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An enantiospecific synthesis of a komarovispirane

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Abstract—The enantiospecific total synthesis of a komarovispirane, containing the complete carbon framework, *trans*-bicyclo[4.3.0]nonanespiro[8.1′]cyclohexane, of the spiroditerpene komarovispirone, starting from the readily available campholenaldehyde is described.

1. Introduction

The creativity of Nature in devising varied molecular architectures is revealed through the isolation of a wide range of natural products, with remarkable skeletal build-up and multifarious functionality. Among natural products, terpenoids (isoprenoids) occupy a special position on account of their widespread occurrence and array of carbocyclic skeleta that they embody. Terpenes, comprising of multiple isoprene units, can be assembled in acyclic, monocyclic, bicyclic, tricyclic, tetracyclic and pentacyclic structures containing small, medium and large sized rings and a wide range of functionalities. Due to this structural diversity, this class of natural products holds special appeal to synthetic chemists and provides a fertile ground for developing and testing new synthetic methodologies, particularly those directed towards the carbocyclic ring construction. As a result, synthetic activity in this area continues to flourish.

Dracocephalum komarovi Lipsky (Labiatae) is a perennial semishrub, which is known as 'buzbosh' in Uzbekistan. In this region, the aerial parts in a tea are to treat various diseases such as inflammatory diseases and hypertony. Initial phytochemical investigations on the dried whole plants of *D. komarovi* by Honda et al.[1] led to the isolation of three icetexane diterpenes cyclocoulterone **1**, komaroviquinone **2** and dracocephalone A **3** (Fig. 1), whose structures were elucidated by extensive analysis of their NMR data.

In 2004, further investigations[2] by the same research group on *D. komarovi* led to the isolation of a novel tricyclic diterpene komarovispirone **4**, containing a new and interesting cyclohexane spiro fused to a bicyclo[4.3.0]nonane carbon framework. It is postulated that komarovispirone **4** is biogenetically derived from komaroviquinone **2** through a ring-contraction rearrangement sequence as outlined in Scheme 1. The stereochemistry of **4** was tentatively assigned as indicated in Scheme 1. In 2006, Honda et al.[3] reported the isolation of three more diterpenes dracocequinone A **5A**, dracocequinone B **5B** and komarovinone A **6** along with cyclocoulterone **1**, komaroviquinone **2**, dracocephalone A **3** and komarovispirone **4**. All compounds **1**–**6** have been found to exhibit trypanocidal activity against the epimastigotes of *Trypanosoma cruzi*, the causative agent of Chagas' disease, American Trypanosomiasis, in Central and South America.

The novel tricyclic structure containing an unusual cyclohexane spiro fused to a bicyclo[4.3.0]nonane carbon framework (komarovispirane **7**) coupled with biological activity has made komarovispirone **4**, and its analogues interesting and challenging synthetic targets. So far there is no report in the literature on either the total synthesis or model studies of komarovispirone **4** and its analogues (komarovispiranes), either in racemic or enantiopure forms. We have initiated an enantiospecific approach for the generation of the complete carbon framework **7** of komarovispirone **4** starting from bicyclo[3.3.0]octanone[4] **8**, which is readily available from campholenaldehyde **9** by employing an intramolecular rhodium carbenoid CH insertion reaction. It was contemplated that the bicyclic ketone **8** would be an ideal substrate to elaborate into komarovispiranes **7**, which requires spiroannulation of a cyclohexane ring at the C-3 carbon and expansion of the second cyclopentane

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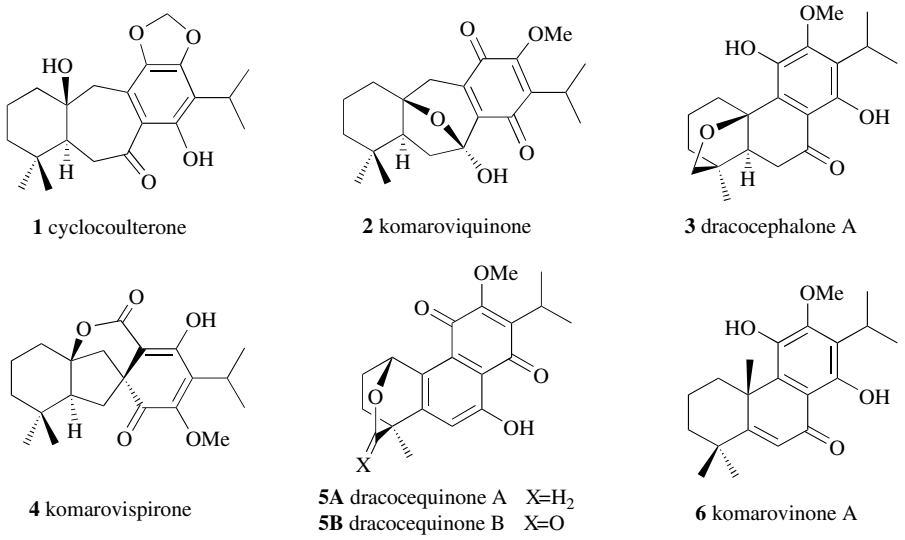
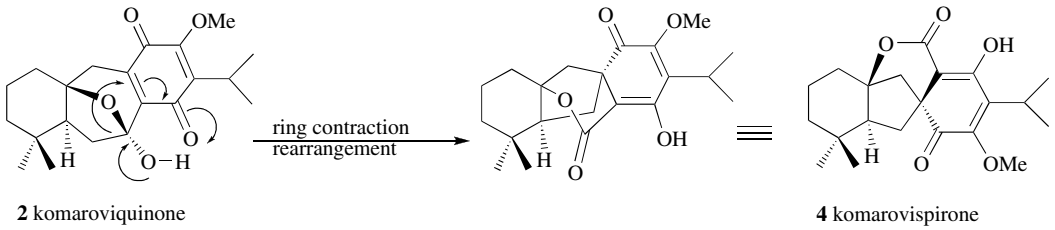
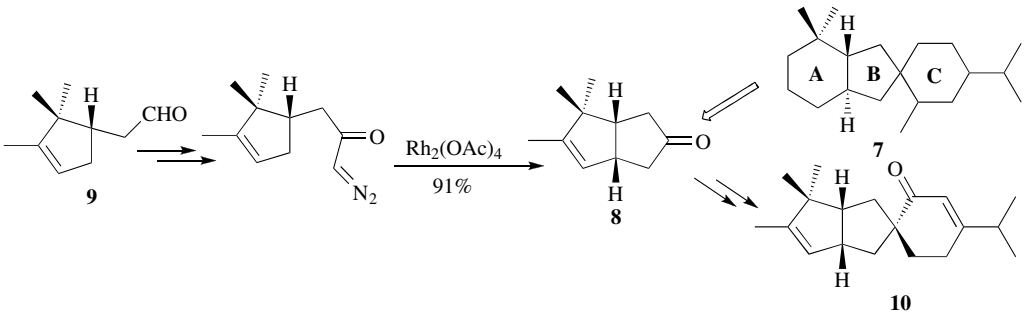


Figure 1.



Scheme 1.

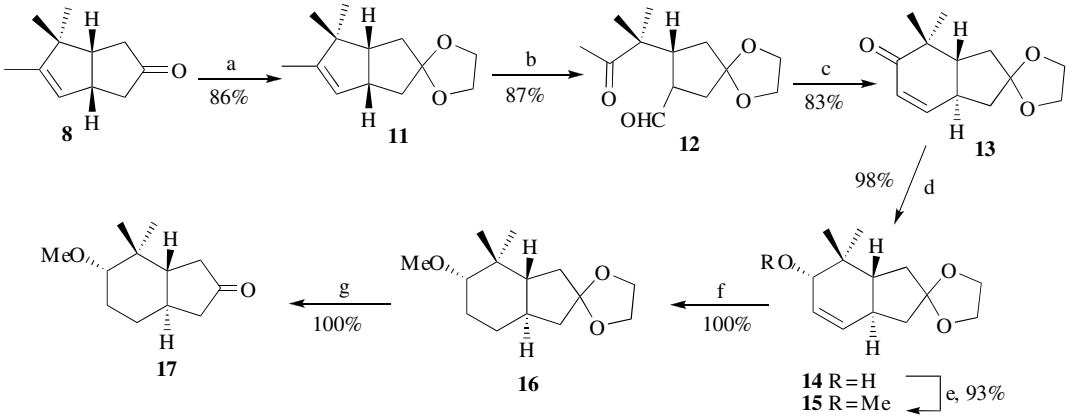


Scheme 2.

ring into a cyclohexane ring (Scheme 2). As a model study, we have recently reported[5] the synthesis of bis-norkomarovispirane **10** via spiroannulation of a cyclohexane to the bicyclic ketone **8**. In continuation, we herein report the enantiospecific total synthesis of a komarovispirane, containing the complete carbon framework of komarovispirone **4**.

2. Results and discussion

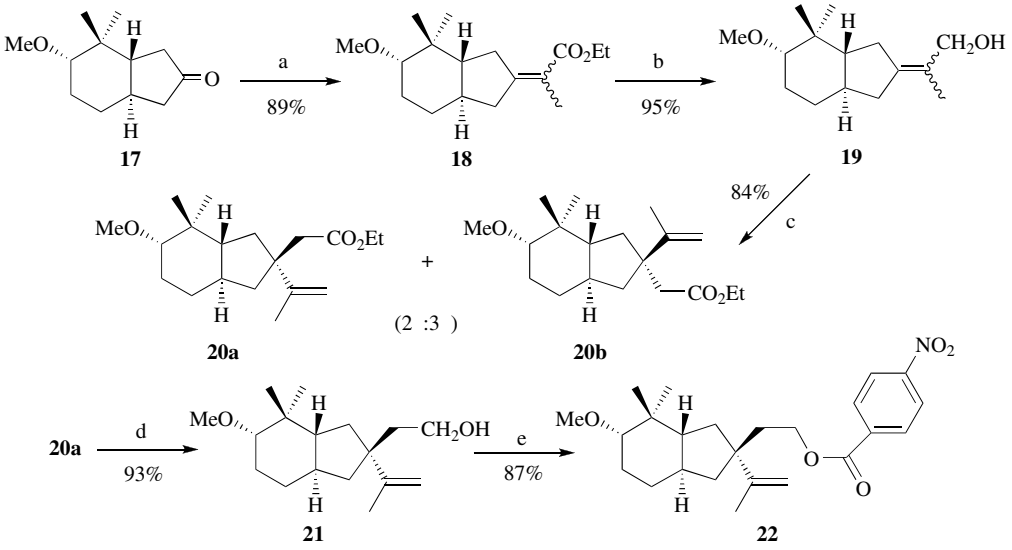
To begin with, we investigated expansion of the cyclopentene ring in diquinane **8** into a cyclohexane ring employing an oxidative cleavage followed by intramolecular aldol condensation, Scheme 3. To avoid regiochemical problems, the ketone group in diquinane **8** was protected as its ethylene ketal by refluxing in benzene with 1,2-ethanediol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) under Dean–Stark conditions to furnish ketal **11**. Ozonolysis of bicyclic ketal **11** followed by reductive work-up furnished keto-aldehyde **12**. Intramolecular aldol condensation of keto-aldehyde **12** with piperidine and acetic acid furnished bicyclic enone **13** containing the requisite *trans*-ring junction, whose structure was established from its spectral data. The *trans* stereochemistry of enone **13** was confirmed at a later stage by single crystal X-ray diffraction studies of an advanced intermediate. Reduction of bicyclic enone **13** with lithium aluminium hydride (LAH) furnished allyl



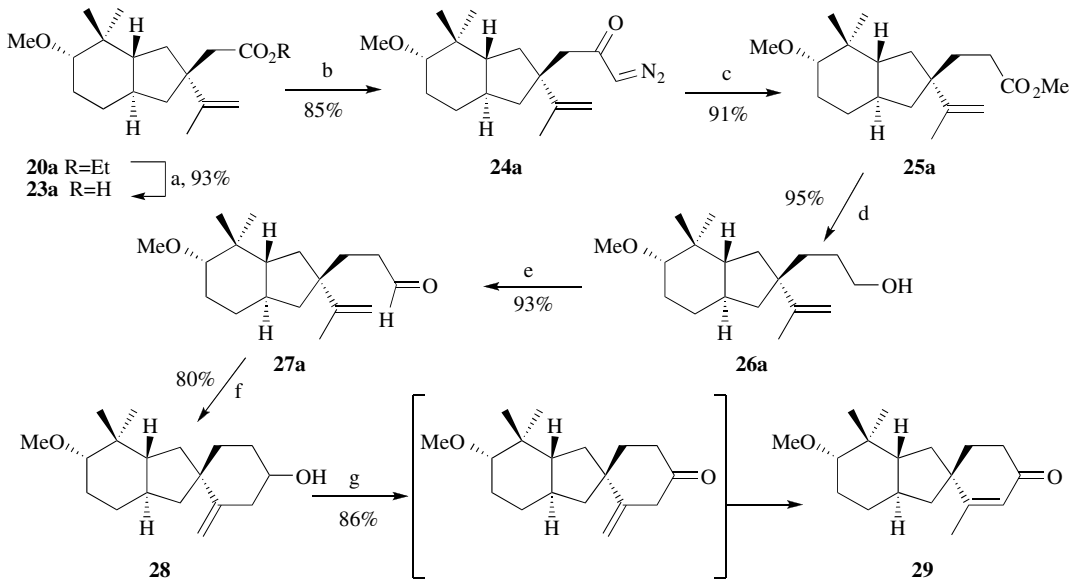
Scheme 3. Reagents and conditions: (a) $(CH_2OH)_2$, PTSA, C_6H_6, reflux, 4 h; (b) O_3/O_2, CH_2Cl_2–MeOH (4:1), −70 °C; Me_2S, rt, 8 h; (c) AcOH, piperidine, C_6H_6, reflux, 7 h; (d) LAH, Et_2O, −70 °C, 1.5 h; (e) NaH, MeI, TBAI, THF, 0 °C→reflux, 4 h; (f) H_2, 10% Pd–C, hexane, 1 atm, 5 h; (g) 3 N HCl, THF, rt, 3 h.

alcohol **14** in a highly regio- and stereoselective manner. Treatment of allyl alcohol **14** with sodium hydride, methyl iodide and a catalytic amount of tetrabutylammonium iodide (TBAI) in THF furnished methyl ether **15**, which on hydrogenation with 10% palladium over carbon as the catalyst furnished the saturated compound **16**. Acid catalyzed hydrolysis transformed ketal **16** into the bicyclic ketone **17**.

After accomplishing the ring expansion of the A-ring to generate the bicyclic ketone **17**, attention was next turned to the spiroannulation of a cyclohexane ring at C-8 carbon. Initially, an intramolecular type II ene reaction[6] based methodology was investigated (Schemes 4 and 5). For the creation of the quaternary carbon atom (latent spiro centre), an orthoester Claisen rearrangement[7] was conceived. Thus, Horner–Wadsworth–Emmons reaction of the bicyclic ketone **17** with triethyl phosphonopropionate and sodium hydride in refluxing THF furnished an *E*,*Z*-mixture of the unsaturated ester **18** in 89% yield, which on regioselective reduction with LAH in ether at low temperature furnished an *E*,*Z*-mixture of allyl alcohol **19**. As either isomer of alcohol **19** is expected to generate the same product in the Claisen rearrangement, no attempt was made to separate the individual isomers. The orthoester Claisen rearrangement of the allyl alcohol **19** with triethyl orthoacetate and a catalytic amount of propionic acid at 180 °C in a sealed tube furnished a 2:3 diastereomeric mixture of esters **20a** and **20b** containing the requisite quaternary carbon atom, which were separated by column chromatography on neutral alumina. To unambiguously establish the stereochemistry of the newly created quaternary carbon atom, an X-ray diffraction study of a crystalline derivative was investigated. Thus, reduction of ester **20a** with LAH in ether generated the primary alcohol **21**, which on treatment with *p*-nitrobenzoyl chloride in pyridine and methylene chloride in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) furnished *p*-nitrobenzoate **22**. Single crystal X-ray diffraction analysis of ester **22**



Scheme 4. Reagents and conditions: (a) $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF, 0 °C→reflux, 4 h; (b) LAH, Et_2O, −70 °C, 2 h; (c) $CH_3C(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 72 h; (d) LAH, Et_2O, 0 °C, 2 h; (e) 4-$NO_2C_6H_4COCl$, py, DMAP, CH_2Cl_2, 0 °C→rt, 4 h.



Scheme 5. Reagents and conditions: (a) 5% NaOH, MeOH–H_2O (1:1), reflux, 5 h; (b) (i) $(COCl)_2$, C_6H_6, rt, 2 h; (ii) CH_2N_2, Et_2O, 0 °C, 3 h; (c) *hv*, MeOH, 1 h; (d) LAH, Et_2O, 0 °C, 1.5 h; (e) PDC, CH_2Cl_2, rt, 7 h; (f) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 7 min; (g) PCC, silica gel, CH_2Cl_2, rt, 4 h.

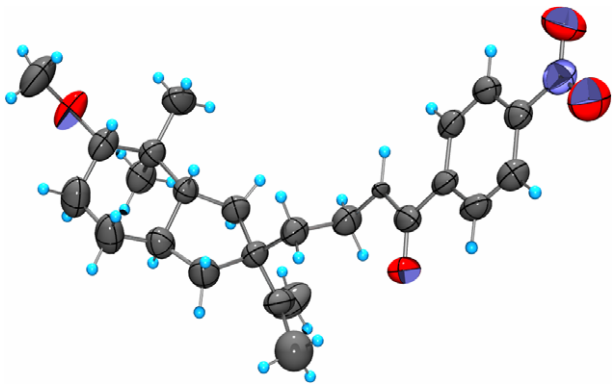


Figure 2. ORTEP diagram of ester **22**.

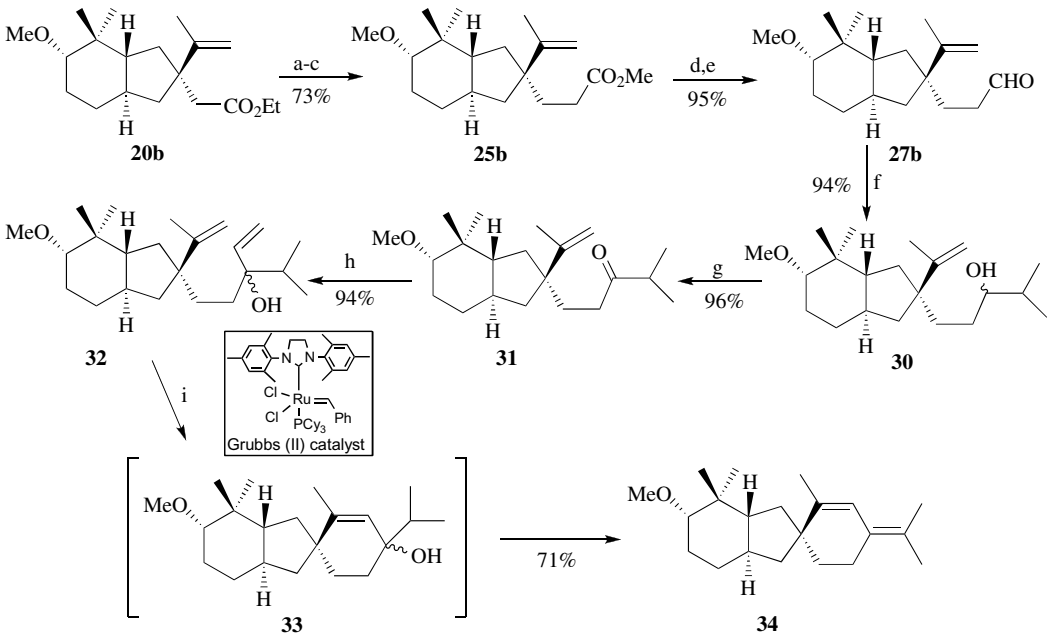
(Fig. 2) unambiguously established not only the stereochemistry of the quaternary carbon but also the *trans*-ring junction as well as the stereochemistry of the methoxy group in esters **20a** and **20b**.

For the spiroannulation of a cyclohexane ring, ester **20a** was first homologated employing an Arndt–Eistert protocol. Accordingly, hydrolysis of ester **20a** with sodium hydroxide in aqueous methanol furnished acid **23a**. Reaction of acid **23a** with oxalyl chloride followed by treatment of the resultant acid chloride with diazomethane furnished diazoketone **24a**. A photochemical Wolff rearrangement by irradiation of diazoketone **24a** with a 450 W medium pressure mercury vapour lamp in methanol generated the homologated ester **25a**. A two step protocol was employed for the conversion of the ester in **25a** into the corresponding aldehyde. Thus, reduction of ester **25a** with LAH in ether followed by oxidation of the primary alcohol **26a** with pyridinium dichromate (PDC) in methylene chloride furnished aldehyde **27a**. Boron trifluoride diethyl etherate catalyzed type II carbonyl ene reaction of aldehyde **27a** in methylene chloride generated spiro alcohol **28**, containing the ABC-ring system of komarovispiranes. Oxidation of alcohol **28** with PCC and silica gel in methylene chloride followed by simultaneous isomerization of the *exo*-cyclic olefin furnished enone **29**, whose structure was established from its spectral data.

In another direction, an RCM[8] based approach was also investigated for the enantiospecific total synthesis of a komarovispirane (Scheme 6), starting from ester **20b**. Ester **20b** was converted into aldehyde **27b** employing the same sequence via the homologated ester **25b**. It was contemplated to introduce the isopropyl group prior to the spiroannulation. Thus, a Grignard reaction of aldehyde **27b** with isopropylmagnesium bromide followed by oxidation of the resultant secondary alcohol **30** generated isopropyl ketone **31**. The addition of vinylmagnesium bromide to ketone **31** furnished the tertiary allyl alcohol **32**. As anticipated, RCM reaction of hydroxydiene **32** with Grubbs' second generation catalyst in refluxing benzene followed by dehydration of the resultant spiroalcohol **33** furnished komarovispiradiene **34**, whose structure was established from its spectral data.

3. Conclusion

In conclusion, we have developed a convenient strategy for the generation of the ABC-ring system of komarovispiranes. The AB-*trans* system was efficiently generated, in six steps, with an average yield of 94% in each step, by ring expansion of diquinane **8**, which was readily available from campholenaldehyde **9**. For the generation of the ABC-ring system of komarovispiranes, a Claisen rearrangement-intramolecular type II carbonyl ene reaction based methodology was developed for the spiroannulation of a cyclohexane to the AB-ring system. An alternate RCM based



Scheme 6. Reagents and conditions: (a) 5% NaOH, MeOH–H_2O (1:1), reflux, 4 h; (b) (i) $(COCl)_2$, C_6H_6, rt, 2 h; (ii) CH_2N_2, Et_2O, 0 °C, 3 h; (c) *hv*, MeOH, 1 h; (d) LAH, Et_2O, 0 °C, 2 h; (e) PDC, CH_2Cl_2, rt, 8 h; (f) *i*-PrMgBr, THF, 0 °C, 0.75 h; (g) PCC, NaOAc, CH_2Cl_2, 0 °C→rt, 6 h; (h) CH_2=CHMgBr, THF, 0 °C→rt, 0.75 h; (i) Grubbs' II generation catalyst (5 mol %), C_6H_6, reflux, 4 h.

methodology was developed for an efficient enantiospecific synthesis of komarovispiradiene **34** starting from the bicyclic ketone **17**.

4. Experimental

Melting points were recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Perkin–Elmer 781 and Jasco FTIR 410 spectrophotometers. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a JNM λ-300 spectrometer. 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, 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 micromass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^{-2} g^{-1}. Ozonolysis experiments were carried out using Fischer 502 ozone generator. Hydrogenation reactions at one atmosphere pressure were carried out using a balloon filled with hydrogen. 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 vapour 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). 10% Silver nitrate impregnated silica gel was prepared as per a standard procedure.

4.1. (1*R*,5*R*)-7,7-Ethylenedioxy-3,4,4-trimethylbicyclo-[3.3.0]oct-2-ene 11

To a magnetically stirred solution of diquinane[4] **8** (800 mg, 4.9 mmol) and 1,2-ethanediol (2.7 mL, 48.8 mmol) in benzene (20 mL, 0.25 M) was added a catalytic amount of *p*-TSA (50 mg) and the reaction mixture was refluxed for 4 h with a Dean–Stark water trap. The reaction mixture was cooled, washed with saturated aqueous $NaHCO_3$ solution (15 mL), followed by brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:6) as eluent furnished ketal **11** (871 mg, 86%) as an oil. $[\alpha]_D^{26} = -21.7$ (*c* 1.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1238, 1122, 1097, 1021; ^1H NMR (300 MHz, $CDCl_3$): δ 5.10 (1H, br s), 3.94–3.80 (4H, m), 3.09–3.00 (1H, m), 2.39 (1H, dt, *J* 11.1 and 8.1 Hz), 1.98 (1H, ddd, *J* 13.5, 9.6 and 1.8 Hz), 1.67–1.59 (3H, m), 1.57 (3H, t, *J* 2.1 Hz,), 1.00 (3H, s), 0.94 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2 (C), 127.3 (CH), 118.4 (C), 64.6 (CH_2), 63.8 (CH_2), 52.4 (CH), 47.0 (C), 43.2 (CH), 40.3 (CH_2), 36.8 (CH_2), 28.2 (CH_3), 22.0 (CH_3), 12.4 (CH_3). HRMS *m*/*z*: (M+H) calcd for $C_{13}H_{21}O_2$, 209.1541; found, 209.1546.

4.2. (7*S*,8*R*)-8-(1,1-Dimethyl-2-oxopropyl)-1,4-dioxaspiro-[4.4]nonane-7-carboxaldehyde 12

Dry ozone in oxygen was passed through a cold (−70 °C) solution of ketal **11** (800 mg, 3.85 mmol) and a catalytic amount of $NaHCO_3$ in 1:4 MeOH–CH_2Cl_2 (15 mL) for 15 min. Me_2S (2.8 mL, 38.5 mmol) was added to the reac-

tion mixture and stirred for 8 h at rt. Water (10 mL) was added to the reaction mixture and extracted with ether (3×5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:4) as eluent furnished keto-aldehyde **12** (803 mg, 87%) as an oil. $[\alpha]_D^{24} = +8.2$ (*c* 19.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2720, 1723, 1701; ^1H NMR (300 MHz, $CDCl_3$): δ 9.53 (1H, d, *J* 2.1 Hz), 3.88 (4H, s), 2.83 (1H, ddd, *J* 10.2, 8.4 and 6.6 Hz), 2.56 (1H, qd, *J* 6.9 and 2.1 Hz), 2.14 (3H, s), 2.03 (1H, s), 2.01 (1H, s), 1.83 (1H, dd, *J* 13.2 and 8.7 Hz), 1.67 (1H, dd, *J* 13.2 and 10.8 Hz), 1.11 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.1 (C), 202.3 (CH), 115.6 (C), 64.9 (CH_2), 64.2 (CH_2), 50.1, (CH), 49.5 (C), 42.6 (CH), 37.0 (CH_2), 36.8 (CH_2), 25.6 (CH_3), 22.2 (CH_3), 21.4 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{13}H_{20}O_4Na$, 263.1259; found, 263.1257.

4.3. (1*R*,6*S*)-2,2-Dimethyl-8,8-ethylenedioxybicyclo-[4.3.0]non-4-en-3-one 13

To a magnetically stirred solution of keto-aldehyde **12** (800 mg, 3.33 mmol) in anhydrous benzene (35 mL, 0.1 M) were added glacial acetic acid (0.1 mL, 0.33 mmol) and piperidine (0.1 mL, 0.33 mmol) and the reaction mixture was refluxed using Dean–Stark water trap for 7 h. The reaction mixture was allowed to cool to rt and washed with aqueous $NaHCO_3$. The aqueous portion was extracted with ether (2×5 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:14) as eluent furnished enone **13** (610 mg, 83%) as an oil. $[\alpha]_D^{25} = +6.4$ (*c* 9.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1675, 1527; ^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (1H, dd, *J* 9.9 and 1.5 Hz,), 5.88 (1H, dd, *J* 9.9 and 3.0 Hz,), 3.97–3.90 (2H, m), 3.90–3.80 (2H, m), 2.64–2.52 (1H, m), 2.23 (1H, dd, *J* 12.9 and 7.5 Hz), 2.05–1.88 (2H, m), 1.75 (1H, t, *J* 12.9 Hz), 1.69 (1H, t, *J* 12.6 Hz), 1.10 (3H, s), 0.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7 (C), 148.9 (CH), 129.3 (CH), 116.0 (C), 64.3 (CH_2), 64.2 (CH_2), 51.7 (CH), 44.6 (C), 41.8 (CH_2), 38.4 (CH), 37.9 (CH_2), 23.1 (CH_3), 17.1 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{13}H_{18}O_3Na$, 245.1154; found, 245.1154.

4.4. (1*R*,3*S*,6*S*)-2,2-Dimethyl-8,8-ethylenedioxybicyclo-[4.3.0]non-4-en-3-ol 14

To a cold (−70 °C), magnetically stirred solution of enone **13** (600 mg, 2.70 mmol) in anhydrous ether (5 mL) was added LAH (103 mg, 2.70 mmol) in portions. The reaction mixture was stirred at the same temperature for 1.5 h and allowed to warm up to 0 °C over a period of 20 min. Ethyl acetate (0.5 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice cold water (1 mL). The suspension was filtered through a sintered funnel and the residue was thoroughly washed with ether (3×5 mL). The ether layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:7) as eluent furnished the secondary alcohol **14** (593 mg, 98%) as an oil. $[\alpha]_D^{24} = +14.8$ (*c* 2.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3430; ^1H NMR (300 MHz, $CDCl_3$): δ 5.72 (1H, d, *J* 9.9 Hz), 5.47 (1H, dt, *J* 9.9 and 2.4 Hz), 3.95–3.74 (4H, m), 3.88–3.82 (1H, m), 2.23–2.12 (1H, m), 2.07 (1H, dd, *J* 12.3 and 6.9 Hz), 1.88–1.42 (5H, m), 1.00 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.9 (CH), 129.5 (CH), 116.3 (C), 77.4 (CH), 64.1 (CH_2), 64.0 (CH_2), 50.5 (CH), 42.5 (CH_2), 38.7 (CH), 37.5 (CH_2), 36.5 (C), 25.6 (CH_3), 13.5 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{13}H_{20}O_3Na$, 247.1310; found, 247.1303.

4.5. (1*R*,3*S*,6*S*)-2,2-Dimethyl-8,8-ethylenedioxy-3-methoxybicyclo[4.3.0]non-5-ene 15

To a magnetically stirred, ice cold suspension of sodium hydride (272 mg, 60% dispersion in oil, 6.8 mmol, washed with dry hexane) and tetrabutylammonium iodide (catalytic) in anhydrous THF (1 mL) was added a solution of alcohol **14** (507 mg, 2.26 mmol) in anhydrous THF (4 mL) and stirred for 40 min at rt. Methyl iodide (0.7 mL, 11.3 mmol) was added to the reaction mixture and refluxed for 4 h. It was then quenched with water (5 mL) and extracted with ether (2×10 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:6) as eluent furnished methyl ether **15** (501 mg, 93%) as an oil. $[\alpha]_D^{25} = +17.8$ (*c* 4.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1635, 1270, 1234; ^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (1H, d, *J* 10.2 Hz), 5.64 (1H, dt, *J* 9.9 and 2.4 Hz), 3.94–3.79 (4H, m), 3.42 (3H, s), 2.25–2.13 (1H, m), 2.08 (1H, dd, *J* 12.6 and 6.6 Hz), 1.84 (1H, dd, *J* 11.4 and 5.7 Hz), 1.65–1.45 (3H, m), 0.99 (3H, s), 0.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.2 (CH), 127.8 (CH), 116.3 (C), 86.9 (CH), 64.1 (CH_2), 64.0 (CH_2), 58.4 (CH_3), 50.8 (CH), 42.6 (CH_2), 38.9 (CH), 37.3 (CH_2), 36.4 (C), 25.9 (CH_3), 13.9 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{14}H_{22}O_3Na$, 261.1467; found, 261.1456.

4.6. (1*R*,3*S*,6*R*)-2,2-Dimethyl-8,8-ethylenedioxy-3-methoxybicyclo[4.3.0]nonane 16

To a solution of allyl methyl ether **15** (500 mg, 2.1 mmol) in hexane (3 mL) was added activated 10% Pd–C (100 mg) and the reaction mixture was stirred at 1 atm pressure under hydrogen atmosphere, created by evacuative displacement of air (balloon), for 5 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:4) as eluent furnished product **16** (504 mg, 100%) as an oil. $[\alpha]_D^{23} = -10.0$ (*c* 0.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1237, 1192; ^1H NMR (300 MHz, $CDCl_3$): δ 3.84–3.66 (4H, m), 3.25 (3H, s), 2.64 (1H, dd, *J* 11.1 and 3.9 Hz), 1.92–1.70 (4H, m), 1.62–1.45 (2H, m), 1.33–1.07 (3H, m), 1.00–0.86 (1H, m), 0.88 (3H, s), 0.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 117.0 (C), 88.0 (CH), 63.8 (2C, CH_2), 57.5 (CH_3), 53.0 (CH), 43.8 (CH_2), 37.7 (CH), 37.6 (C), 37.4 (CH_2), 29.5 (CH_2), 26.0 (CH_2), 26.7 (CH_3), 13.4 (CH_3). HRMS *m*/*z*: (M+Na) calcd for $C_{14}H_{24}O_3Na$, 263.1623; found, 263.1623.

4.7. (1*R*,3*S*,6*R*)-2,2-Dimethyl-3-methoxybicyclo[4.3.0]-nonan-8-one 17

To a solution of ketal **16** (510 mg, 2.13 mmol) in THF (8 mL, 0.25 M) was added 3 M HCl (8 mL) and magnetically stirred for 3 h at rt. The reaction mixture was extracted with ether (3 × 10 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ and brine, 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 bicyclic ketone **17** (409 mg, 100%) as an oil. $[\alpha]_D^{25} = -35.0$ (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1746; ^1H NMR (300 MHz, $CDCl_3$): δ 3.36 (3H, s), 2.80 (1H, dd, *J* 11.1 and 4.2 Hz), 2.34 (1H, dd, *J* 15.9 and 4.8 Hz), 2.18 (1H, dd, *J* 12.1 and 6.9 Hz), 2.05–1.70 (5H, m), 1.48–1.08 (3H, m), 1.00 (3H, s), 0.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.1 (C), 87.6 (CH), 57.8 (CH_3), 52.5 (CH), 45.9 (CH_2), 39.6 (CH_2), 37.8 (C), 37.1 (CH), 29.9 (CH_2), 26.0 (CH_2), 27.0 (CH_3), 13.5 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{12}H_{20}O_2Na$, 219.1361; found, 219.1371.

4.8. Ethyl 2-[(1*R*,3*S*,6*R*)-3-methoxy-2,2-dimethylbicyclo-[4.3.0]non-8-ylidene]propionate 18

A suspension of sodium hydride (300 mg, 7.5 mmol, 60% dispersion in oil) in hexanes under nitrogen atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free sodium hydride was then suspended in dry THF (2 mL), cooled to 0 °C and triethyl phosphonopropionate (1.61 mL, 7.5 mmol) was added and stirred for 40 min at rt. A solution of bicyclic ketone **17** (491 mg, 2.5 mmol) in dry THF (4 mL) was added dropwise to the reaction mixture and refluxed for 4 h. The reaction was then quenched by careful addition of saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3 × 5 mL). The combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:4) as eluent furnished a 3:2 *E*/*Z* mixture of α,β-unsaturated ester **18** (626 mg, 89%) as an oil. $[\alpha]_D^{22} = -5.6$ (*c* 10.1, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1709, 1644; ^1H NMR (300 MHz, $CDCl_3$): (mixture of *E*,*Z*-isomers) δ 4.07 (2H, q, *J* 6.9 Hz), 3.26 (3H, s), 2.99 and 2.83 (1H, dd, *J* 18.0 and 6.6 Hz), 2.70–2.60 (1H, m), 2.60–1.00 2.64 (9H, m), 1.74 and 1.72 (3H, s), 1.21 and 1.20 (3H, t, *J* 6.9 Hz), 0.94 (3H, s), 0.73 and 0.72 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of *E*,*Z*-isomers) δ 167.4 and 167.3 (C), 158.0 and 157.8 (C), 119.4 (C), 88.0 (CH), 59.4 (CH_2), 57.6 (CH_3), 54.9 and 53.3 (CH), 40.5 and 40.1 (CH_2), 39.3 and 37.9 (CH), 37.8 and 37.7 (C), 34.1 and 33.6 (CH_2), 29.4 (CH_2), 26.7 and 26.6 (CH_3), 25.9 (CH_2), 15.7 and 15.6 (CH_3), 14.4 (CH_3), 13.3 and 13.2 (CH_3); HRMS *m*/*z*: (M+H) calcd for $C_{17}H_{29}O_3$, 281.2116; found, 281.2101.

4.9. 2-[(1*R*,3*S*,6*R*)-3-Methoxy-2,2-dimethylbicyclo-[4.3.0]non-8-ylidene]propan-1-ol 19

To a cold (−70 °C), magnetically stirred solution of ester **18** (500 mg, 1.8 mmol) in anhydrous ether (7 mL) was added LAH (102 mg, 2.7 mmol) in portions. The reaction mixture was stirred at the same temperature for 2 h and allowed to warm up to 0 °C over a period of 20 min. Ethyl acetate (1 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice cold water (1 mL). The suspension was filtered through a sintered funnel and the residue was thoroughly washed with ether (3 × 5 mL). The ether layer was washed with brine 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 a 3:2 mixture of allyl alcohol **19** (406 mg, 95%) as an oil. $[\alpha]_D^{24} = -6.8$ (*c* 8.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3374; ^1H NMR (300 MHz, $CDCl_3$): (mixture of *E*,*Z*-isomers) δ 4.15–3.90 (2H, m), 3.34 (3H, s), 2.72 (1H, dd, *J* 11.4 and 4.2 Hz), 2.60–1.00 (11H, m), 1.67 and 1.65 (3H, s), 0.99 and 0.98 (3H, s), 0.78 and 0.76 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of *E*,*Z*-isomers) δ 138.4 and 138.3 (C), 128.9 (C), 88.4 (CH), 64.4 and 64.3 (CH_2), 57.7 (CH_3), 54.8 and 54.3 (CH), 39.2 and 38.7 (CH), 38.0 (C), 37.5 and 36.5 (CH_2), 30.8 (CH_2), 29.8 and 29.7 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 16.6 and 16.5 (CH_3), 13.4 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{15}H_{26}O_2Na$, 261.1830; found, 261.1822.

4.10. Ethyl 2-[(1*R*,3*S*,6*R*)-3-methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non- 8-yl]acetates 20a and 20b

A solution of allyl alcohol **19** (406 mg, 1.71 mmol), triethyl orthoacetate (0.93 mL, 5.12 mmol) and a catalytic amount of propionic acid (ca 5 μL) was placed in a Carius tube and heated to 180 °C for 72 h. The reaction mixture was cooled, diluted with ether, washed with 3 N HCl followed by saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a neutral alumina column using CH_2Cl_2–hexane (1:9) as eluent first furnished the minor 8*R*-ester **20a** (175 mg, 34%) as an oil. $[\alpha]_D^{25} = +4.4$ (*c* 1.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1732, 1638, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 4.74 (1H, s), 4.71 (1H, s), 4.06 (2H, q, *J* 7.2 Hz), 3.34 (3H, s), 2.69 (1H, dd, *J* 11.4 and 3.9 Hz), 2.54 and 2.42 (2H, 2 × d, *J* 14.1 Hz), 2.13 (1H, dd, *J* 13.2 and 6.6 Hz), 1.95–1.00 (9H, m), 1.78 (3H, s), 1.24 (3H, t, *J* 7.2 Hz), 0.96 (3H, s), 0.76 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C), 150.4 (C), 108.9 (CH_2), 88.4 (CH), 59.7 (CH_2), 57.8 (CH_3), 53.9 (CH), 48.3 (C), 46.0 (CH_2), 42.6 (CH_2), 39.1 (CH), 37.8 (C), 37.3 (CH_2), 29.6 (CH_2), 26.7 (CH_3), 26.0 (CH_2), 20.4 (CH_3), 14.3 (CH_3), 13.5 (CH_3). HRMS *m*/*z*: (M+Na) calcd for $C_{19}H_{32}O_3Na$, 331.2249; found, 331.2255.

Further elution of the column with CH_2Cl_2–hexane (1:6) furnished the major 8*S*-ester **20b** (263 mg, 50%) as an oil. $[\alpha]_D^{25} = -4.4$ (*c* 1.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1734, 1637, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (1H, br s), 4.71 (1H, br s), 4.05 (2H, q, *J* 6.9 Hz), 3.33 (3H, s), 2.67 (1H, dd, *J* 11.4 and 4.2 Hz), 2.48 and 2.39 (2H, 2 × d, *J* 14.1 Hz), 2.00–1.80 (4H, m), 1.78 (3H, s), 1.66–1.50 (2H, m), 1.45–1.00 (4H, m), 1.22 (3H, t, *J* 6.9 Hz), 0.96 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4 (C), 150.6 (C), 109.1 (CH_2), 88.5 (CH), 59.8 (CH_2), 57.9 (CH_3), 54.5 (CH), 48.7 (C), 45.7 (CH_2), 43.6 (CH_2), 38.4 (CH), 38.0 (C), 36.0 (CH_2), 29.7 (CH_2), 26.7 (CH_3),

26.2 (CH_2), 20.6 (CH_3), 14.4 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{19}H_{32}O_3Na$, 331.2249; found, 331.2242.

4.11. 2-[(1*R*,3*S*,6*R*,8*R*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]ethyl 4-nitrobenzoate 22

To a cold (0 °C), magnetically stirred solution of ester **20a** (50 mg, 0.16 mmol) in dry ether (2 mL) was added LAH (13 mg, 0.33 mmol) in one portion. The reaction mixture was stirred at the same temperature for 2 h. Ethyl acetate (0.5 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice cold water (0.1 mL). The suspension was filtered through a sintered funnel and the residue was thoroughly washed with ether (3 × 5 mL). The ether layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished alcohol **21** (40 mg, 93%) as an oil. $[\alpha]_D^{26} = +3.9$ (*c* 7.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3372, 1636, 886; ^1H NMR (300 MHz, $CDCl_3$): δ 4.74 (1H, s), 4.70 (1H, s), 3.45 (2H, t, *J* 7.8 Hz), 3.33 (3H, s), 2.68 (1H, dd, *J* 11.4 and 3.9 Hz), 2.11 (1H, dd, *J* 12.9 and 6.6 Hz), 2.05–1.00 (12H, m), 1.75 (3H, s), 0.95 (3H, s), 0.73 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.3 (C), 108.8 (CH_2), 88.6 (CH), 60.2 (CH_2), 57.8 (CH_3), 53.9 (CH), 48.3 (C), 44.4 (CH_2), 42.6 (CH_2), 38.8 (CH), 38.0 (C), 37.9 (CH_2), 29.7 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 20.4 (CH_3), 13.6 (CH_3). To a cold (0 °C), magnetically stirred solution of alcohol **21** (30 mg, 0.113 mmol) in CH_2Cl_2 (0.5 mL) were added *p*-nitrobenzoyl chloride (63 mg, 0.34 mmol), pyridine (0.4 mL) and a catalytic amount of DMAP (5 mg) and stirred at rt for 4 h. The reaction mixture was then diluted with water and extracted with CH_2Cl_2 (2 × 5 mL). The combined CH_2Cl_2 layer was washed with 3 N HCl and brine, and dried over 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 *p*-nitrobenzoate **22** (41 mg, 87%) as a solid, which was recrystallized from a 4:1 mixture of CH_2Cl_2–MeOH. $[\alpha]_D^{22} = +18.9$ (*c* 1.8, $CHCl_3$); mp: 113–115 °C; IR (thin film): ν_{max}/cm^{-1} 1727, 1637, 1608, 890; ^1H NMR (300 MHz, $CDCl_3$): δ 8.29 (2H, d, *J* 9.3 Hz), 8.19 (2H, d, *J* 9.3 Hz), 4.80 (1H, s), 4.78 (1H, s), 4.24 (2H, t, *J* 7.5 Hz), 3.36 (3H, s), 2.73 (1H, dd, *J* 11.7 and 4.2 Hz), 2.24–2.07 (2H, m), 2.00–1.80 (3H, m), 1.79 (3H, s), 1.65–1.50 (2H, m), 1.35–1.00 (5H, m), 0.98 (3H, s), 0.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6 (C), 150.4 (C), 149.7 (C), 135.8 (C), 130.5 (2C, CH), 123.4 (2C, CH), 109.3 (CH_2), 88.5 (CH′), 63.8 (CH_2), 57.9 (CH_3), 53.8 (CH), 48.0 (C), 42.4 (CH_2), 39.7 (CH_2), 38.8 (CH), 37.9 (CH_2), 37.7 (C), 29.5 (CH_2), 26.6 (CH_3), 26.0 (CH_2), 20.2 (CH_3), 13.4 (CH_3). HRMS *m*/*z*: (M+Na) calcd for $C_{24}H_{33}NO_5Na$, 438.2256; found, 438.2242; Anal. Calcd for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.70; H, 8.02; N, 3.74. Crystal data: X-ray data were collected at 296 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ 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. $C_{24}H_{33}NO_5$; MW = 415.52; colourless; crystal system: triclinic; space group $P\bar{1}$; cell parameters, $a = 7.1547(16)$ Å, $b = 7.1730(16)$ Å, $c = 23.765(5)$ Å; α 92.968(4), β 91.578(4), γ 110.248(4), $V = 1141.4(4)$ Å^3, $Z = 2$, $D_c = 1.203$ g cm^{-3}, $F(000) = 444$, $\mu = 0.084$ mm^{-1}. Total number of l.s. parameters = 270, $R_1 = 0.0699$ for 2363 $F_0 > 2\sigma(F_0)$ and 0.1135 for all 3879 data. $wR_2 = 0.2010$, GOF = 0.762, restrained GOF = 0.762 for all data. An ORTEP diagram is depicted in Figure 2. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 621174).

4.12. Methyl 3-[(1*R*,3*S*,6*R*,8*R*)-3-methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]propionate 25a

To a magnetically stirred solution of ester **20a** (200 mg, 0.65 mmol) in methanol (10 mL) was added 10% aq NaOH (10 mL) and refluxed for 5 h. It was then cooled, acidified with 3 M HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent furnished acid **23a** (178 mg, 93%) as an oil. To a magnetically stirred solution of acid **23a** (150 mg, 0.54 mmol) in dry benzene (3 mL) was added oxalyl chloride (0.14 mL, 1.61 mmol) and stirred at rt for 2 h. Evaporation of the excess oxalyl chloride and solvent under reduced pressure gave the acid chloride, which was taken in dry ether (5 mL) and added to a cold (0 °C), magnetically stirred ether solution of diazomethane [excess, prepared from *N*-nitroso-*N*-methylurea (400 mg), 60% KOH solution (10 mL) and ether (10 mL)] and the reaction mixture was stirred at 0 °C for 3 h. Careful evaporation of the excess diazomethane and solvent on a hot water bath and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished diazoketone **24a** (139 mg, 85%) as a greenish yellow oil. A solution of diazoketone **24a** (133 mg, 0.44 mmol) in anhydrous methanol (35 mL) was placed in a Pyrex flask and irradiated with a Hanovia medium pressure mercury vapour lamp for 1 h. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:3) as eluent gave ester **25a** (123 mg, 91%) as an oil. $[\alpha]_D^{26} = +10.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1741, 1635, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 4.75 (1H, s), 4.72 (1H, s), 3.64 (3H, s), 3.33 (3H, s), 2.68 (1H, dd, *J* 11.7 and 4.5 Hz), 2.13–2.03 (3H, m), 1.95–0.95 (11H, m), 1.64 (3H, s), 0.88 (3H, s), 0.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (C), 149.9 (C), 109.7 (CH_2), 88.6 (CH), 57.9 (CH_3), 53.8 (CH_3), 51.4 (CH), 49.4 (C), 42.2 (CH_2), 38.9 (CH), 37.9 (C), 37.4 (CH_2), 36.5 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 20.2 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{19}H_{32}O_3Na$, 331.2249; found, 331.2245.

4.13. 3-[(1*R*,3*S*,6*R*,8*R*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]propan-1-ol 26a

To a cold (0 °C), magnetically stirred solution of ester **25a** (123 mg, 0.4 mmol) in dry ether (3 mL) was added LAH (23 mg, 0.6 mmol). The reaction mixture was stirred at the same temperature for 1.5 h. Ethyl acetate (0.5 mL)

was carefully introduced to consume the excess reagent and the reaction was quenched with ice cold water (0.2 mL). The suspension was filtered through a sintered funnel and the residue was thoroughly washed with ether (3 × 5 mL). The ether layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished alcohol **26a** (106 mg, 95%) as an oil. $[\alpha]_D^{25} = -7.5$ (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3419, 1635, 885. ^1H NMR (300 MHz, $CDCl_3$): δ 4.70 (2H, s), 3.56 (2H, t, *J* 6.0 Hz), 3.33 (3H, s), 2.68 (1H, dd, *J* 11.7 and 4.5 Hz), 2.08 (1H, dd, *J* 12.6 and 6.6 Hz), 1.95–1.00 (14H, m), 1.69 (3H, s), 0.94 (3H, s), 0.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8 (C), 109.0 (CH_2), 88.7 (CH), 63.4 (CH_2), 57.9 (CH_3), 54.0 (CH), 49.6 (C), 42.6 (CH_2), 38.9 (CH), 38.2 (CH_2), 37.9 (C), 37.7 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 26.9 (CH_3), 26.2 (CH_2), 20.4 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{19}H_{32}O_3Na$, 303.2300; found, 303.2254.

4.14. 3-[(1*R*,3*S*,6*R*,8*R*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]propanal 27a

To a magnetically stirred solution of alcohol **26a** (70 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (2 mL) was added PDC (226 mg, 1.25 mmol) and stirred for 7 h at rt. The reaction mixture was then filtered through a small silica gel column and the column was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished aldehyde **27a** (64 mg, 93%) as an oil. $[\alpha]_D^{23} = +15.0$ (*c* 0.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2713, 1726, 1635, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 9.68 (1H, s), 4.69 (1H, s), 4.66 (1H, s), 3.27 (3H, s), 2.62 (1H, dd, *J* 11.7 and 4.5 Hz), 2.18 (2H, t, *J* 7.8 Hz), 2.02 (1H, d, *J* 12.6 and 6.6 Hz), 1.90–1.70 (3H, m), 1.62 (3H, s), 1.60–1.35 (3H, m), 1.30–0.75 (5H, m), 0.89 (3H, s), 0.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6 (CH), 150.0 (C), 109.9 (CH_2), 88.5 (CH), 57.9 (CH_3), 53.9 (CH), 49.3 (C), 42.4 (CH_2), 40.6 (CH_2), 38.9 (CH), 37.9 (C), 37.4 (CH_2), 33.4 (CH_2), 29.8 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 20.3 (CH_3), 13.6 (CH_3).

4.15. (1*R*,3*S*,6*R*,8*R*)-3-Methoxy-2,2-dimethyl-2′-methylenebicyclo[4.3.0]nonanespiro[8.1′]cyclohexan-4′-ol 28

To a cold (0 °C), magnetically stirred solution of aldehyde **27a** (30 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (10 mL, 0.01 M) was added $BF_3{\cdot}Et_2O$ (0.1 mL, 0.28 mmol) and stirred for 7 min. Reaction was then quenched by washing with saturated aqueous $NaHCO_3$ solution. It was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished a 1:1 epimeric mixture of spiro alcohol **28** (24 mg, 80%) as an oil. $[\alpha]_D^{25} = -10.0$ (*c* 1.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3382, 1637, 885; ^1H NMR (300 MHz, $CDCl_3$): (mixture of two isomers) δ 4.78 and 4.69 (1H, s), 4.73 and 4.65 (1H, s), 3.80–3.70 and 3.70–3.60 (1H, m), 3.34 (3H, s), 2.69 (1H, dd, *J* 11.4 and 4.5 Hz), 2.60–2.45 (1H, m), 2.30–0.85 (16H, m), 0.96 and 0.95 (3H, s), 0.77 and 0.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of two isomers) δ 152.1 and 151.5 (C), 107.7 and 106.7 (CH_2), 88.7 (CH), 70.2 and 69.5 (CH), 57.9 (CH_3), 54.2 and 53.8 (CH), 46.4 and 46.2 (C), 43.9 and 42.9 (CH_2), 43.3 and 43.2 (CH_2), 38.4 and 38.1 (CH_2), 38.3 (CH), 38.0 and 37.9 (C), 36.4 and 35.3 (CH_2), 32.5 and 31.5 (CH_2), 29.8 (CH_2), 26.8 (CH_3), 26.1 (CH_2), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{18}H_{32}O_2Na$, 301.2144; found, 301.2077.

4.16. (1*R*,3*S*,6*R*,8*R*)-3-Methoxy-2,2,2′-trimethylbicyclo-[4.3.0]nonanespiro[8.1′]cyclohex-2′-en-4′-one 29

To a magnetically stirred solution of an epimeric mixture of spiro alcohol **28** (21 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (2 mL) was added a homogeneous mixture of PCC (81 mg, 0.38 mmol) and silica gel (81 mg) and stirred for 4 h at rt. The reaction mixture was filtered through a small silica gel column using more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished enone **29** (18 mg, 86%) as an oil. $[\alpha]_D^{25} = -38.3$ (*c* 0.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1672, 1614; ^1H NMR (300 MHz, $CDCl_3$): δ 5.71 (1H, s), 3.36 (3H, s), 2.73 (1H, dd, *J* 11.7 and 4.5 Hz), 2.50–2.28 (2H, m), 2.15–1.86 (4H, m), 1.93 (3H, s), 1.80–1.50 (4H, m), 1.48–1.18 (4H, m), 1.00 (3H, s), 0.82 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6 (C), 167.8 (C), 126.1 (CH), 88.3 (CH), 58.0 (CH_3), 54.0 (CH), 45.3 (C), 45.0 (CH_2), 40.6 (CH), 38.1 (C), 38.0 (CH_2), 35.0 (CH_2), 34.2 (CH_2), 29.9 (CH_2), 26.9 (CH_3), 26.1 (CH_2), 20.3 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{18}H_{28}O_2Na$, 299.1987; found: 299.1989.

4.17. Methyl 3-[(1*R*,3*S*,6*R*,8*S*)-3-methoxy-2,2-dimethyl-8-(methylethenyl)bicyclo[4.3.0]non-8-yl]propionate 25b

To a magnetically stirred solution of ester **20b** (130 mg, 0.42 mmol) in methanol (10 mL) was added 10% aq NaOH (10 mL) and refluxed for 4 h. It was then cooled, acidified with 3 M HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent furnished acid **23b** (113 mg, 95%) as an oil. To a magnetically stirred solution of acid **23b** (100 mg, 0.35 mmol) in dry benzene (3 mL) was added oxalyl chloride (0.15 mL, 1.05 mmol) and stirred at rt for 2 h. Evaporation of the excess oxalyl chloride and solvent under reduced pressure gave an acid chloride, which was taken in dry ether (5 mL) and added to a cold (0 °C), magnetically stirred ether solution of diazomethane [excess, prepared from *N*-nitroso-*N*-methylurea (400 mg), 60% KOH solution (10 mL) and ether (10 mL)] and the reaction mixture was stirred at 0 °C for 3 h. Careful evaporation of the excess diazomethane and solvent on a hot water bath and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished diazoketone **24b** (97 mg, 89%) oil. A solution of diazoketone **24b** (97 mg, 0.32 mmol) in anhydrous methanol (35 mL) was placed in a Pyrex flask and irradiated with a Hanovia medium pressure mercury vapour lamp for 1 h. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:3) as eluent gave propionate **25b** (86 mg, 87%) as an oil.

$[\alpha]_D^{26} = +13.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1740, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 4.74 (1H, s), 4.70 (1H, s), 3.64 (3H, s), 3.33 (3H, s), 2.67 (1H, dd, *J* 11.7 and 4.5 Hz), 2.09 (2H, t, *J* 8.7 Hz), 1.95–1.75 (4H, m), 1.70 (3H, s), 1.68–1.53 (3H, m), 1.33–0.80 (5H, m), 0.88 (3H, s), 0.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C), 150.1 (C), 109.6 (CH_2), 88.4 (CH), 57.8 (CH_3), 54.1 (CH_3), 51.3 (CH), 49.5 (C), 43.6 (CH_2), 38.2 (CH), 37.9 (C), 35.8 (CH_2), 35.5 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 26.7 (CH_3), 26.1 (CH_2), 20.2 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{19}H_{32}O_3Na$, 331.2249; found, 331.2248.

4.18. 3-[(1*R*,3*S*,6*R*,8*S*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]propan-1-ol 26b

To a cold (0 °C), magnetically stirred solution of ester **25b** (76 mg, 0.25 mmol) in dry ether (3 mL) was added LAH (19 mg, 0.5 mmol) and the reaction mixture was stirred at the same temperature for 1.5 h. Ethyl acetate (0.5 mL) was carefully introduced to consume the excess reagent and the reaction was quenched with ice cold water (0.2 mL). The suspension was filtered through a sintered funnel and the residue was thoroughly washed with ether (3×5 mL). The ether layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:6) as eluent furnished alcohol **26b** (68 mg, 99%) as an oil. $[\alpha]_D^{26} = +8.3$ (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3374, 885; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71 (1H, s), 4.69 (1H, s), 3.56 (2H, t, *J* 6.6 Hz), 3.33 (3H, s), 2.68 (1H, dd, *J* 11.4 and 3.9 Hz), 1.95–0.80 (15H, m), 1.62 (3H, s), 0.88 (3H, s), 0.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.0 (C), 109.0 (CH_2), 88.6 (CH), 63.2 (CH_2), 57.8 (CH_3), 54.1 (CH), 49.6 (C), 43.8 (CH_2), 38.3 (CH), 38.0 (C), 37.5 (CH_2), 35.8 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 26.8 (CH_3), 26.2 (CH_2), 20.4 (CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{18}H_{32}O_2Na$, 303.2300; found, 303.2299.

4.19. 3-[(1*R*,3*S*,6*R*,8*S*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]propanal 27b

To a magnetically stirred solution of alcohol **26b** (60 mg, 0.214 mmol) in anhydrous CH_2Cl_2 (3 mL) was added PDC (194 mg, 1.1 mmol) and stirred for 8 h at rt. The reaction mixture was then filtered through a small silica gel column and the column was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:19) as eluent furnished aldehyde **27b** (57 mg, 96%) as an oil. $[\alpha]_D^{26} = +8.7$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2713, 1726, 1635, 889; ^1H NMR (300 MHz, $CDCl_3$): δ 9.73 (1H, s), 4.75 (1H, s), 4.71 (1H, s), 3.32 (3H, s), 2.66 (1H, dd, *J* 11.4 and 3.9 Hz), 2.24 (2H, t, *J* 7.5 Hz), 2.00–1.50 (7H, m), 1.68 (3H, s), 1.40–1.00 (5H, m), 0.95 (3H, s), 0.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3 (CH), 150.2 (C), 109.8 (CH_2), 88.4 (CH), 57.8 (CH_3), 54.1 (CH), 49.4 (C), 43.6 (CH_2), 40.5 (CH_2), 38.2 (CH), 37.9 (C), 35.6 (CH_2), 32.7 (CH_2), 29.7 (CH_2), 26.7 (CH_3), 26.1 (CH_2), 20.2 (CH_3), 13.6 (CH_3).

4.20. 1-[(1*R*,3*S*,6*R*,8*S*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]-4-methylpentan-3-ol 30

To an ice cold solution of aldehyde **27b** (42 mg, 0.16 mmol) in anhydrous THF (1 mL) was added a solution of isopropylmagnesium bromide [freshly prepared from magnesium (62 mg, 2.36 mmol) and isopropyl bromide (0.24 mL, 2.36 mmol) in anhydrous THF (5 mL)] and stirred for 45 min at rt. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with ether (3×5 mL). The combined organic layer was washed with brine 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 a 1:1 epimeric mixture of alcohol **30** (46 mg, 94%) as an oil. $[\alpha]_D^{26} = +8.6$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3444, 885; ^1H NMR (300 MHz, $CDCl_3$): (mixture of two isomers) δ 4.70 (1H, s), 4.68 (1H, s), 3.33 (3H, s), 3.30–3.20 (1H, m), 2.67 (1H, dd, *J* 11.4 and 4.2 Hz), 1.95–1.80 (3H, m), 1.69 (3H, s), 1.70–1.00 (13H, m), 0.96 (3H, s), 0.78 (3H, s), 0.92–0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): (mixture of two isomers) δ 151.2 (C), 108.9 (CH_2), 88.6 (CH), 77.3 and 77.2 (CH), 57.9 (CH_3), 54.1 (CH), 49.7 (C), 44.0 and 43.9 (CH_2), 38.3 (CH), 37.9 (C), 37.7 and 37.6 (CH_2), 35.9 and 35.8 (CH_2), 33.5 (CH), 29.9 (CH_2), 29.8 (CH_2), 26.7 (CH_3), 26.2 (CH_2), 20.4 (CH_3), 19.2 (CH_3), 17.3 and 17.1 (CH_3), 13.6 (CH_3). HRMS *m*/*z*: (M+H) calcd for $C_{21}H_{39}O_2$, 323.2973. Found: 323.2973.

4.21. 1-[(1*R*,3*S*,6*R*,8*S*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]-4-methylpentan-3-one 31

To a magnetically stirred suspension of PCC (84 mg, 0.39 mmol) and NaOAc (32 mg, 0.39 mmol) in anhydrous CH_2Cl_2 (1 mL) was added a solution of an epimeric mixture of alcohol **30** (40 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (2 mL) and stirred vigorously for 6 h at rt. The reaction mixture was then filtered through a small silica gel column and the column was eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica gel column using CH_2Cl_2–hexane (1:3) as eluent furnished ketone **31** (38 mg, 96%) as an oil. $[\alpha]_D^{24} = +5.0$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1714, 1635, 887; ^1H NMR (300 MHz, $CDCl_3$): δ 4.72 (1H, s), 4.68 (1H, s), 3.32 (3H, s), 2.66 (1H, dd, *J* 11.7 and 4.2 Hz), 2.54 (1H, septet, *J* 7.2 Hz), 2.20 (2H, t, *J* 7.8 Hz), 1.90–1.50 (6H, m), 1.67 (3H, s), 1.40–0.80 (6H, m), 1.06 (6H, d, *J* 6.9 Hz), 0.95 (3H, s), 0.77 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.1 (C), 150.7 (C), 109.3 (CH_2), 88.5 (CH), 57.8 (CH_3), 54.2 (CH), 49.5 (C), 43.7 (CH_2), 41.0 (CH), 38.2 (CH), 37.9 (C), 36.5 (CH_2), 35.6 (CH_2), 34.5 (CH_2), 29.7 (CH_2), 26.7 (CH_3), 26.2 (CH_2), 20.3 (CH_3), 18.5 (2C, CH_3), 13.6 (CH_3); HRMS *m*/*z*: (M+H) calcd for $C_{21}H_{37}O_2$, 321.2793; found, 323.2791.

4.22. 5-[(1*R*,3*S*,6*R*,8*S*)-3-Methoxy-2,2-dimethyl-8-(1-methylethenyl)bicyclo[4.3.0]non-8-yl]-3-(1-methylethyl)pent-1-en-3-ol 32

To an ice cold solution of ketone **31** (30 mg, 0.08 mmol) in anhydrous THF (1 mL) was added a solution of vinylmagnesium bromide [freshly prepared from magnesium (30 mg,

1.44 mmol) and vinyl bromide (0.1 mL, 1.44 mmol) in anhydrous THF (5 mL)] and stirred for 45 min at rt. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with ether (3×5 mL). The combined organic layer was washed with brine 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 a 1:1 epimeric mixture of alcohol **32** (31 mg, 94%) as an oil. $[\alpha]_D^{26} = -8.0$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3460, 1637, 918; ^1H NMR (300 MHz, $CDCl_3$): (mixture of two isomers) δ 5.75 (1H, dd, *J* 17.4 and 10.5 Hz), 5.18 (1H, dd, *J* 17.4 and 1.5 Hz), 5.14 (1H, d, *J* 10.5 Hz), 4.70 (1H, s), 4.67 (1H, s), 3.33 (3H, s), 2.67 (1H, dd, *J* 11.4 and 3.9 Hz), 2.00–1.00 (16H, m), 1.67 (3H, s), 0.96 (3H, s), 0.88 (3H, d, *J* 6.6 Hz), 0.85 (3H, d, *J* 6.6 Hz), 0.78 (3H, s); ^{13}C NMR (75 MHz): (mixture of two isomers) δ 150.8 (C), 142.4 (CH), 113.2 (CH_2), 108.9 (CH_2), 88.5 (CH), 77.4 (C), 57.9 (CH_3), 53.9 (CH), 49.6 (C), 42.8 and 42.6 (CH_2), 38.9 and 38.7 (CH), 38.0 (C), 38.0 (CH_2), 36.5 and 36.3 (CH), 35.2 (CH_2), 33.8 and 33.6 (CH_2), 29.9 (CH_2), 26.9 (CH_3), 26.2 (CH_2), 20.4 (CH_3), 17.8 (CH_3), 16.6 (CH_3), 13.7 (CH_3); HRMS *m*/*z*: (M+Na) calcd for $C_{23}H_{40}O_2Na$, 371.2926; found, 371.2941.

4.23. (1*R*,3*S*,6*R*,8*S*)-4′-Isopropylidine-3-methoxy-2,2,2′-trimethylbicyclo[4.3.0]nonanespiro[8.1′]cyclohex-2′-ene 34 (komarovispiradiene)

To a magnetically stirred solution of a 1:1 epimeric mixture of alcohol **32** (16 mg, 0.05 mmol) in anhydrous benzene (1 mL, 0.1 M) was added Grubbs' second generation catalyst (2 mg, 5 mol %) and the reaction mixture was refluxed for 4 h. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using CH_2Cl_2–pentane (1:19) as eluent furnished komarovispiradiene **34** (10 mg, 71%) as an oil. $[\alpha]_D^{23} = +15.0$ (*c* 1.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1260, 1189, 1152, 1137; ^1H NMR (300 MHz, $CDCl_3$): δ 6.11 (1H, s), 3.36 (3H, s), 2.73 (1H, dd, *J* 11.7 and 4.5 Hz), 2.40–2.30 (1H, m), 2.20–2.07 (1H, m), 1.78 (3H, s), 1.75 (3H, s), 1.70 (3H, s), 2.00–1.77 (3H, m), 1.64–1.50 (4H, m), 1.35–0.90 (5H, m), 0.96 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2 (C), 127.6 (C), 123.7 (C), 121.4 (CH), 88.8 (CH), 58.0 (CH_3), 55.9 (CH), 44.2 (C), 42.6 (CH_2), 38.8 (CH_2), 38.2 (CH), 38.0 (C), 37.9 (CH_2), 29.4 (CH_2), 26.6 (CH_3), 26.2 (CH_2), 24.0 (CH_2), 20.5 (CH_3), 19.9 (CH_3), 19.5 (CH_3), 13.3 (CH_3); HRMS *m*/*z*: (M+H) calcd for $C_{21}H_{35}O$, 303.2688; found, 303.2698.

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