

## Rapid Communication

### Enantiospecific synthesis of the complete carbon framework of the diterpenes komarovspiranes

A Srikrishna\* & B Beeraiah

Department of Organic Chemistry, Indian Institute of Science,  
Bangalore 560 012, India

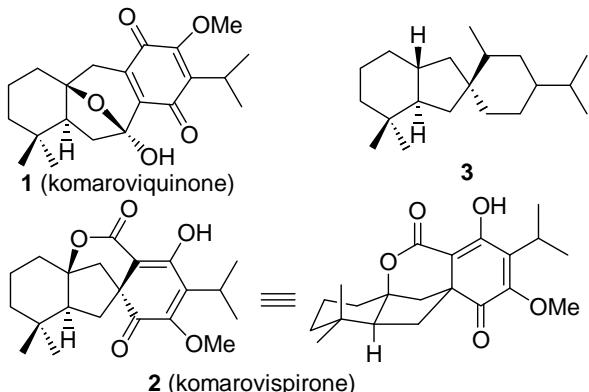
E-mail: ask@orgchem.iisc.ernet.in

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Enantiospecific total synthesis of komarovspiradiene, containing a novel carbon framework *trans*-bicyclo[4.3.0]nonanespiro[8.1']cyclohexane, starting from campholenaldehyde is described.

**Keywords:** Komarovspiranes; enantiospecific synthesis; campholenaldehyde; RCM reaction; bicyclo[4.3.0]nonanespiro[8.1']-cyclohexane; diquinane.

*Dracocephalum komarovi* Lipsky is a perennial semishrub in Uzbekistan, and its extract is known to treat various diseases such as inflammatory diseases and hypertony. Initial phytochemical investigations on the whole plants of *D. komarovi* by Honda and coworkers led to the isolation<sup>1</sup> of komarovquinone **1**, which belong to the icetexane group of diterpenes. Further investigations led to the isolation<sup>2</sup> of a novel tricyclic diterpene komarovspirone **2** containing a new and interesting cyclohexane spirofused to a hydrindane carbon framework, komarovspirane **3**. Both komarovquinone **1** and komarovspirone **2** were found to exhibit trypanocidal activity against epimastigotes *Trypanosoma cruzi*, the causative agent of American trypanosomiasis. Novel structure containing an unusual carbon framework coupled with the biological activity made komarovspirone **2**



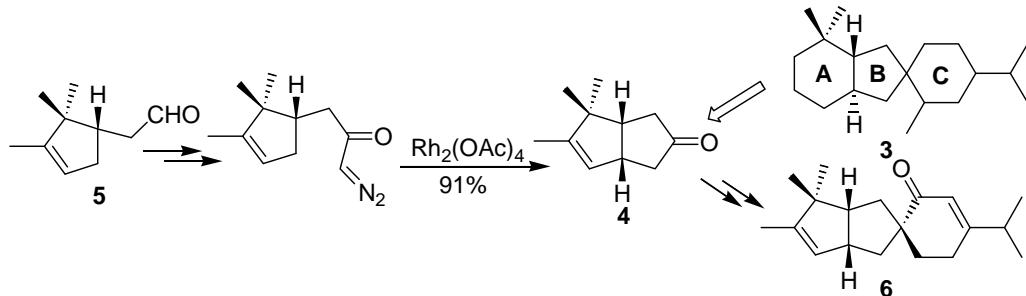
and its analogues interesting synthetic targets. So far there is no report in the literature on the synthesis of the tricyclic carbon framework of komarovspiranes either in racemic or enantiopure form.

An enantiospecific approach for the generation of the complete carbon framework **3** of komarovspirone starting from the bicyclo[3.3.0]octanone **4**, which is readily available from campholenaldehyde **5** employing an intramolecular rhodium carbénoid CH insertion reaction has been initiated<sup>3</sup>. It was contemplated that the bicyclic ketone **4** is an ideal substrate to elaborate into komarovspiranes **3**, which requires spiroannulation of a cyclohexane ring at the C-3 carbon and expansion of the second cyclopentane ring into a cyclohexane ring, **Scheme I**. As a model study, recently we have reported<sup>4</sup> the synthesis of bis-norkomarovspirane **6** via spiroannulation of a cyclohexane to the bicyclic ketone **4**. In continuation, herein we describe enantiospecific synthesis of a komarovspiradiene, containing the complete carbon framework of komarovspirone **2**.

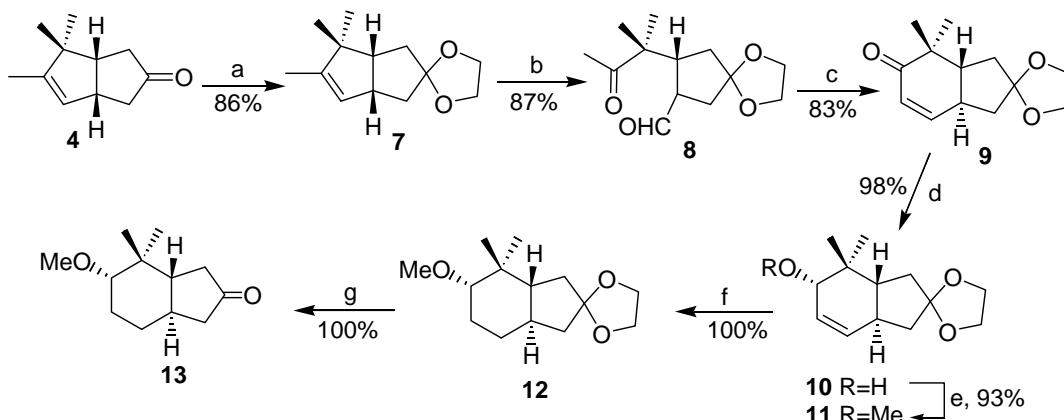
To begin with, we have investigated the expansion of the cyclopentene ring in the diquinane **4** into a cyclohexane ring employing an oxidative cleavage followed by intramolecular aldol condensation (**Scheme II**). To avoid regiochemical problems, the ketone group in diquinane **4** was protected as 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 the ketal **7**. Ozonolysis of the bicyclic ketal **7** followed by reductive work-up furnished the keto-aldehyde **8**, which on intramolecular aldol condensation with piperidine and acetic acid furnished the bicyclic enone **9** containing the requisite *trans*-ring junction, whose structure was established from its spectral data. Reduction of the bicyclic enone **9** with lithium aluminum hydride (LAH) furnished the allyl alcohol **10** in a highly regio- and stereoselective manner. Treatment of the allyl alcohol **10** with sodium hydride, methyl iodide and a catalytic amount of tetrabutylammonium iodide (TBAI) in THF furnished the methyl ether **11**, which on hydrogenation with 10% palladium over carbon as the catalyst furnished the saturated compound **12**. Acid catalysed hydrolysis transformed the ketal **12** into the bicyclic ketone **13**.

After successfully accomplishing the ring expansion of the A-ring to generate the bicyclic ketone **13**, spiroannulation of a cyclohexane ring at the C-8 carbon was addressed. The sequence starting from the bicyclic ketone **13** is depicted in **Schemes III-VI**. Horner-Wadsworth-Emmons reaction of the bicyclic ketone **13** with triethyl phosphonoacetate and sodium hydride in refluxing THF furnished an *E,Z*-mixture of the  $\alpha,\beta$ -unsaturated ester **14**, which on

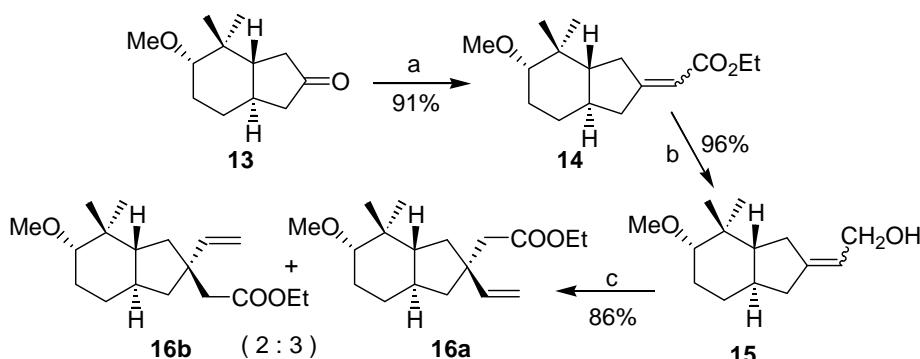
reduction with LAH in ether at low temperature furnished an *E,Z*-mixture of the allyl alcohol **15**. As either isomer of the alcohol **15** is expected to lead to same product in the next step, separation of the isomers was not carried out. An ortho ester Claisen rearrangement<sup>5</sup> of the allyl alcohol **15** was employed for the creation of the quaternary (latent spiro) carbon. Thus, thermal activation of the allyl alcohol **15** and triethyl orthoacetate in the presence of a catalytic



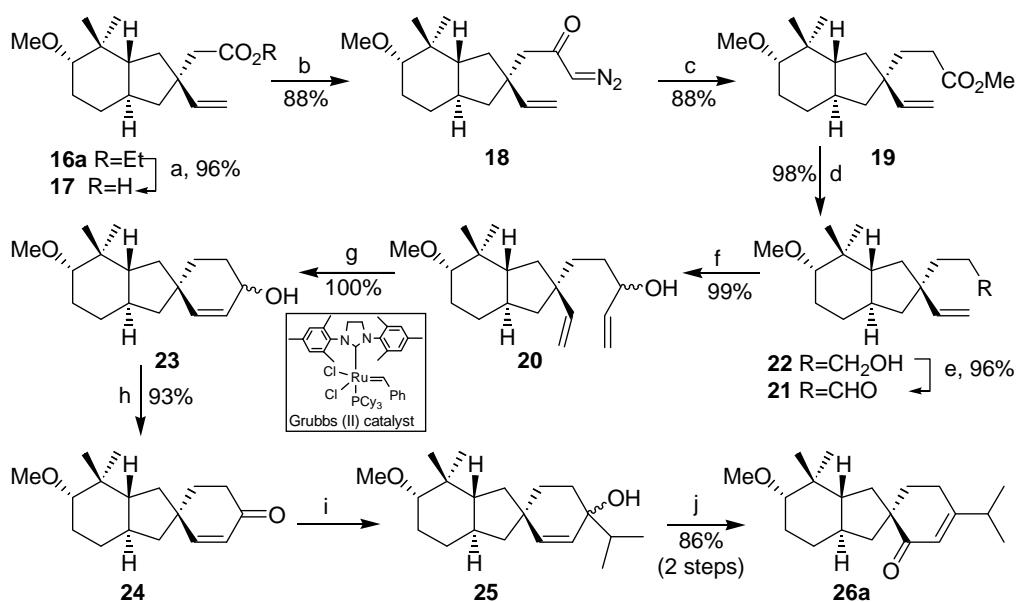
Scheme I



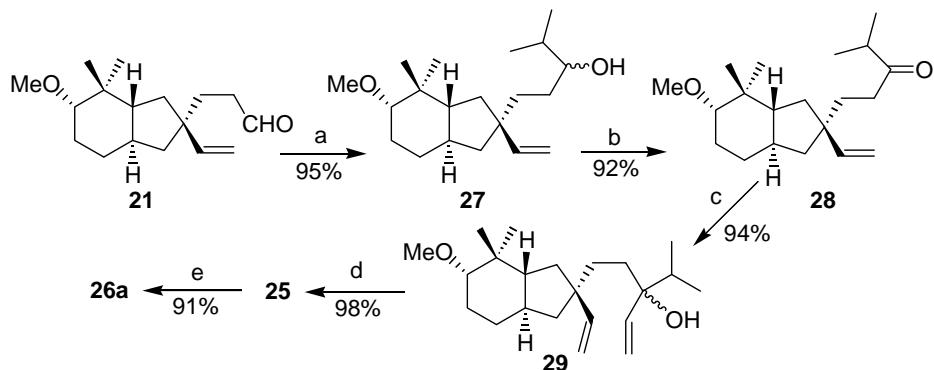
**Scheme II**—Reagents and conditions: (a)  $(\text{CH}_2\text{OH})_2$ , PTSA,  $\text{C}_6\text{H}_6$ , reflux, 4 hr; (b)  $\text{O}_3/\text{O}_2$ ,  $\text{CH}_2\text{Cl}_2\text{-MeOH}$  (4:1),  $-70^\circ\text{C}$ ;  $\text{Me}_2\text{S}$ , RT, 8 hr; (c)  $\text{AcOH}$ , piperidine,  $\text{C}_6\text{H}_6$ , reflux, 7 hr; (d) LAH,  $\text{Et}_2\text{O}$ ,  $-70^\circ\text{C}$ , 1.5 hr; (e)  $\text{NaH}$ ,  $\text{MeI}$ , TBAI,  $\text{THF}$ ,  $0^\circ\text{C} \rightarrow$  reflux, 4 hr; (f)  $\text{H}_2$ , 10%Pd/C, hexane, 1 atm, 5 hr; (g) 3*N* HCl, THF, RT, 3 hr.



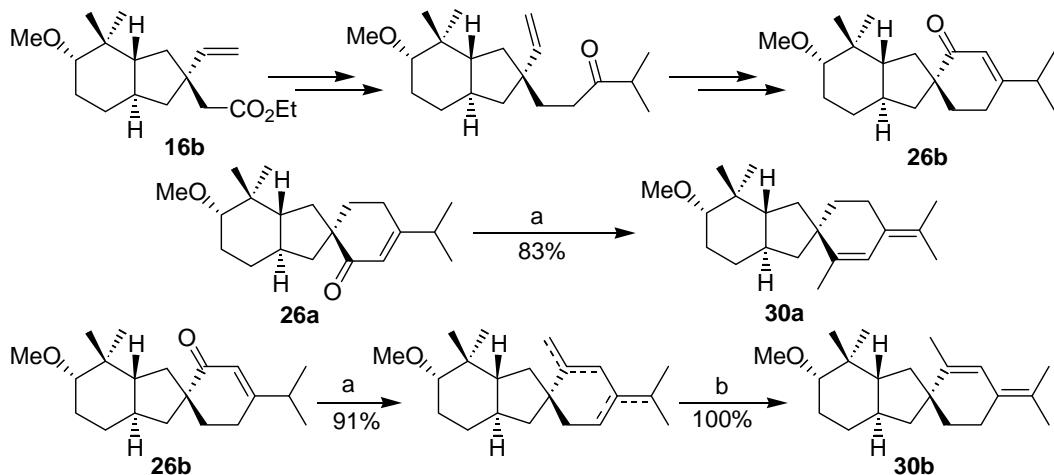
**Scheme III**—Reagents and conditions: (a)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ ,  $\text{NaH}$ ,  $\text{THF}$ ,  $0^\circ\text{C} \rightarrow$  reflux, 4 hr; (b) LAH,  $\text{Et}_2\text{O}$ ,  $-70^\circ\text{C}$ , 2 hr; (c)  $\text{CH}_3\text{C}(\text{OEt})_3$ ,  $\text{EtCO}_2\text{H}$  (catalytic), sealed tube,  $180^\circ\text{C}$ , 60 hr.



**Scheme IV**—Reagents and conditions: (a) 5% NaOH, MeOH-H<sub>2</sub>O (1:1), reflux, 4 hr; (b) i. (COCl)<sub>2</sub>, C<sub>6</sub>H<sub>6</sub>, rt, 2 hr; ii. CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 0 °C, 3 hr; (c) hν, MeOH, 1 hr; (d) LAH, Et<sub>2</sub>O, 0 °C, 1.5 hr; (e) PDC, CH<sub>2</sub>Cl<sub>2</sub>, rt, 7 hr; (f) CH<sub>2</sub>=CHMgBr, THF, 0 °C, 0.75 hr; (g) Grubbs II generation catalyst (5 mol%), C<sub>6</sub>H<sub>6</sub>, reflux, 5 hr; (h) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 hr; (i) i-PrMgBr, THF, 0 °C, 0.5 hr; (j) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 6 hr.



**Scheme V**—Reagents and conditions: (a) i-PrMgBr, THF, 0 °C→rt, 0.5 hr; (b) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, rt, 4 hr; (c) CH<sub>2</sub>=CHMgBr, THF, 0 °C, 0.5 hr; (d) Grubbs II generation catalyst (5 mol%), C<sub>6</sub>H<sub>6</sub>, reflux, 6 hr; (e) PCC, NaOAc, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C→rt, 6 hr.



**Scheme VI**—Reagents and conditions: (a) MeMgI, Et<sub>2</sub>O, 0 °C, 0.5 hr; (b) PTSA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 5 hr.

amount of propionic acid in a sealed tube furnished a 3:2 epimeric mixture of the  $\gamma,\delta$ -unsaturated esters **16a** and **16b**, which were separated by column chromatography on neutral alumina<sup>6</sup>.

For the spiroannulation of a cyclohexane ring, first the ester **16a** was homologated employing an Arndt-Eistert protocol. Thus, hydrolysis of the ester **16a** with sodium hydroxide in aqueous methanol furnished the acid **17**. Reaction of the acid **17** with oxalyl chloride followed by treatment of the resultant acid chloride with diazomethane furnished the diazoketone **18**. Photochemical Wolff rearrangement by irradiation of the diazoketone **18** with a 450W medium pressure mercury vapor lamp in methanol generated the ester **19**.

An RCM reaction<sup>7</sup> was conceived for the spiroannulation of the cyclohexane ring via the hydroxydiene **20**, which was prepared via the aldehyde **21**. Reduction of the ester **19** with LAH in ether, followed by oxidation of the alcohol **22** with pyridinium dichromate (PDC) in methylene chloride furnished the aldehyde **21**. Grignard reaction of the aldehyde **21** with vinylmagnesium bromide in THF furnished the hydroxydiene **20**. RCM reaction of the hydroxydiene **20** with 5 mol% Grubbs' second generation catalyst in refluxing benzene generated the spiroannulated alcohol **23**, which on oxidation with PCC and sodium acetate in methylene chloride furnished the spiroenone **24**. A 1,3-alkylative enone transposition methodology<sup>8</sup> was adopted for the introduction of the isopropyl group. Thus, regioselective 1,2-addition of isopropylmagnesium bromide to the enone **24**, followed by oxidation of the resultant allyl alcohol **25** produced norkomarovispirone **26a**, whose structure was established from its spectral data<sup>#</sup>.

It was considered that the isopropyl group could also be incorporated prior to the spiroannulation with almost equal efficiency, **Scheme V**. Accordingly, Grignard reaction of the aldehyde **21** with isopropylmagnesium bromide followed by oxidation of the resultant secondary alcohol **27** generated the isopropyl ketone **28**. Addition of vinylmagnesium bromide to the ketone **28** furnished the tertiary allyl alcohol **29**. As anticipated, RCM reaction of the hydroxydiene **29** with Grubbs' second generation catalyst in refluxing benzene, followed by oxidation of the resultant spiroalcohol **25** furnished norkomarovispirone **26a**.

In a similar manner, same set of sequence transformed the minor isomer **16b** into norkomarovispirone<sup>#</sup> **26b** in almost equal overall efficiency,

**Scheme VI.** Finally, the last carbon required for komarovispirane was introduced by a Grignard reaction. Thus, reaction of the enone **26a** with methylmagnesium iodide in ether followed by *in situ* dehydration of the resultant alcohol furnished komarovispiradiene **30a**<sup>#</sup>. On the other hand reaction of the enone **26b** with methylmagnesium iodide followed by *in situ* dehydration generated a mixture of three dienes (by NMR), which on isomerisation with PTSA furnished komarovispiradiene **30b**, whose structure was established from its spectral data<sup>#</sup>.

In conclusion, we have developed a convenient and efficient enantiospecific strategy for the synthesis of komarovispiradienes **30**, containing the complete carbon framework **3** of komarovispirone **2**. For the generation of the ABC-ring system of komarovispirane, a Claisen rearrangement-RCM reaction based methodology was developed for the spiroannulation of a cyclohexane ring to AB-ring system **13**, which was generated by ring expansion of the diquinane **4** derived from campholenaldehyde **5**.

### Acknowledgement

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### References and Notes

- Uchiyama N, Kiuchi F, Ito M, Honda G, Takeda Y, Khodzhimato O K & Ashurmetov O A, *J Nat Prod*, **66**, 2003, 128.  
(a) Uchiyama N, Ito M, Kiuchi F, Honda G, Takeda Y, Khodzhimato O K & Ashurmetov O A, *Tetrahedron Lett*, **45**, 2004, 531;  
(b) Uchiyama N, Kiuchi F, Ito M, Honda G, Takeda Y, Khodzhimato O K & Ashurmetov O A, *Tetrahedron*, **62**, 2006, 4355.
- Srikrishna A, Beeraiah B & Satyanarayana G, *Tetrahedron: Asymmetry*, **17**, 2006, 1544.
- Srikrishna A & Beeraiah B, *Tetrahedron Lett*, **48**, 2007, 2291.
- Johnson W S, Werthmann L, Bartlett W R, Brocksom T J, Li T T, Faulkner D J & Petersen M R, *J Am Chem Soc*, **92**, 1970, 741.
- The stereochemistry of the newly created quaternary carbon atom as well as the *trans* ring junction in the two isomers **16** was assigned on the basis of X-ray diffraction analysis of a related example. Srikrishna A & Beeraiah B, *Tetrahedron: Asymmetry*, in press.
- (a) Grubbs R H & Chang S, *Tetrahedron*, **54**, 1998, 4413;  
(b) Fürstner A, *Angew Chem Int Ed*, **39**, 2000, 3013;  
(c) Trnka T M & Grubbs R H, *Acc Chem Res*, **34**, 2001, 18;

(d) Grubbs R H, **2003**, *Handbook of Metathesis*, Wiley-VCH, Vol. 2.

7 (a) Buchi G & Egger B, *J Org Chem*, **36**, **1971**, 2021.

(b) Srikrishna A & Hemamalini P, *Indian J Chem*, **29B**, **1990**, 152.

# Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass) consistent with their structures. Selected spectral data for (1*R*,3*S*,6*R*,8*S*)-4'-isopropyl-3-methoxy-2,2-dimethylbicyclo[4.3.0]nonanespiro[8.1']cyclohex-3'-en-2'-one **26a**:  $[\alpha]_D^{24} : +10.0$  (*c* 0.8,  $\text{CHCl}_3$ ); IR (neat): 1666, 1629, 1103  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.73 (1 H, s), 3.28 (3 H, s), 2.67 (1 H, dd, *J* = 11.1 and 4.2 Hz), 2.40-2.20 (3 H, m), 1.90-1.40 (10 H, m), 1.30-1.10 (2 H, m), 1.02 (6 H, d, *J* = 6.6 Hz), 0.88 (3 H, s), 0.70 (3 H, s); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.3 (C), 169.7 (C), 122.2 (CH), 88.4 (CH), 58.1 (CH<sub>3</sub>), 53.8 (CH), 50.2 (C), 39.4 (CH<sub>2</sub>), 38.5 (CH), 37.8 (C), 36.4 (CH<sub>2</sub>), 35.43 (CH<sub>2</sub>), 35.4 (CH), 29.0 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>), 26.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 20.8 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 13.3 (CH<sub>3</sub>); HRMS: *m/z* Calcd for  $\text{C}_{20}\text{H}_{32}\text{O}_2\text{Na}$  ( $\text{M}+\text{Na}$ ): 327.2300; Found: 327.2296. (1*R*,3*S*,6*R*,8*R*)-4'-Isopropyl-3-methoxy-2,2-dimethylbicyclo[4.3.0]nonanespiro[8.1']cyclohex-3'-en-2'-one **26b**:  $[\alpha]_D^{26} : -10.0$  (*c* 0.4,  $\text{CHCl}_3$ ); IR (neat): 1666, 1633, 1103  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.78 (1 H, s), 3.35 (3 H, s), 2.72 (1 H, dd, *J* = 11.4 and 4.2 Hz), 2.38 (1 H, septet, *J* = 6.6 Hz), 2.30 (2 H, t, *J* = 5.7 Hz), 2.07 (1 H, dd, *J* = 12.3 and 6.6 Hz), 2.00-1.60 (6 H, m), 1.43 (1 H, dd, *J* = 12.3 and 7.2 Hz), 1.35-1.08 (4 H, m), 1.09 (6 H, d, *J* = 6.6 Hz), 0.98 (3 H, s), 0.82 (3

H, s); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.4 (C), 169.5 (C), 122.1 (CH), 88.7 (CH), 58.0 (CH<sub>3</sub>), 54.1 (CH), 50.1 (C), 42.4 (CH<sub>2</sub>), 39.0 (CH), 38.0 (C), 36.6 (CH<sub>2</sub>), 35.3 (CH), 32.9 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 26.7 (CH<sub>3</sub>), 26.0 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 20.74 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 13.5 (CH<sub>3</sub>); HRMS: *m/z* Calcd for  $\text{C}_{20}\text{H}_{32}\text{O}_2\text{Na}$  ( $\text{M}+\text{Na}$ ): 327.2300; Found: 327.2306. (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 **30a**:  $[\alpha]_D^{23} : +15.0$  (*c* 1.4,  $\text{CHCl}_3$ ); IR (neat): 1104  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.11 (1 H, s), 3.36 (3 H, s), 2.73 (1 H, dd, *J* = 11.7 and 4.5 Hz), 2.40-2.30 (1 H, m), 2.20-2.07 (1 H, m), 1.78 (3 H, s), 1.75 (3 H, s), 1.70 (3 H, s), 2.00-1.77 (3 H, m), 1.64-1.50 (4 H, m), 1.35-0.90 (5 H, m), 0.96 (3 H, s), 0.78 (3 H, s); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.2 (C), 127.6 (C), 123.7 (C), 121.4 (CH), 88.8 (CH), 58.0 (CH<sub>3</sub>), 55.9 (CH), 44.2 (C), 42.6 (CH<sub>2</sub>), 38.8 (CH<sub>2</sub>), 38.2 (CH), 38.0 (C), 37.9 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 26.6 (CH<sub>3</sub>), 26.2 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 20.5 (CH<sub>3</sub>), 19.9 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>), 13.3 (CH<sub>3</sub>); HRMS: *m/z* Calcd for  $\text{C}_{21}\text{H}_{35}\text{O}$  ( $\text{M}+\text{H}$ ): 303.2688; Found: 303.2698. (1*R*,3*S*,6*R*,8*R*)-4'-Isopropylidine-3-methoxy-2,2,2'-trimethylbicyclo[4.3.0]nonanespiro[8.1']cyclohex-2'-ene **30b**:  $[\alpha]_D^{24} : +39.3$  (*c* 1.4,  $\text{CHCl}_3$ ); IR (neat): 1104  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.10 (1 H, s), 3.36 (3 H, s), 2.73 (1 H, dd, *J* = 11.4 and 4.2 Hz), 2.40 (1 H, dt, *J* = 15.3 and 4.2 Hz), 2.20-2.05 (1 H, m), 2.00-0.80 (12 H, m), 1.78 (3 H, s), 1.76 (3 H, s), 1.70 (3 H, s), 0.98 (3 H, s), 0.81 (3 H, s); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.6 (C), 127.5 (C), 123.8 (C), 121.1 (CH), 88.7 (CH), 58.0 (CH<sub>3</sub>), 53.8 (CH), 45.2 (CH<sub>2</sub>), 44.0 (C), 40.3 (CH), 39.2 (CH<sub>2</sub>), 37.9 (C), 35.8 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 26.8 (CH<sub>3</sub>), 26.2 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 20.5 (CH<sub>3</sub>), 20.0 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>), 13.4 (CH<sub>3</sub>).