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Enantiospecific total synthesis of aciphyllene

A. Srikrishna *, Vijendra H. Pardeshi

Department of Organic Chemistry, Indian Institute of Science, C. V. Raman Avenue, Bangalore, Karnataka 560012, India

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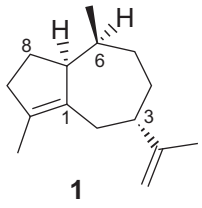
ABSTRACT

Enantiospecific total synthesis of the sesquiterpene aciphyllene and its three epimers have been described starting from the readily available monoterpene (*R*)-limonene employing an intramolecular type II carbonyl ene reaction as the key step.

1. Introduction

Of the various bicyclo[5.3.0]decane containing sesquiterpenes, guaianes constitute a large group and are present in plant, liverwort as well as marine sources. Guaianes, particularly, guaianoloides, are known to exhibit a wide spectrum of biological activities,[1] such as anti-inflammatory, cytotoxic, antinociceptive, antimalarial, antimicrobial, antiviral, antitumaral, and antioxidant activities. Aciphyllene **1**, a guaiane sesquiterpene, was first isolated in 1983 by Kubota and co-workers[2] from the essential oil of the roots of *Lindera glauca*. The structure of aciphyllene **1** was deduced on the basis of spectroscopic analysis. In 1998, Konig and co-workers, reported[3] the isolation of aciphyllene along with a number of sesquiterpene hydrocarbons from the liverwort *Dumortiera hirusta* (Sw.) Nees collected near Sao Fransisco de Paula Rio Grande do Sul (Brazil). Same structure **1** as that given by the research group of Kubota was assigned for aciphyllene isolated from *D. hirusta* on the basis of two dimensional GC and spectral analysis. Subsequently, aciphyllene **1** was also found in several medicinally valuable sources, such as *Shorea robusta*,[4] *Toona sinensis*,[5] and *Pogostemon cablin*.[6–8] Aciphyllene **1** was also found to be a component of the volatile blends let out by ficus trees to attract specific pollinating wasps.[9]



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Although isolation of aciphyllene **1** was reported as early as 1983, it was only in 2007 the first report appeared in the literature on the synthesis of aciphyllenes. In 2007, research group[10] of Pedro reported the semi-synthesis of the putative structure **1** of aciphyllene, Scheme 1. Enantiospecific synthesis of natural guaidienones **2** and **3**, and their diastereomer **4** has been accomplished starting from dihydrocarvone via cyperone. Subsequent deoxygenation of guaiadienone **2** generated **1**, whose NMR spectral data was found to differ with the aciphyllene isolated from *D. hirusta*. Deoxygenation of guaidienone **3** generated **5**, whose NMR data was found to be identical to that of the natural aciphyllene isolated from *D. hirusta*. Similarly, deoxygenation of the guaiadienone **4** generated 6-epiaciphyllene **6**. These studies not only established the revised stereostructure of aciphyllene as (3*R*,6*S*,7*S*)-3-isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-ene, but also established the absolute configuration of aciphyllene. In continuation of our interest on the enantiospecific synthesis of natural products[11] employing the readily available monoterpene (*R*)-limonene as the chiral starting material, herein we describe an enantiospecific

* Corresponding author. Fax: +91 80 23600529; e-mail address: ask@orgchem.iisc.ernet.in (A. Srikrishna).

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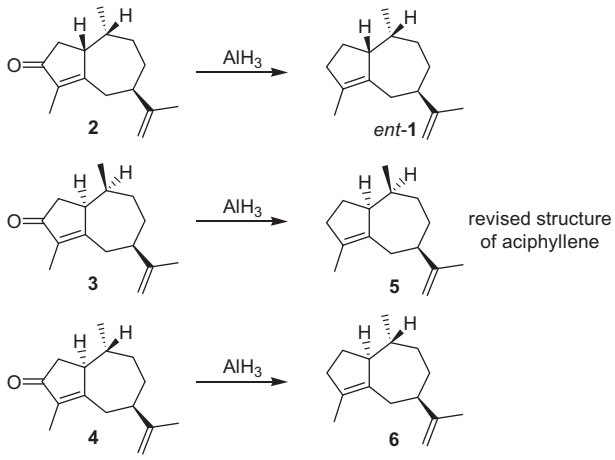
synthesis of aciphyllene and its three diastereomers, employing a type II carbonyl ene reaction as the key reaction.

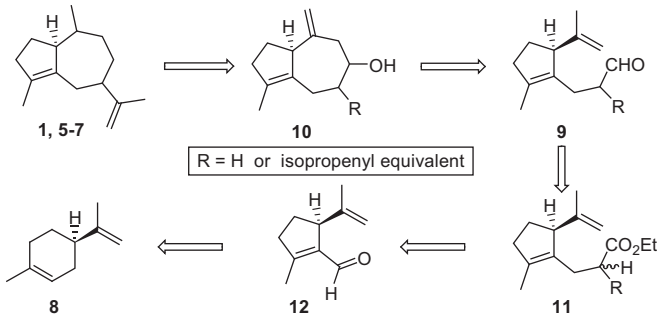


Scheme 1.

2. Results and discussion

As depicted in the retrosynthetic Scheme 2, an ene reaction based approach was conceived for the construction of the seven-membered ring of aciphyllenes **1**, **5**–**7** starting from the readily available monoterpene (*R*)-limonene **8**. It was anticipated that type II carbonyl ene reaction of the aldehyde **9** would generate the bicyclic alcohol **10**, which could be further elaborated into aciphyllenes. The aldehyde **9** could be obtained from the ester **11**, which in turn could be obtained from the aldehyde **12**. A two-step (controlled ozonolysis followed by intramolecular aldol condensation) conversion of (*R*)-limonene **8** into the aldehyde **12** has already been developed by us.[11a]

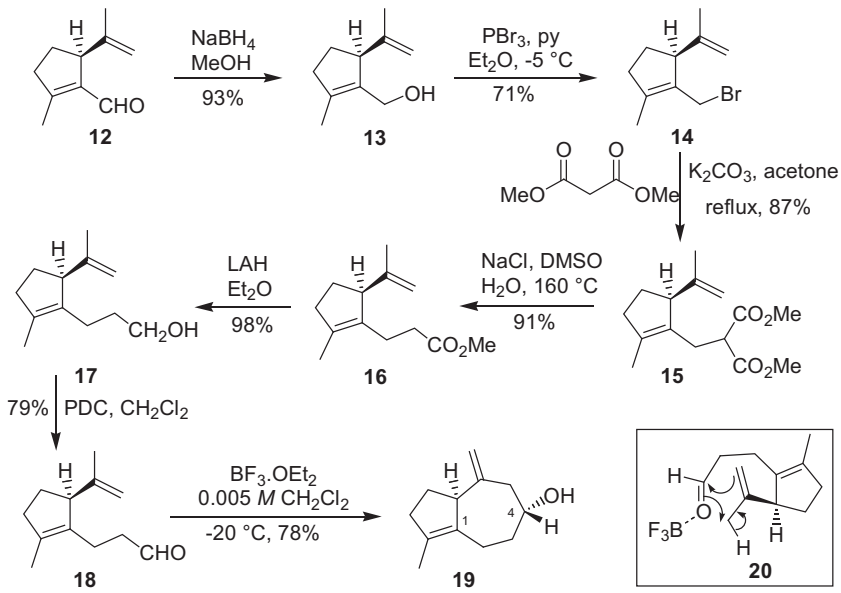
Prior to the synthesis of aciphyllenes, to test the feasibility of the strategy, a model study was investigated for the enantiospecific synthesis of bicyclo[5.3.0]decanol **10** (R=H), Scheme 3. Sodium borohydride reduction of the cyclopentene aldehyde **12** in methanol generated the allylic alcohol **13** in 93% yield, which was treated with phosphorous tribromide in ether in the presence of a catalytic amount of pyridine at −5 °C to furnish the allyl bromide **14**.[13] Two carbon chain extension of the bromide **14** was then carried out by



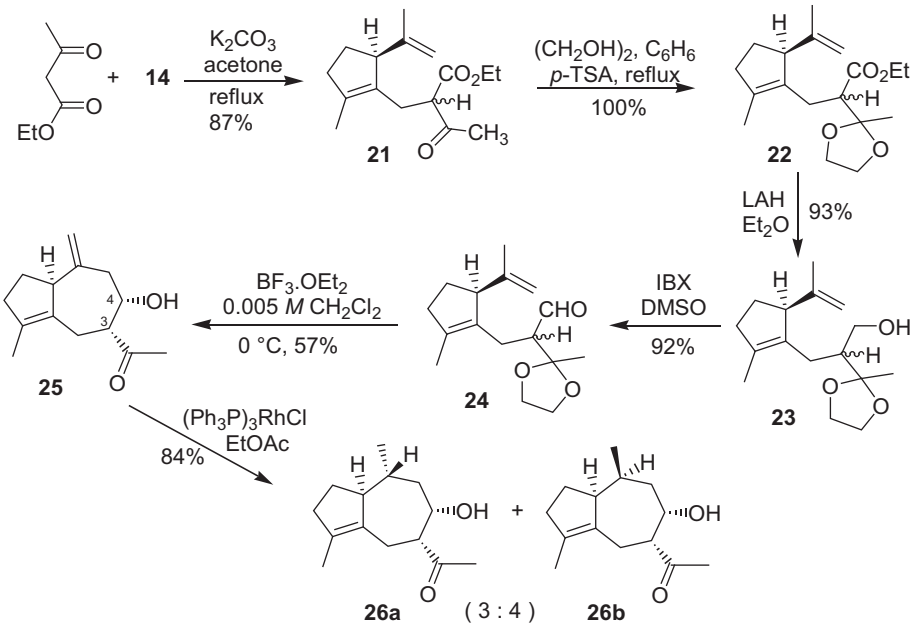
Scheme 2.

using dimethyl malonate. Thus, alkylation of dimethyl malonate with the allyl bromide **14** in refluxing acetone using potassium carbonate as the base furnished the malonate ester **15** in 87% yield. Krapcho's dealkoxycarbonylation reaction[14] of the malonate **15** with sodium chloride, dimethyl sulfoxide, and water in a sealed tube for 12 h at 160 °C furnished the ester **16** in 91% yield. Reaction of the ester **16** with lithium aluminum hydride (LAH) in anhydrous ether furnished the alcohol **17** in 98% yield, which on oxidation with pyridinium dichromate (PDC) in methylene chloride furnished the aldehyde **18**. After exploring various conditions, it was found that the intramolecular type II carbonyl ene reaction proceeds with boron trifluoride etherate. Thus, treatment of a 0.005 M methylene chloride solution of the aldehyde **18** with a catalytic amount of boron trifluoride diethyl etherate for 10 min at −20 °C resulted in the formation of the bicyclic alcohol[15] **19** in 78% yield, in a stereoselective manner, whose structure was established from its spectral data. The stereochemistry at the newly created chiral center was tentatively assigned as 4*R* on the basis of the preferred[12] transition state geometry, cf. **20**.

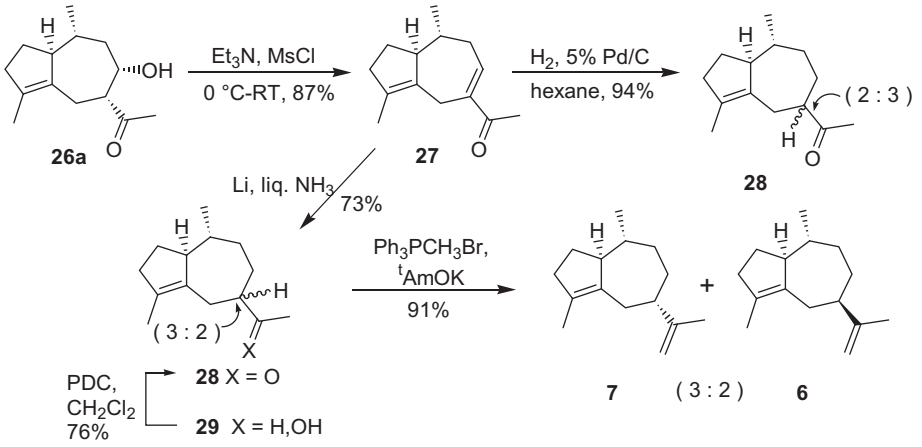
After successfully demonstrating the feasibility of the strategy, it has been extended to the synthesis of aciphyllenes **1**, **5**–**7** starting from the allyl bromide **14**, Schemes 4–6. Alkylation of ethyl acetoacetate with the allyl bromide **14** in refluxing acetone using potassium carbonate as the base furnished a diastereomeric mixture of the β-ketoester **21** in 87% yield, whose structure was revealed from its spectral data. Since the β-ketoesters are prone to equilibrium, no attempt was made to separate the two diastereomers of the ketoester **21**. In order to avoid chemoselectivity problems in



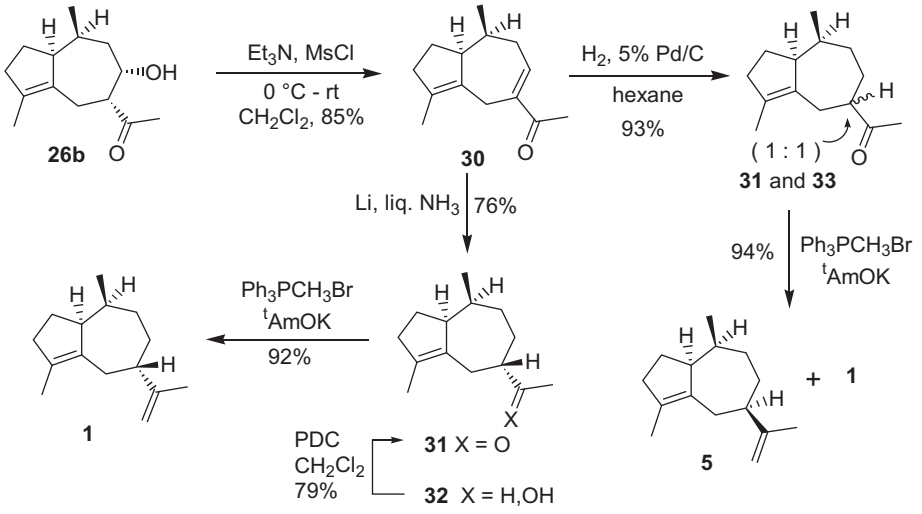
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

subsequent reactions, the keto group in the ketoester **21** was protected as its ethylene ketal by refluxing with 1,2-ethanediol in the presence of a catalytic amount of *p*-toluenesulphonic acid (*p*-TSA) in anhydrous benzene using a Dean–Stark water separator to furnish the ketal-ester **22** in quantitative yield. Regioselective reduction of the ketal-ester **22** with LAH in anhydrous ether at 0 °C furnished an epimeric mixture of the alcohol **23**, in 93% yield, which on oxidation with IBX in DMSO at rt furnished a diastereomeric mixture of the aldehyde **24** in 92% yield. Treatment of a 0.005 M solution of the aldehyde **24** in anhydrous methylene chloride with a catalytic amount of boron trifluoride diethyl etherate at 0 °C for 10 min furnished the bicyclic alcohol **25** in 57% yield, whose structure was assigned on the basis of the spectral data. It was found that the ketal group also got deprotected under the reaction conditions. As in the model study, the reaction proceeded in a highly stereoselective manner and generated mainly one isomer, and presumably during the hydrolysis of the ketal, the C-3 center also isomerised to thermodynamically preferred configuration via chelation of one of the oxygens of the ketal oxygen with boron. Although both the chiral centres (C-3 and 4) in **25** will become achiral at a later stage, tentative stereochemistry 3*R*,4*S* was assigned on the basis of the model study and it was confirmed in the next step.

Next, conversion of the bicyclic hydroxy ketone **25** into aciphyllenes **1**, **5**–**7** was investigated. For which, three transformations were required, namely, selective reduction of the *exo* methylene group, deoxygenation of the hydroxy group, and Wittig methylenation of the acetyl group. They were addressed in the same sequence. Since reaction was not selective with palladium over carbon as the catalyst, Wilkinson's catalyst was chosen for the hydrogenation. Thus, regioselective hydrogenation of the *exo* methylene group in the hydroxy ketone **25** at rt with 1.5 mol % Wilkinson's catalyst in dry ethyl acetate at one atmospheric pressure of hydrogen (balloon) for 15 h furnished a 3:4 mixture of the alcohols **26a** and **26b** in 84% yield, which were separated by column chromatography on silica gel. The structures of the compounds **26a** and **26b** were deduced from their spectral data. The stereochemistry at the newly created chiral center C-6 in the hydroxy ketones **26a** and **26b** was assigned tentatively on the basis of the preferred approach of the hydrogen from the less hindered side. It was further confirmed by the single crystal X-ray diffraction analysis of the hydroxy ketone **26a** (details are given in the Experimental section), the ORTEP diagram is depicted in Figure 1, which also confirmed the stereochemistry at the C-3 and C-4 carbons also of the alcohols **25** and **26b**.

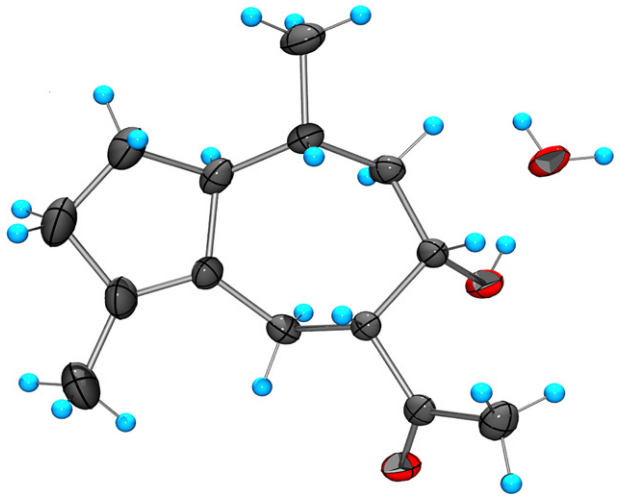


Figure 1. ORTEP diagram of the hydroxy ketone **26a**.

For the deoxygenation of the hydroxy group, a dehydration followed by reduction of the resultant enone was contemplated. First, the sequence was carried out with the minor hydroxy ketone **26a** to generate the diastereomers **6** and **7** of aciphyllene. Reaction of the β-hydroxy ketone **26a** with an excess of methanesulphonyl chloride and triethylamine in anhydrous methylene chloride at rt furnished the enone **27** in 87% yield. For the selective reduction of the enone double bond of the bicyclic dienone **27**, first one electron transfer reduction was explored. Thus, regioselective reduction of the bicyclic enone **27** in THF with lithium in liquid ammonia furnished a 3:2 mixture of ketone **28** along with the diastereomeric mixture of the alcohol **29**, which was treated with PDC in methylene chloride to furnish a 3:2 mixture of the ketone **27**. A controlled hydrogenation was also explored for selective reduction of the enone **28**. Thus, regioselective hydrogenation of the dienone **27** in hexane at rt using 5% palladium over carbon as the catalyst at one atmospheric pressure of hydrogen (balloon) furnished a 2:3 diastereomeric mixture of the ketone **28** in 94% yield. Wittig methylenation[16] of a 3:2 diastereomeric mixture of the ketone **28** with methylenetriphenylphosphorane in dry benzene at rt furnished a 2:3 mixture of 6-epiaciphyllene **6** and *ent*-7-epiaciphyllene **7** in 91% yield, which were found to be inseparable by column chromatography on silica gel as well as on silver nitrate impregnated silica gel. The structures of **6** and **7** were established from the spectral data of the mixture. The ^{1}H and ^{13}C NMR spectra of the minor guaiadiene **6** obtained in the Wittig reaction of **28** was found to be identical with that reported by Pedro and co-workers, confirming the stereostructures of 6- and 7-epiaciphyllenes **6** and **7**.

Next, for the synthesis of aciphyllene **5** and its C-3 epimer **1**, the sequence was carried out with the C-6 epimeric β-hydroxy ketone **26b**. Reaction of the β-hydroxy ketone **26b** with an excess of methanesulphonyl chloride and triethylamine in methylene chloride at rt furnished the enone **30** in 85% yield. Regiospecific reduction of the bicyclic enone **30** in THF with lithium in liquid ammonia furnished the ketone **31** in a highly stereoselective manner (>95%), along with the over reduced product **32**, which on oxidation with PDC in methylene chloride also furnished the ketone **31**. Wittig methylenation of the ketone **31** with methylenetriphenylphosphorane in dry benzene at rt gave 3-epiaciphyllene **1** in 92% yield. The structure of **1** was confirmed by comparing the ^{1}H and ^{13}C NMR spectral data with that reported[10] by Pedro and co-workers. The synthetic sample exhibited optical rotation value {$[\alpha]_D^{27}$ +13.5 (*c* 1.3, $CHCl_3$)} comparable to that reported by Pedro and co-workers. {lit.[10] $[\alpha]_D^{24}$ −13.2 (*c* 0.35, $CHCl_3$)}, as expected, with opposite sign (synthesis of **1** by Pedro and co-workers resulted in the compound with *R* configuration at C-7 position, which is enantiotopic to that in natural aciphyllene **5**). Regioselective hydrogenation of the enone **30** in hexane at rt using 5% palladium over carbon as the catalyst at one atmospheric pressure of hydrogen (balloon) for 30 min furnished a 1:1 mixture of the ketones **31** and **33** in 93% yield. Wittig methylenation of a mixture of the ketones **31** and **33** with methylenetriphenylphosphorane in dry benzene at rt furnished a 1:1 mixture of 3-epiaciphyllene **1** and aciphyllene **5** in 94% yield, which were separated by column chromatography using silver nitrate impregnated silica gel. The structure and absolute configuration of aciphyllene **5** obtained in this study was confirmed by comparing the ^{1}H and ^{13}C NMR spectral data and optical rotation {$[\alpha]_D^{26}$ +50.7 (*c* 1.4, $CHCl_3$), lit. $[\alpha]_D^{24}$ +52.2 (*c* 0.53, $CHCl_3$)} with that of (+)-aciphyllene **5** reported[10] by Pedro and co-workers.

3. Conclusions and summary

Enantiospecific syntheses of aciphyllenes **1**, **5**–**7** have been accomplished employing a chiron based approach. As a model study,

an intramolecular type II carbonyl ene reaction based strategy was developed for the enantiospecific synthesis of the bicyclo[5.3.0] decanol **19**, starting from the readily available monoterpene (*R*)-limonene. The strategy has been further extended to the enantiospecific syntheses of aciphyllenes **1**, **5**–**7** via the hydroxy ketones **26a** and **26b**. A single crystal X-ray diffraction analysis of the hydroxy ketone **26a** established the stereochemistry of all the compounds. Further extrapolation of the present strategy to other related guaiane sesquiterpenes is under progress.

4. Experimental section

4.1. General

Melting points are recorded using Buchi B-540 and M-560 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Jasco FTIR 410 and Perkin–Elmer FTIR spectrum BX and GX spectrophotometers. ^{1}H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were recorded on JNM λ-300 and Brucker Avance 400 spectrometers, using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for 1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 and Jasco P-1020 polarimeters and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^1. Hydrogenation reactions at one atmospheric pressure were carried out using a balloon filled with hydrogen. Analytical thin-layer chromatography (TLC) was performed on glass plates (7.5×2.5 and 7.5×5.0 cm) coated with Acme's silica gel G containing 13% calcium sulfate as binder and various combinations of ethyl acetate/hexane and methylene chloride/hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapor. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). All small-scale dry reactions were carried out using standard syringe-septum technique. Low temperature reactions were carried out using a bath made of sodium chloride and ice, or alcohol and liquid nitrogen. Dry THF was obtained by distillation over sodium/benzophenone ketyl. Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry dichloromethane was prepared by distillation over phosphorous pentoxide or calcium hydride. Dry benzene was obtained by distillation over sodium. Liquid ammonia was obtained in cylinders from Mysore Ammonia Ltd. and distilled over sodamide prior to use.

*4.1.1. (S)-2-Bromomethyl-3-isopropenyl-1-methylcyclopent-1-ene (**14**).* To a magnetically stirred solution of the allyl alcohol[11a,17] **13** (608 mg, 4 mmol) in anhydrous ether (6 mL) was added a catalytic amount of pyridine (10 mg) and cooled to −5 °C. PBr_3 (0.19 mL, 2 mmol) was slowly added to the reaction mixture over a period of 15 min and stirred for 1 h at the same temperature in an argon atmosphere. The reaction mixture was then poured into ice-cold water (5 mL) and extracted with ether (3×8 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using hexane as eluent furnished the bromide[13] **14** (604 mg, 71%) as yellow oil. R_f (hexane) 0.9; $[\alpha]_D^{23}$ +121.7 (*c* 4.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3073, 2963, 2915, 2842, 1664, 1644, 1449, 1438, 1373, 1200, 893 (C=CH_2), 631, 605; ^{1}H NMR (400 MHz): δ 4.77 (1H, s) and 4.75 (1H, s) [C=CH_2], 4.12 and 3.76 (2H, 2×d, *J* 9.7 Hz, CH_2Br), 3.55 (1H, br s, H-3), 2.45–2.25 (2H, m), 2.15–2.00 (1H, m), 1.75–1.65 (1H, m), 1.77 (3H, s) and 1.60 (3H, s) [2×olefinic–CH_3]; ^{13}C NMR (100 MHz): δ 146.8 (C, *C*=CH_2), 141.6 (C), 132.9 (C), 111.8 (CH_2, C=*C*H_2), 54.2 (CH, C-3), 37.9 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 18.7 (CH_3), 14.4 (CH_3).

*4.1.2. Dimethyl 2-[((5S)-5-isopropenyl-2-methylcyclopent-1-en-1-yl) methyl]malonate (**15**).* To a magnetically stirred solution of the bromide **14** (125 mg, 0.58 mmol) in acetone (3 mL) were added K_2CO_3 (400 mg, 2.9 mmol) and dimethyl malonate (0.07 mL, 0.58 mmol), and refluxed for 15 h. Water (5 mL) was then added to the reaction mixture and extracted with ether (3×8 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:5) as eluent furnished the diester **15** (135 mg, 87%) as colorless oil. R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{27}$ +43.9 (*c* 7.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3073, 2954, 2845, 1755, and 1739 (OC=O), 1643, 1436, 1372, 1282, 1241, 1204, 1153, 1051, 1026, 892 (C=CH_2); ^{1}H NMR (400 MHz): δ 4.69 (1H, s) and 4.68 (1H, s) [C=CH_2], 3.70 (3H, s) and 3.65 (3H, s) [2×OCH_3], 3.46 (1H, dd, *J* 10.3 and 5.6 Hz, H-2), 3.28 (1H, br s, H-5′), 2.77 (1H, dd, *J* 13.7 and 10.5 Hz), 2.40–2.15 (3H, m), 2.00–1.90 (1H, m), 1.65–1.55 (1H, m), 1.64 (3H, s) and 1.55 (3H, s) [2×olefinic–CH_3]; ^{13}C NMR (100 MHz): δ 169.4 (C) and 169.3 (C) [2×OC=O], 147.5 (C, *C*=CH_2), 137.5 (C), 131.4 (C), 111.3 (CH_2, C=*C*H_2), 55.2 (CH_3) and 53.3 (CH_3) [2×OCH_3], 52.1 (CH, C-5′), 49.7 (CH, C-2), 37.5 (CH_2), 27.6 (CH_2), 26.1 (CH_2), 18.3 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* Calcd for $C_{15}H_{22}O_4Na$ (M+Na): 289.1416; found: 289.1415.

*4.1.3. Methyl 3-[(S)-5-isopropenyl-2-methylcyclopent-1-en-1-yl]propanoate (**16**).* To a solution of the malonate **15** (90 mg, 0.34 mmol) in DMSO (1 mL) and water (0.2 mL) was added NaCl (59 mg, 1.0 mmol) and heated in a sealed tube for 12 h at 160 °C. Water (5 mL) was added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:5) as eluent furnished the propanoate **16** (64 mg, 91%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{24}$ +113.9 (*c* 4.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3072, 2952, 2845, 1744 (OC=O), 1643, 1436, 1372, 1261, 1169, 1020, 891 (C=CH_2), 805; ^{1}H NMR (400 MHz): δ 4.70 (1H, s) and 4.68 (1H, s) [C=CH_2], 3.64 (3H, s, OCH_3), 3.29 (1H, br s, H-5′), 2.52–2.15 (5H, m), 2.10–1.90 (2H, m), 1.65–1.55 (1H, m), 1.67 (3H, s) and 1.57 (3H, s) [2×olefinic–CH_3]; ^{13}C NMR (100 MHz): δ 173.6 (C, C=O), 148.0 (C, *C*=CH_2), 135.1 (C), 134.1 (C), 110.9 (CH_2, C=*C*H_2), 55.6 (CH_3, OCH_3), 51.3 (CH, C-5′), 37.5 (CH_2), 32.4 (CH_2), 27.7 (CH_2), 22.2 (CH_2), 18.4 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* Calcd for $C_{13}H_{21}O_2$ (M+H): 209.1541; found: 209.1531.

*4.1.4. 3-[(S)-5-Isopropenyl-2-methylcyclopent-1-en-1-yl]propan-1-ol (**17**).* To a cold (0 °C), magnetically stirred solution of the ester **16** (60 mg, 0.29 mmol) in anhydrous ether (2 mL) was added LAH (38 mg, 1 mmol) and stirred for 1 h at rt. Ethyl acetate (0.5 mL) was added to the reaction mixture to consume excess LAH. The reaction was then quenched with 3 N HCl (6 mL) and extracted with ether (3×5 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the alcohol **17** (51 mg, 98%) as colorless oil. R_f (10% EtOAc/hexane) 0.3; $[\alpha]_D^{23}$ +130.3 (*c* 3.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3350 (OH), 3072, 2942, 2856, 1643, 1452, 1442, 1372, 1060, 1041, 889 (C=CH_2); ^{1}H NMR (400 MHz): δ 4.69 (1H, s) and 4.68 (1H, s) [C=CH_2], 3.70–3.50 (2H, m, H-1), 3.31 (1H, br s, H-5′), 2.40–2.10 (3H, m), 2.05–1.90 (1H, m), 1.85–1.75 (1H, m), 1.65–1.50 (4H, m), 1.67 (3H, s) and 1.57 (3H, s) [2×olefinic–CH_3]; ^{13}C NMR (100 MHz): δ 148.3 (C, *C*=CH_2), 135.6 (C), 134.0 (C), 110.7

(CH_2, C=CH_2), 62.9 (CH_2, CH_2OH), 55.8 (CH, C-5′), 37.5 (CH_2), 30.8 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 18.4 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* Calcd for $C_{12}H_{20}ONa$ (M+Na): 203.1413; found: 203.1414.

*4.1.5. 3-[(S)-5-Isopropenyl-2-methylcyclopent-1-en-1-yl]propanal (**18**).* To a magnetically stirred solution of the alcohol **17** (51 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1 mL) was added PDC (338 mg, 0.9 mmol) and stirred for 7 h at rt. The reaction mixture was then filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the aldehyde **18** (40 mg, 79%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{23}$ +133.4 (*c* 4.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3072, 2925, 2846, 2717 (H–C=O), 1728 (C=O), 1643, 1442, 1410, 1373, 1057, 891 (C=CH_2); ^{1}H NMR (400 MHz): δ 9.72 (1H, s, CHO), 4.70 (2H, s, C=CH_2), 3.29 (1H, br s, H-5′), 2.55–1.90 (7H, m), 1.70–1.50 (1H, m), 1.68 (3H, s) and 1.50 (3H, s) [2×olefinic–CH_3]; ^{13}C NMR (100 MHz): δ 202.1 (CH, HC=O), 147.9 (C, *C*=CH_2), 135.2 (C), 133.8 (C), 111.1 (CH_2, C=*C*H_2), 55.7 (CH, C-5′), 42.0 (CH_2, C-2), 37.5 (CH_2), 27.6 (CH_2), 19.5 (CH_2), 18.4 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* Calcd for $C_{12}H_{18}ONa$ (M+Na): 201.1256; found: 201.1249.

*4.1.6. (4R,7S)-10-Methyl-6-methylenebicyclo[5.3.0]dec-1(10)-en-4-ol (**19**).* To a cold (−20 °C) magnetically stirred solution of the aldehyde **18** (40 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (44 mL, 0.005 M) was added $BF_3{\cdot}OEt_2$ (5 mg) and stirred for 10 min at the same temperature. Saturated $NaHCO_3$ solution (8 mL) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×8 mL). The combined organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the alcohol **19** (31 mg, 78%) as colorless oil. R_f (10% EtOAc/hexane) 0.4; $[\alpha]_D^{26}$ −19.2 (*c*, 1.6 $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3441 (OH), 3073, 2926, 2854, 1638, 1439, 1382, 1079, 1056, 1029, 939, 893 (C=CH_2); ^{1}H NMR (400 MHz): δ 5.08 (1H, s) and 4.88 (1H, s) [C=CH_2], 3.96 (1H, br s, H-4), 3.36 (1H, br s, H-7), 2.50–1.70 (8H, m), 1.65 (3H, s, olefinic–CH_3), 1.50–1.20 (3H, m); ^{13}C NMR (100 MHz): δ 148.7 (C, C-6), 138.2 (C, C1), 134.3 (C, C-10), 116.6 (CH_2, C=*C*H_2), 66.9 (CH, C-4), 57.5 (CH, C-7), 39.4 (CH_2), 38.4 (CH_2), 37.9 (CH_2), 31.9 (CH_2), 21.2 (CH_2), 14.8 (CH_3); HRMS: *m*/*z* Calcd for $C_{12}H_{18}ONa$ (M+Na): 201.1255; found: 201.1255.

*4.1.7. Ethyl 2-[((S)-5-isopropenyl-2-methylcyclopent-1-en-1-yl)methyl]-3-oxobutanoate (**21**).* To a magnetically stirred solution of the bromide **14** (430 mg, 2.0 mmol) in acetone (4 mL) were added K_2CO_3 (1.38 g, 10 mmol) and ethyl acetoacetate (0.26 mL, 2.0 mmol), and refluxed for 9 h. Water (5 mL) was then added to the reaction mixture and extracted with ether (3×8 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the ketoester **21** (460 mg, 87%) as pale yellow oil. R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{27}$ +46.3 (*c* 2.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3187, 2966, 2944, 2842, 1734 (OC=O), 1718 (C=O), 1633, 1442, 1365, 1266, 1228, 1179, 1145, 1096, 1036, 891 (C=CH_2); ^{1}H NMR (400 MHz, mixture of two isomers): δ 4.72 (1H, s) and 4.70 (1H, s) [C=CH_2], 4.20–4.00 (2H, m, OC$H_2$$CH_3$), 3.53 and 3.51 (1H, dd, *J* 10.2 and 6.3 Hz, H-2), 3.35 and 3.20 (1H, br s, H-5″), 2.80–2.70 (1H, m), 2.40–2.10 (3H, m), 2.18 and 2.14 (3H, s, H-4), 2.05–1.90 (1H, m), 1.68–1.58 (1H, m), 1.66 (3H, s) and 1.56 (3H, s) [2×olefinic–CH_3], 1.26 and 1.24 (3H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, mixture of two isomers): δ 202.4 and 201.9 (C, C=O), 169.4 and 169.3 (C, OC=O), 147.6 and 147.5 (C, *C*=CH_2), 137.1 (C, C-1′), 131.7 and 131.6 (C, C-10′), 111.3 and 111.2 (CH_2, C=*C*H_2), 61.1 and 60.9 (CH_2, O*C*$H_2$$CH_3$), 57.8 and 57.1 (CH, C-2), 55.5 and 55.1 (CH, C-5"), 37.6 and 37.5 (CH_2), 28.7 and 28.5 (CH_3, *C*H_3C=O), 27.7 and 27.6 (CH_2), 25.7 and 25.4 (CH_2), 18.4 and 18.3 (CH_3), 14.2 and 14.1 (CH_3), 14.2 and 14.1 (CH_3, OCH_2CH_3); HRMS: *m*/*z* Calcd for $C_{16}H_{24}O_3Na$ (M+Na): 287.1623; found: 287.1613.

*4.1.8. Ethyl 3-[(S)-5-isopropenyl-2-methylcyclopent-1-en-1-yl]-2-(2-methyl-1,3-dioxolan-2-yl)propanoate (**22**).* To a solution of the ketoester **21** (528 mg, 2.0 mmol) in dry benzene (15 mL) were added ethylene glycol (0.33 mL, 6 mmol) and *p*-TSA (20 mg), and refluxed for 7 h using Dean–Stark apparatus. Aqueous $NaHCO_3$ (8 mL) was added to the reaction mixture and extracted with ether (3×8 mL). The combined ether extract was washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the ketal-ester **22** (616 mg, 100%) as colorless oil. R_f (10% EtOAc/hexane) 0.45; $[\alpha]_D^{24}$ +95.6 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3073, 2954, 1734 (OC=O), 1643, 1442, 1372, 1346, 1298, 1182, 1131, 1040, 950, 887 (C=CH_2); ^{1}H NMR (400 MHz, mixture of two isomers): δ 4.72 and 4.70 (1H, s) and 4.64 (1H, s) [C=CH_2], 4.20–3.80 (6H, m), 3.37 and 3.10 (1H, br s, H-5"), 2.85–2.55 (2H, m), 2.40–2.10 (3H, m), 2.00–1.85 (2H, m), 1.66 and 1.61 (3H, s), and 1.56 and 1.55 (3H, s) [2×olefinic–CH_3], 1.39 and 1.38 (3H, s, H-4), 1.24 and 1.19 (3H, t, *J* 7.1 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, mixture of two isomers): δ 172.6 and 172.1 (C, OC=O), 147.8 and 148.2 (C, *C*=CH_2), 135.9 and 135.7 (C, C-1′), 133.8 and 132.6 (C, C-2′), 111.0 and 110.7 (CH_2, C=*C*H_2), 109.8 and 109.6 (C, O–C–O), 64.7 and 64.6 (CH_2), 64.5 (CH_2), 60.2 and 60.0 (CH_2), 56.9 and 54.8 (CH, C-2), 52.8 and 51.2 (CH, C-5′), 37.6 and 37.4 (CH_2), 28.0 and 27.4 (CH_2), 25.7 and 25.5 (CH_2), 21.5 and 21.1 (CH_3), 18.1 and 18.7 (CH_3), 14.3 and 14.2 (CH_3), 14.1 (CH_3, OCH_2CH_3); HRMS: *m*/*z* Calcd for $C_{18}H_{28}O_4Na$ (M+Na): 331.1885; found: 331.1884.

*4.1.9. 3-[(S)-5-Isopropenyl-2-methylcyclopent-1-en-1-yl]-2-(2-methyl-1,3-dioxolan-2-yl)-propan-1-ol (**23**).* To a cold (0 °C), magnetically stirred solution of the ester **22** (616 mg, 2.0 mmol) in anhydrous ether (4 mL) was added LAH (152 mg, 4 mmol) and stirred for 2 h at rt. Ethyl acetate (0.5 mL) was added to the reaction mixture to consume excess LAH. The reaction was then quenched with 3 N HCl (6 mL) and extracted with ether (3×8 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:5) as eluent furnished the alcohol **23** (495 mg, 93%) as colorless oil. R_f (10% EtOAc/hexane) 0.35; $[\alpha]_D^{26}$ +115.9 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3535 (OH), 3070, 2941, 2892, 1643, 1441, 1377, 1211, 1140, 1090, 1048, 948, 889 (C=CH_2), 866; ^{1}H NMR (400 MHz, mixture of two isomers): δ 4.70 and 4.67 (2H, 2×s, C=CH_2), 4.10–3.80 (4H, m, O*C*H_2*C*H_2O), 3.60–3.10 (4H, m), 2.40–2.15 (2H, m, H-1), 2.05–1.80 (4H, m), 1.68 and 1.64 (3H, s), and 1.56 (3H, s) [2×olefinic–CH_3], 1.30 (3H, s, *tert*-CH_3); ^{13}C NMR (100 MHz, mixture of two isomers): δ 148.6 and 148.0 (C, *C*=CH_2), 135.8 and 135.4 (C, C-1′), 134.5 and 133.6 (C, C-10′), 112.9 (C, O–C–O), 111.0 and 110.9 (CH_2, C=*C*H_2), 64.5 and 64.4 (CH_2), 64.2 and 64.1 (CH_2), 63.2 and 62.4 (CH_2), 58.2 and 55.0 (CH, C-5′), 47.3 and 45.3 (CH, C-3), 37.7 and 37.5 (CH_2), 28.0 and 27.4 (CH_2), 24.4 and 24.0 (CH_2), 20.8 and 20.5 (CH_3), 18.6 and 18.2 (CH_3), 14.3 and 14.2 (CH_3); HRMS: *m*/*z* Calcd for $C_{16}H_{26}O_3Na$ (M+Na): 289.1781; found: 289.1780.

*4.1.10. 3-[(S)-5-Isopropenyl-2-methylcyclopent-1-en-1-yl]-2-(2-methyl-1,3-dioxolan-2-yl)propanal (**24**).* To a magnetically stirred solution of the alcohol **23** (495 mg, 1.86 mmol) in DMSO (3 mL) was added IBX (625 mg, 2.23 mmol) and stirred for 3 h at rt. Aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture and extracted with ether (3×8 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the aldehyde **24** (452 mg, 92%) as

colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{27}$ +71.4 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3072, 2949, 2888, 2844, 2730 (H–C=O), 1727 (HC=O), 1643, 1442, 1379, 1212, 1153, 1086, 1045, 948, 890 (C=CH_2); ^1H NMR (400 MHz, mixture of two isomers): δ 9.61 and 9.46 (1H, d, *J* 3.8 Hz, H–C=O), 4.75–4.60 (2H, m, C=*C*H_2), 4.10–3.85 (4H, m, OCH_2CH_2O), 3.24 and 3.13 (1H, br s, H-5′), 2.75–2.55 (1H, m, H-2), 2.40–2.15 (3H, m), 2.05–1.85 (2H, m), 1.65–1.55 (1H, m), 1.66 (3H, s) and 1.54 (3H, s) [2×olefinic–CH_3], 1.28 (3H, s, H-4); ^{13}C NMR (100 MHz, mixture of two isomers): δ 202.5 and 202.1 (CH, HC=O), 148.1 and 147.7 (C, *C*=CH_2), 136.1 and 135.9 (C, C-1′), 133.4 and 132.0 (C, C-10′), 111.2 and 111.1 (CH_2, C=*C*H_2), 109.6 and 109.5 (C, C-3), 64.7 and 64.6 (CH_2), 64.6 (CH_2), 59.6 and 57.7 (CH, C-2), 56.7 and 55.0 (CH, C-5′), 37.5 and 37.4 (CH_2), 27.9 and 27.4 (CH_2), 22.7 and 22.5 (CH_3), 22.2 and 22.1 (CH_2), 18.6 and 18.3 (CH_3), 14.3 and 14.2 (CH_3); HRMS: *m*/*z* Calcd for $C_{16}H_{24}O_3Na$ (M+Na): 287.1624; found: 287.1613.

*4.1.11. (3R,4S,7S)-3-Acetyl-10-methyl-6-methylenebicyclo[5.3.0]dec-1(10)-en-4-ol (**25**).* To a cold (0 °C), magnetically stirred solution of the aldehyde **24** (264 mg, 1 mmol) in anhydrous CH_2Cl_2 (200 mL, 0.005 M) was added $BF_3{\cdot}Et_2O$ (5 mg) and stirred for 10 min at the same temperature. Saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3×8 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent furnished the bicyclic hydroxy ketone **25** (150 mg, 57%) as colorless oil. R_f (20% EtOAc/hexane) 0.5; $[\alpha]_D^{25}$ +66.4 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3518 (OH), 2924, 2851, 1707 (C=O), 1645, 1444, 1350, 1276, 1159, 1096, 1015, 897 (C=CH_2), 779; ^1H NMR (400 MHz): δ 5.10 (1H, s) and 4.90 (1H, s) [C=CH_2], 4.35 (1H, br s, H-4), 3.41 (1H, br s, C-7), 2.55–2.35 (3H, m), 2.35–2.10 (4H, m), 2.24 (3H, s, CH_3C=O), 2.02 (1H, dt, *J* 14.2 and 7.7 Hz, H-3), 1.91 (1H, t, *J* 13.2 Hz), 1.65 (3H, s, olefinic–CH_3), 1.55–1.35 (1H, m); ^{13}C NMR (100 MHz): δ 209.4 (C, C=O), 146.5 (C, C-6), 135.1 (C), 134.9 (C), 116.5 (CH_2, C=*C*H_2), 66.7 (CH, C-4), 60.0 (CH, C-3), 56.6 (CH, C-7), 37.9 (CH_2), 37.0 (CH_2), 31.0 (CH_2), 28.3 (CH_3, *C*H_3C=O), 21.5 (CH_2), 14.1 (CH_3, C_{10}–CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{20}O_2Na$ (M+Na): 243.1361; found: 243.1358.

*4.1.12. (3R,4S,6R,7S)-3-Acetyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-en-4-ol (**26a**) and (3R,4S,6S,7S)-3-acetyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-en-4-ol (**26b**).* Wilkinson's catalyst (9 mg, 1.5 mol %) was added to a magnetically stirred solution of the hydroxy ketone **25** (150 mg, 0.68 mmol) in dry ethyl acetate (1 mL) and stirred for 15 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon). The catalyst was then filtered off through a short silica gel column using ethyl acetate/hexane (1:4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as eluent first furnished the (6*S*,7*S*)-isomer **26b** (72 mg, 48%) as colorless oil. R_f (20% EtOAc/hexane) 0.52; $[\alpha]_D^{26}$ +173.7 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3468 (OH), 2953, 2918, 2873, 1700 (C=O), 1455, 1440, 1380, 1357, 1307, 1265, 1165, 1050, 962, 865; ^1H NMR (400 MHz): δ 4.17 (1H, s), 3.32 (1H, s), 2.95–2.70 (2H, m), 2.60–1.90 (5H, m), 2.21 (3H, s, CH_3C=O), 1.90–1.20 (4H, m), 1.65 (3H, s, olefinic–CH_3), 0.85 (3H, d, *J* 7.2 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 212.5 (C, C=O), 138.2 (C, C-1), 133.1 (C, C-10), 67.9 (CH, C-4), 59.2 (CH, C-3), 52.4 (CH, C-7), 36.4 (CH_2), 36.1 (CH_2), 28.9 (CH, C-6), 25.5 (CH_2), 25.4 (CH_3, *C*H_3C=O), 22.0 (CH_2), 19.5 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517; found: 245.1505.

Further elution of the column using ethyl acetate/hexane (1:5) as eluent furnished the (6*R*,7*S*)-isomer **26a** (54 mg, 36%) as a solid, which was recrystallised along with one molecule of water from a mixture of ethyl acetate and hexane. Mp 74.5–76.5 °C; R_f (20% EtOAc/hexane) 0.48; $[\alpha]_D^{26}$ +129.1 (*c* 4.3, $CHCl_3$); IR (KBr): ν_{max}/cm^{-1} 3422 (OH), 2954, 2924, 2858, 2835, 2803, 1694 (C=O), 1463, 1438, 1373, 1277, 1250, 1202, 1188, 1166, 1139, 1025, 964, 934; ^1H NMR (400 MHz): δ 4.08 (1H, br s, H-4), 2.88 (1H, br s, H-3), 2.71 (1H, ddd, *J* 9.1, 6.8, and 2.9 Hz, H-7), 2.54 (1H, d, *J* 15.2 Hz), 2.36 (1H, dd, *J* 15.2 and 9.2 Hz), 2.30–2.10 (2H, m), 2.17 (3H, s, CH_3C=O), 1.99 (1H, dt, *J* 12.3 and 7.1 Hz), 1.89 (1H, dd, *J* 13.8 and 5.6 Hz), 1.80–1.60 (2H, m), 1.64 (3H, s, olefinic–CH_3), 1.35–1.20 (2H, m), 0.92 (3H, d, *J* 6.6 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 211.9 (C, C=O), 136.4 (C, C-1), 133.0 (C, C-10), 71.5 (CH, C4), 57.3 (CH, C-3), 54.9 (CH, C-7), 43.3 (CH_2, C-2), 36.4 (CH_2), 35.2 (CH, C-6), 29.9 (CH_2), 29.1 (CH_3), 23.1 (CH_2), 21.8 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517; found: 245.1516.

*4.1.13. X-ray data for the compound **26a** monohydrate.* X-ray data were collected at 295 K on an SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods (SIR 92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms were refined isotropically. Mol. For. $C_{14}H_{24}O_3$; MW=240.44; colorless; Crystal system: Monoclinic; Space group *P* 2 1; cell parameters, *a*=5.1049(3) Å, *b*=7.7340(3) Å, *c*=18.0134 (9) Å; α 90, β 93.23(5), γ 90, *V*=710.08(6) $Å^3$, *Z*=2, D_c=1.124 g cm^{-3}, *F*(000)=264, μ=0.094 mm^{-1}. Total number of least square refinement parameters=160, *R*1=0.0472 for 1775 $F_0 > 2\sigma(F_0)$ and 0.0930 for all 3041 data. *wR*2=0.0958, GOF=0.890, restrained GOF=0.890 for all data. An ORTEP diagram is depicted in Figure 1. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 783504).

*4.1.14. 1-[(6R,7S)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl] ethanone (**27**).* To a cold (0 °C), magnetically stirred solution of the hydroxy ketone **26a** (54 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2 mL) were added Et_3N (0.18 mL, 1.3 mmol) and MsCl (0.10 mL, 1.3 mmol), and stirred for 6 h at rt 3 N HCl (8 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3×6 mL). The combined organic layer was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the enone **27** (43 mg, 87%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{27}$ +17.5 (*c* 2.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3048, 2952, 2928, 2871, 2841, 1667 (C=O), 1638, 1456, 1376, 1342, 1299, 1260, 1234, 1165, 956, 896; ^1H NMR (400 MHz): δ 6.95 (1H, t, *J* 7.3 Hz, H-4′), 3.82 and 2.49 (2H, 2×d, *J* 14.6 Hz, H-2′), 2.45–2.30 (2H, m), 2.28 (3H, s, CH_3C=O), 2.28–2.00 (5H, m), 1.65 (3H, s, olefinic–CH_3), 1.45–1.20 (2H, m), 1.00 (3H, d, *J* 6.6 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 197.3 (C, C=O), 143.6 (C), 143.0 (CH, C-4′), 132.4 (C), 132.0 (C), 58.7 (CH, C-7′), 38.4 (CH, C-6′), 36.0 (CH_2), 35.5 (CH_2), 29.1 (CH_2), 24.9 (CH_3, *C*H_3C=O), 23.6 (CH_2), 22.4 (CH_3), 14.0 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412; found: 227.1405.

*4.1.15. 1-[(6R,7S)-6,10-Dimethylbicyclo[5.3.0]dec-1(10)-en-3-yl] ethanones (**28**).* Lithium metal (14 mg, 2 mmol) was added to freshly distilled liquid ammonia (20 mL). To the resultant blue colored solution was added a solution of the enone **27** (43 mg, 0.19 mmol) in dry THF (1 mL) over a period of 5 min and the reaction mixture was slowly allowed to attain rt over a period of 1 h. Aqueous NH_4Cl (5 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (7 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:9) as eluent first furnished a 3:2 diastereomeric mixture of the ketone **28** (17 mg, 39%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{27}$ +66.5 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2950, 2924, 2858, 1711 (C=O), 1459, 1439, 1376, 1352, 1263, 1163, 1019, 954; ^1H NMR (400 MHz, mixture of two isomers): δ 2.60–2.50

(2H, m), 2.40–1.75 (6H, m), 2.16 (3H, s, CH_3C=O), 1.70–1.10 (5H, m), 1.62 and 1.60 (3H, s, olefinic–CH_3), 0.94 and 0.91 (3H, d, *J* 6.7 Hz, sec-CH_3); ^{13}C NMR (100 MHz, mixture of two isomers): δ 211.0 and 211.3 (C, C=O), 136.6 and 135.9 (C, C-1′), 132.8 and 133.6 (C, C-10′), 57.3 and 55.9 (CH), 50.4 and 51.1 (CH), 39.6 and 39.1 (CH, C-6′), 38.3 (CH_2), 36.5 and 36.3 (CH_2), 31.7 and 31.3 (CH_2), 29.9 and 29.8 (CH_2), 28.1 and 27.9 (CH_3, CH_3C=O), 27.7 and 26.9 (CH_2), 22.1 and 21.7 (CH_3), 13.9 and 14.4 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{22}ONa$ (M+Na): 229.1568; found: 229.1570.

Further elution of the column with CH_2Cl_2/hexane (1:5) furnished a mixture of the alcohol **29** (15 mg, 34%). To a magnetically stirred solution of the alcohol **29** in anhydrous CH_2Cl_2 (0.5 mL) was added PDC (150 mg, 0.4 mmol) and stirred for 8 h at rt. The reaction mixture was then filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:5) as eluent furnished a 3:2 diastereomeric mixture of the ketone **28** (12 mg, 76%) as colorless oil.

*4.1.16. Hydrogenation of the enone **27**.* To a magnetically stirred solution of the enone **27** (40 mg, 0.20 mmol) in hexane (1 mL) was added 5% Pd/C (12 mg) and stirred for 30 min at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon). The catalyst was then filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:5) as eluent furnished a 2:3 mixture of the bicyclic ketone **28** (38 mg, 94%) as colorless oil.

*4.1.17. (3S,6R,7S)-3-Isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-ene (ent-7-epiaciphyllene **7**) and (3R,6R,7S)-3-isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-ene (6-epiaciphyllene **6**).* To a magnetically stirred freshly prepared solution of ^{t}AmO^{-}K^{+} [prepared from potassium (58 mg, 1.50 mmol) and *tert*-amyl alcohol (3 mL), followed by evaporation of the excess *tert*-amyl alcohol under reduced pressure] in dry benzene (3 mL) was added methyltriphenylphosphonium bromide (640 mg, 1.80 mmol). The reaction mixture was stirred for 30 min at rt and the resultant yellow colored solution was allowed to settle. The dark yellow colored supernatant solution of methylenetriphenylphosphorane was taken in a syringe and added to a magnetically stirred solution of a 3:2 diastereomeric mixture of the ketone **28** (30 mg, 0.15 mmol) in dry benzene (0.5 mL) and stirred for 1 h at rt. Water (5 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using hexane as eluent furnished a 3:2 mixture of *ent*-7-epiaciphyllene **7** and 6-epiaciphyllene **6** (27 mg, 91%) as colorless oil. R_f (hexane) 0.9; $[\alpha]_D^{27}$ +58.7 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3074, 2950, 2923, 2858, 1644, 1457, 1441, 1376, 1020, 887 (C=CH_2); ^{1}H NMR (400 MHz, $CDCl_3$, 3:2 mixture of **7** and **6**): δ 4.71 and 4.68 (1H, s) and 4.68 and 4.62 (1H, s) [C=CH_2], 2.55–1.80 (6H, m), 1.75–1.20 (7H, m), 1.75 and 1.74 (3H, s) and 1.63 and 1.61 (3H, s) [2×olefinic–CH_3], 0.96 (d, *J* 6.8 Hz) and 0.91 (d, *J* 6.5 Hz), [3H, sec-CH_3]; ^{13}C NMR (100 MHz, $CDCl_3$, peaks due to **6** and **7**): δ 152.5 and 151.3 (C, *C*=CH_2), 138.0 and 138.2 (C, C-1), 132.1 and 131.9 (C, C-10), 107.6 and 108.1 (CH_2, C=*C*H_2), 55.7 and 57.2 (CH, C-7), 45.2 and 45.1 (CH, C-3), 39.8 and 36.5 (CH_2), 39.2 (CH, C-6), 36.3 and 32.0 (CH_2), 36.1 and 31.1 (CH_2), 34.5 and 30.5 (CH_2), 30.1 and 30.2 (CH_2), 21.6 and 22.2 (CH_3), 20.3 and 20.6 (CH_3), 14.5 and 13.9 (CH_3).

*4.1.18. 1-[(6S,7S)-6,10-Dimethylbicyclo[5.3.0]deca-1(10),3-dien-3-yl] ethanone (**30**).* To a cold (0 °C), magnetically stirred solution of the hydroxy ketone **26b** (72 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (2 mL) were added Et_3N (0.22 mL, 1.6 mmol) and MsCl (0.12 mL, 1.6 mmol), and stirred for 7 h at rt. 3 N HCl (8 mL) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×6 mL). The combined organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:19) as eluent furnished the bicyclic enone **30** (56 mg, 85%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{26}$ +297 (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2955, 2928, 2877, 2841, 1666 (C=O), 1635, 1440, 1379, 1349, 1258, 1232, 1174, 1019; ^{1}H NMR (400 MHz): δ 6.77 (1H, br s, H-4′), 3.75 and 2.45 (2H, 2×d, *J* 16.0 Hz, H-2′), 2.86 (1H, br s, H-7′), 2.40–2.10 (6H, m), 2.28 (3H, s, CH_3C=O), 1.90–1.80 (1H, m), 1.59 (3H, s, olefinic–CH_3), 1.60–1.40 (2H, m), 0.82 (3H, d, *J* 6.9 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 198.2 (C, C=O), 142.7 (CH, C-4′), 142.2 (C), 133.4 (C), 132.8 (C), 54.5 (CH, C-7′), 36.9 (CH_2), 33.7 (CH, C6′), 32.8 (CH_2), 25.3 (CH_3, CH_3C=O), 24.9 (CH_2), 24.3 (CH_2), 16.5 (CH_3), 13.8 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{20}ONa$ (M+Na): 227.1412; found: 227.1422.

*4.1.19. 1-[(3S,6S,7S)-6,10-Dimethylbicyclo[5.3.0]dec-1(10)-en-3-yl] ethanone (**31**).* Lithium metal (14 mg, 2 mmol) was added to magnetically stirred freshly distilled (over sodamide) liquid ammonia (20 mL). To the resultant blue colored solution was added a solution of the enone **30** (56 mg, 0.27 mmol) in dry THF (1 mL) over a period of 5 min, and the reaction mixture was slowly allowed to attain rt over a period of 1 h. Aqueous NH_4Cl (5 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:9) as eluent first furnished the ketone **31** (15 mg, 25%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{28}$ +97.0 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2954, 2924, 2871, 2856, 1711 (C=O), 1455, 1376, 1353, 1266, 1158, 1100, 1019; ^{1}H NMR (400 MHz): δ 2.76 (1H, br s), 2.56 (1H, d, *J* 13.4 Hz), 2.35–1.20 (11H, m), 2.17 (3H, s, CH_3C=O), 1.65 (3H, s, olefinic–CH_3), 0.90 (3H, d, *J* 7.2 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 211.6 (C, C=O), 137.5 (C, C-1′), 135.5 (C, C10′)-, 55.4 (CH), 52.7 (CH), 36.2 (CH_2), 35.8 (CH), 32.7 (CH_2), 29.6 (CH_2), 28.1 (CH_3, CH_3C=O), 27.9 (CH_2), 25.3 (CH_2), 19.7 (CH_3), 13.8 (CH_3); HRMS: *m*/*z* Calcd for $C_{14}H_{22}ONa$ (M+Na): 229.1568; found: 229.1560.

Further elution of the column with CH_2Cl_2/hexane (1:5) gave a diastereomeric mixture of the alcohol **32** (29 mg, 51%) as colorless oil. To a magnetically stirred solution of a mixture of the secondary alcohol **32** (29 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added PDC (263 mg, 0.7 mmol) and stirred for 8 h at rt. The reaction mixture was then filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2/hexane (1:5) as eluent furnished the ketone **31** (23 mg, 79%) as colorless oil.

*4.1.20. (3S,6S,7S)-3-Isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-ene (3-epiaciphyllene **1**).* To a magnetically stirred freshly prepared solution of ^{t}AmO^{-}K^{+} [prepared from potassium (23 mg, 0.6 mmol) and *tert*-amyl alcohol (1 mL) followed by evaporation of the excess *tert*-amyl alcohol under reduced pressure] in dry benzene (2 mL) was added methyltriphenylphosphonium bromide (285 mg, 0.8 mmol). The reaction mixture was stirred magnetically for 30 min at rt. The resultant yellow colored solution was allowed to settle. The dark yellow colored supernatant solution of methylenetriphenylphosphorane was taken in a syringe and added to a magnetically stirred solution of the ketone **31** (11 mg, 0.13 mmol) in dry benzene (0.5 mL) and stirred for 1 h at rt. Water (5 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using hexane as eluent furnished 3-epiaciphyllene **1** (10 mg, 92%) as colorless oil. R_f

(hexane) 0.9; $[\alpha]_D^{27}$ +13.5 (*c* 1.3, $CHCl_3$); {lit.[10] $[\alpha]_D^{24}$ −13.2 (*c* 0.35, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 3080, 2954, 2919, 2871, 2855, 1643, 1454, 1375, 1019, 886 (C=CH_2); ^{1}H NMR (400 MHz): δ 4.69 (1H, s) and 4.65 (1H, s) [C=CH_2], 2.77 (1H, br s), 2.44 (1H, d, *J* 11.2 Hz), 2.26–2.14 (1H, m), 2.10 (1H, dd, *J* 11.2 and 8.8 Hz), 2.00–1.66 (5H, m), 1.74 (3H, s) and 1.63 (3H, s) [2×olefinic–CH_3], 1.45–1.20 (3H, m), 0.89 (3H, d, *J* 7.2 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 151.7 (C, *C*=CH_2), 139.2 (C, C-1), 132.6 (C, C10), 108.0 (CH_2, C=*C*H_2), 52.9 (CH), 50.2 (CH), 36.7 (CH_2), 36.2 (CH_2), 36.1 (CH, C-6), 31.7 (CH_2), 30.0 (CH_2), 25.2 (CH_2), 20.6 (CH_3), 20.1 (CH_3), 13.8 (CH_3).

*4.1.21. 1-[(3S,6S,7S)-6,10-Dimethylbicyclo[5.3.0]dec-1(10)-en-3-yl] ethanone (**31**) and 1-[(3R,6S,7S)-6,10-dimethylbicyclo[5.3.0]dec-1 (10)-en-3-yl]ethanone (**33**).* To a magnetically stirred solution of the enone **31** (30 mg, 0.15 mmol) in hexane (1 mL) was added 5% Pd/C (7 mg) and stirred for 30 min at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon). The catalyst was then filtered through a short silica gel column using CH_2Cl_2. Evaporation of the solvent and purification of the residue using CH_2Cl_2/hexane (1:5) as eluent furnished a 1:1 mixture of the bicyclic ketones **31** and **33** (28 mg, 93%) as colorless oil. R_f (10% EtOAc/hexane) 0.7; $[\alpha]_D^{25}$ +103.7 (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2951, 2924, 2871, 1710 (C=O), 1442, 1378, 1353, 1161, 1019; ^{1}H NMR (400 MHz, mixture of **31** and **33**): δ 2.87 and 2.75 (1H, br s), 2.60–2.30 (1H, m), 2.30–2.05 (4H, m), 2.14 (3H, s, CH_3C=O), 2.00–1.80 (3H, m), 1.80–1.70 (2H, m), 1.63 and 1.58 (3H, s, olefinic–CH_3), 1.55–1.20 (4H, m), 0.89 and 0.76 (3H, d, *J* 7.1 Hz, sec-CH_3); ^{13}C NMR (100 MHz, mixture 3**1** and **33**): δ 211.4 and 211.2 (C, C=O), 137.5 and 133.9 (C), 133.4 (C), 55.4 and 53.1 (CH), 52.7 and 51.7 (CH), 37.4 and 36.3 (CH_2), 36.6 and 35.8 (CH, C-6), 36.2 and 32.7 (CH_2), 36.2 and 32.7 (CH_2), 30.9 and 29.6 (CH_2), 28.3 and 28.1 (CH_2), 28.0 and 27.9 (CH_3, CH_3C=O), 27.8 and 25.3 (CH_2), 19.7 and 14.2 (CH_3), 13.8 and 13.1 (CH_3).

*4.1.22. (3S,6S,7S)-3-Isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1 (10)-ene (3-epiaciphyllene **1**) and (3R,6S,7S)-3-isopropenyl-6,10-dimethylbicyclo[5.3.0]dec-1(10)-ene (aciphyllene **5**).* To a magnetically stirred freshly prepared solution of $^tAmO^-K^+$ [prepared from potassium (51 mg, 1.30 mmol) and *tert*-amyl alcohol (3 mL) followed by evaporation of the excess *tert*-amyl alcohol under reduced pressure] in dry benzene (3 mL) was added methyltriphenylphosphonium bromide (530 mg, 1.60 mmol). The reaction mixture was stirred for 30 min at rt and the resultant yellow colored solution was allowed to settle. The dark yellow colored supernatant solution of methylenetriphenylphosphorane was taken in a syringe and added to a magnetically stirred solution of a 1:1 mixture of the ketones **31** and **33** (27 mg, 0.13 mmol) in dry benzene (0.5 mL) at rt and stirred for 1 h. Water (5 mL) was then added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (8 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silver nitrate impregnated silica gel column using hexane as eluent first furnished 3-epiaciphyllene **1** (13 mg, 48%) as colorless oil, which exhibited all the spectral data identical to that of the sample obtained earlier. Further elution of the column with hexane gave aciphyllene **5** (12 mg, 46%) as colorless oil. R_f (hexane) 0.9; $[\alpha]_D^{26}$ +50.7 (*c* 1.4, $CHCl_3$); {lit.[10] $[\alpha]_D^{24}$ +52.2 (*c* 0.53, $CHCl_3$)}; IR (neat): ν_{max}/cm^{-1} 3072, 2920, 1644, 1448, 1378, 1019, 886; ^{1}H NMR (400 MHz): δ 4.64 (1H, s) and 4.60 (1H, s) [C=CH_2], 2.99–2.92 (1H, m), 2.42 (1H, br d, *J* 14.1 Hz), 2.30–1.40 (11H, m), 1.73 (3H, s) and 1.58 (3H, s) [2×olefinic–CH_3], 0.76 (3H, d, *J* 7.1 Hz, sec-CH_3); ^{13}C NMR (100 MHz): δ 152.8 (C, *C*=CH_2), 135.1 (C, C-1), 132.5 (C, C-10), 107.5 (CH_2, C=*C*H_2), 53.2 (CH, C-7), 45.7 (CH, C-3), 37.4 (CH_2), 37.0 (CH_2), 36.9 (CH, C-6), 35.1 (CH_2), 31.9 (CH_2), 28.5 (CH_2), 20.2 (CH_3), 14.1 (CH_3), 12.9 (CH_3).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.045.

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