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Enantiospecific approach to the tricyclic core structure of tricycloillicinone, ialibinones, and takaneones via ring-closing metathesis reaction

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ABSTRACT

Enantiospecific synthesis of the tricyclic core structure present in the biologically active natural products tricycloillicinone, ialibinones, and takaneones, starting from the readily available campholenaldehyde employing a transannular RCM reaction as the key step, has been accomplished.

1. Introduction

During a search for potent neurotropic substances from *Illicium tashiroi* collected from Ishigaki Island, Fukuyama and co-workers isolated a novel C_6–C_3 prenylated compound and named as tricycloillicinone **1** on the basis of its biogenetic relationship to illicinones. The tetracyclic structure of **1**, comprising of an interesting 3,4,4-trimethyltricyclo[5.3.1.0^{1,5}]-undecane **2**, which is isomeric to that present in cedranoid sesquiterpenes, was elucidated on the basis of extensive spectral studies.[1] It was found that **1** could significantly increase choline acetyltransferase (ChAT) activity in culture of P10 rat septal neurons. The tricyclic structure **2** was also present in two groups of acylphloroglucinoid natural products. In the traditional medicine of Papua New Guinea, leaves of the plant *Hypericum papuanum* Ridley are used for the treatment of sores, and its extract is known to exhibit antibacterial activity. In their search for the biologically active compounds, in 2001, Sticher and co-workers reported the bioassay guided isolation of five tricyclic acylphloroglucinol derivatives (along with several bicyclic derivatives) ialibinones A–E **3a–d** and **4**, and also their hydroxy derivatives **5a–c** from the petroleum ether extract of *H. papuanum* Ridley.[2] Compounds **3** and **5** showed good antibacterial activity against *Bacillus cereus*, *Staphylococcus epidermidis*, and *Micrococcus luteus*, and cytotoxic activity against KB cell line. Recent widespread interest in the antidepressant activity of *Hypericum* species led Takaishi and co-workers to investigate on the bioactive natural products from *H. sikokumontanum*, which resulted in the isolation of three tricyclic compounds takaneones A–C **6a–c**.[3] Takaneones **6b–c** showed almost equal cytotoxicities against both K562/Adr multi-drug resistant cancer cells as well as sensitive cell lines (e.g., KB and K 562).

2. Results and discussion

Presence of an interesting tricyclic carbon framework **2**, coupled with potential neurotropic properties made tricycloillicinone **1** a challenging synthetic target. So far there are three approaches reported in the literature.[4–6] First total synthesis of tricycloillicinone **1** in racemic form was reported by the research group of Danishefsky in 1998.[4] In 2003, Terashima and Furuya reported an enantioselective synthesis of tricycloillicinone **1**.[5] Very recently,[6] Danishefsky co-workers reported an improved biomimetic method for the generation of racemic tricycloillicinone **1** via illicinone A. In contrast, there is no report in the literature on either model studies or total synthesis of ialibinones and takaneones either in racemic or optically active forms. (*S*)-Campholenaldehyde **7** is a readily available cyclopentane based chiral starting material. It has been employed in the synthesis of a variety of industrially (fragrance) important monocyclic compounds.[7] However, it has been under utilized in the synthesis of polycyclic compounds in organic

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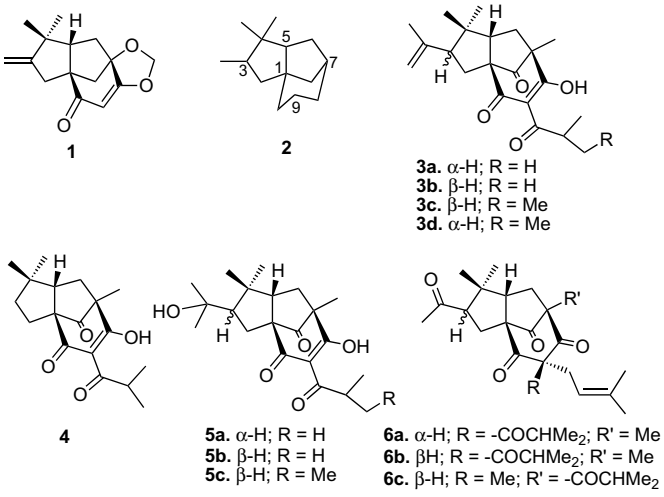


synthesis.[8] Recently, we have reported an efficient route for the enantiospecific conversion of (*S*)-campholenaldehyde **7** into diquinanes, e.g., **8**, employing an intramolecular rhodium carbenoid CH insertion reaction.[9] In continuation of our interest in the enantiospecific synthesis of polycyclic compounds starting from (*S*)-campholenaldehyde **7**, herein we report an enantiospecific approach to the tricyclic core structure present in the natural products tricycloillicinone, ialibinones, and takaneones employing a ring-closing metathesis (RCM) reaction as the key step.

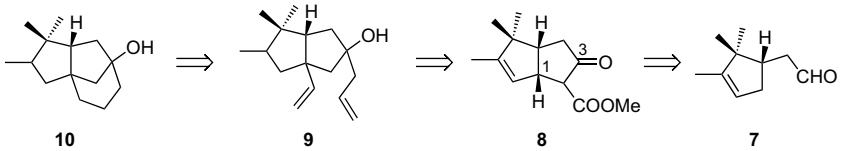
It was contemplated (Scheme 1) that an RCM reaction of the hydroxydiene **9**, containing *syn* oriented vinyl and allyl groups at the C-1 and C-3 carbons of a diquinane, could lead to the tricyclic system **10** containing an oxygen functionality at the C-7 carbon atom as in tricycloillicinone **1**. For the generation of the hydroxydiene **9**, the diquinane **8** was chosen as a suitable precursor, whose synthesis from campholenaldehyde **7** has already been developed.

The synthetic sequence starting from the β-ketoester **8**, which was prepared[9] from campholenaldehyde **7** in three steps employing an intramolecular rhodium carbenoid CH insertion[10] of the α-diazo-β-ketoester **11**, is depicted in Scheme 2. For the introduction of a vinyl group at the C-1 carbon of the diquinane **8** a cuprate based methodology[11] was conceived via the dienone **12**. For the introduction of the requisite olefin at C-1, a regioselective selenation-deselenation sequence was employed. Thus, reaction of the β-ketoester **8** with phenylselenyl chloride in the presence of pyridine in methylene chloride furnished the selenide **13** in 88% yield in a highly regio- and stereoselective manner, which on oxidation with 30% hydrogen peroxide at ice temperature furnished the requisite diene ester **12** in 90% yield. Reaction of the diene ester **12** with vinylmagnesium bromide in the presence of copper iodide in THF at low temperature furnished the vinylated β-ketoester **14** in 62% yield, which was found to exist predominantly in the enol form **14b**. Krapcho's decarboxylation[12] of the β-ketoester **14** with sodium chloride and DMSO in the presence of water at 180 °C furnished the diquinane **15** in 87% yield. A Barbier reaction was explored for the introduction of the allyl group at the C-3 position *syn* to the vinyl group. Thus, sonochemically accelerated reaction of the ketone **15** with lithium and allyl bromide furnished the tertiary alcohol **16** in 91% yield in a stereoselective (~9:1) manner. The stereochemistry of the major isomer **16** was assigned on the basis of the preferential approach of the nucleophile from the *exo* face of the convex shaped diquinane **15**. The key RCM reaction[13] for the generation of the tricyclic ring system of tricycloillicinone containing an oxygen functionality at the C-7 carbon was carried out employing Grubbs' first generation catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$]. Reaction of a 0.05 M methylene chloride solution of the hydroxydiene **16** with 10 mol % of Grubbs' first generation catalyst at room temperature for 8 h furnished the tricyclic compound **17** in 90% yield. Structure of **17** was established from its spectral data. To rule out the possibility of di- and trimeric structures for the product (a serious competing side reaction encountered during RCM mediated construction of bridged compounds)[14] formed in the RCM reaction of the hydroxydiene **16**, RCM was also carried out with the corresponding acetate **18**. Acylation of the tertiary alcohol **16** with acetic anhydride and pyridine in methylene chloride in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) generated the acetate **18**.

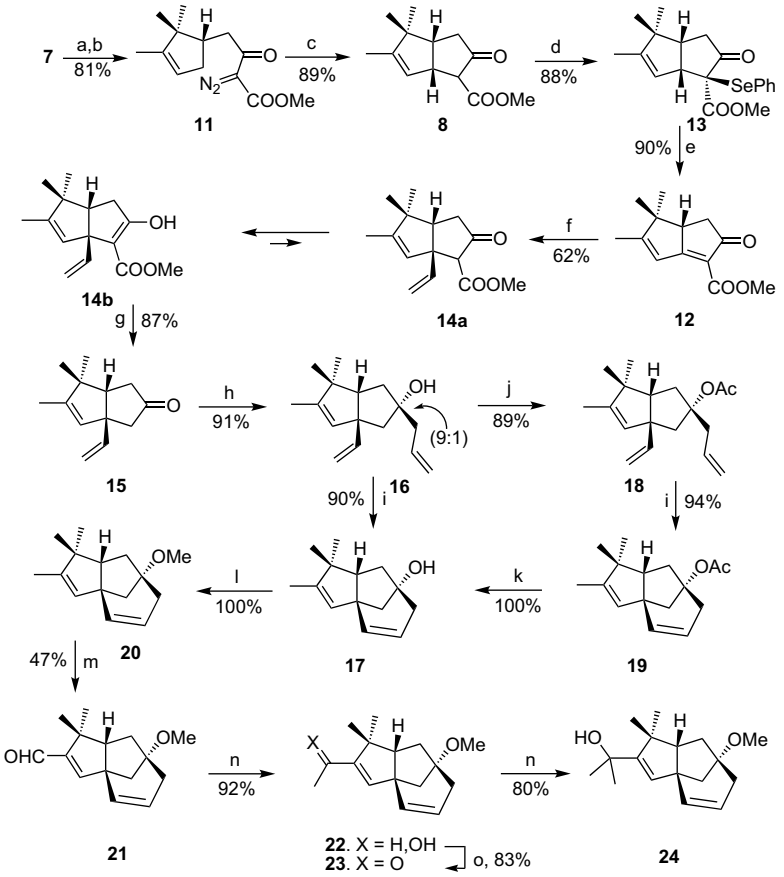
The RCM reaction of the acetate **18** with 10 mol % of Grubbs' first generation catalyst in methylene chloride at room temperature furnished the tricyclic acetate **19**, whose structure was established from its spectral data. The high-resolution mass spectrum confirmed the monomeric nature of **19**. Hydrolysis of the tricyclic acetate **19** with potassium carbonate in methanol at room temperature furnished the alcohol **17**, which was found to be identical with that generated via the RCM reaction of the hydroxydiene **16**.

Since there are three and two carbon side chains present at the C-3 carbon of the tricyclo[5.3.1.$0^{1,5}$]undecane system in ialibinones **3**,**5** and takaneones **6**, after successfully developing enantiospecific synthesis of the tricyclic core of tricycloillicinone **1**, it was conceived to elaborate the side chain at C-3 position in **17**. The tertiary hydroxy group in **17** was protected as its methyl ether by reacting with sodium hydride and methyl iodide in the presence of tetrabutylammonium iodide (TABI) in THF to furnish quantitatively the ether **20**. A selenium dioxide mediated allylic oxidation was opted for functionalizing the methyl group at the C-3 carbon of the tricyclic compound **20**. Thus, refluxing an aqueous dioxane solution of the ether **20** with selenium dioxide for 50 min furnished the aldehyde **21** in moderate yield. Grignard reaction of the aldehyde **21** with methylmagnesium bromide in THF generated predominantly one isomer of the secondary alcohol **22** in 92% yield, which on oxidation with pyridinium dichromate (PDC) in methylene chloride at room temperature for 3 h furnished the ketone **23** in 83% yield. Grignard reaction of the ketone **23** with methylmagnesium bromide in THF at ice temperature for 2 h furnished the tertiary alcohol **24** in 80% yield. Structures of the ketone **23** and the tertiary alcohol **24** were established from their spectral data.

In summary, we have accomplished enantiospecific synthesis of the tricyclic core structure present in the biologically active natural products tricycloillicinone **1**, ialibinones **3**,**5** and takaneones **6**. A transannular RCM reaction was employed as the key step for the construction of the tricyclo[5.3.1.$0^{1,5}$]undecane system starting from campholenaldehyde **7** via the diquinane **8**.



Scheme 1.



Scheme 2. Reagents: (a) $SnCl_2\cdot 2H_2O$, N_2CHCO_2Me, CH_2Cl_2; (b) TsN_3, NEt_3, CH_3CN; (c) $Rh_2(OAc)_4$, CH_2Cl_2; (d) PhSeCl, pyridine, CH_2Cl_2; (e) 30% aq H_2O_2, CH_2Cl_2; (f) CH_2=CHMgBr, CuI, THF; (g) DMSO, NaCl, H_2O; (h) CH_2=$CHCH_2$Br, Li, THF,))); (i) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2; (j) Ac_2O, pyridine, DMAP, CH_2Cl_2; (k) K_2CO_3, MeOH; (l) NaH, MeI, TBAI; (m) SeO_2, dioxane, H_2O; (n) MeMgBr, THF; (o) PDC, CH_2Cl_2.

3. Experimental section

3.1. General

Melting points are recorded using Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Jasco FTIR spectrum BX spectrophotometer. ^{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. A 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for recording NMR spectra. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Elemental analyses were carried out using Carlo Erba 1106 CHN analyzer, at the Department of Organic Chemistry, Indian Institute of Science. Optical rotations were measured using a Jasco P-1020 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatographies (TLC) were 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, methylene chloride, and hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapor or anisaldehyde–H_2SO_4 or MeOH–H_2SO_4 spray followed by heating. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

3.2. Methyl (1*R*,2*S*,5*R*)-6,6,7-trimethyl-3-oxo-2-phenylselenobicyclo[3.3.0]oct-7-ene-2-carboxylate 13

To a magnetically stirred ice cold solution of PhSeCl (218 mg, 1.14 mmol) and pyridine (0.15 mL, 1.90 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise a solution of the keto ester **8** (211 mg, 0.95 mmol) in dry CH_2Cl_2 (2 mL) and stirred for 1 h at the same temperature. The reaction was then quenched with 3 *N* HCl (4 mL) and extracted with CH_2Cl_2 (3×8 mL). The CH_2Cl_2 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 (1:20) as eluent furnished the selenide **13** (315 mg, 88%) as colorless oil. R_f (1:19 EtOAc–hexane) 0.5; $[\alpha]_D^{23}$: −10.8 (*c* 3.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3056, 2957, 2867, 1752, 1730, 1579, 1475, 1438, 1300, 1274, 1238, 1155, 1073, 1021, 999, 742, 691; ^{1}H NMR (300 MHz): δ 7.55 (2H, d, *J* 6.9 Hz) and 7.45–7.25 (3H, m) [Ar–H], 5.03 (1H, s, olefinic H), 3.71 (3H, s, OCH_3), 3.40 (1H, br s, H-1), 2.65–2.56 (2H, m, H-4), 2.40–2.25 (1H, m), 1.58 (3H, s, olefinic CH_3), 1.02 (3H, s) and 1.01 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz): δ 204.0 (C, C=O), 168.9 (C, OC=O), 150.2 (C, C-7), 137.5 (2C, CH), 130.1 (C, CH), 129.0 (2C, CH), 126.7 (C), 121.1 (CH, C-8), 60.0 (C, C-2), 53.8 (CH_3, OCH_3), 52.2 (CH), 47.8 (C, C-6), 47.1 (CH), 38.1 (CH_2, C-4), 26.2 (CH_3), 21.5 (CH_3), 12.8 (CH_3); HRMS: *m*/*z* calcd for $C_{19}H_{22}O_3SeNa$ (M+Na): 401.0632. Found: 401.0627.

3.3. Methyl (5*R*)-6,6,7-trimethyl-3-oxobicyclo[3.3.0]octa-1,7-diene-2-carboxylate 12

To a magnetically stirred, ice cold solution of the selenide **13** (315 mg, 0.83 mmol) in CH_2Cl_2 (4 mL) was added 30% aq H_2O_2

(4 mL) and stirred for 1 h at the same temperature. It was then diluted with water (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extract was washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:2) as eluent furnished the α,β-unsaturated keto ester **12** (165 mg, 90%) as oil. R_f (1:2 EtOAc–hexane) 0.4; $[\alpha]_D^{23}$: −40.3 (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2958, 2928, 2869, 1741, 1705, 1614, 1577, 1464, 1435, 1378, 1361, 1275, 1222, 1191, 1125, 1066, 1028, 861; ^{1}H NMR (300 MHz): δ 6.72 (1H, s, olefinic H), 3.74 (3H, s, OCH_3), 2.97 (1H, t, *J* 6.7 Hz, H-5), 2.47 (1H, dd, *J* 17.2 and 7.1 Hz) and 2.27 (1H, dd, *J* 17.2 and 5.6 Hz) [H-4], 2.01 (3H, s, olefinic CH_3), 1.20 (3H, s) and 0.89 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (75 MHz): δ 202.1 (C, C=O), 193.0 (C, C-1), 177.7 (C, C-7), 162.5 (C, OC=O), 124.2 (CH, C-8), 119.3 (C, C-2), 55.6 (CH_3, OCH_3), 51.2 (CH, C-5), 48.0 (C, C-6), 38.1 (CH_2, C-4), 24.9 (CH_3), 23.5 (CH_3), 15.0 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{16}O_3Na$ (M+Na): 243.0995. Found: 243.0996.

3.4. Methyl (1*R*,5*R*)-6,6,7-trimethyl-3-oxo-1-vinylbicyclo[3.3.0]oct-7-ene-2-carboxylate 14

To a cold (−30 °C), magnetically stirred suspension of CuI (22 mg, 0.11 mmol) in dry THF (2 mL) was added a solution of vinylmagnesium bromide (2.5 mL, 1 M solution in THF, 2.5 mmol) over a period of 20 min. After stirring the reaction mixture for 30 min at −30 °C, a solution of the keto ester **12** (250 mg, 1.14 mmol) in dry THF (3 mL) was added and stirred for 1 h at the same temperature. It was then quenched with saturated aq NH_4Cl (10 mL) and extracted with ether (3×10 mL). The 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 (1:20) as eluent furnished the keto ester **14** (174 mg, 62%) as colorless oil, which was found to exist in the enol form **14b**. R_f (1:19 EtOAc–hexane) 0.4; $[\alpha]_D^{25}$: 2.0 (*c* 8.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3261, 3081, 3046, 2956, 2866, 1760, 1732, 1651, 1615, 1446, 1354, 1281, 1218, 1167, 1042, 993, 912, 845, 804; ^{1}H NMR (300 MHz, for the enol form **14b**): δ 10.55 (1H, s, OH), 5.87 (1H, dd, *J* 18.0 and 9.9 Hz, *H*C=CH_2), 5.41 (1H, s, H-8), 4.88 (1H, d, *J* 9.9 Hz) and 4.87 (1H, d, *J* 18.0 Hz) [HC=*CH*$_2$], 3.72 (3H, s, OCH_3), 2.64 (1H, dd, *J* 18.3 and 8.7 Hz), 2.51–2.42 (1H, m), 2.21 (1H, dd, *J* 9.3 and 3.0 Hz), 1.64 (3H, s, olefinic CH_3), 1.05 (3H, s, *tert*-CH_3), 0.93 (3H, s, *tert*-CH_3); ^{13}C NMR (75 MHz, signals due to enol form **14b**): δ 176.1 (C, *C*O$_2$CH$_3$), 170.0 (C, C-3), 147.6 (C, C-7), 144.7 (CH, H*C*=CH_2), 126.6 (CH, C-8), 111.3 (CH_2, HC=*CH*$_2$), 104.6 (C, C-2), 62.5 (C), 55.2 (CH_3, OCH_3), 50.8 (CH, C-5), 47.8 (C), 32.2 (CH_2, C-4), 29.2 (CH_3), 22.8 (CH_3), 12.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310. Found: 271.1302.

3.5. (1*S*,5*R*)-6,6,7-Trimethyl-1-vinylbicyclo[3.3.0]oct-7-en-3-one 15

A solution of the keto ester **14** (180 mg, 0.73 mmol), NaCl (126 mg, 2.18 mmol), DMSO (2 mL), and water (0.01 mL) was placed in a Carius tube and heated to 180 °C for 2 h. The reaction mixture was cooled to rt, diluted with ether (10 mL), washed with water (5 mL) and 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 diquinane ketone **15** (120 mg, 87%) as oil. R_f (1:19 EtOAc–hexane) 0.5; $[\alpha]_D^{23}$: −46.1 (*c* 4.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3080, 2960. 1743, 1632, 1442, 1400, 1175, 1000, 911, 837; ^{1}H NMR (400 MHz): δ 5.98 (1H, dd, *J* 17.3 and 10.4 Hz, *H*C=CH_2), 5.24 (1H, s, H-8), 4.97 (1H, d, *J* 17.3 Hz), 4.95 (1H, d, *J* 10.4 Hz), 2.45–2.20 (5H, m), 1.66 (3H, s, olefinic CH_3), 1.08 (3H, s) and 0.91 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (100 MHz): δ 218.0 (C, C=O), 148.0 (C, C-7), 145.8 (CH, *C*H=CH_2), 128.1 (CH, C-8), 111.7 (CH_2, HC=*CH*$_2$), 56.3 (C), 56.0 (CH, C-1), 48.6 (CH_2, C-2), 48.3 (C), 40.2 (CH_2, C-4), 28.4 (CH_3), 23.3 (CH_3), 12.5 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}ONa$ (M+Na): 213.1255. Found: 213.1263.

3.6. (1*S*,3*S*,5*R*)-3-Allyl-6,6,7-trimethyl-1-vinylbicyclo-[3.3.0]oct-7-en-3-ol 16

To a suspension of lithium (12 mg, 1.74 mmol) in anhydrous THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a solution of the ketone **15** (33 mg, 0.17 mmol) and allyl bromide (0.2 mL, 1.74 mmol) in THF (2 mL) and the reaction mixture was sonicated for 1 h. Then the reaction mixture was decanted from the excess lithium, quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3×3 mL). The 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 (1:9) as eluent furnished a 1:9 diastereomeric mixture of the alcohol **16** (37 mg, 91%) as oil. R_f (1:9 EtOAc–hexane) 0.5; $[\alpha]_D^{22}$: −21.4 (*c* 2.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3406, 3080, 2928, 2862, 1638, 1513, 1435, 1370, 1304, 1220, 995, 910, 840; ^{1}H NMR (400 MHz, signals due to the major isomer): δ 5.95 (1H, dd, *J* 17.2 and 10.4 Hz, vinylic *H*C=CH_2), 6.01–5.84 (1H, m, *H*C=CH_2), 5.25 (1H, s, H-8), 5.20–5.10 (2H, m), 4.91 (1H, d, *J* 17.2 Hz), 4.86 (1H, d, *J* 10.4 Hz), 2.55–2.21 (4H, m), 2.00–1.75 (4H, m), 1.66 (3H, s, olefinic CH_3), 1.05 (3H, s) and 1.03 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (100 MHz, signals due to the major isomer): 148.1 (C, C-7), 146.6 (CH), 134.7 (CH), 130.0 (CH), 117.6 (CH_2), 110.7 (CH_2), 81.7 (C, C-3), 60.1 (C), 58.3 (CH, C-5), 50.1 (CH_2), 48.4 (C), 44.6 (CH_2), 41.9 (CH_2), 30.2 (CH_3), 23.6 (CH_3), 12.6 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{24}ONa$ (M+Na): 255.1725. Found: 255.1715.

3.7. (1*S*,5*R*,7*S*)-3,4,4-Trimethyltricyclo[5.3.1.0^{1,5}]undec-2,9-dien-7-ol 17

To a magnetically stirred solution of the alcohol **16** (20 mg, 0.08 mmol) in dry CH_2Cl_2 (2 mL) was added Grubbs' first generation catalyst (6 mg, 10 mol %) and the reaction mixture was stirred at rt for 8 h. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the tricyclic compound **17** (16 mg, 90%) as solid. Mp: 91–92 °C; R_f (1:9 EtOAc–hexane) 0.5; $[\alpha]_D^{21}$: +43.0 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3363, 3025, 2955, 2861, 1640, 1462, 1359, 1333, 1158, 1067, 1007, 950, 831, 712; ^{1}H NMR (400 MHz): δ 5.86 (1H, d, *J* 9.2 Hz, H-10), 5.42 (1H, dt, *J* 9.2 and 3.4 Hz, H-9), 5.31 (1H, s, H-2), 2.45 (1H, dq, *J* 17.4 and 2.4 Hz), 2.37 (1H, d, *J* 17.4 Hz), 2.27 (1H, dd, *J* 7.8 and 7.5 Hz), 2.00–1.90 (2H, m), 1.73 and 1.68 (2H, 2×d, *J* 10.0 Hz), 1.64 (3H, s, olefinic CH_3), 1.74–1.63 (1H, m, OH), 1.00 (6H, s, 2×*tert*-CH_3); ^{13}C NMR (100 MHz): δ 149.3 (C, C-3), 139.8 (CH, C-10), 127.0 (CH, C-2), 123.1 (CH, C-9), 81.3 (C, C-7), 62.7 (CH, C-5), 56.9 (C, C-1), 48.3 (CH_2), 47.2 (C, C-4), 44.2 (CH_2), 40.4 (CH_2), 29.4 (CH_3), 24.2 (CH_3), 13.0 (CH_3). Anal. Calcd: for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.00; H, 9.90.

3.8. (1*S*,3*S*,5*R*)-3-Allyl-6,6,7-trimethyl-1-vinylbicyclo-[3.3.0]oct-7-en-3-yl acetate 18

To a magnetically stirred ice cold solution of the alcohol **16** (25 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) were added DMAP (5 mg), pyridine (0.2 mL, 3.90 mmol), and Ac_2O (0.4 mL, 3.9 mmol) and stirred for 2 h at rt; 3 N HCl (4 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (2×5 mL). The combined organic 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 acetate **18** (26 mg, 89%) as oil. R_f (1:19 EtOAc–hexane) 0.5; $[\alpha]_D^{21}$: +15.0 (*c* 0.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3081, 2961, 2930, 2867, 1738, 1436, 1367, 1238, 1210, 1116, 1020, 994, 913, 843; ^{1}H NMR

(400 MHz): δ 5.94 (1H, dd, *J* 17.6 and 10.4 Hz, vinylic *H*C=CH$_2$), 5.85–5.70 (1H, m), 5.15–4.80 (5H, m), 2.77 (1H, dd, *J* 14.6 and 7.3 Hz), 2.55 (1H, dd, *J* 14.6 and 7.2 Hz), 2.40–1.80 (5H, m), 1.92 (3H, s, CH$_3$C=O), 1.62 (3H, s, olefinic CH$_3$), 1.04 (3H, s) and 0.98 (3H, s) [2×*tert*-CH$_3$]; ^{13}C NMR (100 MHz): δ 169.8 (C, OC=O), 146.9 (CH), 145.0 (C), 133.4 (CH), 129.0 (CH), 117.9 (CH$_2$), 110.6 (CH$_2$), 89.6 (C), 58.0 (C), 57.1 (CH), 47.8 (C, C-4), 47.4 (CH$_2$), 40.1 (CH$_2$), 39.5 (CH$_2$), 29.5 (CH$_3$), 22.5 (CH$_3$), 21.8 (CH$_3$), 12.5 (CH$_3$); HRMS: *m*/*z* calcd for $C_{18}H_{26}O_2Na$ (M+Na): 297.1830. Found: 297.1833.

3.9. (1*S*,5*R*,7*S*)-3,4,4-Trimethyltricyclo[5.3.1.0^{1,5}]undeca-2,9-dien-7-yl acetate 19

To a magnetically stirred solution of the acetate **18** (13 mg, 0.05 mmol) in dry CH_2Cl_2 (2 mL) was added Grubbs' first generation catalyst (4 mg, 10 mol %) and the reaction mixture was stirred at rt for 9 h. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the tricyclic acetate **19** (11 mg, 94%) as oil. R_f (1:19 EtOAc–hexane) 0.4; $[\alpha]_D^{23}$: +21.0 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3028, 2958, 2866, 1736, 1438, 1367, 1261, 1245, 1047, 1016, 913, 830; ^{1}H NMR (400 MHz): δ 5.85 (1H, d, *J* 9.2 Hz, H-10), 5.41 (1H, dt, *J* 9.2 and 3.4 Hz, H-9), 5.31 (1H, s, H-2), 2.85 (1H, d, *J* 17.3 Hz), 2.55 (1H, dq, *J* 17.3 and 2.8 Hz), 2.55–2.40 (1H, m), 2.32 (1H, dd, *J* 9.4 and 6.0 Hz), 2.10–2.00 (2H, m), 2.03 (3H, s, COCH$_3$), 1.78 (1H, d, *J* 10.0 Hz), 1.64 (3H, s, olefinic CH$_3$), 1.00 (3H, s) and 0.98 (3H, s) [2×*tert*-CH$_3$]; ^{13}C NMR (100 MHz): δ 169.9 (C, OC=O), 149.4 (C, C-3), 139.1 (CH, C-10), 126.7 (CH), 123.1 (CH), 88.4 (C, C-7), 62.4 (CH, C-5), 55.2 (C, C-1), 47.2 (C, C-4), 45.8 (CH$_2$), 40.2 (CH$_2$), 37.7 (CH$_2$), 29.4 (CH$_3$), 24.1 (CH$_3$), 21.9 (CH$_3$), 12.9 (CH$_3$); HRMS: *m*/*z* calcd for $C_{16}H_{22}O_2Na$ (M+Na): 269.1517. Found: 269.1508.

3.10. Hydrolysis of the tricyclic acetate 19

To a magnetically stirred solution of the tricyclic acetate **19** (12 mg, 0.05 mmol) in MeOH (0.5 mL) was added K_2CO_3 (138 mg, 1.0 mmol) and stirred for 6 h at rt. Water (2 mL) was added to the reaction mixture and extracted with ether (2×5 mL). The combined organic 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: 9) as eluent furnished the alcohol **17** (10 mg, 100%), which exhibited TLC and spectral data (IR and ^{1}H NMR) identical to the sample obtained by RCM reaction of **16**.

3.11. (1*S*,5*R*,7*S*)-7-Methoxy-3,4,4-trimethyltricyclo-[5.3.1.0^{1,5}]undeca-2,9-diene 20

To an ice cold, magnetically stirred suspension of NaH (60% dispersion in oil, 59 mg, 1.50 mmol, washed with dry hexane) and tetrabutylammonium iodide (10 mg, catalytic) in THF (1 mL) was added a solution of the alcohol **17** (30 mg, 0.15 mmol) in THF (2 mL) and stirred for 30 min at rt. To the alkoxide thus formed was added methyl iodide (0.1 mL, 1.50 mmol) and the reaction mixture was stirred for 15 h at rt. Water (2 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 over a silica gel column using CH_2Cl_2–hexane (1:9) as eluent furnished the methyl ether **20** (32 mg, 100%) as oil. R_f (1:9 CH_2Cl_2–hexane) 0.5; $[\alpha]_D^{22}$: +26.1 (*c* 3.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3027, 2957, 2863, 2826, 1463, 1440, 1360, 1335, 1197, 1160, 1082, 711; ^{1}H NMR (400 MHz): δ 5.82 (1H, d, *J* 9.2 Hz, H-10), 5.40 (1H, dt, *J* 9.2 and 3.4 Hz, H-9), 5.27 (1H, s, H-2), 3.26 (3H, s, OCH$_3$), 2.48 (1H, dq, *J* 17.3 and 2.7 Hz), 2.30–2.20 (2H, m), 1.99 (1H, ddd, *J* 12.8, 5.6 and 3.1 Hz), 1.83 (1H, dd, *J* 12.8 and 9.8 Hz), 1.64 (2H, s), 1.60 (3H, s, olefinic CH$_3$), 0.96 (6H, s, 2×*tert*-CH$_3$); ^{13}C NMR (100 MHz): δ 149.1 (C, C-3), 139.7 (CH, C-10), 127.2 (CH), 123.2 (CH), 85.6 (C, C-7), 62.5 (CH, C-5), 56.2 (C, C-1), 50.7 (CH$_3$, OCH$_3$), 47.4 (C, C-4), 44.4 (CH$_2$), 39.9 (CH$_2$), 36.2 (CH$_2$), 29.4 (CH$_3$), 24.1 (CH$_3$), 13.0 (CH$_3$); HRMS: *m*/*z* calcd for $C_{14}H_{19}$ (M−OMe): 187.1468. Found: 187.1461.

3.12. (1*S*,5*R*,7*S*)-7-Methoxy-4,4-dimethyltricyclo-[5.3.1.0^{1,5}]undeca-2,9-dien-3-carboxaldehyde 21

To a solution of the methyl ether **20** (16 mg, 0.07 mmol) in dioxane (0.5 mL) and water (two drops) was added SeO_2 (25 mg, 0.22 mmol) and refluxed for 50 min. The reaction mixture was cooled, diluted with ether (2 mL), and quenched with satd aq NH_4Cl (1 mL). The organic layer was separated and the aqueous phase was extracted with ether (3×3 mL). The combined organic phase was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the aldehyde **21** (8 mg, 47%) as oil. R_f (1:19 EtOAc–hexane) 0.5; $[\alpha]_D^{22}$: −22.0 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3031, 2957, 2928, 2712, 1682, 1610, 1514, 1463, 1361, 1342, 1324, 1251, 1214, 1162, 1118, 1080, 1022, 996, 830; ^{1}H NMR (400 MHz): δ 9.64 (1H, s, HC=O), 6.63 (1H, s, H-2), 5.87 (1H, d, *J* 9.2 Hz, H-10), 5.51 (1H, dt, *J* 9.2 and 3.4 Hz, H-9), 3.23 (3H, s, OCH$_3$), 2.47 (1H, dq, *J* 17.5 and 3.0 Hz), 2.38 (1H, dd, *J* 9.6 and 5.6 Hz), 2.30 (1H, d, *J* 17.5 Hz), 2.03 (1H, ddd, *J* 13.0, 5.5 and 3.0 Hz), 1.82 (1H, dd, *J* 13.0 and 10.1 Hz), 1.72 (2H, s), 1.17 (3H, s) and 1.13 (3H, s) [2×*tert*-CH$_3$]; ^{13}C NMR (100 MHz): δ 190.3 (CH, CH=O), 154.4 (CH, C-2), 154.3 (C, C-3), 136.0 (CH, C-10), 125.1 (CH, C-9), 85.1 (C, C-7), 63.7 (CH, C-5), 57.5 (C, C-1), 50.9 (CH$_3$, OCH$_3$), 45.9 (C, C-4), 44.0 (CH$_2$), 40.0 (CH$_2$), 35.4 (CH$_2$), 29.5 (CH$_3$), 24.1 (CH$_3$); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_2Na$ (M+Na): 255.1725. Found: 255.1738.

3.13. 1-[(1*S*,5*R*,7*S*)-7-Methoxy-4,4-dimethyltricyclo-[5.3.1.0^{1,5}]undeca-2,9-dien-3-yl]ethanol 22

To a magnetically stirred, ice cold solution of the aldehyde **21** (12 mg, 0.05 mmol) in THF (1 mL) was added MeMgBr (0.3 mL, 0.9 mmol, 3 M in THF) and stirred for 1 h at rt. The reaction mixture was poured into ice cold satd aq NH_4Cl solution (3 mL) and extracted with ether (3×3 mL). The ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the secondary alcohol **22** (11 mg, 92%) as oil. R_f (1:9 EtOAc–hexane) 0.5; $[\alpha]_D^{23}$: −14.5 (*c* 1.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3370, 2927, 2856, 1514, 1465, 1376, 1240, 1215, 1117, 1052, 1024, 829; ^{1}H NMR (400 MHz): δ 5.80 (1H, d, *J* 9.2 Hz, H-10′), 5.67 (1H, s, H-2′), 5.40 (1H, dt, *J* 9.2 and 3.3 Hz, H-9′), 4.19 (1H, q, *J* 6.3 Hz, CHOH), 3.22 (3H, s, OCH$_3$), 2.46 (1H, dq, *J* 17.3 and 2.7 Hz), 2.30–2.20 (2H, m), 1.96 (1H, ddd, *J* 13.0, 5.5 and 3.0 Hz), 1.80 (1H, dd, *J* 13.0 and 9.6 Hz), 1.70–1.55 (3H, m), 1.30 (3H, d, *J* 6.3 Hz, *sec*-CH$_3$), 1.05 (3H, s) and 0.96 (3H, s) [2×*tert*-CH$_3$]; ^{13}C NMR (100 MHz): δ 157.3 (C, C-3′), 138.9 (CH, C-10′), 127.8 (CH, C-2′), 123.7 (CH, C-9′), 85.7 (C, C-7′), 64.2 (CH), 63.0 (CH), 56.1 (C, C-1′), 50.8 (CH$_3$, OCH$_3$), 47.4 (C, C-4′), 44.3 (CH$_2$), 39.9 (CH$_2$), 36.0 (CH$_2$), 30.3 (CH$_3$), 25.3 (CH$_3$), 24.3 (CH$_3$); HRMS: *m*/*z* calcd for $C_{16}H_{24}O_2Na$ (M+Na): 271.1674. Found: 271.1646.

3.14. (1*S*,5*R*,7*S*)-3-Acetyl-7-methoxy-4,4-dimethyltricyclo[5.3.1.0^{1,5}]undeca-2,9-diene 23

To a magnetically stirred solution of the secondary alcohol **22** (11 mg, 0.044 mmol) in CH_2Cl_2 (1 mL) was added PDC (150 mg, 0.44 mmol) and stirred for 3 h at rt. The reaction mixture was then filtered through a small silica gel column and eluted the column with an excess of CH_2Cl_2 (10 mL). Evaporation of the solvent and

purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished the ketone **23** (9 mg, 83%) as oil. R_f (1:19 EtOAc–hexane) 0.5; $[\alpha]_D^{24}$: −12.9 (*c* 0.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3028, 2962, 2930, 2864, 1671, 1605, 1463, 1361, 1281, 1259, 1201, 1162, 1122, 1087, 1024, 954, 706; ^1H NMR (400 MHz): δ 6.67 (1H, s, H-2), 5.93 (1H, d, *J* 9.3 Hz, H-10), 5.56 (1H, td, *J* 9.3 and 3.5 Hz, H-9), 3.31 (3H, s, OCH_3), 2.55 (1H, dq, *J* 17.4 and 2.8 Hz), 2.40–2.30 (2H, m), 2.30 (3H, s, CH_3CO), 2.10 (1H, ddd, *J* 12.3, 5.0 and 3.0 Hz), 1.88 (1H, dd, *J* 12.3 and 10.0 Hz), 1.80 and 1.76 (2H, 2×d, *J* 10.0 Hz), 1.20 (6H, s, 2×*tert*-CH_3); ^{13}C NMR (100 MHz): δ 197.2 (C, C=O), 152.4 (C, C-3), 146.4 (CH, C-2), 136.6 (CH, C-10), 124.8 (CH, C-9), 85.2 (C, C-7), 62.9 (CH, C-5), 56.7 (C, C-1), 51.0 (CH_3, OCH_3), 47.2 (C, C-4), 43.9 (CH_2), 40.1 (CH_2), 35.4 (CH_2), 29.9 (CH_3), 27.9 (CH_3), 24.4 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{22}O_2Na$ (M+Na): 269.1517. Found: 269.1507.

3.15. 2-[(1*S*,5*R*,7*S*)-7-Methoxy-4,4-dimethyltricyclo-[5.3.1.0^{1,5}]undeca-2,9-dien-3-yl]propan-2-ol 24

To a magnetically stirred, ice cold solution of the ketone **23** (7 mg, 0.03 mmol) in THF (1 mL) was added MeMgBr (0.2 mL, 0.6 mmol, 3 M in THF) and stirred for 2 h at rt. The reaction mixture was poured into ice cold satd aq NH_4Cl solution (3 mL) and extracted with ether (3×3 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 over a silica gel column using ethyl acetate–hexane (1:9) as eluent furnished the alcohol **24** (6 mg, 80%) as oil. R_f (1:19 EtOAc–hexane) 0.4; $[\alpha]_D^{23}$: −17.1 (*c* 0.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3364, 3029, 2964, 2928, 2857, 1514, 1464, 1375, 1243, 1213, 1122, 1088, 1072, 1020, 945, 830; ^1H NMR (400 MHz): δ 5.84 (1H, d, *J* 9.1 Hz, H-10′), 5.61 (1H, s, H-2′), 5.46 (1H, dt, *J* 9.1 and 3.4 Hz, H-9′), 3.31 (3H, s, OCH_3), 2.52 (1H, dq, *J* 17.2 and 2.7 Hz), 2.40–2.25 (2H, m), 2.07 (1H, ddd, *J* 13.1, 5.2 and 3.1 Hz), 1.82 (1H, dd, *J* 13.1 and 10.8 Hz), 1.74 and 1.67 (2H, 2×d, *J* 10.0 Hz), 1.70–1.55 (1H, m, OH), 1.45 (6H, s, 2×*tert*-CH_3), 1.22 (3H, s) and 1.21 (3H, s) [2×*tert*-CH_3]; ^{13}C NMR (100 MHz): δ 159.4 (C, C-3′), 139.3 (CH, C-10′), 128.1 (CH, C-2′), 123.4 (CH, C-9′), 85.8 (C, C-7′), 72.7 (C, C-2), 64.2 (CH, C-5′), 55.0 (C, C-1′), 50.9 (CH_3, OCH_3), 48.8 (C, C-4′), 43.9 (CH_2), 40.1 (CH_2), 35.5 (CH_2), 32.7 (CH_3), 32.6 (CH_3), 31.2 (CH_3), 26.3 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830. Found: 285.1826.

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