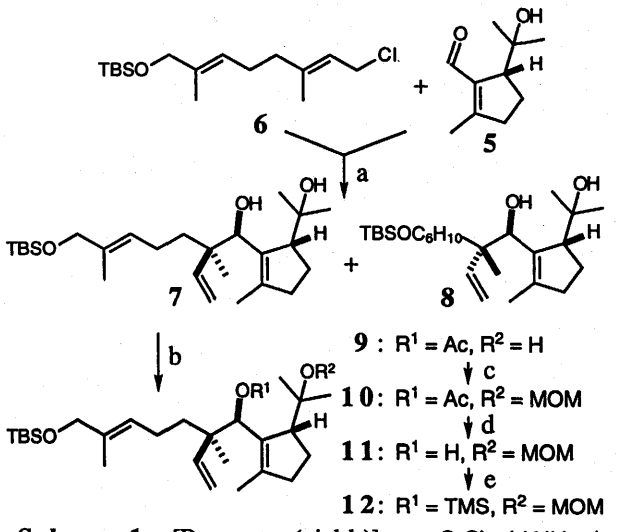


4 : Clavudiol A

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 clavudiol 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: $CrCl_3$–$LiAlH_4$ / THF–DMF (84%; **7** : **8** = 3 : 1), b: Ac_2O / pyridine (100%), c: MOMCl–*i*-Pr_2NEt / CH_2Cl_2 (83%), d: $LiAlH_4$ / THF (100%), e: TMSCl / pyridine (96%).

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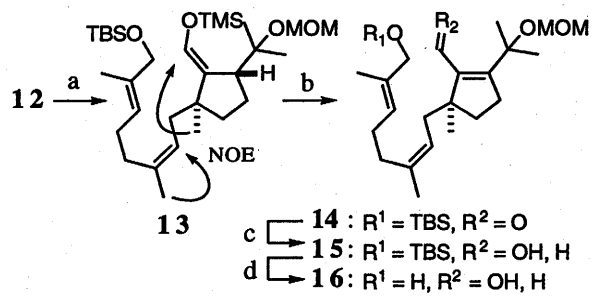
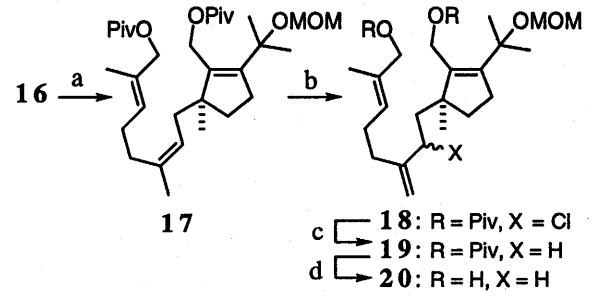
Thus, the $CrCl_2$ mediated coupling reaction[12] of (3*R*)-8-hydroxyirid-1-en-7-al (**5**)[10] and 10-(*t*-butyldimethylsilyloxy)geranyl chloride (**6**)[10] afforded mainly two condensates, **7** and **8**, in a ratio of 3 : 1. Selective acetylation of the secondary hydroxy group of the major condensate **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**.



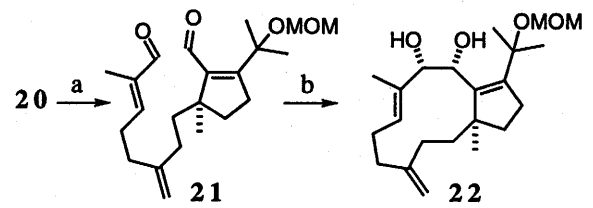
Scheme 2. [Reagents (yields)]. a: 200 °C / xylene (100%), b: $^1O_2$, then Ph_3P / acetone (57%), c: $LiAlH_4$ / THF (91%), d: Bu_4NF / THF (98%).

As has been already reported,[10] 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 stereochemical outcomes were diagnostic to conclude that the rearrangement proceeded on the less-crowded β-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 photooxygenation and subsequent reductive work-up on the enol silyl ether moiety. The aldehyde was reduced (**14**→**15**) and the *t*-butyldimethylsilyl (TBS) group was deprotected to produce a diol **16**.



Scheme 3. [Reagents (yields)]. a: trimethylacetyl (Piv) chloride / pyridine (100%), b: $Ca(OCl)_2$–$KHSO_4$ / CH_2Cl_2–H_2O (98%), c: $CrCl_3$–$LiAlH_4$–*i*-PrOH / THF–DMF (83%), d: $LiAlH_4$ / THF (100%).

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.[13] Firstly, two primary hydroxy groups of **16** were protected with the trimethylacethyl (pivaloyl; abbreviated as Piv in Scheme 3) groups for the purpose of retarding the reactivity of adjacent double bonds toward the electrophilic reagent. When the dipivaloate **17** was treated with hypochlorous acid, generated from calcium hypochlorite and potassium hydrogen sulfate, the C-3–C-4 double bond reacted predominantly as expected to afford a diastereomeric mixture of allylic chlorides **18**. Then, **18** was treated with $CrCl_2$ in the presence of 2-propanol as a proton source to furnish the isomerization of the double bond leading to **19**.



Scheme 4. [Reagents (yields)]. a: $BaMnO_4$ / CH_2Cl_2 (71%), b: $TiCl_4$–Zn / THF (58%).

The eleven-membered ring formation was carried out by a rather straightforward fashion. The pivaloyl protecting groups of **19** were reductively removed and the resulting diol **20** was oxidized by $BaMnO_4$ to give a dial **21**. The following reaction, low valent Ti-mediated intramolecular pinacol coupling reaction[14] on **21**, gave a crystalline cyclizate **22** as a sole product. Since the conformational mobility of the eleven-membered ring caused difficulties in the spectroscopic structure elucidation of **22**, an X-ray crystallographic analysis was carried out. As shown in Figure 1, **22** was in fact a desired cyclizate having a 9*S*,10*R*-glycol.

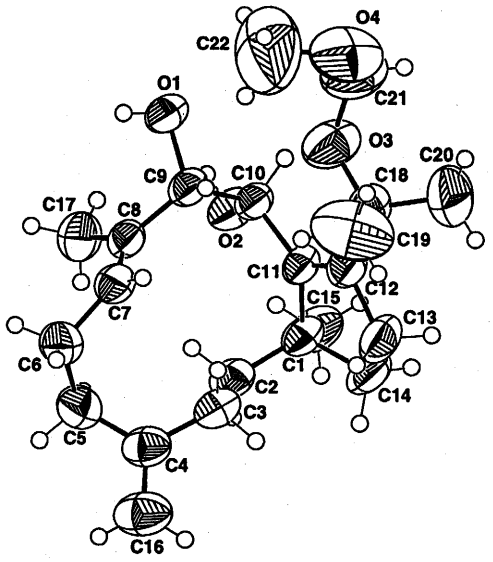
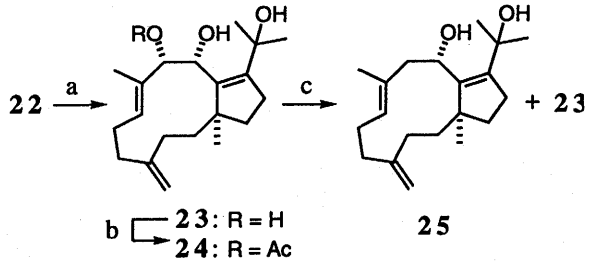


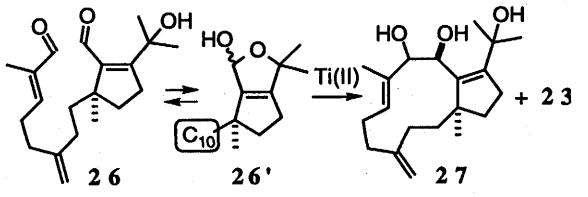
Fig. 1. Crystal structure of **22** showing 50% probability displacement ellipsoids.

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. [Reagents (yields)]. a: AcOH / THF–H_2O (89%), b: Ac_2O / pyridine (90%), c: Ca / liq. NH_3 (**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.



In summary, the synthesis of the dolabellane derivative having unsaturation in the five-membered ring has been realized. The method, Cr(II)-alcohol mediated reduction of the allylic halide, used for the double bond isomerization from the more substituted olefin to the less substituted olefin (**17** → **19**) should have wide applicability in the terpenoid synthesis. The application of this method is also underway.

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 $CDCl_3$ 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.

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 $CrCl_3$ (5.90 g, 37.3 mmol) in anhydrous THF (30 cm^3) was added $LiAlH_4$ (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 cm^3). 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 cm^3) and **5** (2.88 g, 17.1 mmol) dissolved in anhydrous DMF (30 cm^3) 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.
7: $[\alpha]_D^{21}$ +13.5 (*c*2.30, $CHCl_3$); MS: *m/z* 403 (M^+–33) and 228 (base peak); IR (NaCl): ν 3198, 2930, 2854, 1463, 1364, 1253, 1172, 1110, 1067, 1012, 908, 836, and 775 cm^{-1}; ^1H NMR: δ 0.05 (6H, s), 0.90 (9H, s), 0.93 (3H, s), 1.03 (3H, s), 1.25 (3H, s), 1.35 (3H, m), 1.47–1.57 (2H, m), 1.56 (3H, br s), 1.73 (3H, br s), 1.80–2.00 (3H, m), 2.08 (1H, m), 2.30 (1H, m), 3.02

(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); ^{13}C 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: ^{1}H 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); ^{13}C 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-7-[(3R)-8-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]irid-1-en-8-ol (9). A solution of **7** (250 mg, 0.572 mmol) in CH_2Cl_2 (5 cm^3) was treated with acetic anhydride (0.3 cm^3) and pyridine (1 cm^3) and stirred for 20 h. The mixture was then diluted with aqueous $NaHCO_3$ and extracted with ether. The organic extract was washed with aqueous $KHSO_4$, aqueous $NaHCO_3$, and brine, dried, and evaporated in vacuo. Chromatography of the residue on silica gel gave **9** (274 mg, 0.572 mmol, 100%) as a colorless oil.

9: IR (NaCl): ν 3550, 2930, 2854, 1755, 1463, 1372, 1219, 1067, 1013, 955, 837, and 775 cm^{-1}; ^{1}H NMR: δ 0.05 (6H, s), 0.90 (12H, s), 1.04 (3H, s), 1.22 (3H, br s), 1.27–1.35 (2H, m), 1.55 (3H, br s), 1.62 (1H, m), 1.86 (3H, br s), 1.77–2.02 (3H, m), 2.08 (3H, s), 2.09 (1H, m), 2.31 (1H, m), 3.15 (1H, br d, *J*=9 Hz), 3.94 (2H, br s), 3.98 (2H, br s), 5.00 (1H, dd, *J*=17.6, 1.1 Hz), 5.16 (1H, dd, *J*=10.6, 1.1 Hz), 5.30 (1H, br t, *J*=7 Hz), 5.84 (1H, s), and 5.94 (1H, dd, *J*=17.6, 10.6 Hz); ^{13}C NMR: δ –5.2 (2C), 13.3, 15.3, 18.4 (2C), 21.0, 22.0, 24.5, 26.0 (3C), 27.5, 29.3, 37.0, 38.0, 44.6, 58.0, 68.6, 73.4, 76.1, 114.3, 124.5, 131.1, 134.4, 143.7, 147.2, and 169.0.

Methoxymethylation of the tertiary hydroxy group of 9. Formation of (3R,7S)-7-acetoxy-7-[(3R)-8-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]-8-(methoxymethoxy)irid-1-ene (10). To a CH_2Cl_2 solution (5 cm^3) of **9** (161 mg, 0.369 mmol) were added diisopropylethylamine (0.4 cm^3) and chloromethyl methyl ether (0.2 cm^3) at 0 ℃, and then the mixture was stirred for 35 h at ambient temperature. The mixture was then diluted with aqueous $NaHCO_3$ and extracted with ether. The combined organic layers were washed successively with water and brine, dried, and concentrated under reduced pressure. The residue was purified by a silica-gel chromatography, affording **10** (160 mg, 0.307 mmol, 83%) as a colorless oil.

10: IR (NaCl): ν 2930, 2854, 1738, 1463, 1368, 1240, 1142, 1042, 914, 837, and 776 cm^{-1}; ^{1}H NMR: δ 0.05 (6H, s), 0.90 (9H, s), 0.95 (3H, s), 1.08 (3H, s), 1.27 (3H, s), 1.26–1.37 (2H, m), 1.55 (3H, br s), 1.68–2.09 (5H, m), 1.87 (3H, br s), 2.03 (3H, s), 2.33 (1H, m), 3.16 (1H, br d, *J*=9 Hz), 3.36 (3H, s), 3.98 (2H, br s), 4.67 (1H, d, *J*=7.3 Hz), 4.72 (1H, d, *J*=7.3 Hz), 4.99 (1H, dd, *J*=17.8, 1.3 Hz), 5.12 (1H, dd, *J*=10.8, 1.3 Hz), 5.30 (1H, br t, *J*=6 Hz), 5.63 (1H, s), and 6.04 (1H, dd, *J*=17.8, 10.8 Hz); ^{13}C NMR: δ –5.2 (2C), 13.3, 15.6, 18.3, 18.4, 21.2, 22.0, 24.3, 25.1, 26.0 (3C), 26.8, 37.2, 38.6, 44.4, 55.1, 55.1, 68.7, 76.2, 80.0, 90.9, 113.5, 124.6, 132.0, 134.3, 144.3, 147.3, and 170.3.

Reductive deprotection of the acetyl group of 10. Formation of (3R,7S)-7-[(3R)-8-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]-8-(methoxymethoxy)-irid-1-en-7-ol (11). To an anhydrous THF solution (15 cm^3) of **10** (1.155 g, 2.28 mmol) was added an excess $LiAlH_4$ at 0 ℃ and the mixture was stirred for 2 h at ambient temperature. The mixture was then treated with aqueous NH_4Cl and extracted with ether. The combined ethereal layers were washed with water and brine, dried, and concentrated in vacuo. The residue was chromatographed on a silica gel to afford **11** (1.060 g; 2.28 mmol; 100%) as a colorless oil.

11: Found: C 70.18, H 10.88%; Calcd for $C_{28}H_{52}O_4Si$: C 69.95, H 10.90%; $[\alpha]_D^{21}$ –7.6 (*c*1.58, $CHCl_3$); MS: *m/z* 269 (M^+–211) and 151 (base peak); IR (NaCl): ν 3386, 2930, 2854, 1468, 1370, 1253, 1148, 1129, 1066, 1022, 836, and 775 cm^{-1}; ^{1}H NMR: δ 0.05 (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), 2.32 (1H, m), 3.06 (1H, br d, *J*=10 Hz), 3.39 (3H, s), 3.98 (2H, br s), 4.27 (1H, d, *J*=8.4 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); ^{13}C 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-t-butyldimethylsilyloxy-3,7-dimethyl-1,6-octadien-3-yl]-8-(methoxymethoxy)-7-trimethylsilyloxyirid-1-ene (12). To a CH_2Cl_2 solution (5 cm^3) of **11** (883 mg, 1.84 mmol) was added pyridine (1.5 cm^3) and TMSCl (0.7 cm^3) and the mixture was stirred for 15 h at ambient temperature. The reaction mixture was treated with aqueous $NaHCO_3$, and extracted with ether. The combined organic layers were washed with water, aqueous $KHSO_4$, aqueous $NaHCO_3$, 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

$C_{31}H_{60}O_4Si_2$: C 67.33, H 10.94%; $[\alpha]_D^{21}$ –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); ^{13}C 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-(t-butyldimethylsilyloxy)-18-methoxymethoxy-10-trimethylsilyloxy-9,10-seco-dolabella-3(Z),7(E),10(E)-triene (****13****).* An anhydrous xylene solution (8 cm^3) of **12** (964 mg, 1.74 mmol) was heated in a degassed sealed tube containing 500 mg of MS 4A at 200 ℃ 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.

13: Found: C 67.45, H 10.80%; Calcd for $C_{31}H_{60}O_4Si$: C 67.33, H 10.94%; $[\alpha]_D^{21}$ –42.6 (*c*1.22, $CHCl_3$); MS: *m/z* 538 (M^+–14) and 226 (base peak); ^1H NMR: δ 0.07 (6H, s), 0.17 (9H, s), 0.92 (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); ^{13}C NMR: δ –5.3 (2C), –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, 134.6, and 135.9.

Photooxygenation of ***13****. Formation of (1S)-9-(t-butyldimethylsilyloxy)-18-methoxymethoxy-9,10-seco-dolabella-3(Z),7(E),11-trien-10-al (****14****).* Into an acetone (2 cm^3) 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 ℃ for 13 min under oxygen atmosphere. Then Ph_3P (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 $NaHCO_3$, extracted with ether, washed with water, aqueous $KHSO_4$, aqueous $NaHCO_3$, 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: $[\alpha]_D^{21}$ –11.5 (*c*1.22, $CHCl_3$); MS: *m/z* 478 (M^+) 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); ^{13}C NMR: –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 (1S)-9-(t-butyldimethylsilyloxy)-18-methoxymethoxy-9,10-seco-dolabella-3(Z),7(E),11-trien-10-ol (****15****).* An anhydrous THF (5 cm^3) solution of **14** (99 mg, 0.207 mmol) was treated with $LiAlH_4$ (8 mg, 1 eq.) at 0 ℃ and the at ambient temperature for 2 h. The reaction was quenched by an addition of aqueous NH_4Cl solution and extracted with ether, washed with water and brine, and dried over Na_2SO_4. After the evaporation of solvents, the residue was chromatographed on silica gel provided **15** (91 mg, 0.189 mmol, 91%) as a colorless oil.

15: Found: C 69.99, H, 10.00%; Calcd for $C_{28}H_{52}O_4Si$: C 69.95, H 10.90%; $[\alpha]_D^{21}$ –5.0 (*c*1.0, $CHCl_3$); MS: *m/z* 420 (M^+–60) and 287 (base peak); IR (NaCl): ν 3470, 2952, 2930, 2856, 1462, 1381, 1364, 1254, 1146, 1071, 1034, 923, 837, and 776 cm^{-1}; ^1H NMR: δ 0.06 (6H, s), 0.91 (9H, s), 1.06 (3H, s), 1.40 (3H, s), 1.41 (3H, s), 1.47 (1H, m), 1.60 (3H, br s), 1.69 (3H, d, *J*=1.1 Hz), 1.75 (1H, m), 1.97–2.18 (6H, m), 2.21–2.28 (2H, m), 3.41 (3H, s), 3.48 (1H, dd, *J*=7.3, 5.9 Hz), 4.00 (2H, br s), 4.02 (1H, dd, *J*=13.2, 7.3 Hz), 4.13 (1H, dd, *J*=13.2, 5.9 Hz), 4.75 (1H, d, *J*=7.0 Hz), 4.78 (1H, d, *J*=7.0 Hz), 5.08 (1H, br t, *J*=7.0 Hz), and 5.38 (1H, m); ^{13}C NMR: δ –5.3 (2C), 13.4, 18.4, 23.6, 25.8, 25.9 (3C), 26.0, 27.3, 27.4, 31.7, 32.5, 34.9, 37.6, 51.7, 55.7, 56.6, 68.6, 78.3, 91.8, 122.1, 124.3, 134.5, 136.3, 142.3, and 143.3.

Deprotection of the primary TBS ether of ***15****. Formation of (1S)-18-methoxymethoxy-9,10-seco-dolabella-3(Z),7(E),11-triene-9,10-diol (****16****).* An anhydrous THF (8 cm^3) solution of **15** (398 mg, 0.827 mmol) was treated with tetrabutylammonium fluoride (1 M in THF, 1.3 cm^3; 1.5 eq.) at ambient temperature for 15 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_2SO_4. After the evaporation of solvents, the residue was chromatographed on silica gel to give **16** (298 mg, 0.813 mmol, 98%) as a colorless oil.

16: $[\alpha]_D^{21}$ –5.9 (*c*1.70, $CHCl_3$); MS: *m/z* 213 (M^+–153), 109 (base peak); IR (NaCl): ν 3420, 2930, 1453, 1381, 1145, 1084, 1033, and 923 cm^{-1}; ^1H NMR: δ 1.05 (3H, s), 1.40 (3H, s), 1.40 (3H, s), 1.48 (1H, m), 1.67 (3H, d, *J*=0.7 Hz), 1.69 (3H, d, *J*=1.1 Hz), 1.75 (1H, m), 1.98–2.19 (6H, m), 2.22–2.29 (2H, m), 3.41 (3H, s), 3.42 (1H, br), 3.98 (2H, br s), 4.08 (2H, br s), 4.75 (1H, d, *J*=7.2 Hz), 4.76 (1H, d, *J*=7.2 Hz), 5.09 (1H, br t, *J*=6.6 Hz), and 5.41 (1H, m); ^{13}C NMR: δ 13.6, 23.5, 25.8, 25.9, 27.4, 27.4, 31.6, 32.5, 35.0, 37.7, 51.5, 55.7,

56.5, 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-triene (****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_2SO_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%; Calcd for $C_{32}H_{54}O_6$: C 71.87, H 10.18%; $[\alpha]_D^{20}$ –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*=1.1 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*=11.7 Hz), 4.78 (1H, d, *J*=11.7 Hz), 5.11 (1H, tm, *J*=6.6 Hz), and 5.43 (1H, m); ^{13}C 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-triene (****18****).* Into a CH_2Cl_2 (20 cm^3) of **17** (441 mg, 0.824 mmol) were added water (2 cm^3), calcium hypochrolite (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 ℃. 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_2SO_3, water, and brine. After drying over $MgSO_4$, the solvents were evaporated to give **18** (464 mg, 0.817 mmol, 98%), a mixture of diastereomers, as a colorless oil, which was used directly without any purifications.

18: ^1H NMR: δ 1.19 (9H, s), 1.22 (9H, s), 1.26 (1.5H, s), 1.27 (1.5H, s), 1.39 (6H, s), 1.66 (3H, br s), 3.35 (3H, s), 4.45 (2H, br s), 4.64 (1H, s), 4.65 (1H, s), 4.69 (1H, d, J=12 Hz), 4.76 (1H, br s), 4.79 (1H, d, J=12 Hz), 4.87 (0.5H, br s), 4.88 (0.5H, br s), 5.09 (0.5H, br s), 5.11 (0.5H, br s), 5.47 (1H, m).

Reductive dechlorination of ***18****. Formation of (1S)-18-methoxymethoxy-9,10-di(trimethylacetoxy)-9,10-seco-dolabella-4(16),7(E),11-triene (****19****).* To a suspension of $CrCl_3$ (500 mg, 3.16 mmol) in anhydrous THF (5 cm^3) was added $LiAlH_4$ (60 mg, 1.58 mmol) at 0 ℃ and the mixture was stirred for 1 h. Then isopropyl alcohol (0.5 cm^3), anhydrous DMF (3 cm^3), and a THF (10 cm^3) of **18** (464 mg, 0.817 mmol) were added into a resulted suspension. After 18 h of stirring at ambient temperature, the mixture was diluted with water and 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 **19** (368 mg, 0.688, 83%) as a colorless oil.

19: Found: C 71.91, H, 10.20%; Calcd for $C_{32}H_{54}O_6$: C 71.87, H 10.18%; MS: *m/z* 473 (M^+–61) and 133 (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); ^{13}C 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-triene-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 ℃ and the at ambient temperature for 1 h. The reaction was quenched by an addition of aqueous NH_4Cl solution and extracted with ether, washed with water and brine, and dried over Na_2SO_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: 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), 3.42 (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); ^{13}C 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-triene-9,10-dial (****21****).* Into a solution of **20** (129 mg, 0.352 mmol) in anhydrous CH_2Cl_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 a 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-triene-9,10-*

diol (22). Into a suspension of $TiCl_2$, prepared from $TiCl_4$ (4 cm^3) and Zn dust (600 mg) in cold anhydrous THF (80 cm^3), a solution of **21** (91 mg, 0.211 mmol) in THF (18 cm^3) was added slowly using a micro-feeder during a period of 8 h at –30 ℃. The stirring was continued at this temperature for 7 h and the at ambient temperature for 4 h. The reaction mixture was treated with an aqueous K_2CO_3 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 ℃; Found: C 72.46, H 9.92%; Calcd for $C_{22}H_{54}O_6$: C 72.49, H 9.95%; $[\alpha]_D^8$ –58.0 (*c*0.40, $CHCl_3$); MS: *m/z* 302 (M^+–62) and 149 (base peak); IR (KBr): ν 3418, 2934, 2854, 1448, 1258, 1116, 1085, 1030, 902, and 887 cm^{-1}; ^1H NMR: δ 1.30 (3H, s), 1.40 (3H, s), 1.43 (3H, s), 1.63 (1H, m), 1.85 (3H, br s), 1.95–2.25 (4H, m), 2.25–2.43 (2H, m), 3.41 (3H, s), 4.51 (1H, br d, *J*=2.6 Hz), 4.67 (1H, br d, *J*=1.3 Hz), 4.73 (1H, br d, *J*=1.3 Hz), 4.78 (2H, s), 5.54 (1H, br s), and 5.63 (1H, br t, *J*=7.5 Hz); ^{13}C NMR: δ 13.7, 26.5, 26.9, 28.5, 32.1, 32.5, 33.5, 36.2, 37.3, 39.9, 53.1, 55.7, 78.0, 78.7, 81.2, 91.5, 110.5, 129.1, 134.8, 139.1, 143.8, and 152.6.

Deprotection of methoxymethyl group of 22. Formation of (1S,9S,10R)-dolabella-4(16),7(E),11-triene-9,10,18-triol (23). A solution of **22** (45 mg, 0.123 mmol) in a mixture of THF (1 cm^3), acetic acid (1 cm^3), and water (1 cm^3) was stirred at ambient temperature for 4 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution extracted with ether and washed with brine, dried, and evaporated. Chromatography of the residue on silica gel gave **23** (35 mg, 0.109 mmol, 89%) as a colorless oil.

23: $[\alpha]_D^{20}$ –52.0 (*c*0.27, $CHCl_3$); ^1H NMR: δ 1.30 (3H, s), 1.41 (6H, s), 1.85 (3H, br s), 1.98–2.23 (6H, m), 2.23–2.45 (2H, m), 4.60 (1H, br d, *J*=2.6 Hz), 4.67 (1H, br s), 4.73 (1H, br s), 5.65 (1H, m), and 5.67 (1H, br s); ^{13}C NMR: δ 13.8, 28.6, 31.1, 31.2, 32.0, 32.5, 33.9, 36.2, 37.6, 40.1, 52.9, 73.8, 78.1, 81.5, 110.5, 129.2, 134.8, 137.8, 144.0, and 152.7.

Selective acetylation of 23. Formation of (1S,9S,10R)-9-acetoxydolabella-4(16),7(E),11-triene-10,18-diol (24). A solution of **23** (35 mg, 0.109 mmol) in pyridine (2 cm^3) and acetic anhydride (1 cm^3) was stirred at room temperature for 16 h. The mixture was then treated with aqueous $NaHCO_3$ and extracted with ether, which was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel to give **24** (35 mg, 0.097 mmol, 90%) as colorless needles.

24: mp 127–128 ℃; Found: C 72.67, H 9.43%; Calcd for $C_{22}H_{34}O_4$: C 72.89, H 9.45%; $[\alpha]_D^{20}$ –39 (*c*0.38, $CHCl_3$); MS: *m/z* 345 (M^+–17) and 151 (base peak); IR (KBr): ν 3426, 2938, 2852, 1714, 1366, 1262, 1116, 959, and 879 cm^{-1}; ^1H NMR: δ 1.30 (3H, s), 1.37 (3H, s), 1.47 (3H, s), 1.77 (1H, m), 1.87 (3H, br s), 2.09 (3H, s), 1.97–2.26 (6H, m), 2.26–2.44 (3H, m), 4.68 (1H, d, *J*=1 Hz), 4.74 (1H, d, *J*=1 Hz), 5.61 (1H, d, *J*=2 Hz), 5.73 (1H, br t, *J*=7 Hz), and 5.80 (1H, d, *J*=2 Hz); ^{13}C 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, 136.8, 144.7, 152.4, and 170.6.

Dissolving metal reduction of 24. Formation of 10-epi-clavudiol (25). Calcium metal was dissolved into liq. NH_3 (5 cm^3) at –78 ℃. Into the resultant blue-colored solution, THF (3 cm^3) and a solution of **24** (2.9 mg, 0.008 mmol) in THF (3 cm^3) were added successively and stirred at –78 ℃ for 1 h. After destroying an excess Ca metal by an addition of PhCOONa, liq. NH_3 was evaporated off at room temperature. The residue was diluted with aqueous NH_4Cl 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 ℃; HRFABMS: *m/z* 327.2301 ($M+Na^+$); Calcd for $C_{20}H_{32}O_2$·Na: 327.2300; $[\alpha]_D^{24}$ –72 (*c*0.25, $CHCl_3$); MS: *m/z* 286 (M^+–18) and 107 (base peak); IR (KBr): ν 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, dd, *J*=9.9, 6.6 Hz); ^{13}C 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, 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**.

Formula	$C_{22}H_{36}O_4$
Formula weight	M_r = 364.51
Crystal size / mm	0.35 x 0.30 x 0.25
Crystal system	Tetragonal
Space group	$P4_12_12$
a / Å	9.245(2)
c / Å	51.206(2)
V / Å^3	4376.6(13)
Z	8
D_{calc} / g cm^{-3}	1.106
μ / mm^{-1}	0.588
No. of reflections	3719
No. of obsd refl. [$I > 2\sigma(I)$]	2726
Refined parameters	236
Refinement	F^2 (*SHELXL93*)
$R[F^2 > 2\sigma(F^2)]$	0.0632
$wR(F^2)$	0.2028

The measurement was made on an Enraf-Nonius FR590

diffractometer with graphite monocromated Cu $K\alpha$ radiation (λ = 1.54184 Å}). The data were collected at a temperature 23±2 ℃ using ω-2θ scan technique to a maximum 2θ value of 129.8°. The structure was solved by direct method (*SIR92*[15]) and was refined using full-matrix least squares (*SHELXL93*[16]) based on F^2 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) U_{eq} of the riding atoms. The crystallographic data are listed in Table 1.

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