Total Synthesis of (±)-Gleenol and (±)-Axenol *via* a Functionalized Spiro[4.5]decane

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Total synthesis of the biologically important axane sesquiterpenes, gleenol (1) and axenol (2), was accomplished through a readily available spiro[4.5]decane. The key features of the synthesis of 1 and 2 include Claisen rearrangement to afford the multi-functionalized spiro[4.5]decane 4 as a single diastereomer in excellent yield, installation of the C7 isopropyl group *via* ketene dithioacetal instead of direct alkylation and a diastereoselective reduction of ketone under the Birch conditions.

Key words Claisen rearrangement; axane sesquiterpene; spiro[4.5]decane; total synthesis

Vetivane sesquiterpenes and axane sesquiterpenes are attractive naturally occurring products because of their unique structures as well as interesting biological activities.[1—4] For example, (−)-hinesol is a specific inhibitor of H^+, K^+-ATPase and an active ingredient of cerebral circulation and metabolism improvers,[5] while axamide-3 is reported to completely inhibit larval metamorphosis (Fig. 1).[6] Therefore, the total synthesis of these sesquiterpenes has been reported by several groups.[7—11] Recently, we have developed an efficient approach to the stereoselective synthesis of spiro[4.5]decanes through Claisen rearrangement (Chart 1).[12—17] The significant feature of this reaction is that the Claisen rearrangement of bicyclic 2-(alkenyl)dihydropyran **3** bearing a siloxy group at the C4 position led to the highly functionalized spiro[4.5]-decane **4** in good yield as a single diastereomer. Making use of this reaction, we have already achieved total synthesis of vetivane sesquiterpenes in racemic[18] and enantio-enriched versions.[19] Our attention is next centered on the synthesis of the structurally related sesquiterpenes, gleenol (**1**) and axenol (**2**). (+)-Geenol (**1**), isolated from marine sponge,[3] shows several important biological activities such as termiticidal, antihelmintic and growth regulation effects on plant seeds.[20] Although axenol (**2**) does not show any significant biological activity, it is utilized as a key intermediate for the synthesis of axisonitlile-3[10] which is a candidate for antimalarial agent.[21] In this communication, we report herein total synthesis of racemic **1** and **2** *via* a functionalized spiro[4.5]decane **4** which can be readily prepared utilizing our Claisen rearrangement methodology.

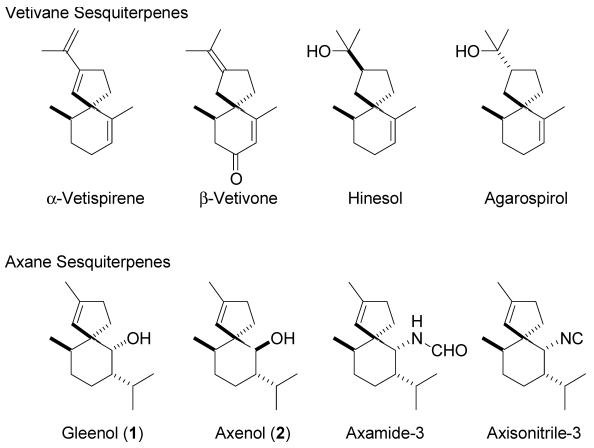

Fig. 1. Spirocyclic Sesquiterpenes

The synthetic strategy is shown in Chart 2. Spiro[4.5]decane **4** bearing functional groups, obtained by Claisen rearrangement of alkenyl dihydropyran **3**, would be converted into α,β-unsaturated ester **5**, a useful intermediate for the synthesis of vetivane sesquiterpene,[18] or its derivative ketone **6**. Gleenol (**1**) and axenol (**2**) could be readily synthesized from **5** and **6** after alkylation at the C7 position. Preliminary attempts of the C7-alkylation of the α,β-unsaturated ester **5** with several different electrophiles were found not to proceed at all (Chart 3). On the basis of these results, we decided to use ketone **6** instead of **5** as a key intermediate.

Synthesis of the alkylation precursor **6** starts with the formation of α,β-unsaturated ester **7** prepared from spiro[4.5]-decane **4** *via* a five-step sequence according to our previous publication (Chart 4).[18] Reduction of the methoxycarbonyl group in **7** with DIBAL afforded the primary alcohol **8**, and halogenation of the resulting hydroxyl group followed by reductive dehalogenation with $LiAlH_4$, led to trisubstituted

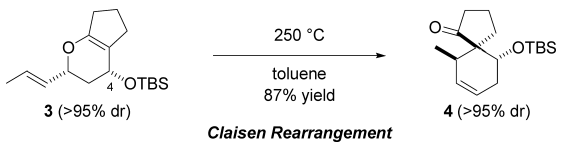

Chart 1

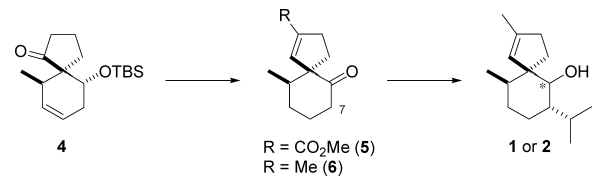

Chart 2. Synthetic Strategy toward **1** and **2**

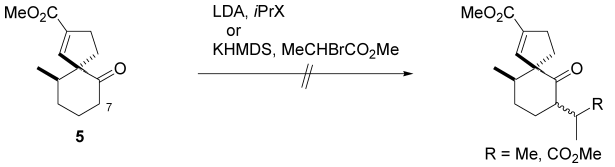

Chart 3. Attempted Alkylation at C7 on α,β-Unsaturated Ester **5**

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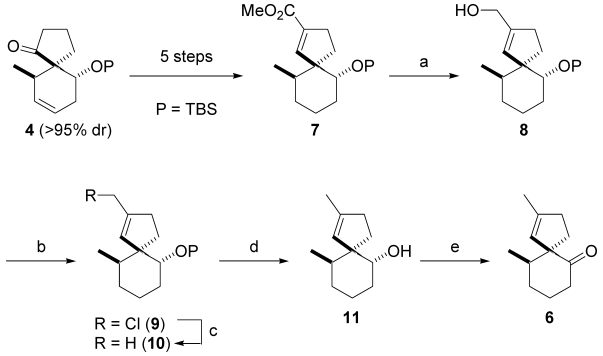
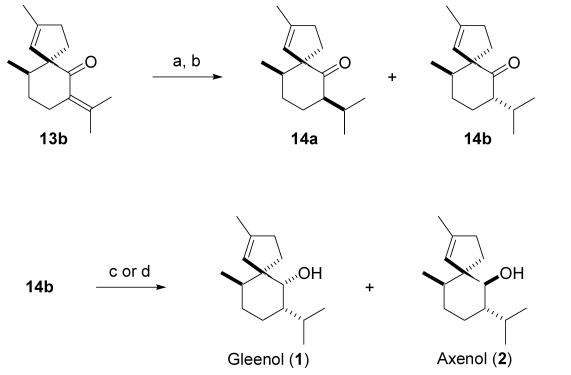


Reagents and conditions: (a) DIBAL, Et_2O, −78 °C; (b) CCl_4, PPh_3, MeCN, 0 °C to RT, 89% (2 steps); (c) $LiAlH_4$, THF, reflux, 96%; (d) HF, MeCN–THF (1 : 1); (e) Dess–Martin periodinane, CH_2Cl_2, RT, 78% (2 steps).

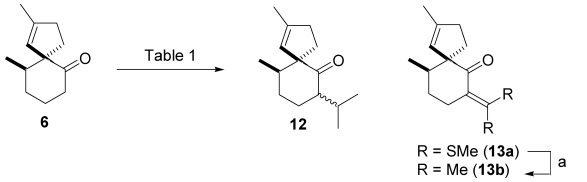
Chart 4



Reagents and conditions: (a) Li, NH_3, *t*BuOH, −78 °C; (b) Dess–Martin periodinane, CH_2Cl_2, RT, 87% (2 steps), **14a** : **14b** = 27 : 73; (c) $LiAlH_4$, THF, 0 °C, **1**: 33%, **2**: 43%; (d) Li, NH_3, *t*BuOH, −78 °C, **2**: 93%.

Chart 5

Table 1



Entry	Conditions	Results
1	KH, *i*PrI, THF, RT to reflux	**12**: 0% (complex mixture)
2	NaOH aq., acetone, 80 °C	**13b**: 0%, mainly **6**
3	LiOAr,[a] CS_2, then MeI	**13a**: 5%, **6**: 78%
4	LHMDS, CS_2, then MeI, 0 °C to RT	**13a**: 92%

Reagents and conditions: (a) Me_2CuLi, Et_2O, −78 °C, 93%. *a*) Ar=2,6-di-*tert*-butyl-4-methylphenyl.

alkene **10** in 89% overall yield from **7**. Reported transformation from **7** to **10** by the three step procedure [(i) DIBAL, (ii) $SO_3 \cdot py$, (iii) $LiAlH_4$] was next examined,[22] however the yield was moderate (43%). Removal of the *tert*-butyldimethylsilyl group in **10** with hydrogen fluoride in CH_3CN–THF, followed by oxidation with Dess–Martin periodinane,[23] gave the desired ketone **6** in 78% yield from **10**.

With the requisite ketone **6** now in hand, we turned our attention to installation of the C7 isopropyl group (Table 1). Treatment of **6** with potassium hydride and isopropyl iodide was found to afford complicated mixtures; none of alkylated product **12** was formed (entry 1). Aldol condensation of **6** with acetone in the presence of sodium hydroxide did not provide **13b** (entry 2). A more satisfactory procedure toward **13b** involved the use of ketene dithioacetal **13a** (entries 3, 4).[24] The reaction of **6** with LHMDS, CS_2 and MeI furnished the desired ketene dithioacetal **13a** in 92% yield; in contrast, the reaction with lithium 2,6-di-*tert*-butyl-4-methylphenoxide as a base provided only 5% of **13a** together with recovered **6** in 78% yield. Finally, exposure of **13a** to Me_2CuLi provided the corresponding α,β-unsaturated ketone **13b** in 93% yield.

Total synthesis of **1** and **2** was accomplished in three steps from **13b** (Chart 5). As Birch reduction of enone **13b** furnished a mixture of 1,4-reduction product and a saturated alcohol, oxidation of the mixture with Dess–Martin periodinane gave α-isopropylketone **14a** and **14b** as a mixture of epimers (23 : 77 by ^{1}H-NMR integration of the olefinic proton).[25] This mixture was subjected to epimerization using an ethanolic solution of potassium hydroxide in a sealed tube at 100 °C, to furnish a 17 : 83 mixture of epimers **14a** and **14b**, obtained in 80% yield after silica gel column chromatography. The final task was a diastereoselective reduction of ketone **14b**. Spitzner and Oesterreich reported that highly stereoselective reduction of **14b** furnishing **1** was achieved with L-Selectride at −78 °C (77% yield, >95% diastereomeric ratio (dr)).[8] Unfortunately, we could not reproduce their result even if freshly prepared L-Selectride was used. We eventually used $LiAlH_4$ to obtain **1** in 33% yield along with **2** in 43% yield. On the other hand, Birch reduction of **14b** was found to provide **2** as a sole product.

In conclusion, we have achieved the total synthesis of the biologically important axane sesquiterpenes, gleenol (**1**) and axenol (**2**), through a readily available spiro[4.5]decane utilizing Claisen rearrangement methodology. Results from our research have demonstrated the utility of the Claisen rearrangement approach to the synthesis of this structural type. As spiro[4.5]decane **4** can be prepared as an enantiomerically pure form,[19] asymmetric total synthesis of **1** and **2** could be achieved.

Experimental

General Techniques ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-LD400 spectrometer operating at either 400 MHz (^{1}H) or 100 MHz (^{13}C). Chemical shifts are reported in δ units and are referenced to the solvent, *i.e.*, 7.26/77.1 for $CDCl_3$. Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet) or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Jasco FT-IR410 spectrometer. Electron impact mass spectra were performed on a Hitachi M-80B mass spectrometer. Electrospray ionization mass spectra were recorded on an Applied Biosystems API QSTAR pulsar i as high resolution, using poly(ethylene glycol) as internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck 1.05715.0009) plates. Flash column chromatography was performed on a PSQ100B silica gel (Fuji Silysia Co., Ltd., Japan) or on a Silica Gel 60 N (spherical, neutral) 63—210 μm (Kanto Chemical Co., Inc., Japan) and PSQ100B was usually used. THF and Et_2O were purchased from Wako Pure Chemical Industries Ltd. in anhydrous grade. CH_2Cl_2 was distilled from CaH_2 immediately before use. Reagents were used as received. All moisture sensitive reactions were performed under a static argon atmosphere in oven-dried of flame-dried glassware.

Allyl Chloride 9 To a solution of α,β-unsaturated ester **7** (509 mg, 1.50 mmol) in Et_2O (29.5 ml) was added DIBAL (0.97 M in hexane, 3.81 ml) at −78 °C, then the resulting mixture was stirred for 25 min at that tempera-

ture. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, and allowed to warm to room temperature (RT). To this mixture was added hexane, anhydrous Na_2SO_4 and Celite, then stirred for 30 min. The resulting mixture was filtrated, and concentrated under reduced pressure to afford crude allyl alcohol **8**: *Rf* 0.34 (hexane/EtOAc=5 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.50 (tt, J=1.7, 1.5 Hz, 1H), 4.19 (br s, 2H), 3.56 (dd, J=2.9, 3.9 Hz, 1H), 2.28—2.23 (m, 2H), 1.95—1.84 (m, 2H), 1.78—1.65 (m, 2H), 1.63—1.50 (m, 2H), 1.47—1.39 (m, 2H), 1.34 (br s, 1H), 1.17—1.05 (m, 1H), 0.893 (s, 9H), 0.767 (d, J=7.1 Hz, 3H), 0.0287 (s, 6H). To a solution of crude allyl alcohol **7** in CH_3CN (29.5 ml) was added CCl_4 (0.285 ml, 2.95 mmol) at RT. After the mixture was cooling to 0 °C, to the resulting mixture was added Ph_3P (775 mg, 2.95 mmol) at 0 °C. This mixture was allowed to warm to RT and stirred for 14 h 35 min. The reaction mixture was concentrated under reduced pressure, and filtrated by a pad of silica gel (hexane/EtOAc=50 : 1). Purification by silica gel column chromatography (hexane as eluent) gave 440 mg (89% yield from **7**, >95% dr by ^{1}H-NMR analysis) of allyl chloride **9** as a colorless clear oil: *Rf* 0.81 (hexane/EtOAc=5 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.61 (br s, 1H), 4.12 (br s, 2H), 3.57 (t, J=3.5 Hz, 1H), 2.34 (tt, J=0.8, 7.5 Hz, 2H), 1.98—1.84 (m, 2H), 1.80—1.65 (m, 2H), 1.61—1.53 (m, 2H), 1.48—1.40 (m, 2H), 1.16—1.04 (m, 1H), 0.890 (s, 9H), 0.777 (d, J=7.1 Hz, 3H), 0.0299 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 141.8, 132.5, 74.3, 59.0, 43.7, 35.2, 33.2, 32.4, 31.4, 31.2, 25.9, 20.1, 18.1, 16.4, −4.1, −4.9; IR (neat, cm^{-1}) 3044, 2931, 2856, 2708, 1731; HR-ESI-MS Calcd for $C_{18}H_{33}ONaSiCl$: 351.1881, Found: 351.1874.

Trisubstituted Alkene 10 To a solution of allyl chloride **9** (425 mg, 1.29 mmol) in THF (25.8 ml) was added $LiAlH_4$ (54 mg, 1.29 mmol) at RT, then the resulting mixture was heated at 75 °C for 2 h 10 min. After this mixture was cooling to 0 °C, the reaction was quenched with a saturated aqueous solution of NH_4Cl at 0 °C. The aqueous layer was extracted two times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane) gave 366 mg of trisubstituted alkene **10** (96% yield) as a colorless clear oil: *Rf* 0.75 (hexane/EtOAc=50 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.18 (tq, J=1.7, 1.5 Hz, 1H), 3.52 (dd, J=2.8, 4.1 Hz, 1H), 2.17—2.13 (m, 2H), 1.88—1.78 (m, 2H), 1.72 (dt, J=1.5, 1.0 Hz, 3H), 1.71—1.64 (m, 2H), 1.60—1.50 (m, 2H), 1.42—1.36 (m, 2H), 1.14—1.04 (m, 1H), 0.890 (s, 9H), 0.744 (d, J=7.1 Hz, 3H), 0.0226 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.1, 127.0, 75.1, 59.0, 36.4, 35.1, 33.7, 31.6, 31.1, 25.9, 20.3, 18.2, 17.0, 16.5, −4.1, −5.0; IR (neat, cm^{-1}) 3040, 2930, 2857, 2734, 2708, 1658; HR-EI-MS Calcd for $C_{18}H_{34}OSi$: 294.2379, Found: 294.2372.

Ketone 6 To a solution of **10** (303 mg, 1.03 mmol) in distilled CH_3CN (10.3 ml) and THF (10.3 ml) was added an aqueous solution of HF (46—48%, *ca.* 6 ml) at RT, then the resulting mixture was stirred at that temperature for 55 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to affoed crude alcohol **11**: *Rf* 0.27 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.20 (tq, J=1.7, 1.5 Hz, 1H), 3.63 (dt, J=6.3, 3.2 Hz, 1H), 2.27—2.22 (m, 2H), 2.05—1.98 (m, 1H), 1.81—1.47 (m, 7H), 1.75 (br s, 3H), 1.41 (d, J=3.2 Hz, 1H), 1.25—1.18 (m, 1H), 0.858 (d, J=7.1 Hz, 3H). To a solution of crude alcohol **11** in CH_2Cl_2 (20.5 ml) was added Dess–Martin periodinane (871 mg, 2.05 mmol) at RT, then the resulting mixture was stirred at that temperature for 15 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc=30 : 1) gave 143 mg of ketone **6** (78% yield from **10**, >95% dr by ^{1}H-NMR analysis) as a colorless clear oil: *Rf* 0.33 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.33 (tq, J=1.7, 1.5 Hz, 1H), 2.64 (ddd, J=5.4, 9.3, 13.4 Hz, 1H), 2.47 (ddd, J=5.9, 11.7, 13.4 Hz, 1H), 2.36—2.16 (m, 3H), 2.04—1.96 (m, 1H), 1.78—1.50 (m, 5H), 1.73 (dt, J=1.5, 1.2 Hz, 3H), 0.898 (d, J=6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 212.7, 144.6, 123.2, 69.0, 42.4, 39.4, 36.1, 31.3, 29.0, 25.5, 16.9, 16.5; IR (neat, cm^{-1}) 2929, 2860, 1706, 1653; HR-ESI-MS Calcd for $C_{12}H_{18}ONa$: 201.1249, Found: 201.1257.

Ketene Dithioacetal 13a To a solution of ketone **6** (90 mg, 0.506 mmol) in Et_2O (5.1 ml) was added LHMDS (1.0 M in THF, 1.04 ml) at 0 °C, then this mixture was stirred at that temperature for 30 min. To the resulting mixture was added CS_2 (0.153 ml, 2.53 mmol) at 0 °C, then the mixture was allowed to warm to RT and stirred for 3 h. To the resulting mixture was added MeI (0.0724 ml, 1.16 mmol) dropwise at RT, then this mixture was stirred for 3 h 35 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc=30 : 1) gave 131 mg of ketene dithioacetal **13a** (92% yield, >95% dr by ^{1}H-NMR analysis) as a clear yellow oil: *Rf* 0.40 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.18 (tq, J=1.7, 1.5 Hz, 1H), 3.17 (dt, J=15.0, 4.9 Hz, 1H), 2.64 (ddd, J=5.5, 9.4, 13.4 Hz, 1H), 2.54 (ddd, J=4.9, 10.8, 15.0 Hz, 1H), 2.39—2.30 (m, 1H), 2.34 (s, 3H), 2.28—2.19 (m, 1H), 2.26 (s, 3H), 1.92—1.77 (m, 2H), 1.74 (dt, J=1.5, 1.2 Hz, 3H), 1.68 (ddd, J=5.5, 9.4, 13.4 Hz, 1H), 1.62—1.52 (m, 1H), 0.915 (d, J=6.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.5, 144.6, 144.0, 137.5, 122.4, 69.7, 41.7, 36.4, 32.7, 30.8, 29.9, 17.9, 17.2, 16.9, 16.3; IR (neat, cm^{-1}) 3041, 2962, 2920, 2855, 2731, 1694, 1559; HR-ESI-MS Calcd for $C_{15}H_{22}ONaS_2$: 305.1004, Found: 305.0997.

To a suspension of CuI (250 mg, 1.31 mmol) in Et_2O (7.5 ml) was added MeLi (0.66 M in Et_2O, 2.78 ml) dropwise at −20 °C. After the resulting mixture was cooling to −78 °C, to this mixture was added ketene dithioacetal **13a** (124 mg, 0.438 mmol) in Et_2O (10 ml) at −78 °C, and stirred for 17 min. The reaction mixture was quenched with MeOH and a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc=30 : 1) gave 89 mg of α,β-unsaturated ketone **13b** (93% yield) as a colorless clear oil: *Rf* 0.45 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.19 (tq, J=1.7, 1.5 Hz, 1H), 2.69 (dt, J=14.4, 5.1 Hz, 1H), 2.58 (ddd, J=5.5, 9.2, 13.2 Hz, 1H), 2.36—2.19 (m, 3H), 1.91—1.82 (m, 1H), 1.80—1.76 (m, 1H), 1.75 (d, J=1.0 Hz, 6H), 1.73 (dt, J=1.5, 1.2 Hz, 3H), 1.67 (ddd, J=5.5, 9.2, 13.2 Hz, 1H), 1.59—1.48 (m, 1H), 0.906 (d, J=6.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 207.6, 144.0, 136.0, 133.3, 123.2, 69.6, 41.3, 36.4, 30.9, 29.9, 28.8, 22.2, 20.8, 16.9, 16.5; IR (neat, cm^{-1}) 3041, 2961, 2917, 2856, 2731, 1728, 1685, 1649; HR-ESI-MS Calcd for $C_{15}H_{22}ONa$: 241.1562, Found: 241.1568.

Ketone 14a and 14b The apparatus was flame-dried while flushing with Ar and then maintained under positive Ar pressure. Lithium wire (13 mg, 1.91 mmol) was added after glassware had cooled to −78 °C. The dry ice condenser was filled, and then ammonia (*ca.* 5 ml) was added to the reaction vessel. To this blue mixture was added a solution of α,β-unsaturated ketone **13b** (199 mg, 0.910 mmol) and distilled *t*-BuOH (0.0870 ml, 0.910 mmol) in THF (4 ml) at −78 °C, then stirred at that temperature for 50 min. The reaction mixture was quenched with a solid NH_4Cl, then H_2O was added. The resulting mixture was allowed to warm to RT, then stirred for additional 15 min. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to afford crude mixture. To a solution of curde mixture in CH_2Cl_2 (9.1 ml) was added Dess–Martin periodinane (386 mg, 0.910 mmol) at RT, then the resulting mixture was stirred at that temperature for 14 h 30 min. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$, and $Na_2S_2O_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc=100 : 1) gave 174 mg of a mixture of saturated ketone **14a** and **14b** (87% yield from **13b**, a 23 : 77 mixture of epimers by ^{1}H-NMR analysis) as a colorless clear oil: *Rf* 0.58, 0.52 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.47 (q, J=1.7 Hz, 0.23H), 5.31 (q, J=1.5 Hz, 0.77H), 2.79 (ddd, J=13.4, 9.5, 5.1 Hz, 0.77H), 2.31—1.95 (m, 6.1H), 1.90—1.83 (m, 0.23H), 1.74 (q, J=1.0 Hz, 0.77H), 1.72 (q, J=1.0 Hz, 2.3H), 1.71—1.49 (m, 3.1H), 1.33 (dq, J=3.8, 12.9 Hz, 0.77H), 0.887—0.842 (m, 9H).

Ketone 14b To a solution of a mixture of saturated ketone **14a** and **14b** (174 mg, 0.788 mmol) in EtOH (7.9 ml) was added powdered KOH (66.3 mg, 1.18 mmol) at RT, then this mixture was heated at 100 °C for 15 h. After the resulting mixture was cooling to RT, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/*i*-Pr_2O=40 : 1) gave 139 mg of desired ketone **14b** (80% yield, >95% dr by ^{1}H-NMR analysis) as a colorless clear oil along with 28 mg of **14a** (16% yield) as a colorless clear oil. Ketone **14b**: *Rf* 0.58 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.31 (tq, J=1.7, 1.5 Hz, 1H), 2.79 (ddd, J=5.1, 9.6, 13.4 Hz, 1H), 2.31—2.22 (m, 2H), 2.19—2.01 (m, 3H), 1.72 (dt, J=1.5, 1.2 Hz, 3H), 1.70—1.59 (m, 2H), 1.57—1.49 (m, 2H), 1.38—1.26 (m, 1H), 0.880 (d, J=6.8 Hz, 3H), 0.876 (d, J=6.8 Hz, 3H), 0.851 (d, J=6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 212.6, 144.8, 123.0, 69.7, 53.3, 43.6, 36.0, 31.8, 28.6, 28.2, 26.3,

21.4, 18.8, 17.0, 16.6; IR (neat, cm^{-1}) 3041, 2956, 2930, 2871, 2731, 1704, 1653; HR-ESI-MS Calcd for $C_{15}H_{24}ONa$: 243.1719, Found: 243.1725.

Reduction of 14b with $LiAlH_4$ (Condition c in Chart 5) To a solution of **14b** (10 mg, 0.0458 mmol) in distilled THF (1.83 ml) was added $LiAlH_4$ (1.0 M in THF, 0.0688 ml) at 0 °C, then the resulting mixture was stirred at that temperature for 20 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (petroleum ether/Et_2O=20 : 1) gave 3.4 mg of (±)-gleenol (**1**) (33% yield, >95% dr by ^{1}H-NMR analysis) as a colorless clear oil and 4.4 mg of (±)-axenol (**2**) (43% yield, >95% dr by ^{1}H-NMR analysis) as a colorless clear oil.

Reduction of 14b with Li/NH_3 (Condition d in Chart 5) The apparatus was flame-dried while flushing with Ar and then maintained under positive Ar pressure. Lithium wire (14 mg, 2.05 mmol) was added after glassware had cooled to −78 °C. The dry ice condenser was filled, and then ammonia (*ca.* 5 ml) was added to the reaction vessel. To this blue mixture was added a solution of ketone **14b** (42 mg, 0.188 mmol) and distilled *t*-BuOH (0.0180 ml, 0.188 mmol) in THF (2 ml) at −78 °C, then stirred at that temperature for 50 min. The reaction was quenched with a solid state of NH_4Cl, then H_2O was added. The resulting mixture was allowed to warm to RT, then stirred for additional 15 min. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica gel column chromatography (hexane/EtOAc=40 : 1) gave 39 mg of (±)-axenol (**2**) (93% yield, >95% dr by ^{1}H-NMR analysis) as a colorless clear oil. Gleenol (**1**): *Rf* 0.45 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.17 (tq, J=1.7, 1.4 Hz, 1H), 3.54 (br s, 1H), 2.24—2.19 (m, 2H), 1.90 (ddd, J=7.0, 9.2, 13.2 Hz, 1H), 1.80 (ddd, J=5.6, 8.1, 13.2 Hz, 1H), 1.76—1.64 (m, 2H), 1.74 (dt, J=1.4, 1.2 Hz, 3H), 1.59—1.43 (m, 2H), 1.33—1.23 (m, 2H), 1.17—1.03 (m, 2H), 0.922 (d, J=6.8 Hz, 3H), 0.916 (d, J=6.8 Hz, 3H), 0.749 (d, J=6.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.8, 125.6, 76.5, 58.9, 45.4, 36.3, 34.1, 34.0, 31.8, 29.3, 24.4, 21.2, 20.8, 17.0, 16.3; IR (neat, cm^{-1}) 3480, 3401, 2925, 2870, 2730, 1718, 1656; HR-ESI-MS Calcd for $C_{15}H_{26}ONa$: 245.1875, Found: 245.1878. Axenol (**2**): *Rf* 0.55 (hexane/EtOAc=10 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.14 (tq, J=1.7, 1.5 Hz, 1H), 3.07 (t, J=10.3 Hz, 1H), 2.33—2.25 (m, 1H), 2.22—2.15 (m, 2H), 2.09 (ddd, J=5.4, 10.3, 13.1 Hz, 1H), 1.79 (dt, J=1.5, 1.2 Hz, 3H), 1.78 (ddd, J=4.9, 9.8, 13.1 Hz, 1H), 1.59—1.55 (m, 1H), 1.52—1.48 (m, 1H), 1.41—1.32 (m, 1H), 1.25—1.17 (m, 1H), 1.14—0.979 (m, 3H), 0.898 (d, J=7.1 Hz, 3H), 0.798 (d, J=7.1 Hz, 3H), 0.787 (d, J=7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 147.3, 121.8, 78.4, 61.3, 47.1, 40.8, 36.8, 33.2, 31.9, 26.2, 23.2, 21.1, 17.2, 16.9, 15.8; IR (neat, cm^{-1}) 3558, 3479, 3037, 2956, 2929, 2871, 1655; HR-ESI-MS Calcd for $C_{15}H_{26}ONa$: 245.1875, Found: 245.1867.

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References and Notes

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