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INTRAMOLECULAR PHOTOCYCLOADDITION OF 2-CYCLOALKENYL-1,3-DIOXIN-4-ONE. STEREOSELECTIVE SYNTHESIS OF *CIS*-EUDESMANE-4,11-DIOLS

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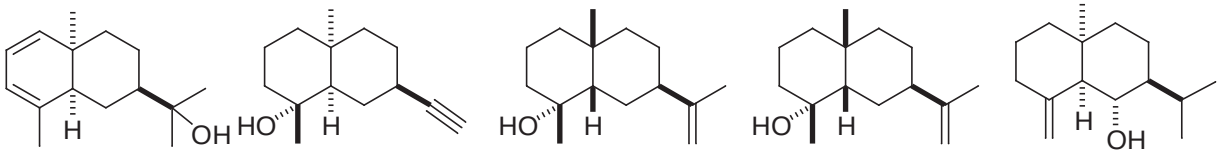
Abstract—Two isomeric eudesmane-4,11-diols having a *cis*-decalin skeleton were synthesized *via* intramolecular photocycloaddition of 6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-1,3-dioxin-4-one. Comparison of their NMR spectra with the natural diol, isolated from the Pakistanii medicinal plant, *Pluchea arguta (Compositae)*, indicated that it should be a *trans*-eudesmanoid.

The photocycloaddition reaction of α,β-unsaturated carbonyl compounds is one of the most useful photoreactions.[2] The enol form of 1,3-diketones or keto aldehydes reacts with olefins to give 1,5-dicarbonyl compounds *via* retro-aldol reaction, which is known as de Mayo reaction.[3] The application of this reaction to β-keto esters has been failed because of low enol-keto ratio, but Baldwin[4] used 2,2,6-trimethyl-1,3-dioxin-4-one as a synthetic equivalent of acetoacetate where the enol is fixed as a cyclic enol ether. Similarly, an equivalent of formylacetate was developed by Kaneko *et al*.[5] Takeshita *et al*. applied this to intramolecular reaction for the synthesis of valeranone.[6] Here we report the synthesis of *cis*-eudesmane-4,11-diols *via* intramolecular photocycloaddition of 6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-1,3-dioxin-4-one.

Eudesmanoid is one of the most common families of naturally occurring sesquiterpenoids, but most of



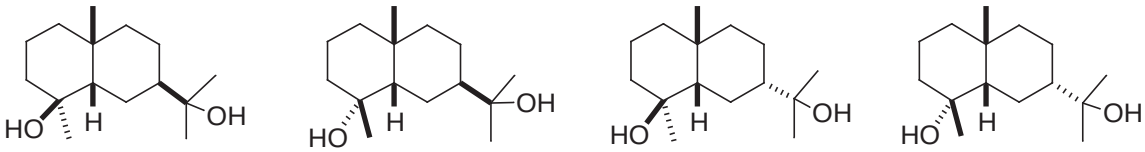
Occidentalol Chamaecynone Amiteol 5-Epi-paradisol 10-Epi-junenol

†Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

them have a *trans*-fused decalin skeleton and only a few are known to have a *cis*-fused one. Occidentalol,[7] chamaecynone,[8] and related acetylenic norsesquiterpenoids,[9] which belong to this class of compounds obtained from the plant origins, show interesting stereochemical feature and biological activity. Recently, some *cis*-eudesmane terpenoids were isolated from the zoological origin; amiteol,[10] 5-epiparadisol[11] 10-epijunenol[12] and evuncifer ether[13] from termites, and brominated *cis*-eudesmanoids, lankalapuol A and B from sea hare.[14]

In 1994, a sesquiterpenediol isolated from the Pakistani medicinal plant, *Pluchea arguta (Compositae)* was assigned to 4,5-epicryptomeridiol (**A**) by Ahmad *et al*.[15] But Ando *et al.*[16] synthesized 4,5-diepi- and 5-epicryptomeridiols (**A** and **B**), and proved them not to be identical to the diol (**X**) isolated from the above plant. They suggested that it should be a *trans*-fused eudesmane sesquiterpene.

As the Ando's suggestion on the structure of **X** was based on the ^{13}C-NMR chemical shift, the structure of **X** is still disputable problem, considering that the bulky 7α-substituent could cause the conformation of *cis*-decalin ring to change from that having 7β-substituent. Herein we report the synthesis of the rest of *cis*-eudesmane-4,11-diols, (**C** and **D**), to compare the NMR spectral data with those of the isomers.

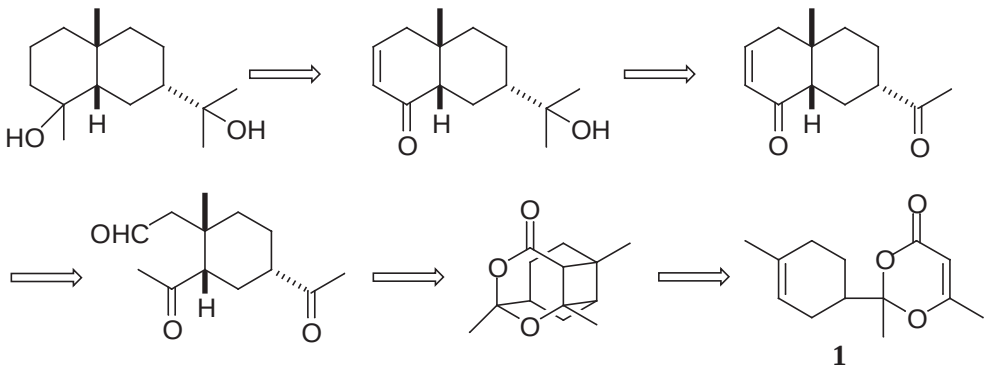


A **B** **C** **D**

RESULTS AND DISCUSSION

In constructing a decalin ring, intramolecular cycloaddition is expected to be useful in *cis*-ring fusion, avoiding the *trans*-addition which often occurs in enone-olefin photocycloaddition reaction, and also in controlling the stereochemistry of a substituent at C-7 of eudesmanoid (see Figure 1).

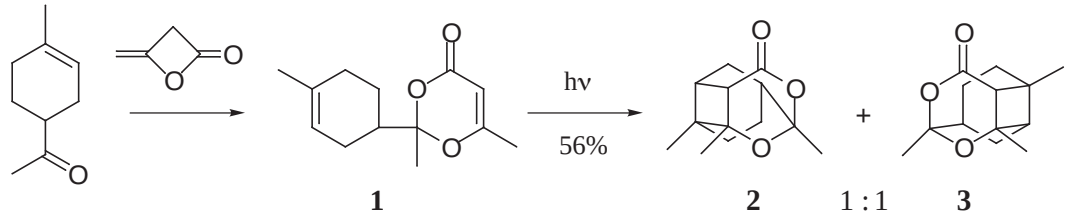
Dioxin-4-one (**1**) was prepared by the reaction of diketene with 4-acetyl-1-methyl-1-cyclohexene as a 1:1 mixture of stereoisomers. The ultraviolet light irradiation of **1** in acetone-acetonitrile (9:1) gave a 1:1



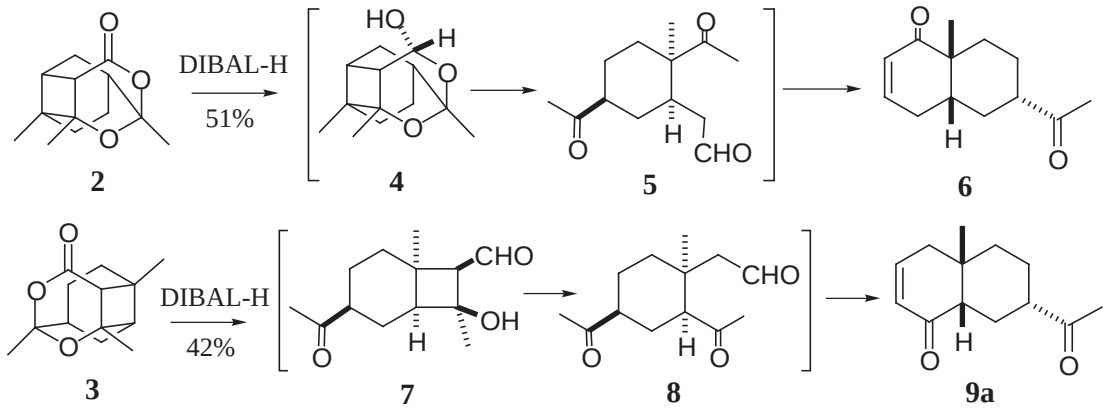
1

Figure 1. Retrosynthesis for *cis*-fused eudesmanediols.

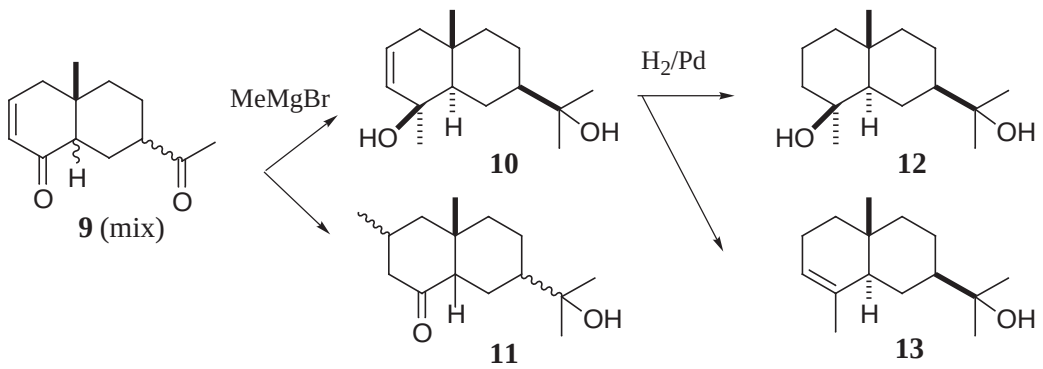
mixture of tetracyclic lactones (**2** and **3**) in 56% yield. From the ^{1}H-NMR spectra, **2** and **3** were easily distinguished. The former has a methine proton on the four membered ring as a doublet (J = 9.2 Hz) at δ 3.24, and the latter has a singlet with long range coupling at δ 2.73 (J = 1.5 Hz).



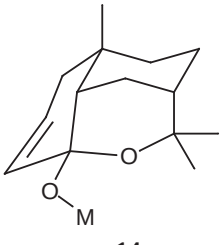
Reduction of **2** with AlH(i-Bu)$_2$ (DIBAL-H) gave a mixture of hemiacetal (**4**) and diketo aldehyde (**5**), which was converted to enone (**6**) by acid catalized aldol reaction. The stereochemistry of **6** was confirmed by NOE-experiment and the observation of H-7 of **6** as tt at δ 2.35 showing an axial orientation of the methine proton.

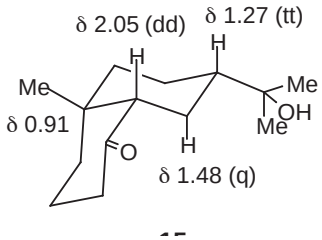


On the other hand, reduction of **3** gave a mixture of aldol (**7**) and ketoaldehyde (**8**). Acidic cyclization of the mixture of **7** and **8** gave a mixture of three isomers of octalones (**9**). The stereochemistry of the major isomer of **9** was proved to be the desired one (**9a**) by the NMR analysis; that is, the *cis*-ring fusion was confirmed by the NOE observed between the angular methyl protons and the methine proton at C-5, and the coupling pattern of 6α-proton, as a quartet with 13 Hz of J value, required both 5- and 7- methine protons to be axial. Therefore, the configuration of these two methine protons and angular methyl group was concluded to be *cis*. Analyzing by MM2 calculation of steric energy, **9a** was the most stable isomer



among the four epimers, but the differences between **9a** and the other two, (±)-5β,7β,10β and (±)-5α,7β,10β isomers, were small, $\Delta\Delta E$ = 0.23 and 0.03 kcal/mol. In fact the longer reaction time decreased the ratio of **9a** from 0.7 to 0.3. The occurrence of a *trans*-octalone ((±)-5α,7β,10β–isomer) was proved by the formation of (±)-4-epicryptomeridiol (**12**)[16] by hydrogenation of unsaturated diol (**10**), obtained after methylation of a crude mixture of **9**.

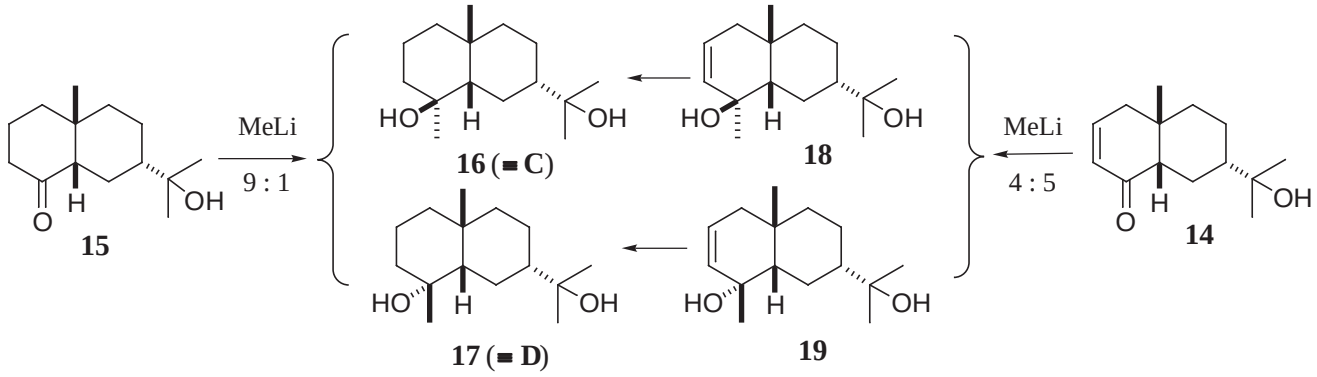




Methylation of **9a** with methyllithium (MeLi) at –78 °C gave **14** in 73% yield. Further methylation did not occur at this temperature due to the formation of acetal (**14a**).

Hydrogenation of **14** gave a saturated ketone (**15**), and the structure of **15** was fully analyzed by ^{1}H-, ^{13}C-, and 2D-NMR-spectra. Observation of NOE between the angular methyl and the 5-methine proton at δ 2.05 supported the *cis*-fused ring. Further the 6α-proton was observed at δ 1.48 as a quartet (J = 12.6 Hz). This implies that the angular 5-methine and 7-methine protons must be axial. Then, its conformation was depicted as shown in the right figure.

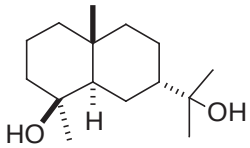
Subsequent methylation with methylmagnesium bromide gave a single diol (**16**). When **15** was methylated with MeLi, **16** and its isomer (**17**) were obtained in a 9:1 ratio. This selectivity must be caused by the steric inhibition by the axial methyl group in **15**. Similar face selectivity was reported by Baker *et al*.[11] in the reaction of 7-isopropenyl analog of **15**, which gave only the α-methylated product. On the other hand, methylation of **14** with MeLi gave unsaturated diols (**18** and **19**) in 37 and 47% yields, which were converted to saturated diols, **16** and **17**, respectively, by subsequent hydrogenation.



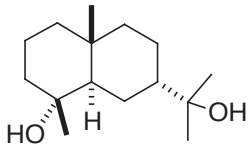
The structure of **17** was assigned as (±)–4α,5β,7α,10β isomer (**D**) by the NOE observed between the 4-methyl and the 10-methyl protons. Then **16** was attributed to the (±)–4β,5β,7α,10β isomer (**C**). This conclusion was independently supported by the similar discussion on the NMR spectra of **18** and **19**.

The NMR spectra of **16** and **17** were not coincident with that of a sesquiterpenediol (**X**) isolated from *Pluchea arguta* (Table 1). Therefore, **X** must not be a *cis*-eudesmanoid, but a *trans*-eudesmanediol[17] **E** or

F as Ando suggested.

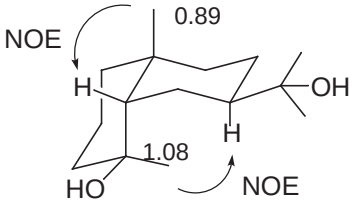


F



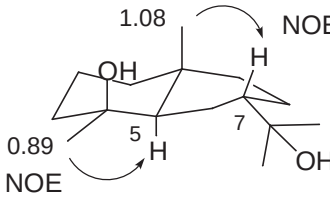
F

Taking account of the reported NOE observed between the methyl proton signal at δ 1.08 and the 7-methine proton at δ 1.65, **E** having twist boat conformation of the B-ring is the only rational structure, but the assignment of 15-methyl and 14-methyl protons in ^{1}H-NMR (δ 0.89 and 1.08) should be inverted as shown in the figure below. By the MM2 calculation, the chair-twist boat conformation of **E** is slightly less stable ($\Delta\Delta E$ = 1.1 kcal/mol) than chair-chair conformation, but more than ten percent of **E** may exist in the former conformation, and this explains the observed NOEs.

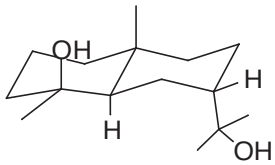


A

The assignment by Ahmad for **X**



E (chair-twist boat)



E (chair-chair)

The authors' assignment for **X**

Table 1. NMR spectral data of four *cis*-eudesmane-4,11-diols

	A (Ando *et al.*[16])	**B**	**C** (=**16**)	**D** (=**17**)	**X** (Ahmad *et al.*[15])
^{1}H-NMR	1.02	0.94	1.17	1.02	0.89
(Methyl)	1.20	1.17	1.18	1.19	1.08
	1.21	1.20	1.19	1.19	1.26
	1.32	1.26	1.20	1.44	1.27
^{13}C-NMR					
1	41.45	41.73	29.81	29.44	41.47
2	19.91	17.42	18.38	20.31	20.28
3	44.06	42.59	34.37	35.28	43.65
4	73.25	73.26	72.77	72.98	72.65
5	50.72	47.61	52.14	53.16	48.84
6	21.41	22.00	26.70	24.67	20.69
7	43.27	42.99	49.30	49.13	41.98
8	21.46	22.25	22.64	23.12	21.40
9	33.10	32.38	42.94	43.10	41.65
10	33.76	32.74	33.19	34.03	34.34
11	73.93	73.58	74.34	72.98	74.70
12	26.96	25.93	26.64	27.04	29.54
13	27.28	27.69	27.49	27.10	29.84
14	29.98	31.34	30.77	30.50	21.95
15	27.96	29.45	31.41	31.31	18.66

In conclusion, two isomers of racemic *cis*-eudesmane-4,11-diols were prepared by the intramolecular photocycloaddition of 6-methyl-2-(4-methyl-3-cyclohexen-1-yl)-1,3-dioxin-4-one. Intramolecular

reaction is, thus, useful in the *cis*-ring fusion and in controlling the stereochemistry of the substituent at C-7 of eudesmane sesquiterpenoids.

EXPERIMENTAL

All the mp were not corrected. IR spectra were obtained with JASCO IR-700 spectrophotometer. NMR spectra were measured in $CDCl_3$ solution with JEOL GSX-270 and LA-600 spectrometer at 270 or 600 MHz for ^1H and 67.8 or 180.8 MHz for ^{13}C. MS spectra were obtained with JEOL JMS-AM-20 and JMS-20 spectrometers.

Synthesis of 6-methyl-2-(4-methyl-3-cyclohexenyl)-1,2-dioxin-3-one (1).

In 15 mL of dry benzene, 4-acetyl-1-methyl-1-cyclohexene (0.80 g, 5.8 mmol), freshly distilled diketene (0.49 g) and *p*-toluenesulfonic acid (TsOH, 5 mg) were refluxed for 20 h under a N_2 atmosphere. The cooled mixture was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. After silica-gel chromatography with hexane-EtOAc (10:1), **1** (0.90 g, 70%) was obtained as a 10:9 mixture of two stereoisomers (**1a** and **1b**).

1: yellow oil. ^1H-NMR: δ 1.45 (1H, m), 1.60 and 1.61 (3H, s; **1a**,**b**), 1.66 (3H, s), 1.89–2.22 (6H, m), 1.97 and 1.98 (3H, d, J = 0.7 Hz; **1a**,**b**), 5.20 (1H, t, J = 0.7 Hz), 5.38 (1H, s); ^{13}C-NMR: **1a**: δ 19.5, 20.0, 22.9, 23.1, 25.6, 30.2, 41.6, 93.7, 109.7, 119.4, 134.0, 161.2, 168.6. **1b**: δ 19.6, 20.0, 23.0, 23.1, 25.8, 30.2, 41.9, 93.8, 109.8, 119.5, 134.1, 161.8, 168.6. IR: ν/cm^{-1} 2924, 1738, 1642, 1439, 1354, 1267, 1236, 1214, 1179, 1157, 1132, 1115, 802. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.90; H, 8.18.

Photoreaction of 1.

An acetone-acetonitrile (9:1) solution of **1** (796 mg in 200 mL) in a quartz-flask was irradiated for 5 h by means of 1 kW-high pressure mercury lamp cooled by running water. After solvent was removed in vacuum, a 1:1 mixture of **2** and **3** (398 mg, 56%) was isolated by chromatography. After recrystallization from pentane, **2** was separated.

2: colorless plates, mp 115 –117 °C. ^1H-NMR: δ 1.06 (3H, s), 1.23 (3H, s), 1.33–1.43 (2H, m), 1.59 (3H, s), 1.60–1.78 (3H, m), 1.83 (1H, m), 2.31 (2H, m), 3.24 (1H, d, J = 9.2 Hz). ^{13}C-NMR: δ 20.7, 22.2, 24.8, 25.1, 25.8, 27.1, 36.3, 39.2, 42.1, 43.8, 82.2, 108.7, 169.5. IR: ν/cm^{-1} 2948, 1735, 1460, 1385, 1296, 1260, 1150, 1062, 1012, 890, 868, 849 cm^{-1}. MS: *m/z* (%) 222 (M^+, 6), 204 (3), 180 (13), 162 (17), 138 (96), 123 (38), 105 (7), 95 (88), 85 (80). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.02; H, 8.27.

3: pale yellow liquid. ^1H-NMR: δ 0.89 (1H, m), 1.24 (3H, s), 1.40 (3H, s), 1.58 (3H, s), 1.45–1.80 (4H, m), 1.90–2.17 (2H, m), 2.39 (1H, m), 2.73 (1H, d, J = 1.5 Hz). ^{13}C-NMR: δ 20.9, 21.3, 26.7, 29.6, 29.7, 32.2, 35.3, 36.1, 42.5, 52.5, 69.2, 106.0, 170.7. IR: ν/cm^{-1} 2924, 1741, 1381, 1294, 1219, 1128, 1066, 970.

MS: *m/z* (%) 222 (M^+, 1), 180 (1), 164 (3), 151 (3), 138 (79), 123 (46), 110 (20), 95 (100), 85 (74), 80 (7). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.41; H, 8.38.

Reduction of 2 and cyclization to octalone (6).

A toluene solution of AlH(*i*-Bu)$_2$ (1.0 M, 1 mmol, 1.0 mL) was added to an ether solution (6 mL) of **2** (40 mg) at –78 °C and reacted for 1 h. After usual work up, a mixture of **4** and **5** was obtained, which was heated with TsOH (2 mg) to give **6** (18.8 mg, 51%) after silica gel chromatography with hexane-EtOAc (10:1). Pure **4** and **5** were separated by chromatography for analysis.

4: colorless prisms, mp 103-105 °C (pentane). ^{1}H-NMR: δ 1.01 (3H, s), 1.28 (3H, s), 1.43 (3H, s), 1.48 (1H, ddd, *J* = 13.5, 5.5, 2.0 Hz), 1.55–1.60 (1H, m), 1.62 (1H, dd, *J* = 11.0, 3.0 Hz), 1.77 (1H, dm, *J* = 12.0 Hz). 1.87 (1H, dm, *J* = 13.5, 2.0 Hz), 2.08 (1H, dd, *J* = 6.0, 1.5 Hz), 2.10 (1H, dd, *J* = 5.5, 1.5 Hz), 2.56 (1H, ddd, *J* = 6.0, 1.8, 0.7 Hz), 2.61 (1H, dd, *J* = 8.8, 2.0 Hz), 5.36 (1H, dd, *J* = 6.0, 2.2 Hz). IR(KBr): ν/cm^{-1} 2904, 1459, 1685, 1215, 1187, 1158, 1128, 1087, 1048, 1001, 934, 896, 873, 835, 655. MS: *m/z* (%) 224 (M^+, 4), 216 (5), 185 (4), 164 (9), 161 (12), 139 (20), 138 (100), 123 (39), 109 (7), 105 (9), 95 (42), 87 (22). Exact MS: *m/z* 224.1428. Calcd for $C_{13}H_{20}O_3$: 224.1412.

5: pale yellow oil. ^{1}H-NMR: δ 1.18 (3H, s), 1.21 (1H, ddd, *J* = 10.1, 5.1, 3.0 Hz), 1.45 (1H, dt, *J* = 14.0, 3.0 Hz), 1.70-1.90 (3H, m), 1.93 (1H, ddd, *J* = 8.8, 4.4, 2.8 Hz), 2.08 (3H, s), 2.11 (3H, s), 2.18 (1H, td, *J* = 14.3, 3.0 Hz), 2.44 (1H, tt, *J* = 12.0, 4.0 Hz), 2.67 (1H, dd, *J* = 19.0, 2.6 Hz), 2.92 (1H, ddd, *J* = 19.0, 8.8, 1.5 Hz), 9.79 (1H, s). ^{13}C-NMR: δ 24.9, 25.0, 25.9, 27.8, 30.9, 37.4, 39.4, 46.3, 50.3, 51.3, 202.2, 210.7, 212.3. IR($CHCl_3$): ν/cm^{-1} 2936, 1700, 1455, 1427, 1357, 1244, 1175, 1124, 1098, 1060, 964, 811. MS: *m/z* (%) 223(M^+-1, 0.3), 197 (13), 179 (45), 163 (17), 151 (52), 138 (100), 123 (37), 108 (60), 93 (58). Exact MS: *m/z* 224.1405. Calcd for $C_{13}H_{20}O_3$: 224.1412.

6: pale yellow oil. ^{1}H-NMR: δ 1.02 (1H, td, *J* = 13.5, 3.7 Hz), 1.16 (3H, s), 1.26 (1H, qd, *J* = 13.2, 3.3 Hz), 1.54 (1H, q, *J* = 12.8 Hz), 1.64 (1H, dt, *J* = 13.5, 4.3 Hz), 1.82 (1H, ddt, *J* = 13.2, 4.0, 2.2 Hz), 1.94 (1H, ddd, *J* = 12.8, 5.4, 1.0 Hz), 2.09 (3H, s), 2.11 (1H, dd, *J* = 19.8, 5.9 Hz), 2.35 (1H, tt, *J* = 12.3, 3.7 Hz), 2.48 (1H, dt, *J* = 13.2, 2.3 Hz), 2.84 (1H, dddd, *J* = 19.8, 5.5, 3.0, 2.5 Hz), 5.90 (1H, dd, *J* = 9.9, 2.9 Hz), 6.74 (1H, dddd, *J* = 9.9, 5.9, 2.1, 1.5 Hz). ^{13}C-NMR: δ 25.1, 25.8, 27.7, 30.1, 30.9, 33.8, 41.7, 46.1, 51.4, 127.8, 145.9, 202.8, 211.1. IR($CHCl_3$): ν/cm^{-1} 3584, 2930, 1707, 1673, 1460, 1429, 1388, 1354, 1231, 1212, 1175, 1122, 949, 809, 649. MS: *m/z* (%) 206 (M^+, 24), 188 (21), 164 (3), 149 (4), 138 (36), 123 (44), 109 (36), 95 (100), 85 (35), 68 (68). Exact MS: *m/z* 206.1310. Calcd for $C_{13}H_{18}O_2$: 206.1307.

Reduction of 3 and cyclization to octalone (9).

A toluene solution of AlH(*i*-Bu)$_2$ (1.0 M, 5 mmol, 5.0 mL) was added to ether solution (6 mL) of **3** (104 mg, 0.47 mmol) at –78 °C and reacted for 30 min. After usual work up, a mixture of **7** and **8** was obtained,

which was heated with TsOH to give **9** (41 mg, 42%) containing three isomers after chromatography on silica gel eluted by hexane-EtOAc. The major **9a** was purified by TLC.

7 (oil, as a mixture with **8**): ^{1}H-NMR: δ 1.05 (3H, s), 1.30-1.47 (2H, m), 1.45 (3H, s), 1.65-1.70 (2H, m), 1.77 (1H, ddd, *J* = 15.2, 9.5, 4.0 Hz), 2.00 (1H, ddd, *J* = 12.8, 11.0, 7.0 Hz), 2.20 (3H, s), 2.21 (1H, m), 2.40 (1H, m), 2.63 (1H, dd, *J* = 10.3, 8.0 Hz), 2.77 (1H, t, *J* = 2.6 Hz), 9.80 (1H, d, *J* = 2.9 Hz). ^{13}C-NMR: δ 21.3, 22.6, 27.4, 29.1, 30.5, 33.2, 34.7, 37.4, 53.3, 56.3, 73.6, 205.8, 212.6.

8 (oil, as a mixture with **7**): ^{1}H-NMR: δ 1.19 (3H, s), 2.08 (3H, s), 2.11 (3H, s), 2.70 (1H, dm, *J* = 19.2 Hz), 2.90 (1H, ddd, *J* = 19.2, 8.8, 1.5 Hz), 9.78 (1H, dd, *J* = 1.5, 0.7 Hz). ^{13}C-NMR: δ 24.9, 25.9, 27.8, 30.6, 30.8, 37.4, 39.4, 46.3, 50.2, 51.3, 202.2, 210.7, 212.3.

9a: pale yellow oil. ^{1}H-NMR: δ 1.01 (3H, s), 1.29 (1H, td, *J* = 13.5, 4.0 Hz), 1.39 (1H, q, *J* = 13.0 Hz), 1.59 (1H, dd, *J* = 12.4, 3.7 Hz), 1.64 (1H, dt, *J* = 13.7, 3.6 Hz), 1.84 (1H, dm, *J* = 13.0 Hz), 1.87 (1H, dd, *J* = 19.5, 5.8 Hz), 1.80-1.90 (1H, m), 2.06 (1H, dd, *J* = 13.2, 4.0 Hz), 2.16 (3H, s), 2.38 (1H, tt, *J* = 12.3, 3.5 Hz), 2.66 (1H, dt, *J* = 19.5, 2.5 Hz), 5.98 (1H, ddd, *J* = 10.0, 3.0, 1.0 Hz), 6.96 (1H, ddd, *J* = 10.0, 5.8, 2.3 Hz). ^{13}C-NMR: δ 23.8, 27.9, 28.4, 32.3, 34.7, 37.4, 49.4, 55.0, 76.5, 127.4, 148.0, 202.3, 210.7. IR($CHCl_3$): ν/cm^{-1} 2932, 1708, 1673, 1461, 1387, 1251, 1185, 1136, 957, 916, 884, 797. MS: *m/z* (%) 206 (M^+, 100), 164 (99), 147 (62), 137 (10), 123 (52), 108 (94), 95 (80), 79 (45), 68 (54), 53 (17). Exact MS: *m/z* 206.1307. Calcd for $C_{13}H_{18}O_2$: 206.1307.

Reaction of 9 with MeMgBr and the formation of (±)-4-epicryptomeridiol (12).

To a THF solution (3 mL) of the isomeric mixture of **9** (55 mg, 0.26 mmol), cerium trichloride (12 mg, 0.05 mmol) and a THF solution of MeMgBr (1M, 5.3 mmol, 5.3 mL) was added at 0 °C and stirred for 1 h. After usual work-up, unsaturated diol (**10**) (19 mg, 30%) and a ketone (**11**) (25 mg, 40%) were obtained by chromatographic separation on silica gel eluted by hexane-EtOAc (8:2). Diol (**10**) (6.3 mg) was hydrogenated using Pd/C (2 mg) as catalyst in EtOAc (3 mL). After chromatography on silica gel with hexane-EtOAc (10:1), **12** (3.4 mg, 52%) and **13** (2.3 mg, 38%) were obtained. The NMR spectral data for **12** were well agreed with those of (+)-4-epicryptomeridiol.[16]

10: pale yellow oil. ^{1}H-NMR: δ 1.00 (3H, s), 1.15-1.35 (9H, m), 1.22 (3H, s), 1.23 (3H, s), 1.24 (3H, s), 1.65 (1H, m), 1.72-1.88 (2H, m), 5.65 (2H, m). ^{13}C-NMR: δ 18.9, 22.1, 22.8, 26.9, 27.2, 29.0, 31.9, 41.6, 42.5, 49.7, 49.8, 69.5, 73.0, 126.2, 134.0. IR($CHCl_3$): ν/cm^{-1} 3414, 2966, 1455, 1371, 1149, 915, 731. MS: *m/z* (%) 238 (M^+, 4), 224 (70), 223 (100), 206 (66), 205 (57), 187 (64), 177 (71), 165 (55), 163 (50), 162 (52), 148 (46), 146 (46), 145 (43), 137 (68), 136 (56), 120 (57), 108 (41), 91 (39), 84 (55), 60 (67). Exact MS: m/z 238.1950. Calcd for $C_{15}H_{26}O_2$: 238.1933.

11: colorless needles, mp 87-89 °C (hexane). ^{1}H-NMR: δ 0.91 (3H, s), 1.03 (3H, d, *J* = 6.2 Hz), 1.12 (1H, m), 1.18 (3H, s), 1.19 (3H, s), 1.20-1.30 (4H, m), 1.60-1.85 (5H, m), 2.00-2.20 (3H, m). ^{13}C-NMR: δ 22.3,

22.7, 27.2, 27.4, 27.8, 28.7, 29.1, 35.5, 38.2, 39.7, 45.2, 48.2, 58.6, 72.4, 215.7. IR($CHCl_3$): ν/cm^{-1} 3444, 2954, 2870, 1703, 1455, 1236, 1189, 1161, 947, 909. MS: *m/z* (%) 238 (M^+, 4), 223 (9), 220 (7), 205 (11), 180 (61), 165 (88), 147 (8), 126 (100), 109 (9), 60 (49). Exact MS: *m/z* 238.1931. Calcd for $C_{15}H_{26}O_2$: 238.1933.

12: colorless needles, mp 87-89 °C. ^{1}H-NMR: δ 1.02 (3H, s), 1.17 (3H, s), 1.21 (3H, s), 1.22 (3H, s), 1.68 (1H, dm, *J* = 15.0 Hz), 1.82 (2H, m). ^{13}C-NMR: δ 18.1, 18.7, 21.4, 22.4, 26.8, 27.5, 30.3, 33.6, 41.4, 41.5, 43.8, 50.0, 51.7, 72.1, 73.1. IR($CHCl_3$): ν/cm^{-1} 3584, 3376, 2924, 2846, 1459, 1368, 1185, 1149, 1120, 1072, 1018, 951, 907, 872.

13: pale yellow oil. ^{1}H-NMR: δ 0.77 (3H, s), 1.20 (3H, s), 1.21 (3H, s), 1.62 (3H, br s), 1.86 (1H, m), 5.31 (1H, m). ^{13}C-NMR: δ 15.6, 21.2, 22.4, 23.0, 24.4, 26.8, 27.6, 32.2, 37.9, 40.2, 46.7, 50.0, 73.1, 121.0, 135.2. IR($CHCl_3$): ν/cm^{-1} 2924, 1455, 1377, 1142, 1116, 913, 851, 799.

The reaction of 9a with MeLi.

To 128.5 mg (0.62 mmol) of **9a** in dry ether (10 mL) was added 1.2 equivalents of MeLi at –78 °C under N_2 atmosphere. After usual work-up, **14** (87.3 mg, 73%) was obtained after chromatography using silica gel and hexane-EtOAc (8:2).

14: pale yellow liquid. ^{1}H-NMR: δ 0.99 (3H, s), 1.14 (1H, q, *J* = 12 Hz), 1.17 (3H, s), 1.19 (3H, s), 1.26 (td, *J* = 12.5, 4.0 Hz), 1.32 (1H, tt, *J* = 12.3, 3.2 Hz), 1.36 (1H, qd, *J* = 13.0, 3.0 Hz), 1.60 (1H, dt, *J* = 13.5, 3.3 Hz), 1.77 (2H, m), 1.85 (1H, dd, *J* = 19.5, 5.7 Hz), 2.03 (1H, dd, *J* = 13.0, 4.0 Hz), 2.66 (1H, dm, *J* = 19.5 Hz), 5.97 (1H, ddt, *J* = 10.1, 3.0, 0.9 Hz), 6.86 (1H, ddd, *J* =10.1, 5.7, 2.2 Hz). ^{13}C-NMR: δ 22.6, 27.0, 27.6, 27.9, 28.0, 32.4, 34.8, 38.3, 47.2, 55.9, 72.4, 127.4, 148.1, 203.2. IR($CHCl_3$): ν/cm^{-1} 3610, 3474, 2924, 2852, 1667, 1464, 1387, 1257, 905, 734. MS: *m/z* (%) 223 (M^++1, 16), 205 (30), 179 (22), 163 (32), 161 (23), 136 (61), 122 (68), 119 (61), 110 (61), 94 (100), 92 (50), 91 (80), 81 (62), 79 (57), 68 (51). Exact MS: *m/z* 222.1645. Calcd for $C_{14}H_{22}O_2$: 222.1620.

Catalytic hydrogenation of 14.

Using Pd/C (2 mg) as catalyst, **14** (26.8 mg) was hydrogenated for 1 h in EtOAc (2 mL). After chromatography using silica gel and hexane-EtOAc (8:2), 6.5 mg of **14** and 18.8 mg (0.084 mmol, 92%) of **15** were isolated.

15: colorless plates, mp 88-90 °C. ^{1}H-NMR: δ 0.91 (3H, s), 1.08 (1H, dq, *J* = 13.8, 4.0 Hz), 1.18 (3H, s), 1.19 (3H, s), 1.25 (1H, td, *J* = 13.5, 3.8 Hz), 1.19 (3H, s), 1.27 (1H, tt, *J* = 12.2, 3.2 Hz), 1.41 (1H, qd, *J* = 13.0, 3.9 Hz), 1.48 (1H, q, *J* = 12.6 Hz), 1.64 (1H, dt, *J* = 14.5, 3.1 Hz), 1.67 (1H, m), 1.70 (1H, dt, *J* = 12.0, 3.0 Hz), 1.86 (1H, qt, *J* = 13.6, 4.6 Hz), 1.93 (1H, m), 2.05 (1H, dd, *J* = 12.8, 4.0 Hz), 2.14 (1H, td, *J* = 13.7, 4.8 Hz), 2.17 (1H, dm, *J* = 16.5 Hz), 2.46 (1H, ddd, *J* = 14.8, 13.7, 7.5 Hz). ^{13}C-NMR: δ 21.8, 22.3, 27.2, 27.4, 27.7, 27.8, 28.6, 36.0, 36.7, 39.7, 48.2, 59.4, 75.4, 216.0. IR($CHCl_3$): ν/cm^{-1} 3442, 2946,

1701, 1468, 1380, 1309, 1223, 1157, 1027, 938. MS: *m/z* (%) 224 (M^+, 0.5), 209 (4), 206 (42), 191 (29), 173 (14), 166 (21), 163 (23), 151 (31), 149 (23), 135 (17), 131 (7), 121 (7), 111 (100), 98 (11), 81 (11), 57 (7), 59 (10). Exact MS: *m/z* 224.1789. Calcd for $C_{14}H_{24}O_2$: 224.1776.

Methylation of 15 with MeMgBr.

A THF solution of MeMgBr (1 M, 6 mmol, 6 mL) was added to **15** (22.6 mg, 0.1 mmol) in THF (3 mL) at 0 °C. After usual work-up, **15** (13.7 mg) and **16** (9.3 mg, 97%) were isolated.

16: colorless plates, mp 128-129 °C (EtOAc). ^{1}H-NMR: δ 0.90 (1H, dm, *J* = 13.6 Hz), 0.95 (1H, q, *J* = 12.6 Hz), 1.17 (3H, s), 1.18 (3H, s), 1.19 (3H, s), 1.20 (3H, s), 1.20-1.55 (10H, m), 1.61-1.71 (3H, m), 1.83-1.88 (1H, m). ^{13}C-NMR: δ 18.4, 22.6, 26.6, 26.7, 27.5, 29.8, 30.8, 31.4, 33.2, 34.4, 42.9, 49.3, 52.1, 72.8, 74.3. IR($CHCl_3$): ν/cm^{-1} 3584, 3358, 2936, 1464, 1375, 1181, 1124, 1051, 910, 847, 734. MS: *m/z* (%) 240 (M^+, 0.03), 197 (2.6), 179 (20), 151 (23), 138 (40), 123 (5.6), 107 (100), 93 (53). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.86; H, 11.66.

Methylation of 15 with MeLi.

An ether solution of MeLi (0.7 mmol) was added to **15** (46.2 mg, 0.21 mmol) in ether (5 mL) at -78 °C. After usual work-up, **16** (15.9 mg, 89%) and **17** (2.6 mg, 0.01 mmol, 10%) were obtained together with **15** (24.9 mg).

17: colorless plates. mp 150-152 °C (EtOAc). ^{1}H-NMR: δ 0.85 (1H, br d, *J* = 13 Hz), 1.02 (3H, s), 1.08 (1H, q, *J* = 12.5 Hz), 1.19 (3H, s), 1.193 (3H, s), 1.20-1.45 (8H, m), 1.44 (3H, s), 1.50-1.70 (4H, m), 2.03 (1H, dm, *J* = 12.5 Hz). ^{13}C-NMR: δ 20.3, 23.1, 24.7, 27.0, 27.1, 29.4, 30.5, 31.3, 34.0, 35.3, 43.1, 49.1, 53.2, 73.0, 73.0. IR(KBr): ν/cm^{-1} 3520, 2925, 1480, 1390, 1190, 1105. MS: *m/z* (%) 222 ([M-H_2O]$^+$, 0.03), 204 (12), 189 (12), 164 (18), 149 (28), 135 (13), 121 (9), 109 (100). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.75; H, 11.60.

Methylation of 14 with MeLi.

An ether solution of **14** (12.9 mg) was reacted with MeLi (0.3 mmol) at -78 °C for 30 min. After usual work-up, **18** (2.5 mg, 37%) and **19** (3.2 mg, 47%) were obtained together with unreacted **14** (6.5 mg). Subsequent hydrogenation of **18** and **19** gave **16** and **17** in 83 and 62% yields, respectively.

18: colorless needles. mp 136-138 °C (EtOAc). ^{1}H-NMR: δ 0.69 (1H, q, *J* = 12.8 Hz), 1.15 (3H, s), 1.17 (3H, s), 1.18 (3H, s), 1.21 (1H, m), 1.24 (3H, s), 1.24-1.31 (3H, m), 1.36 (1H, td, *J* = 13.4, 4.2 Hz), 1.43-1.50 (3H, m), 1.61 (dm, *J* = 1.34 Hz), 1.77 (1H, dm, *J* = 12.8 Hz), 2.25 (1H, d, *J* = 18.0 Hz), 5.53 (1H, dt, *J* = 10.0, 1.4 Hz), 5.69 (1H, ddd, *J* = 10.0, 5.5, 2.2 Hz). ^{13}C-NMR: δ 22.7, 26.6, 26.8, 27.5, 29.0, 30.8, 31.2, 32.2, 40.6, 48.9, 51.7, 71.7, 72.8, 126.7, 131.4. IR($CHCl_3$): ν/cm^{-1} 3370, 2925, 1450, 1380, 1095, 900, 735. MS: *m/z* (%) 220 ([M-H_2O]$^+$, 0.5), 205 (12), 187 (9), 159 (8), 137 (67), 136 (64), 121 (18), 107 (57), 106 (35), 84 (100).

19: pale yellow oil. ^{1}H-NMR: δ 0.79 (1H, q, *J* = 12.6 Hz), 1.01 (3H, s), 1.19 (6H, s), 1.15-1.20 (1H, m), 1.2-1.38 (4H, m), 1.41 (3H, s), 1.43-1.50 (2H, m), 1.63 (1H, m), 2.08 (1H, dm, *J* = 13.0 Hz), 2.28 (1H, dm, *J* = 18.0 Hz), 5.45 (1H, dm, *J* = 10.0, Hz), 5.65 (1H, ddd, *J* = 10.0, 5.5, 2.0 Hz). ^{13}C-NMR: δ 22.7, 24.8, 27.1, 27.2, 30.4, 30.7, 31.2, 33.8, 41.0, 48.7, 51.3, 71.6, 72.9, 126.0, 132.3. IR($CHCl_3$): ν/cm^{-1} 3584, 3352, 2924, 1657, 1460, 1377, 1105, 1033, 915. MS: *m/z* (%) 220 ([M-H_2O]$^+$, 0.6), 205 (24), 189 (18), 187 (16), 37 (66), 136 (71), 106 (100), 91 (37), 84 (80).

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17. Two reports were published on the isolation of *trans* diol (**F**), but the NMR spectra of the two compounds were totally different.[18,19] One of the diols, obtained from *Ursinia trifida*,[18] showed the resemblance in NMR spectra to **X** except of the chemical shift of the 4-carbon (δ 77.0). We assigned

this to **E**, and the other from *Isodon grandifolia*[19] to **F**. Thus, the set of eight isomers of eudesmane-4,11-diol becomes complete.

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