Total Syntheses of (−)-Methyl Atis-16-en-19-oate, (−)-Methyl Kaur-16-en-19-oate, and (−)-Methyl Trachyloban-19-oate by a Combination of Palladium-Catalyzed Cycloalkenylation and Homoallyl−Homoallyl Radical Rearrangement

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Asymmetric total syntheses of (−)-methyl atis-16-en-19-oate (**1c**), (−)-methyl kaur-16-en-19-oate (**2c**), and (−)-methyl trachyloban-19-oate (**3c**) have been achieved by employing a hybrid strategy of palladium-catalyzed cycloalkenylation and homoallyl−homoallyl radical rearrangement. The common synthetic intermediate **5** was prepared from 2-allylcyclohexanone (**4**) with 98% ee using d'Angelo's asymmetric Michael addition. A series of functional group modifications in **5** via palladium-catalyzed cycloalkenylation led to (+)-**14**, which had already been prepared by us as racemate. (−)-Methyl atis-16-ene-19-oate (**1c**) was generated via homoallyl-homoallyl radical rearrangement. On the other hand, Wolff−Kishner reduction of **18** followed by esterification yielded (−)-methyl kaur-16-en-19-oate (**2c**) together with (−)-methyl trachyloban-19-oate (**3c**).

1. Introduction

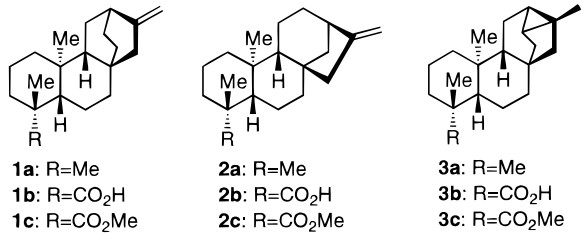
Although diterpenes belonging to atisirene (**1a**), kaurene (**2a**), and trachylobane (**3a**) families arise biogenetically from (−)-copalyl pyrophosphate,[1] each family has a unique tetra- or pentacyclic carbon framework, comprising a number of contiguous stereogenic centers, as shown in Scheme 1.

In our own quest for a diastereoselective avenue toward tetra- and pentacyclic diterpenoids such as (±)-**1c**, (±)-**2c**, and (±)-**3c**, we already demonstrated the total synthesis of these compounds by a combination of palladium-catalyzed cycloalkenylation and homoallyl−homoallyl radical rearrangement.[2] This success prompted us to extend the strategy for the syntheses of optically active **1c**, **2c**, and **3c** via the same key intermediate **14** in the case of racemate.

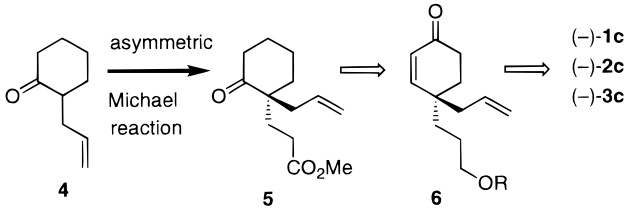
2. Synthesis of the Chiral Key Intermediate (+)-5

Among a number of methodologies for the enantioselective construction of quaternary stereogenic center,[3] we adopted the asymmetric Michael reaction, developed by d'Angelo,[4] for the following reasons: (i) cyclohexanone derivatives are easily obtained with high enantioselectivity, (ii) both enantiomers of the chiral auxiliary, 1-phenylethylamine, are commercially available in high purity and at moderate price, and (iii) the C_3 carbon unit

Scheme 1



Scheme 2



can be introduced in a single step (in the previous racemate synthesis, the C_2 alkyl side chain was homologated).

We planned an alternative strategy for the synthesis of chiral **1c**, **2c**, and **3c** as shown in Scheme 2, in which 1,3-transcarbonylation of the chiral keto ester **5** could give the enone ester **6**. Although the present synthetic strategy is a modification of our racemate synthesis, we focused on the minimization of purification steps by chromatography to make this synthesis practically viable.

The synthesis started with the generation of chiral quaternary center next to the carbonyl group of cyclohexanone by applying asymmetric Michael reaction. Thus, 2-allylcyclohexanone **4**[5] was condensed with (−)-(*S*)-1-phenylethylamine (>98% ee) in the presence of 5 Å molecular sieves in refluxing toluene,[6] and the result-

(1) (a) Wenkert, E. *Chem. Ind. (London)* **1955**, 282. (b) Coates, B. E.; Norton, K. *J. Org. Chem.* **1971**, *36*, 3722, and references therein. (c) Recent syntheses of the atisirene family: Berettoni, M.; Chiara, G. D.; Iacoangeli, T.; Surdo, P. L.; Bettolo, M.; di Mirabello, L. M.; Nicolini, L.; Scarpelli, R. *Helv. Chim. Acta* **1996**, *79*, 2035 and references therein. (d) Our own synthetic study: Ihara, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151 and references therein.

(2) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916.

(3) *For a recent review*: Corey, E. J.; Gunzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 389.

(4) *A review*: d'Angelo. J. D.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459, and references therein.

(5) Conia, J. M.; Leydendecker, F. *Bull. Soc. Chim. Fr.* **1967**, 830.

(6) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.

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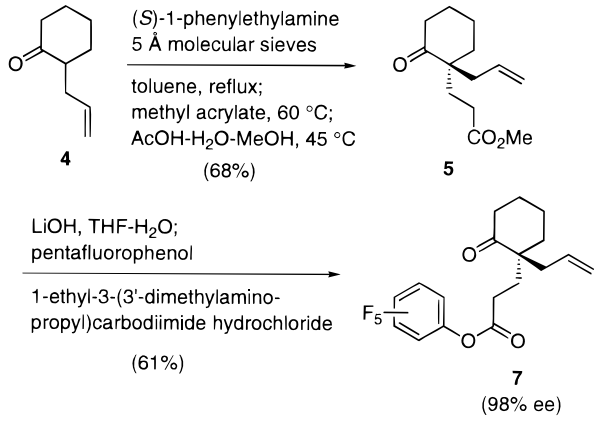
Scheme 3



ing crude imine was subjected to Michael reaction with methyl acrylate, followed by hydrolysis with acetic acid to afford the keto ester **5** in 68% yield. To determine the ee, the compound **5** was converted to the corresponding pentafluorophenyl ester **7** by sequential alkaline hydrolysis and reesterification with pentafluorophenol in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride and DMAP. The chromatographic analysis of **7** with chiral HPLC (SUMICHIRAL OA-4600) showed that the above asymmetric Michael reaction proceeded in 98% ee (Scheme 3).

With the convenient access to the keto ester **5** secure, 1,3-transcarbonylation of **5** was next investigated as depicted in Scheme 4. Thus, the compound **5** was reduced with $LiAlH_4$ followed by treatment with 1 equiv of pivaloyl chloride. The reaction mixture was quenched with methanesulfonyl chloride to provide the crude mesylate **8**, which was then heated at 110 °C with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) without additional solvents. The desired cyclohexene **9** was eventually obtained in 78% overall yield. The allylic oxidation of **9** was carried out using catalytic amounts of chromic acid in the presence of 70% aqueous *tert*-butyl hydroperoxide as reoxidant[7] to furnish the enone **10** in 64% yield.[8]

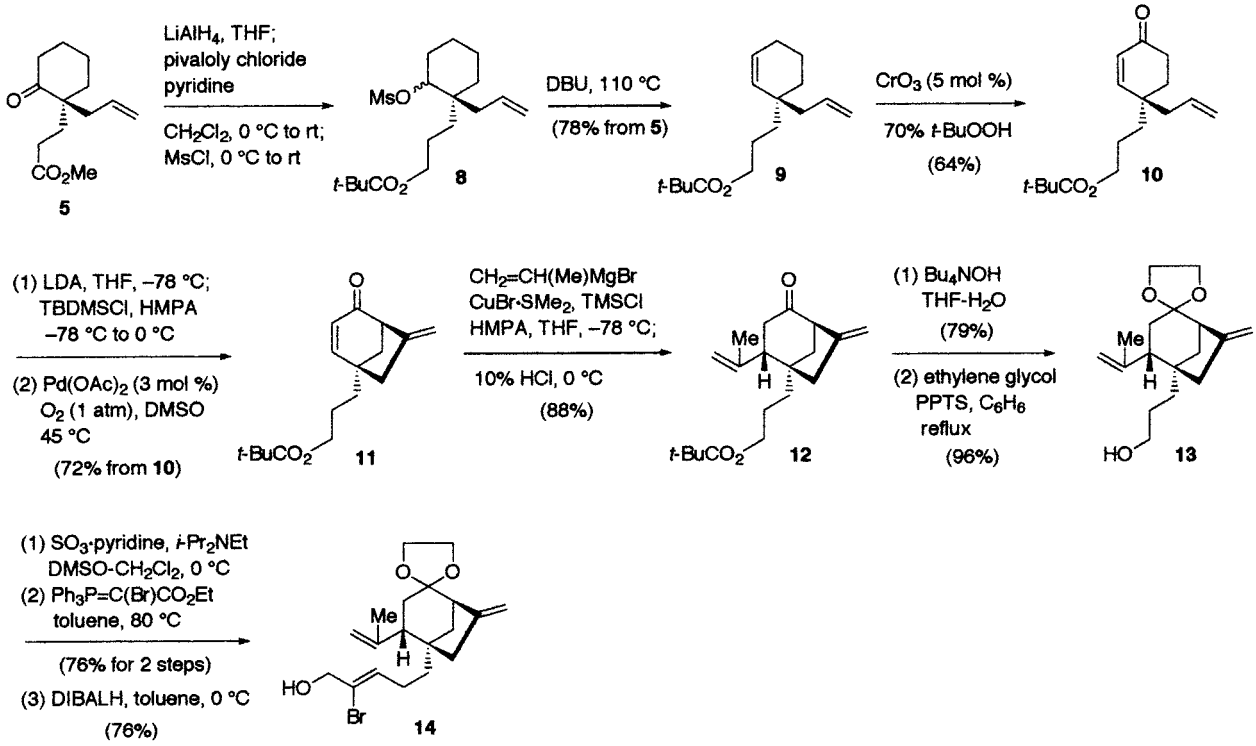
Palladium-catalyzed cycloalkenylation reaction of **10** via the corresponding TBDMS enol ether gave rise to the bicyclo[3.2.1]octenone **11** (72% overall yield from **10**), which was subjected to stereoselective introduction of isopropenyl group (88% yield), followed by hydrolysis of the pivaloate moiety (79% yield) and protection of the carbonyl group (96% yield), to afford the alcohol **13**. Successive oxidation of **13**, Wittig olefination (76% overall yield from **13**) and DIBALH reduction (76% yield) led to the allylic alcohol (+)-**14** (Scheme 4). The spectral data of synthetic (+)-**14** were identical with those of the racemic compound.[2]

With an efficient access to (+)-**14** and our previous experience with the transformation of (±)-**14** into (±)-**1c**, **2c** and **3c**, the completion of syntheses of chiral target natural products seemed imminent. Oxidation of **14** with MnO_2 followed by Wittig olefination provided the tetraene **15** (70% overall yield for 2 steps), which was subjected to intramolecular Diels−Alder reaction at 200 °C in a sealed tube to give the cycloadducts (**16a** and **16b**, 70%) as an 85:15 stereoisomeric mixture. Without separation of the stereoisomers, the mixture was carbomethoxylated (82% yield) and then reduced with magnesium in MeOH to yield the desired ester **17** (63% yield). Subsequent methylation of **17** and hydrolysis furnished the keto ester **18** (Scheme 5).

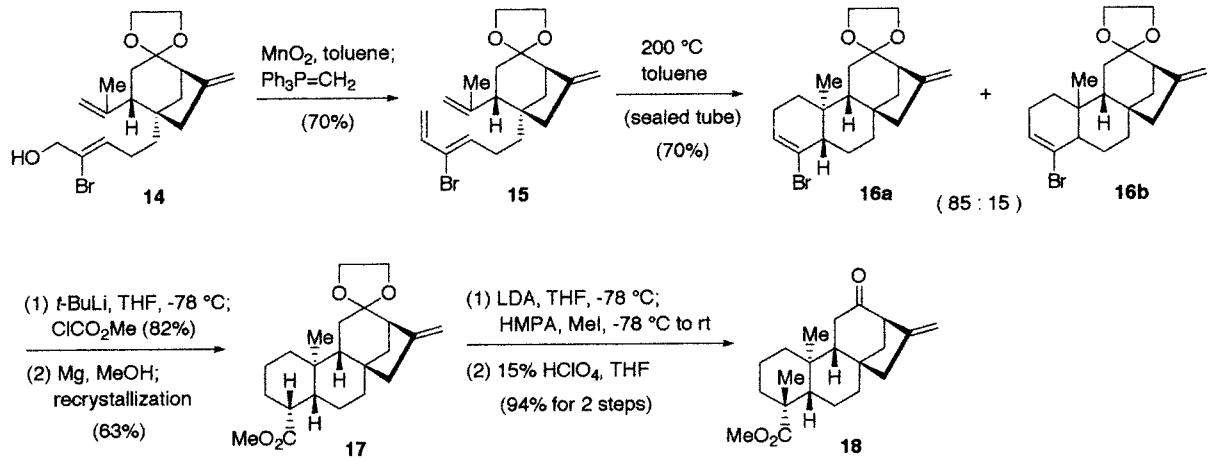
3. Completion of Total Syntheses of (−)-Methyl Atis-16-en-19-oate (1c), (−)-Methyl Kaur-16-en-19-oate (2c), and (−)-Methyl Trachyloban-19-oate (3c)

Transformation of **18** into structurally different natural products, such as atisirene, kaurene, and trachylobane, is shown in Scheme 6. First, **18** was reduced with $NaBH_4$

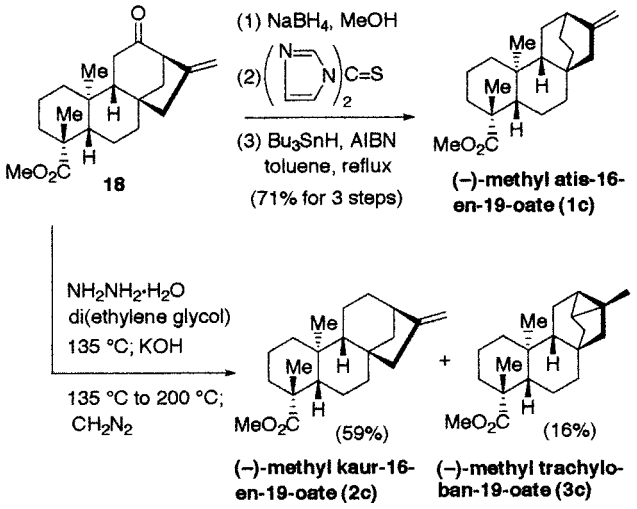
Scheme 4



Scheme 5



Scheme 6



to give the alcohols, which were acylated with 1,1′-thiocarbonyldiimidazole and DMAP. The resulting thioimidazolides were subjected to deoxygenation with Bu_3SnH and AIBN to provide (−)-methyl atis-16-en-19-oate (**1c**)[9] in 71% yield. On the other hand, Wolff−Kishner reduction of **18** followed by esterification afforded (−)-methyl kaur-16-en-19-oate (**2c**, 59%)[9] and (−)-methyl trachyloban-19-oate (**3c**, 16%).[9] The spectral data (^1H NMR, IR, MS) of synthetic (−)-**1c**, (−)-**2c**, and (−)-**3c** were identical with those of the racemates synthesized by us.[2]

In conclusion, asymmetric total syntheses of atisirane, kaurane, and trachylobane diterpenes have been achieved from a common chiral intermediate. Since the common intermediate was easily obtainable by applying d'Angelo's aymmetric Michael reaction with high enantiomeric excess, the present synthetic route would be suitable for the other members of atisirene, kaurene, and trachylobane family and also the related diterpene alkaloids.

Experimental Section

General Methods. Unless otherwise noted, all reactions were performed in oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical Co., Inc. Toluene, pyridine, and diisopropylamine (*i*-Pr_2NH) were distilled from CaH_2. Hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under reduced pressure. Benzene (C_6H_6) and methanol (MeOH) were distilled under argon immediately prior to use. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure with the aid of a rotary evaporator. Flash chromatography was carried out using Merck 60 (230−400 mesh) or Cica 60 (spherical/40−100 μm) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using a ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH), or ammonium molybdate (in 10% H_2SO_4). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$. *J* values are reported in hertz.

(+)-Methyl 3-[(1*R*)-2-Oxo-1-(2-propenyl)cyclohexyl]-propanoate (5). A mixture of 2-allylcyclohexanone (**4**)[5] (20.1 g, 145 mmol), (*S*)−(−)-phenylethylamine (22.0 mL, 172 mmol) and 5 Å molecular sieves (60 g) in toluene (60 mL) was refluxed for 20 h, and then cooled to room temperature. [The reaction was monitored by IR and ^1H NMR.] Molecular sieves were filtered off and toluene was mostly evaporated. To the residue was added freshly distilled methyl acrylate (20.0 mL, 222 mmol) and the resulting viscous mixture was stirred at room temperature for a week. After evaporation of excess methyl acrylate, MeOH (30 mL), water (60 mL) and AcOH (12.0 mL, 210 mmol) were added, and then the resulting mixture was vigorously stirred at room temperature for 1 h, and saturated with NaCl. Hexane (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with hexane, and the combined organic layers were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and then dried. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (9:1 v/v) as an eluent furnished the Michael adduct **5** (22.2 g, 68% from **4**) as a colorless oil. IR 1720 and 1715 cm^{-1}. ^1H NMR δ 1.66−1.88 (7H, m), 1.19 (1H, dd, J = 5.0 and 10.5), 2.00−2.44 (6H, m), 3.66 (3H, s), 5.02−5.11 (2H, m) and 5.66 (1H, ddt, J = 6.5, 10.5 and 15.0). ^{13}C NMR δ 20.52, 26.85, 28.44, 29.53, 36.00 38.84, 38.98, 50.68, 51.50, 118.37 133.27, 174.01 and 214.18. $[\alpha]^{25}_D$ +3.6 (c 3.5, $CHCl_3$). MS *m*/*z* 224 (M^+). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.39; H, 9.07.

(−)-Pentafluorophenyl 3-[(1*R*)-2-Oxo-1-(2-propenyl)-cyclohexyl]propanoate (7). A mixture of the ester **5** (64.5 mg, 0.288 mmol) and lithium hydroxide monohydrate (23.5 mg,

(7) Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 4665.
(8) Although the TBDMS analogue of **9** was also synthesized, the TBDMS group was susceptible to Cr(VI)-catalyzed allylic oxidation.
(9) Pyrek, J. S. *Tetrahedron* **1970**, *26*, 5029.

0.560 mmol) in water−THF (2:1 v/v, 3 mL) was stirred at room temperature for 13 h. After evaporation of the solvent, the residue was acidified with 10% HCl (0.5 mL) and extracted with $CHCl_3$. After being dried, evaporation of the solvent gave the crude acid, which was dissolved in CH_2Cl_2 (2.0 mL). To the resulting solution were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (67.0 mg, 0.350 mmol), DMAP (46.8 mg, 0.383 mmol), and pentafluorophenol (2.4 mg, 0.393 mmol) at 0 °C, and then the resulting mixture was stirred at room temperature for 7 h. After evaporation of the solvent, to the residue were added hexane (20 mL) and water (10 mL), and the layers were separated. The aqueous layer was extracted with hexane, and the combined organic layers were washed with saturated aqueous NaCl and dried. Removal of the solvent and chromatography of the residue on silica gel with hexanes−EtOAc (5:1 v/v) as an eluent afforded the pentafluoroester **7** (66 mg, 61% from **5**) as a colorless oil. The analysis of **7** by chiral HPLC [SUMICHIRAL OA-4600, hexane−$CHCl_3$ (100:1 v/v as an eluent)] revealed that the ee of **7** was more than 98%: IR 1720 and 1715 cm^{-1}; ^1H NMR δ 1.65−1.95 (7H, m), 2.00 (1H, ddd, J = 2.0, 6.5 and 8.5), 2.25−2.76 (6H, m), 5.11 (1H, dq, J = 1.0 and 15.0), 5.10−5.16 (1H, m) and 5.67 (1H, ddt, J = 6.5, 10.5 and 15.0); ^{13}C NMR δ 20.65, 26.94, 28.11, 29.49, 35.88, 39.15, 39.18, 50.87, 119.02, 132.79, 169.83 and 214.09; $[\alpha]^{27}_D$ −14.1 (c 1.1, $CHCl_3$); MS m/z 376 (M^+); HRMS calcd for $C_{18}H_{17}F_5O_3$ 376.1098, found 376.1081.

(−)-3-[(1*R*)-1-(2-Propenyl)-2-cyclohexenyl]propyl 2,2-Dimethylpropanoate (9). To a stirred suspension of $LiAlH_4$ (4.14 g, 109 mmol) in THF (600 mL) was added dropwise a solution of the keto ester **5** (22.5 g 100 mmol) in THF (40 mL) at 0 °C. Stirring was continued at the same temperature for 20 min, and then the reaction was quenched by successive addition of water (4.1 mL), 15% NaOH (4.1 mL), and water (12.3 mL). The mixture was stirred at room temperature for 30 min, and then $MgSO_4$ (10 g) was added. The resulting suspension was filtered through Celite. Removal of the solvent provided an oil, and the solvent was completely removed with toluene as an azeotropy. The residue was used without further purification.

To a stirred solution of the above crude diol (16.7 g, 84.2 mmol) and pyridine (34.0 mL, 420 mmol) in CH_2Cl_2 (300 mL) was added dropwise freshly distilled pivaloyl chloride (11.0 mL, 89.9 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 2 h, and then warmed to room temperature. After 2 h, the reaction mixture was cooled to 0 °C and Et_3N (23 mL, 165 mmol) and freshly distilled methanesulfonyl chloride were successively added dropwise to the mixture. Stirring was continued at room temperature for 1 h, and water (100 mL) and Et_2O (300 mL) were added at 0 °C. The resulting layers were separated, and then the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried. After removal of the solvent, residual pyridine was removed with toluene as an azeotropy, and then to the residue was added DBU (50.0 mL, 334.3 mmol). The resulting mixture was heated at 110 °C for 7 h and cooled to room temperature. Water (150 mL) and Et_2O (150 mL) were added to the reaction mixture and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with 10% HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried. Removal of the solvent and chromatography of the residue on silica gel with hexanes−EtOAc (20:1 v/v) as an eluent furnished the olefin **9** (20.6 g, 78% from **5**) as a colorless oil: IR 1720, 1670 and 1630 cm^{-1}; ^1H NMR δ 1.20 (9H, s), 1.28−1.49 (4H, m), 1.53−1.66 (4H, m), 1.89−1.98 (2H, m), 2.07 (2H, dd, J = 1.0 and 6.5), 4.01 (2H, t, J = 6.5) 5.01 (1H, dt, J = 1.0 and 15.0), 5.00−5.07 (1H, m) 5.41 (1H, dt, J = 2.0 and 9.5), 5.68 (1H, dt, J = 3.5 and 9.5) and 5.77 (1H, ddt, J = 6.5, 10.0 and 15.0); ^{13}C NMR δ 18.79, 23.13, 24.97, 27.11, 32.12, 35.59, 36.61, 38.61, 44.32, 64.91, 117.11, 126.87, 134.82, 135.10 and 178.59; $[\alpha]^{26}_D$ −3.4 (*c* 8.8, $CHCl_3$); MS m/z 264 (M^+). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.08; H, 10.86.

(−)-3-[(1*S*)-4-Oxo-1-(2-propenyl)-2-cyclohexenyl]propyl 2,2-Dimethylpropanoate (10). To a stirred suspension of CrO_3 (723 mg, 7.23 mmol) in CH_2Cl_2 (72 mL) cooled to 0 °C was added dropwise a 70% aqueous solution of *tert*-butyl hydroperoxide (20.0 mL, 146 mmol). The resulting red solution was stirred at the same temperature for 10 min, and then a solution of **9** (9.52 g, 36.0 mmol) in CH_2Cl_2 (17 mL) was added dropwise to the mixture at such a rate as to keep the internal temperature below 6 °C. The reaction mixture was stirred at 0 °C for 2 h, and then the ice−water bath was replaced with a water bath (10 °C) and stirring was continued for 18 h. The reaction was quenched by the dropwise addition of 10% aqueous solution of $NaHSO_3$ (50 mL) at 0 °C, and the resulting greenish mixture was diluted with Et_2O (150 mL). After 1.5 h of vigorous stirring at room temperature, the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated $NaHCO_3$ and brine and dried. Removal of the solvent and chromatography of the residue on silica gel with hexanes−EtOAc (5:1 v/v) as an eluent afforded the starting material (581 mg, 6%) followed by the enone **10** (6.43 g, 64%), each as a colorless oil: IR 1720 and 1675 cm^{-1}; ^1H NMR δ 1.20 (9H, s), 1.48−1.73 (4H, m), 1.90 (2H, t, J = 6.5), 2.25 (2H, d, J = 6.5), 2.46 (2H, dt, J = 4.0 and 6.5), 4.06 (2H, t, J = 6.5), 5.08−5.18 (2H, m), 5.77 (1H, ddt, J = 6.5, 10.0 and 15.0), 5.96 (1H, d, J = 9.5) and (1H, d, J = 9.5); ^{13}C NMR δ 23.20, 26.97, 30.76, 33.62, 33.73, 37.95, 38.51, 42.05, 64.12, 118.85, 128.46, 133.11, 157.25, 178.40 and 199.10; $[\alpha]^{25}_D$ −9.9 (c 14.7, $CHCl_3$); MS m/z 278 (M^+). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.36; H, 9.47.

(+)-3-[(1*R*,5*S*)-7-Methylidene-2-oxobicyclo[3.2.1]octan-2-en-5-yl]propyl 2,2-Dimethylpropanoate (11). To a stirred solution of LDA [prepared in situ from $^iPr_2NH$ (3.6 mL, 25.7 mmol) and 1.54 M hexane solution of BuLi (15.0 mL, 23.4 mmol) at 0 °C] in THF (50 mL) cooled to −78 °C was added dropwise a solution of **10** (4.40 g, 15.8 mmol) in THF (8 mL). After 50 min, a solution of TBDMSCl (3.81 g, 24.5 mmol) and HMPA (3.3 mL, 19.0 mmol) in THF (3 mL) was added, and the resulting mixture was allowed to warm to 0 °C. After removal of the solvent, the residue was diluted with hexane, washed with H_2O and brine, and dried over K_2CO_3. Removal of the solvent and chromatography of the residue on silica gel with hexanes−EtOAc (25:1 v/v) as an eluent provided a colorless oil, which was heated to 80 °C under 1 mmHg for 30 min to furnish the analytically pure TBDMS enol ether (6.20 g, 100%) as a colorless oil: ^1H NMR δ 0.13 (6H, s), 0.93 (9H, s), 1.19 (9H, s), 1.28−1.49 (2H, m), 1.54−1.71 (2H, m), 4.01 (2H, t, J = 6.0), 4.75 (1H, dt, J = 1.5 and 4.0), 4.97−5.08 (2H, m), 5.49 (1H, d, J = 9.5), 5.66 (1H, dd, J = 2.0 and 9.5) and 5.76 (1H, ddt, J = 6.5, 10.0 and 15.5); ^{13}C NMR δ −4.50, 18.01, 23.77, 25.69, 27.21, 32.31, 34.50, 36.81, 38.75, 42.88, 64.91, 101.38, 117.52, 125.64, 134.97, 136.54, 147.58 and 178.81; $[\alpha]^{25}_D$ −1.1 (c 11.2, $CHCl_3$). Anal. Calcd for $C_{23}H_{38}SiO_3$: C, 70.36; H, 10.27. Found: C, 70.31; H, 10.27.

A mixture of the TBDMS enol ether (5.83 g, 14.9 mmol) and $Pd(OAc)_2$ (104 mg, 0.461 mmol, 3 mol %) in DMSO (150 mL, 0.1 M) was stirred under O_2 (1 atm) for 15 h. The reaction mixture was diluted with Et_2O and filtered through Celite to remove Pd black. Water (300 mL) was added to the filtrate, and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with ice-cold 10% HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (6:1 v/v) as an eluent furnished the bicyclic enone **11** (3.13 g, 72%) as a colorless oil: IR 1720 and 1715 cm^{-1}; ^1H NMR δ 1.56−1.84 (5H, m), 2.13 (1H, d, J = 10.5), 2.39 (1H, t, J = 2.0), 3.47 (1H, br d, J = 5.0), 4.11 (1H, t, J = 6.0), 5.05 (1H, br s), 5.28 (1H, br s), 5.84 (1H, dd, J = 1.5 and 9.0) and 5.99 (1H, dd, J = 2.0 and 9.0); ^{13}C NMR δ 24.92, 27.11, 33.83, 38.66, 42.11, 44.53, 46.33, 58.59, 64.18, 112.35, 126.96, 145.36, 157.94, 178.65 and 198.75; $[\alpha]^{25}_D$ +87.0 (c 21.4, $CHCl_3$); MS m/z 276 (M^+). Anal. Calcd for $C_{17}H_{24}O_3$: C, 63.14; H, 8.83. Found: C, 63.10; H, 8.88.

(+)-3-[(1*R*,4*S*,5*S*)-5-(2-Methoxymethoxyethyl)-4-methylethenyl-7-methylidene-2-oxobicyclo[3.2.1]octan-5-yl]-propyl 2,2-Dimethylpropanoate (12). To a stirred solution

of isopropenylmagnesium bromide [from 2-bromopropene (3.5 mL, 39.4 mmol) and Mg (1.02 mg, 42.0 mmol)] and HMPA (8.9 mL, 51.2 mmol) in THF (80 mL) was added CuBr·SMe_2 (710 mg, 3.42 mmol) at −78 °C. After 5 min, a solution of the enone **11** (7.08 g, 25.6 mmol) and TMSCl (6.5 mL, 51.2 mmol) in THF (25 mL) was added dropwise at the same temperature, and stirring was continued for a further 30 min, and then 10% HCl was added at −78 °C. The resulting mixture was allowed to warm to 0 °C and then diluted with Et_2O. The aqueous layer was further extracted with Et_2O, and the combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (8:1 v/v) as an eluent afforded the ketone **12** (7.19 g, 88%) as a colorless oil: IR 1720 and 1715 cm^{-1}; ^1H NMR δ 1.20 (9H, s), 1.29−1.41 (1H, m), 1.59−1.72 (3H, m), 1.77 (3H, br t, J = 0.5), 1.78−1.87 (1H, m), 2.12 (1H, dd, J = 1.0 and 15.0), 2.27 (1H, d, J = 12.0), 2.50 (2H, br t, J = 2.0), 2.73 (1H, dd, J = 2.0 and 9.0), 2.91 (1H, dd, J = 9.0 and 15.0), 3.26 (1H, br d, J = 5.0), 4.05 (2H, dt, J = 2.0 and 5.5), 4.71 (1H, br s), 4.88 (1H, br d, J = 1.5), 4.94 (1H, br s) and 5.05 (1H, br t, J = 2.5); ^{13}C NMR δ 23.08, 24.46, 27.14, 33.98, 38.71, 39.42, 40.83, 43.64, 45.49, 50.81, 60.16, 64.16, 108.66, 115.06, 147.56, 148.68, 178.73 and 210.78; $[\alpha]^{25}_D$ +82.3 (*c* 1.7, $CHCl_3$); MS *m*/*z* 318 (M^+). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.49. Found: C, 75.51; H, 9.49.

(+)-(1*R*,4*S*,5*S*)-5-(2-Hydroxypropyl)-4-methylethenyl-7-methylidenebicyclo[3.2.1]octan-2-one 2-Ethylene Acetal (13). To a stirred solution of the ester **12** (108 mg, 0.340 mmol) in THF (3 mL) was added a 40 w/w % aqueous solution of tetrabutylammonium hydroxide (0.33 mL, 0.503 mmol). After 10 h, tetrabutylammonium hydroxide (0.15 mL, 0 229 mmol) was added to the mixture, and stirring was continued for an additional 4 h. The solvent was evaporated, and to the residue was added saturated aqueous NaCl. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous NaCl and dried. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (1:1 v/v) as an eluent furnished the hydroxy ketone (71.7 mg, 79%) as a colorless oil: IR 3400 and 1715 cm^{-1}; ^1H NMR δ 1.19 (9H, s), 1.20−1.76 (5H, m), 1.91 (3H, s), 2.08 (1H, dd, J = 9.0 and 14.5), 2.28 (1H, ddd, J = 2.0, 6.5 and 8.5), 2.41 (1H, br d, J = 9.0), 2.59 (1H, br d, J = 5.0), 3.86−4.07 (6H, m), 4.75−4.79 (1H, m), 4.87−4.93 (2H, m) and 5.00−5.05 (1H, m); ^{13}C NMR δ 23.07, 28.05, 33.48, 39.19, 40.74, 43.35, 45.37, 50.62, 59.99, 62.74, 108.39, 114.68, 147.59, 148.62 and 211.36; $[\alpha]^{25}_D$ +3.61 (c 3.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.90; H, 8.89.

A solution of the above hydroxy ketone (4.27 g, 18.2 mmol), ethylene glycol (20 mL, 210 mmol), and PPTS (59.3 mg, 0.236 mmol) in C_6H_6 (150 mL) was refluxed under a Dean−Stark water separator for 6 h. The reaction mixture was cooled to room temperature, and then water was added and the layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl and dried. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (3:1 v/v) as an eluent afforded the ethylene acetal **13** (4.89 g, 96%) as a colorless oil: IR 3400 cm^{-1}; ^1H NMR δ 1.20−1.81 (6H, m), 1.76 (3H, t, J = 0.7), 2.10 (1H, dd, J = 1.2 and 14.5), 2.25 (1H, br d, J = 12.0), 2.47−2.52 (2H, m), 2.73 (1H, dd, J = 2.1 and 8.5), 2.80 (1H, dd, J = 8.5 and 14.5), 3.25 (1H, d, J = 5.0), 3.63 (2H, t, J = 5.8), 4.70 (1H, s), 4.86 (1H, d, J = 1.5), 4.92 (1H, br s) and 5.03 (1H, br t, J = 2.3); $[\alpha]^{25}_D$ +7.2 (c 1.1, $CHCl_3$); MS *m*/*z* 278 (M^+). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.32; H, 9.55.

(+)-(1*R*,4*S*,5*S*)-5[(*Z*)-4-Bromohexa-3,5-dienyl]-4-methylethenyl-7-methylidenebicyclo[3.2.1]octane-2-one 2-Ethylene Acetal (14). To a stirred solution of the alcohol **13** (4.87 g, 17.5 mmol) and $^iPr_2NEt$ (9.0 mL, 51.7 mmol) in DMSO−CH_2Cl_2 (1:5 v/v, 60 mL) was added SO_3·Py (5.61 g, 35.2 mmol). Stirring was continued for 30 min, and then the reaction mixture was diluted with Et_2O. The organic layer was washed with water, 10% aqueous $CuSO_4$, water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and evaporated to provide an oil, which was dissolved in toluene (27 mL), and to the solution was added the bromo-containing Wittig reagent (9.73 g, 22.8 mmol). The resulting mixture was heated at 80 °C for 3 h and then cooled to room temperature. The solvent was evaporated, and to the residue was added hexane and triturated. The mixture was filtered through Celite. Removal of the solvent and flash chromatography of the residue on silica gel with hexanes−EtOAc (12:1 v/v) as an eluent furnished the chiral nonracemic ester (5.85 g, 76%) as a colorless oil.

Following the procedure for the racemic compound, the above ester (3.19 g, 7.49 mmol) was reduced with DIBALH (0.94 M in hexane, 17.5 mL, 16.5 mmol) in toluene (50 mL) at 0 °C to give rise to the (*Z*)-allylic alcohol **14** (2.11 g, 76%) as a colorless oil. Spectral data of **14** were consistent with those of the corresponding racemate: $[\alpha]^{25}_D$ +3.61 (*c* 3.5, $CHCl_3$); MS *m*/*z* 382 (M^+). Anal. Calcd for $C_{19}H_{27}BrO_3$: C, 59.53; H, 7.10; Br, 20.85. Found: C, 59.52; H, 7.17; Br, 20.79.

Conversion of (+)-14 to (−)-Methyl Atisirenoate by the Same Reaction Sequence as the Racemate (−)-Methyl 20-Nor-12-oxokaur-16-en-19-oate 12-Ethylene Acetal (17). The alcohol (+)-**14** (2.18 g, 5.70 mmol) was oxidized with MnO_2 (2.15 g) in toluene (200 mL) for 17.5 h, followed by methylenation with $Ph_3P{=}CH_2$ (7.85 mmol) in THF (40 mL) to afford **15** (1.52 g, 70%) as a colorless oil: MS *m*/*z* 378 (M^+).

Diels−Alder reaction of **15** (1.55 g, 4.01 mmol) furnished 1.08 g (70%) of **16a**, MS *m*/*z* 378 (M^+), and **16b** (85:15 mixture by ^1H NMR) as a colorless oil. In contrast to the corresponding racemate, **16a** could not be crystallized. Therefore, the cycloadducts were directly carbomethoxylated (82%), followed by reduction with Mg (1.18 g, 48.5 mmol) in MeOH (12 mL) to provide (−)-**17** (472 mg, 63%) as a white solid. An analytical sample was obtained by recrystallization of the solid from Et_2O−hexane as colorless needles: mp 170.0−172.0 °C; $[\alpha]^{28}_D$ −44.2 (*c* 2.1, $CHCl_3$); MS *m*/*z* 360 (M^+). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.39; H, 8.96.

(+)-Methyl 12-Oxokaur-16-en-19-oate (18). The ester **17** (189 mg, 0.525 mmol) was methylated with MeI (1 mL, 16.1 mmol) in the presence of LDA (5.28 mmol) and HMPA (0.1 mL, 0.575 mmol). After extractive workup, the crude product was treated with 15% $HClO_4$ (5 mL) in THF (10 mL) to afford the keto ester **18** (162 mg, 94% from **17**) as a white solid. An analytical sample was obtained by recrystallization of the solid from Et_2O−hexane as colorless prisms: mp 170.0−172.0 °C; $[\alpha]^{26}_D$ +40.1 (*c* 4.1, $CHCl_3$); MS *m*/*z* 330 (M^+). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.12; H, 9.29.

(−)-Methyl Atis-16-en-19-oate (1c). The ketone **18** (152 mg, 0.461 mmol) was reduced with $NaBH_4$ (57.9 mg, 1.53 mmol) in MeOH (10 mL) to give the crude alcohol, which was acylated with 1,1′-thiocarbonyldiimidazole (202 mg, 90%, 1.02 mmol) and DMAP (117 mg, 0.954 mmol) in CH_2Cl_2 (1.5 mL). The thioimidazolde (190 mg, 93%) obtained was deoxygenated with Bu_3SnH (0.24 mL, 0.866 mol) and AIBN (5.5 mg, 0.0335 mmol) in degassed toluene (43 mL) to furnish (−)-**1c** (111 mg, 76%) as a white solid: mp 102.5−105.0 °C (needles, MeOH) [lit.[10] mp 126 °C]; $[\alpha]^{24}_D$ −58.6 (*c* 0.96, $CHCl_3$) [lit.[10] $[\alpha]^{20}_D$ −62.5 (*c* 0.96, $CHCl_3$) and $[\alpha]^{20}_D$ −60.6 (*c* 0.64, $CHCl_3$)[11]]; MS *m*/*z* 316 (M^+). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.43; H, 10.44.

The synthetic compound was in all respects (^1H NMR, ^{13}C NMR, IR) indistinguishable from an authentic sample of (−)-**1c** provided by Professor R. M. Coates.

(−)-Methyl Kaur-16-en-19-oate (2c) and (−)-Methyl Trachyloban-19-oate (3c). The ketone **18** (94.9 mg, 0.287 mmol) was dissolved in di(ethylene glycol) (4 mL), and then hydrazine monohydrate (1 mL, 20.6 mmol) was added. The resulting mixture was refluxed at 135 °C for 2 h. After the mixture was cooled to room temperature, KOH (172 mg, 2.61 mmol) was added at room temperature and the mixture was

(10) (a) Coates, R. M.; Bertram, E. F. *J. Chem. Soc., Chem. Commun.* **1969**, 797. (b) *Idem J. Org. Chem.* **1971**, *36*, 2625.
(11) Bohlman, F.; Abraham, W.; Sherdlick, W. S. *Phytochemistry* **1980**, *19*, 869.

allowed to warm to 200 °C over a period of 10 h. After 6.5 h of heating, 5% HCl (4 mL) was added at room temperature, and then the resulting mixture was extracted with EtOAc. The organic layer was washed with water (2 mL) and saturated aqueous NaCl and dried. Evaporation of the solvent left a white solid, which was dissolved in Et_2O (4 mL). The resulting solution was treated with an ethereal solution of diazomethane at room temperature. After 1 h of stirring at the same temperature, AcOH was added until the evolution of nitrogen gas ceased. Saturated aqueous K_2CO_3 (1 mL) was added, and the mixture was extracted with Et_2O. The ethereal layer was washed with saturated aqueous NaCl and dried. Removal of the solvent and chromatography of the residue on silica gel impregnated with 30% silver nitrate with benzene−petroleum ether (3:1 v/v) as an eluent provided (−)-methyl trachyloban-19-oate (**3c**) (14.9 mg, 16%) [mp 96.5−98.0 °C [lit.[9] mp 98−100 °C]; $[\alpha]^{24}_D$ −73.4 (*c* 0.89, $CHCl_3$) [lit.[9] $[\alpha]_D$ −70.5 ($CHCl_3$)]; MS *m*/*z* 316 (M^+); HRMS calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2422] and (−)-methyl kaur-16-en-19-oate (**2c**) (53.3 mg, 59%): mp 72.0−73.5 °C [lit.[9] mp 73.5−74.5 °C]; $[\alpha]^{24}_D$ −96.4 (*c* 0.94, $CHCl_3$) [lit.[9] $[\alpha]_D$ −104 ($CHCl_3$)]; MS *m*/*z* 316 (M^+); HRMS calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2405.

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