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# Alternative syntheses of versatile chiral intermediate for drimane sesquiterpenes and labdane diterpenes using (*R*,*R*)-cycloheptane-1,2-diol as a chiral auxiliary

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**Abstract**—The resolution of the enantiomers of (±)-β-keto ester **6** using (*R*,*R*)-cycloheptane-1,2-diol as a chiral auxiliary for acetal formation was carried out with the enantiomerically pure (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanols **7** and (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylates **6** being obtained. Both (10*R*)- and (10*S*)-15,16-epoxy-8(17),13(16),14-labdatriene **4** were synthesized from (8a*R*)- and (8a*S*)-hydroxy ketone (**7**), respectively, with the absolute configuration of the natural (−)-**4** unequivocally being established as (5*R*,9*R*,10*R*). On the other hand, both (10*R*)- and (10*S*)-15,16-epoxy-7,13(16),14-labdatriene **5** were synthesized from (8a*R*)- and (8a*S*)-β-keto ester **6**, respectively, and the relative structure of natural (+)-**5** unequivocally determined as depicted in Scheme 1.


## 1. Introduction

The chiral structural unit **1** possessing a decalin ring system attached with three methyl groups, is an important nucleus found in a variety of natural products such as drimane sesquiterpenes and labdane diterpenes (Scheme 1). Among them, *widendiol* A **2**[1] was reported to inhibit the cholesteryl ester transferprotein (CETP) while hyatellaquinone **3** was reported to inhibit the reverse transcriptase of the human immunodeficiency virus (HIV).[2] On the other hand, there are many furanoditerpenes possessing a β-substituted furan in nature. Both (−)-15,16-epoxy-8(17),13(16),14-labdatriene **4**[3] and (+)-15,16-epoxy-7,13(16),14-labdatriene **5**[4] have been isolated from the Philippine sponge, *Cacospongia* sp and the extract of the aerial part of *Acrisione denticulata*, respectively. The *ent*-type of the former **4**[5] has also been isolated from the aerial part of *Blepharispermum zanguebaricum*. However, the absolute structure of two furanoditerpenes **4** and **5** has not yet been determined. The key optically active intermediate for the synthesis of the above mentioned natural products appeared either to be (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylate **6**,[6] or (8a*S*)- and (8a*R*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol **7**.[6] Enzymatic syntheses of the same type chiral synthons as **6** were reported.[7] The synthesis of (8a*S*)- and (8a*R*)-**7** was based on the enantioselective acetylation of (±)-**7** in the presence of vinyl acetate using a lipase. However, the enantiomeric excess (ee) for (8a*S*)-**7** was only 53%.[7c] Nevertheless, the resolution of the same type of chiral synthons as **6** using a chiral auxiliary has been reported.[8] In case of the resolution of (±)-β-keto ester **6**[9] using commercially available (2*R*,3*R*)-2,3-butanediol or 1,4-di-*O*-benzyl-L-threitol as the chiral auxiliary for the acetal formation, satisfactory results were obtained.[8c] When the chiral auxiliary used was cheap or was effectively recovered from each of the diastereomers after separation of the diastereomeric mixture, the resolution method proved promising for the preparation of the desired chiral compound. Herein, we report an alternative resolution of (±)-**6** using (*R*,*R*)-cycloheptane-1,2-diol, obtained based on enzymatic hydrolysis of *meso*-1,2-cycloheptane diacetate.[10] The determination of the absolute structure of the above-mentioned (−)-**4** was based on the enantioselective synthesis of the chiral form of **4** from (8a*S*)-**7** and/or (8a*R*)-**7**. Additionally, the synthesis of (10*S*)- and (10*R*)-**5** from (8a*S*)- and (8a*R*)-**6** is also described.

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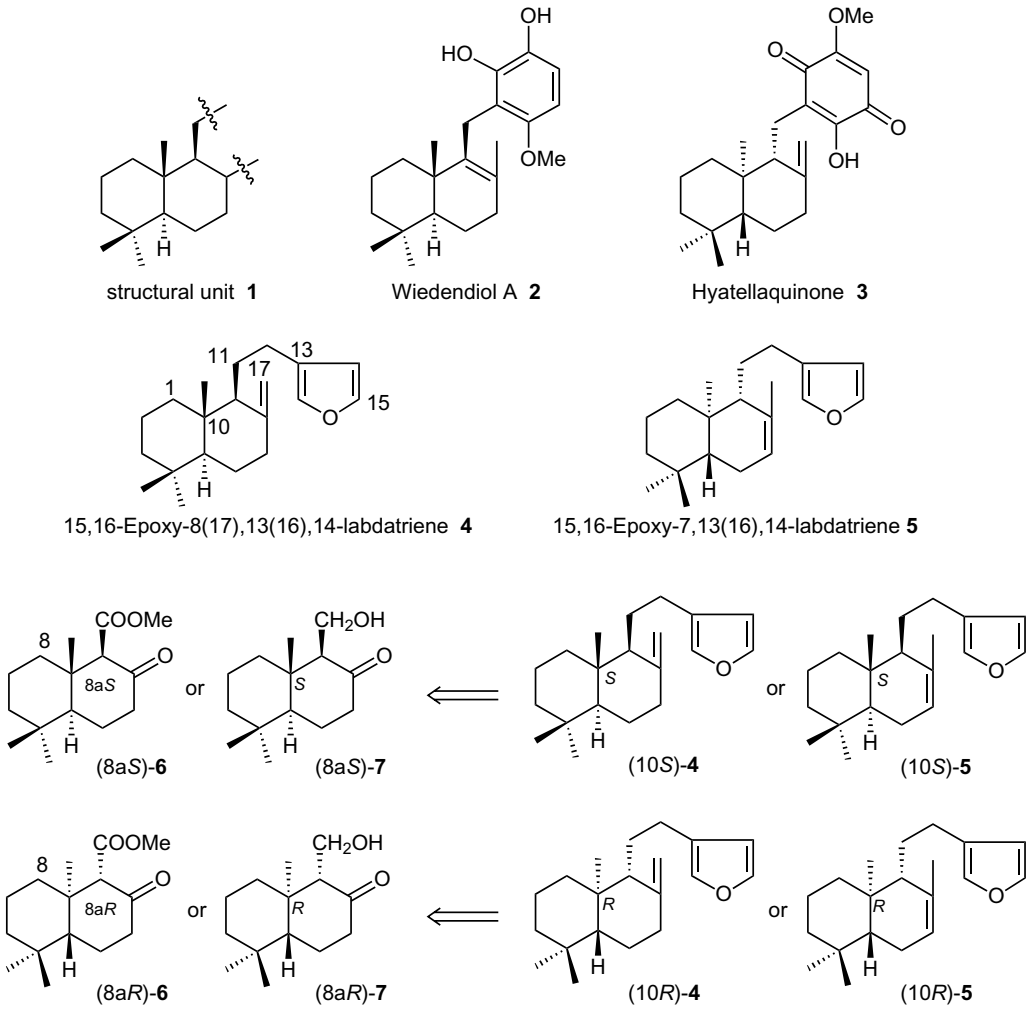


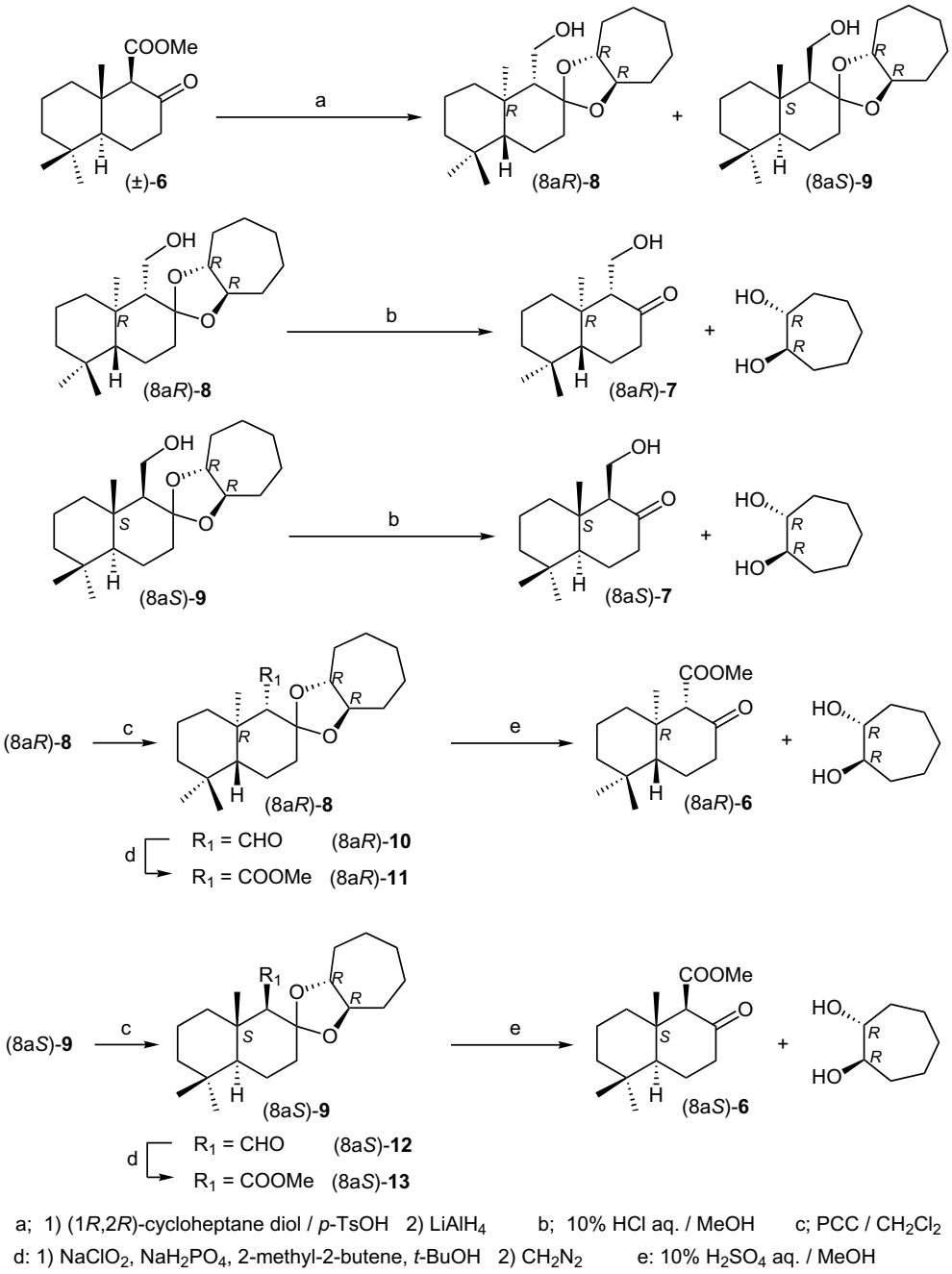

**Scheme 1.**

## 2. Synthesis of (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanols 7

The reaction of (±)-β-keto ester **6**[9] and (*R*,*R*)-cycloheptane-1,2-diol[10] in the presence of *p*-toluenesulfonic acid (*p*-TsOH) followed by a $LiAlH_4$ reduction gave a diastereomeric mixture of alcohols **8** and **9** (Scheme 2), which were separated by silica gel chromatography to give the less polar alcohol **8** {$[\alpha]_D = -12.8$ (*c* 0.90, $CHCl_3$), 47% overall yield from (±)-**6**} and the more polar alcohol **9** {$[\alpha]_D = -38.3$ (*c* 0.92, $CHCl_3$), 44% overall yield from (±)-**6**}. Acid treatment of **8** gave the (+)-hydroxy ketone **7** {$[\alpha]_D = +38.4$ ($CHCl_3$), 89% yield} and 87% of (*R*,*R*)-cycloheptane-1,2-diol. The physical data {$^1$H NMR and $[\alpha]_D$} of (+)-**7** was identical to that of the previously reported (+)-(8a*R*)-**7** {$[\alpha]_D = +38.5$ ($CHCl_3$)}[8c] enabling us to determine the absolute configuration of **8** as (1*R*,4a*R*,8a*R*). Similarly, the absolute configuration of **9** was confirmed as being (1*S*,4a*S*,8a*S*) because acid hydrolysis of **9** provided a (−)-hydroxy ketone **7** {$[\alpha]_D = -38.4$ ($CHCl_3$), 97% yield} and 97% of (*R*,*R*)-cycloheptane-1,2-diol, with the physical data {$^1$H NMR and $[\alpha]_D$} of (−)-**7** being identical to that of the reported (−)-(8a*S*)-**7** {$[\alpha]_D = +38.3$ ($CHCl_3$)}.[8c] The present resolution procedure seemed to be highly advantageous because the (*R*,*R*)-cycloheptane-1,2-diol could be recovered in high yield from the chiral acetals (**8** and **9**) by treatment with acid and could then be again used for chiral acetal formation.

## 3. Synthesis of (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylates 6

Oxidation of (8a*R*)-**8** with pyridinium chlorochromate (PCC) gave an aldehyde (8a*R*)-**10** {$[\alpha]_D = -23.3$ ($CHCl_3$), 92% yield}, which was then subjected to oxidation with $NaClO_2$ followed by esterification to afford methyl ester (8a*R*)-**11** (90% yield). The methyl ester (8a*R*)-**11** was treated with 10% aqueous $H_2SO_4$ to provide the (8a*R*)-β-keto ester **6** {$[\alpha]_D = +59.4$ ($CHCl_3$), 74% yield} along with 86% of (*R*,*R*)-cycloheptane-1,2-diol. Physical data {$^1$H NMR and $[\alpha]_D$} of (8a*R*)-**6** was identical with those of the reported (+)-(8a*R*)-**6** {$[\alpha]_D = +55.0$ ($CHCl_3$)}[8c]. The alcohol (8a*S*)-**9** was also converted to the (8a*S*)-β-keto ester **6** {$[\alpha]_D = -55.6$ ($CHCl_3$), 62% overall yield} along with (*R*,*R*)-cycloheptane-1,2-diol (74% overall yield). Physical data ($^1$H

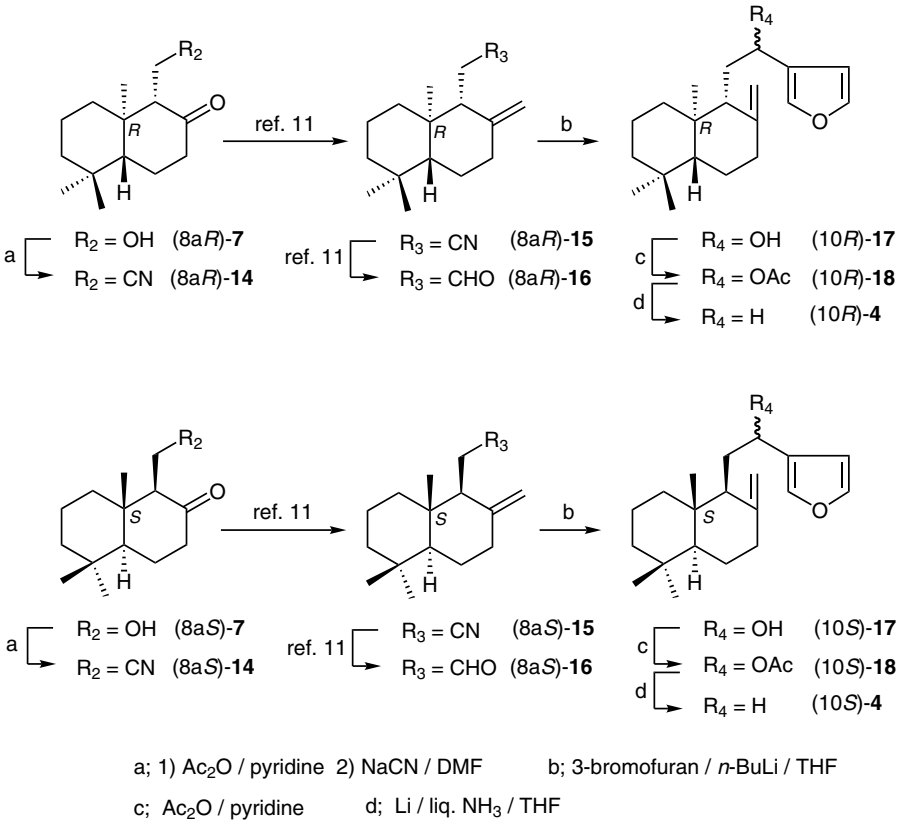



**Scheme 2.**

NMR and $[\alpha]_D$) of (8a*S*)-**6** was identical with that of the reported (−)-(8a*S*)- **6** $\{[\alpha]_D = -54.3\ (CHCl_3)\}$.[8c]

## 4. Synthesis of (10*R*)- and (10*S*)-15,16-epoxy-8(17),13(16),14-labdatrienes 4

Acetylation of (8a*R*)-**7** followed by treatment with NaCN in dimethylformaldehyde (DMF) (Scheme 3) gave a γ-ketonitrile (8a*R*)-**14** $\{[\alpha]_D = +45.1\ (CHCl_3)\}$, 97% overall yield from (8a*R*)-**7**), of which the physical data was identical with that of the reported (8a*S*)-**14** $\{[\alpha]_D = -43.4\ (CHCl_3)\}$[7a] except for the sign of specific rotation. Wittig olefination of (8a*R*)-**14** followed by reduction with diisobutylaluminium hydride (Dibal-H) according to the reported method[11] yielded the corresponding aldehyde (8a*R*)-**16** $\{[\alpha]_D = +27.1\ (CHCl_3)\}$ in 87% overall yield from (8a*R*)-**14**. The spectral data {$^1$H NMR and $[\alpha]_D$} of (8a*R*)-**16** was identical to that of the reported (8a*S*)-**16**[11] $\{[\alpha]_D = -25.5\ (CHCl_3)\}$ except for the sign of specific rotation. Aldehyde (8a*R*)-**16** was reacted with 3-lithiofuran prepared, from 3-bromofuran and *n*-BuLi in situ at −78 °C, to afford a diastereomeric mixture of secondary alcohol (10*R*)-**17**. Acetylation of




**Scheme 3.**

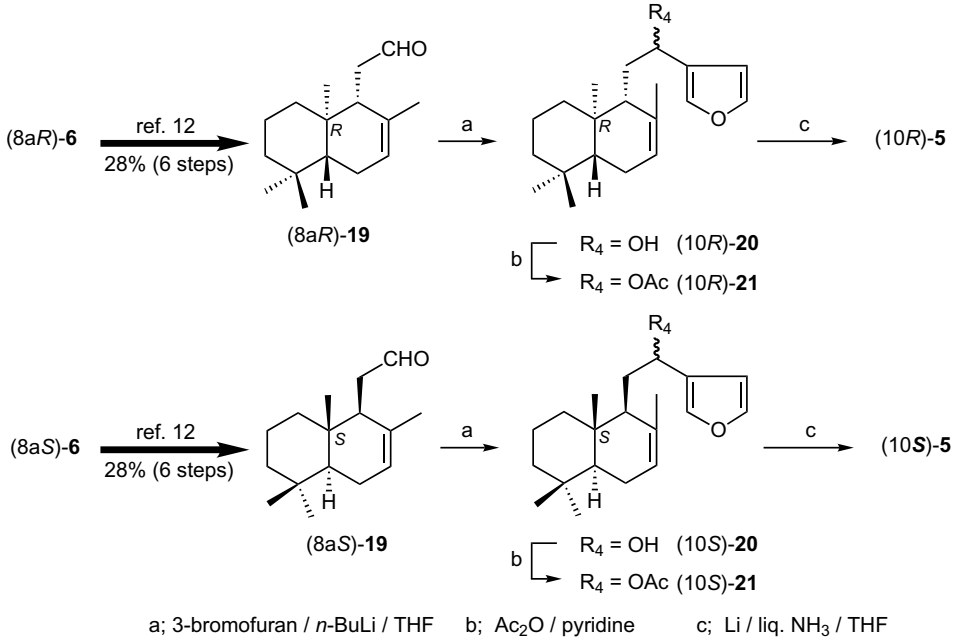
**17** followed by a Birch reduction gave a furanoditerpene (10*R*)-**4** {$[\alpha]_D = -42.6$ ($CHCl_3$)} in 38% overall yield from (8a*R*)-**16**. Similarly, antipodal furanoditerpene (10*S*)-**4** {$[\alpha]_D = +49.3$ ($CHCl_3$), 28% overall yield in six steps} was also synthesized from (8a*S*)-**7** in the same way as for (10*R*)-**4**. The NMR ($^1H$ and $^{13}C$ NMR) data of both enantiomers (10*R*)-**4** and (10*S*)-**4** were identical with those[3,5] of the natural (−)-**4** and the sign of specific rotation of (10*R*)-**4** was the same as that of the natural (−)-**4**. Hence, the absolute structure of the natural (−)-**4** was unequivocally determined as (5*R*,9*R*,10*R*) as depicted in Scheme 1.

## 5. Synthesis of (10*R*)- and (10*S*)-15,16-epoxy-7,13(16),14-labdatrienes 5

Conversion of (8a*R*)-**6** to aldehyde (8a*R*)-**19** (28% overall yield in six steps) was achieved by our previously reported procedure (Scheme 4).[12] The reaction of (8a*R*)-**19** with 3-lithiofuran prepared from 3-bromofuran and *n*-BuLi in situ at −78 °C, furnished a diastereomeric mixture of secondary alcohol (10*R*)-**20** (Scheme 4). Acetylation of **20** followed by a Birch reduction gave a furanoditerpene (10*R*)-**5** {$[\alpha]_D = -14.2$ ($CHCl_3$)} in 46% overall yield from (8a*R*)-**19**. Similarly, antipodal furanoditerpene (10*S*)-**5** {$[\alpha]_D = +11.6$ ($CHCl_3$)} in 9% overall yield in nine steps was also synthesized from (8a*S*)-**6** in the same way as for (10*R*)-**5**. The $^1H$ NMR data of both enantiomers (10*R*)-**5** and (10*S*)-**5** was identical with that of natural (+)-**5** {$[\alpha]_D = +3.2$ ($CHCl_3$)}.[4] The relative structure of natural (+)-**5** was unequivocally determined as depicted in Scheme 1, while the absolute structure of (+)-**5** could not be determined because of both low intensity of specific rotation and no information in respect to $^{13}C$ NMR data of natural (+)-**5** (Schemes 3 and 4).

## 6. Conclusion

In conclusion, the resolution of the enantiomers of (±)-β-keto ester **6** using (*R*,*R*)-cycloheptane-1,2-diol as a chiral auxiliary for acetal formation was achieved and the enantiomerically pure (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanols **7** were obtained. Moreover, the enantiomerically pure (8a*R*)- and (8a*S*)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-carboxylates **6** were also obtained. Both (10*R*)- and (10*S*)-15,16-epoxy-8(17),13(16),14-labdatriene **4** were synthesized from (8a*R*)- and (8a*S*)-hydroxy ketone **7**, respectively, with the absolute configuration of natural (−)-**4** being established as (5*R*,9*R*,10*R*). On the other hand, both (10*R*)- and (10*S*)-15,16-epoxy-7,13(16),14-labdatriene **5** were synthesized from (8a*R*)- and (8a*S*)-β-keto ester **6**, respectively. The relative structure of natural (+)-**5** was unequivocally determined as depicted in Scheme 1, while the absolute structure of (+)-**5** could not be determined.




**Scheme 4.**

## 7. Experimental

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence. The fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded on a JASCO FT/IR-300E spectrometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

### 7.1. (−)-(1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-[(1*R*,2*R*)-cycloheptane acetal] 8 and (−)-(1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-[(1*R*,2*R*)-cycloheptane acetal] 9

(1) To a solution of (±)-β-ketoester **6** (1.76 g, 7.0 mmol) in benzene (50 mL) was added (*R*,*R*)-cycloheptane-1,2-diol (1.00 g, 7.7 mmol) and *p*-toluenesulfonic acid (0.132 g, 0.7 mmol) and the whole mixture stirred for 1 h at reflux. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude acetal, which was used without further purification. (2) To a suspension of $LiAlH_4$ (0.794 g, 20.9 mmol) in ether (25 mL) was added dropwise a solution of the crude acetal in ether (15 mL) at 0 °C. After the reaction mixture was stirred at room temperature for 30 min, acetone (2 mL) and water were added to the reaction mixture. The precipitate was filtered with the aid of celite and the filtrate extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (40 g) to give colorless crystals (less polar fraction) **8** (1.10 g, 47%) from *n*-hexane/AcOEt (60:1) eluate and colorless crystals (more polar fraction) **9** (1.04 g, 44%) from *n*-hexane/AcOEt (40:1) eluate, respectively. Both crystals were recrystallized from *n*-hexane to afford colorless prisms. **8**: mp 109.5–110.5 °C; IR (KBr): 3527 cm$^{-1}$; $[\alpha]_D^{24} = -12.8$ (*c* 0.90, $CHCl_3$); $^1$H NMR: $\delta$ 0.81 (3H, s), 0.84 (3H, s), 0.88 (3H, s), 0.91–0.94 (1H, m), 1.08–1.20 (2H, m), 1.37–1.64 (15H, m), 1.80–1.83 (1H, m), 1.95–1.99 (1H, m), 2.13–2.26 (2H, m), 3.30 (1H, d, $J = 10.4$ Hz), 3.62 (1H, t, $J = 10.0$ Hz), 3.77–3.88 (3H, m). $^{13}$C NMR: $\delta$ 15.57, 18.63, 19.35, 21.83, 25.00, 25.00, 25.03, 29.13, 31.47, 33.33, 33.76, 38.39, 39.06, 39.59, 41.87, 55.09, 58.89, 59.42, 78.87, 83.70, 112.37. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.81; H, 10.91. **9**: mp 119–120 °C; IR (KBr): 3519 cm$^{-1}$; $[\alpha]_D^{24} = -38.3$ (*c* 0.92, $CHCl_3$); $^1$H NMR: $\delta$ 0.81 (3H, s), 0.86 (3H, s), 0.87 (3H, s), 0.90–0.94 (1H, m), 0.93–1.20 (2H, m), 1.37–1.66 (15H, m), 1.80–1.84 (1H, m), 1.91–1.95 (1H, m), 2.10–2.20 (2H, m), 3.01 (1H, dd, $J = 2.0$, 8.9 Hz), 3.61–3.69 (2H, m), 3.86–3.94 (2H, m). $^{13}$C NMR: $\delta$ 15.77, 18.62, 20.15, 21.69, 24.98, 25.05, 25.11, 28.83, 31.04, 33.28, 33.69, 37.73, 38.49, 39.52, 41.91, 55.04, 58.87, 59.88, 80.26, 80.33, 112.27. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.78; H, 10.86.

### 7.2. (+)-(1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-dDecahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol 7 and (−)-(1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol 7

(1) To a solution of (−)-**8** (0.248 g, 0.73 mmol) in MeOH (10 mL) was added 10% aqueous HCl (3 mL) and the whole mixture stirred for 30 min at room temperature.

The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g) to give colorless crystals (8a*R*)-**7** (0.147 g, 89%) from *n*-hexane/AcOEt (10:1) eluate and (*R*,*R* )-cycloheptane-1,2-diol (0.083 g, 87%) from *n*-hexane/AcOEt (2:1) eluate. Recrystallization of (8a*R*)-**7** from *n*-hexane gave colorless needles (8a*R*)-**7**. (8a*R*)-**7**: mp 71.0–72.0 °C; IR (KBr): 3261, 1707 $cm^{-1}$; $[\alpha]_D^{27} = +38.4$ (*c* 0.99, $CHCl_3$); Spectral data ($^1H$ and $^{13}C$ NMR) of (8a*R*)-**3** were identical with those of the reported data,[8c] respectively. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.69; H, 10.93. FAB MS *m*/*z*: 225 ($M^+$+1). (2) To a solution of (−)-**9** (0.254 g, 0.75 mmol) in MeOH (10 mL) was added 10% aqueous HCl (3 mL) and the whole mixture stirred for 30 min at room temperature. The reaction mixture was worked up in the same way as for (−)-**8** to give colorless crystals (8a*S*)-**7** (0.164 g, 97%) and (*R*,*R*)-cycloheptane-1,2-diol (0.096 g, 97%). Recrystallization of (8a*S*)-**7** from *n*-hexane gave colorless needles (8a*S*)-**7**. (8a*S*)-**7**: mp 71.0–72.0 °C; IR (KBr): 3261, 1707 $cm^{-1}$; $[\alpha]_D^{28} = -38.4$ (*c* 0.84, $CHCl_3$); Spectral data ($^1H$ and $^{13}C$ NMR) of (8a*S*)-**7** were identical with those of the reported data,[8c] respectively. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.70; H, 10.86. FAB MS *m*/*z*: 225 ($M^+$+1).

### 7.3. (1*R*,4a*R*,8a*R*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthalene-carboxylate 6

(1) To a solution of (8a*R*)-**8** (0.250 g, 0.74 mmol) in $CH_2Cl_2$ (5 mL) was added PCC (0.321 g, 1.49 mmol) and Florisil (0.325 g), and the reaction mixture stirred for 3 h at room temperature. The reaction mixture was filtered with the aid of celite with the filtrate giving a crude residue. It was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 100:1) to give colorless crystals (8a*R*)-**10** (0.230 g, 92%), which were recrystallized from *n*-hexane to afford colorless prisms. (8a*R*)-**10**: mp 100–101 °C; IR (KBr): 1717 $cm^{-1}$; $[\alpha]_D^{25} = -23.3$ (*c* 0.99, $CHCl_3$); $^1H$ NMR: $\delta$ 0.86 (3H, s), 0.88 (3H, s), 1.12–1.21 (2H, m), 1.25 (3H, s), 1.36–1.69 (16H, m), 2.00–2.05 (2H, m), 2.07–2.13 (1H, m), 2.20–2.26 (1H, m), 3.62–3.68 (1H, m), 3.81–3.87 (1H, m), 9.82 (1H, d, $J = 4.8$ Hz). $^{13}C$ NMR: $\delta$ 16.37, 18.09, 19.43, 21.85, 24.90, 24.94, 25.10, 28.59, 31.21, 33.25, 33.63, 38.99, 39.57, 39.97, 41.65, 54.45, 68.04, 79.25, 83.00, 109.01, 205.21. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.10; H, 10.31. (2) To a solution of (8a*R*)-**10** (0.225 g, 0.67 mmol) and 2-methyl-2-butene (3.4 mL, 32 mmol) in *tert*-BuOH (15 mL) was added $NaClO_2$ (80%, 0.76 g, 6.72 mmol) and $NaH_2PO_4$ (0.565 g, 4.7 mmol) in $H_2O$ (5 mL) at room temperature; the whole mixture was stirred for 12 h at room temperature. The reaction mixture was acidified with aqueous 2M HCl and extracted with $CH_2Cl_2$. The organic layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer gave a crude residue, which was treated with $CH_2N_2$–ether solution. The reaction mixture was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt = 50:1) to give colorless crystals (8a*R*)-**11** (0.221 g, 90%), which were recrystallized from *n*-hexane to afford colorless prisms. (8a*R*)-**11**: mp 114.5–115.5 °C; IR (KBr): 1742 $cm^{-1}$; $^1H$ NMR: $\delta$ 0.85 (3H, s), 0.86 (3H, s), 1.11–1.19 (3H, m), 1.25 (3H, s), 1.36–1.69 (15H, m), 1.89 (1H, dt, $J = 2.9$, 12 Hz), 2.04–2.12 (1H, m), 2.17–2.25 (1H, m), 2.42 (1H, s), 3.63 (3H, s), 3.68–3.74 (1H, m), 3.82–3.88 (1H, m). $^{13}C$ NMR: $\delta$ 14.67, 18.33, 19.67, 21.62, 24.86, 25.03, 25.08, 28.98, 30.93, 33.11, 33.55, 39.04, 39.89, 40.17, 41.85, 50.65, 54.93, 62.87, 79.01, 81.84, 108.58, 171.42. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.30; H, 9.93. (3) To a solution of (8a*R*)-**11** (0.204 g, 0.56 mmol) in MeOH (10 mL) was added 10% aqueous $H_2SO_4$ (1 mL) and the whole mixture refluxed for 48 h with stirring. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g) to give (8a*R*)-**6** (0.105 g, 74%) from *n*-hexane/AcOEt (20:1) eluate and (*R*,*R*)-cycloheptane-1,2-diol (0.063 g, 86%) from *n*-hexane/AcOEt (2:1) eluate. (8a*R*)-**6**: $[\alpha]_D^{23} = +59.4$ (*c* 0.49, $CHCl_3$); Spectral data ($^1H$ and $^{13}C$ NMR) of (8a*R*)-**6** were identical with those of the reported data,[8c] respectively.

### 7.4. (1*S*,4a*S*,8a*S*)-1,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthalene-carboxylate 6

(1) To a solution of (8a*S*)-**9** (0.246 g, 0.73 mmol) in $CH_2Cl_2$ (5 mL) was added PCC (0.316 g, 1.46 mmol) and Florisil (0.320 g), and the reaction mixture then stirred for 3 h at room temperature. The reaction mixture was worked up in the same way for (8a*R*)-**8** to give colorless crystals (8a*S*)-**12** (0.245 g, 99%), which were recrystallized from *n*-hexane to afford colorless prisms. (8a*S*)-**12**: mp 97–98 °C; IR (KBr): 1717 $cm^{-1}$; $[\alpha]_D^{25} = -28.9$ (*c* 0.17, $CHCl_3$); $^1H$ NMR: $\delta$ 0.81–0.82 (1H, m), 0.86 (3H, s), 0.88 (3H, s), 1.09–1.19 (2H, m), 1.25 (3H, s), 1.35–1.66 (15H, m), 1.94 (1H, dt, $J = 3$, 13.3 Hz), 1.99 (1H, d, $J = 4.7$ Hz), 2.10–2.20 (2H, m), 3.45–3.51 (1H, m), 3.81–3.87 (1H, m), 9.96 (1H, d, $J = 4.7$ Hz). $^{13}C$ NMR: $\delta$ 16.22, 18.12, 20.09, 21.78, 24.83, 24.93, 25.03, 28.49, 30.45, 33.18, 33.56, 37.83, 39.14, 39.89, 41.61, 54.09, 68.79, 80.33, 80.79, 109.55, 205.91. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 74.81; H, 10.23%. FAB MS *m*/*z*: 357 (M+Na). (2) To a solution of (8a*S*)-**12** (0.245 g, 0.73 mmol) and 2-methyl-2-butene (3.7 mL, 34.8 mmol) in *tert*-BuOH (15 mL) was added $NaClO_2$ (80%, 0.83 g, 7.3 mmol) and $NaH_2PO_4$ (0.646 g, 5.1 mmol) in $H_2O$ (5 mL) at room temperature; the whole mixture was stirred for 12 h at room temperature. The reaction mixture was acidified with aqueous 2M HCl and extracted with $CH_2Cl_2$. The organic layer was worked up in the same way for (8a*R*)-**10** to give colorless crystals (8a*S*)-**13** (0.226 g, 84%), which were recrystallized from *n*-hexane to afford colorless prisms. (8a*S*)-**13**: mp 102.5–103.5 °C; IR (KBr): 1730 $cm^{-1}$; $^1H$ NMR: $\delta$ 0.84 (3H, s), 0.86–0.90 (1H, m), 0.87 (3H, s), 1.15–1.19 (1H, m), 1.20 (3H, s), 1.26–1.70

(16H, m), 1.83 (1H, dt, $J = 2.8$, 12.3 Hz), 2.05–2.18 (2H, m), 2.44 (1H, s), 3.41–3.47 (1H, m), 3.64 (3H, s), 3.72–3.78 (1H, m). $^{13}$C NMR: $\delta$ 14.76, 18.36, 20.33, 21.50, 24.92, 25.07, 25.12, 28.54, 30.44, 33.11, 33.48, 38.58, 39.90, 39.68, 41.87, 50.75, 54.56, 63.69, 80.23, 80.98, 108.58, 170.78. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.18; H, 10.01. (3) To a solution of (8a*S*)-**13** (0.166 g, 0.45 mmol) in MeOH (10 mL) was added 10% aqueous $H_2SO_4$ (1 mL) and the whole mixture then refluxed for 48 h with stirring. The reaction mixture was worked up as in the same way for (8a*R*)-**11** to give (8a*S*)-**6** (0.084 g, 73%) from *n*-hexane/AcOEt (20:1) eluate and (*R*,*R*)-cycloheptane-1,2-diol (0.053 g, 88%) from *n*-hexane/AcOEt (2:1) eluate. (8a*S*)-**6**: $[\alpha]_D^{23} = -55.6$ (*c* 0.23, $CHCl_3$); Spectral data ($^1$H and $^{13}$C NMR) of (8a*S*)-**6** were identical with those of the reported data,[8c] respectively.

### 7.5. (1*R*,4a*R*,8a*R*)-1,2,3,4,4a,5,6,7,8,8a-Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthaleneacetaldehyde 16 and (1*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,7,8,8a-decahydro-5,5,8a-trimethyl-2-methylene-1-naphthaleneacetaldehyde 16

(1) To a solution of (8a*R*)-**7** (0.407 g, 1.81 mmol) in pyridine (5 mL) was added $Ac_2O$ (0.560 g, 5.5 mmol) and the reaction mixture stirred for 12 h at room temperature. The reaction mixture was diluted with $H_2O$ and extracted with $Et_2O$. The organic layer was washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave the crude acetate, which was used without purification in the next reaction. A mixture of the crude acetate and NaCN (0.14 g, 2.85 mmol) in dimethylformamide (DMF; 10 mL) was stirred for 1.5 h at 60 °C. The reaction mixture was diluted with brine and extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt (10:1)) to give a colorless oil (8a*R*)-**14** (0.410 g, $[\alpha]_D^{22} = +45.1$ (*c* 1.03, $CHCl_3$), 97% overall yield from (8a*R*)-**7**). Spectral data {$^1$H NMR and $[\alpha]_D$} of (8a*R*)-**7** were identical with those of the reported (8a*S*)-**7** {$[\alpha]_D^{23} = -43.4$ (*c* 1.00, $CHCl_3$)}[7a] except for the sign of specific rotation. (2) The Wittig olefination of (8a*R*)-**14** (0.410 g, 1.76 mmol) followed by reduction with Dibal-H according to the reported procedure[11] gave a colorless oil (8a*R*)-**16** (360 mg, $[\alpha]_D^{22} = +27.1$ (*c* 0.92, $CHCl_3$), 87% overall yield from (8a*R*)-**14**. Spectral data ($^1$H and $^{13}$C NMR) of (8a*R*)-**16** were identical with those of the reported data.[11] (3) The antipode (8a*S*)-**7** (0.337 g, 1.5 mmol) was also converted into the aldehyde (8a*S*)-**16** (0.297 g, 84% overall yield from (8a*S*)-**7**) in the same way as for (8a*R*)-**7**.

### 7.6. (10*R*)-15,16-Epoxy-8(17),13(16),14-labdatriene 4

(1) To a solution of 3-bromofuran (0.400 g, 2.7 mmol) in tetrahydrofuran (THF; 3 mL) was added dropwise *n*-BuLi (1.58 M in *n*-hexane, 2 mL, 3.12 mmol) at −78 °C. After the reaction mixture was stirred for 1 h, a solution of (8a*R*)-**16** (0.208 g, 0.89 mmol) in THF (7 mL) was added dropwise. After the reaction mixture was stirred for 2 h at −78 °C, a saturated aqueous $NH_4Cl$ solution was added, and the resulting mixture extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt (10:1)) to give a diastereomeric mixture of alcohol (10*R*)-**17** (0.250 g), which was used without further purification. (2) To a solution of the crude alcohol (0.250 g) in pyridine (3 mL) was added $Ac_2O$ (0.260 g, 2.5 mmol), the reaction mixture was stirred for 13 h at room temperature. The reaction mixture was diluted with $H_2O$ and extracted with $Et_2O$. The organic layer was washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g *n*-hexane/AcOEt (200:1)) to give a diastereomeric mixture of acetate (10*R*)-**18** (0.167 g). (3) A suspension of Li (0.080 g, 6.9 mmol) in liquid $NH_3$ (20 mL) then stirred for 5 min at −78 °C. A solution of the crude acetate (0.167 g) in THF (10 mL) was added to the above reaction mixture, and the whole mixture was stirred for 1 h at −78 °C. After an excess of $NH_3$ was removed at room temperature, the reaction mixture was diluted with aqueous $NH_4Cl$ solution and extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g, *n*-hexane) to give a colorless oil (10*R*)-**4** (0.097 g, 38% overall yield from (8a*R*)-**16**). (10*R*)-**4**: IR ($CCl_4$): 3080, 1641, 883 cm$^{-1}$. $[\alpha]_D^{23} = -42.6$ (*c* 0.95, $CHCl_3$); $^1$H NMR: $\delta$ 0.69 (3H, s), 0.80 (3H, s), 0.86 (3H, s), 0.98 (1H, dt, $J = 4$, 12.9 Hz), 1.07 (1H, dd, $J = 2.8$, 12.6 Hz), 1.16 (1H, dt, $J = 4.1$, 13.2 Hz), 1.27–1.77 (9H, m), 1.98 (1H, dt, $J = 5.2$, 12.9 Hz), 2.19–2.27 (1H, m), 2.40 (1H, ddd $J = 2$, 4.2, 12.8 Hz), 2.51–2.58 (1H, m), 4.56 (1H, br s), 4.86 (1H, br d $J = 1.1$ Hz), 6.26 (1H, br s), 7.19 (1H, br s), 7.34 (1H, t, $J = 1.7$ Hz). $^{13}$C NMR: $\delta$ 14.52, 19.40, 21.74, 23.65, 24.12, 24.47, 33.59, 33.61, 38.36, 39.05, 39.62, 42.17, 55.50, 56.13, 106.26, 111.00, 125.63, 138.69, 142.62, 148.55. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.87; H, 10.58. EI MS *m*/*z*: 286 ($M^+$).

### 7.7. (10*S*)-15,16-Epoxy-8(17),13(16),14-labdatriene 4

(10*S*)-15,16-Epoxy-8(17),13(16),14-labdatriene **4** was synthesized from (8a*S*)-**16** (0.208 g, 0.89 mmol) in the same way as for (8a*R*)-**16** to give (10*S*)-**4** (0.074 g, 29% overall yield from (8a*S*)-**16**). (10*S*)-**4**: $[\alpha]_D^{26} = +49.3$ (*c* 1.00, $CHCl_3$). Spectral data of $^1$H NMR and $^{13}$C NMR of (10*S*)-**4** were identical with those of the abovementioned (10*R*)-**4**. EI MS *m*/*z*: 286 ($M^+$).

### 7.8. (10*R*)-15,16-Epoxy-7,13(16),14-labdatriene 5

(1) To a solution of 3-bromofuran (0.292 g, 2.0 mmol) in THF (2 mL) was added dropwise *n*-BuLi (1.58 M in *n*-hexane, 1.1 mL, 1.7 mmol) at −78 °C. After the reaction mixture was stirred for 30 min, a solution of (8a*R*)-

**19** (0.155 g, 0.66 mmol) in THF (3 mL) was added dropwise. After the reaction mixture was stirred for 1 h at −78 °C, a saturated aqueous $NH_4Cl$ solution was added and the resulting mixture extracted with $Et_2O$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (3 g, *n*-hexane/AcOEt 2:1) to give a diastereomeric mixture of alcohol (8a*R*)-**20** (0.236 g), which was used without further purification. (2) To a solution of the crude alcohol (0.236 g) in pyridine (3 mL) was added $Ac_2O$ (0.40 g, 3.9 mmol) and the reaction mixture then stirred for 12 h at room temperature. The reaction mixture was diluted with $H_2O$ and extracted with $Et_2O$. The organic layer was washed with 2 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (10 g *n*-hexane/AcOEt 100:1) to give a diastereomeric mixture of acetate (8a*R*)-**21** (0.221 g). (3) A suspension of Li (0.070 g, 10 mmol) in liquid $NH_3$ (20 mL) was stirred for 5 min at −78 °C. A solution of the crude acetate (0.221 g) in THF (10 mL) was added to the above reaction mixture, and the whole mixture was stirred for 1 h at −78 °C. After an excess of $NH_3$ was removed at room temperature, the reaction mixture was then diluted with aqueous $NH_4Cl$ solution and extracted with $Et_2O$. The organic layer was washed with brine, dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (5 g, *n*-hexane) to give a colorless oil (10*R*)-**2** (0.087 g, 46% overall yield from (8a*R*)-**19**). (10*R*)-**5**: IR ($CCl_4$): 875 $cm^{-1}$; $[\alpha]_D^{24} = -14.2$ (*c* 0.28, $CHCl_3$); $^1H$ NMR: $\delta$ 0.76 (3H, s), 0.85 (3H, s), 0.87 (3H, s), 1.10–1.20 (2H, m), 1.38–1.95 (10H, m), 1.73 (3H, br s), 2.32–2.40 (1H, m), 2.58–2.64 (1H, m), 5.41 (1H, br s), 6.28 (1H, s), 7.22 (1H, s), 7.35 (1H, br s). $^{13}C$ NMR: $\delta$ 13.57, 18.80, 21.87, 22.21, 23.83, 27.05, 27.81, 32.97, 33.17, 36.72, 39.16, 42.30, 50.12, 54.37, 111.05, 122.49, 125.39, 135.09, 138.73, 142.66. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.56; H, 10.91. EI MS *m*/*z*: 286 ($M^+$).

### 7.9. (10*S*)-15,16-Epoxy-7,13(16),14-labdatriene 5

(10*S*)-15,16-Epoxy-8(17),13(16),14-labdatriene **5** was synthesized from (8a*S*)-**19** (0.110 g, 0.47 mmol) in the same way as for (8a*R*)-**19** to give (10*S*)-**5** (0.041 g, 31% overall yield from (8a*S*)-**19**). (10*S*)-**5**: $[\alpha]_D^{24} = +11.6$ (*c* 0.31, $CHCl_3$); $^1H$ NMR data of (10*S*)-**5** were identical with those of the above-mentioned (10*R*)-**5**. EI MS *m*/*z*: 286 ($M^+$).

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