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Synthetic approaches to komarovispiranes. Enantiospecific synthesis of bicyclo[3.3.0]octanespiro[3.1′]cyclohexanes

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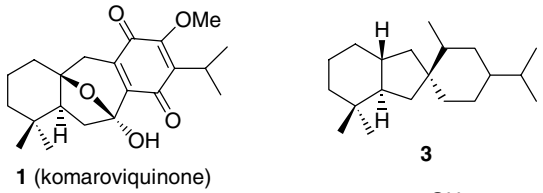
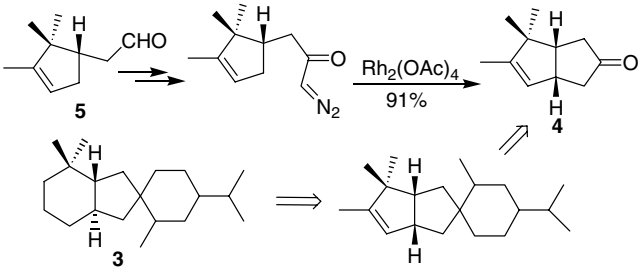
Abstract—A ring-closing metathesis based spiroannulation of cyclopentane and cyclohexanes at the C-3 carbon atom of a bicyclo-[3.3.0]octane, as a model study directed towards the enantiospecific synthesis of the novel diterpenes komarovispiranes, is described.

Dracocephalum komarovi Lipsky is a perennial semi-shrub 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 co-workers led to the isolation[1] of komaroviquinone **1**, which belongs to the icetexane group of diterpenes. Further investigations led to the isolation[2] of a novel tricyclic diterpene komarovispirone **2** containing a new and interesting cyclohexane spirofused to a hydrindane carbon framework **3**, komarovispirane. Both komaroviquinone **1** and komarovispirone **2** were found to exhibit trypanocidal activity against the epimastigotes *Trypanosma cruzi*, the causative agent of American trypanosomiasis. The novel structure containing an unusual carbon framework coupled with the biological activity have made komarovispirone **2** and its analogues interesting synthetic targets. So far there is no report in the literature on either the total synthesis or model studies of komarovispiranes.



Recently, we reported[3] an efficient method for the enantiospecific generation of bicyclo[3.3.0]octanone **4** starting from campholenaldehyde **5** employing an intramolecular rhodium carbenoid CH insertion reaction. It was contemplated that bicyclic ketone **4** is an ideal substrate to elaborate into komarovispiranes **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 1. As a model study, we first investigated the spiroannulation of a cyclohexane to bicyclic ketone **4**, which is the subject of this letter.

A ring-closing metathesis (RCM)[4] based strategy was considered for the spiroannulation of the six membered ring. For the creation of the requisite spiro centre, a



Scheme 1.

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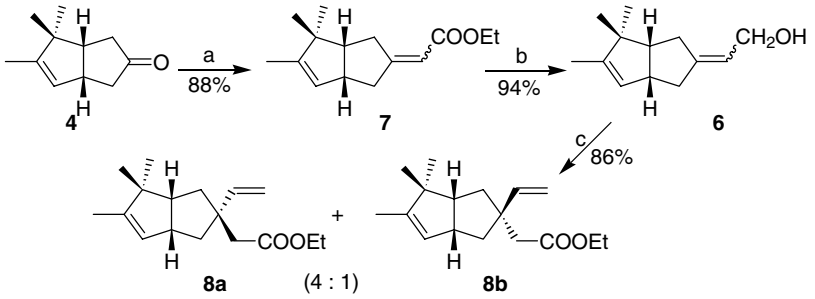
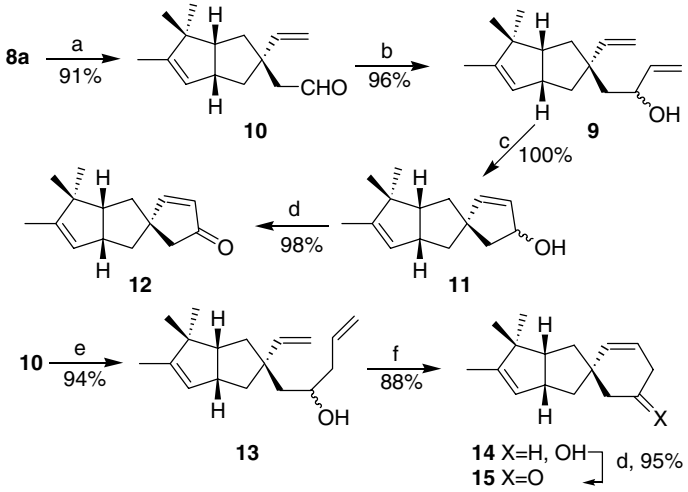


Scheme 2. Reagents, conditions and yields: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C→reflux, 4 h; (b) LAH, Et_2O, −70 °C, 2 h; (c) $CH_3C(OEt)_3$, $EtCO_2H$ (catalytic), sealed tube, 180 °C, 60 h.

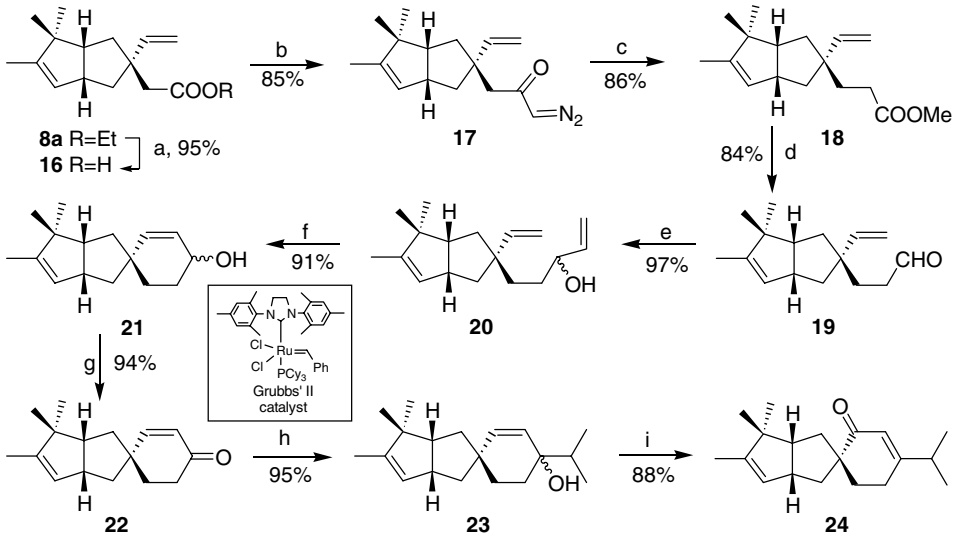
Claisen rearrangement of allyl alcohol **6** was conceived, Scheme 2. Synthesis of the bicyclic ketone **4** has been accomplished as reported earlier.[3] Horner–Wadsworth–Emmons reaction of bicyclic ketone **4** with triethyl phosphonoacetate and sodium hydride in refluxing THF furnished an ~3:2 *E*,*Z* mixture of α,β-unsaturated ester **7** in 88% yield,[5] which on reduction with lithium aluminium hydride (LAH) in ether at low temperature generated, regioselectively, allyl alcohol **6** in 94% yield. Johnson's orthoester variant[6] of the Claisen rearrangement was chosen for creation of the quaternary carbon atom. Thus, thermal activation of a mixture of allyl alcohol **6** and triethyl orthoacetate in the presence of a catalytic amount of propionic acid in a sealed tube at 180 °C for 60 h furnished a 4:1 diastereomeric mixture of acetates **8a** and **8b**, which were separated by column chromatography on silver nitrate impregnated silica gel.[8] The stereochemistry of acetates **8a** and **8b** were assigned on the basis of the preferred geometry in the transition state during the Claisen rearrangement.

To test the feasibility of the RCM strategy, initially spiroannulation of a cyclopentane ring was investigated via the RCM reaction of hydroxydiene **9**, Scheme 3. Accordingly, the ester group in **8a** was transformed into the corresponding aldehyde by a two-step reduction–oxidation protocol to furnish aldehyde **10** in 91% overall yield. Grignard reaction of aldehyde **10** with vinylmagnesium bromide in THF furnished hydroxydiene **9** in 96% yield. RCM reaction of hydroxydiene **9** with Grubbs' first generation catalyst $[Cl_2Ru(PCy_3)_2{=}CHPh]$ in methylene chloride at room temperature for 10 min quantitatively furnished spiro alcohol **11**, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride gave spiroenone **12** in near quantitative yield. The structure of spiroenone **12** was established from its spectral data.[8]

After successfully accomplishing the spirocyclopentannulation, the strategy was extended to the spirocyclohexannulation. Thus, sonochemically accelerated Barbier reaction of aldehyde **10** with zinc and allyl bromide in THF furnished hydroxydiene **13** in 94% yield. RCM reaction of hydroxydiene **13** with Grubbs' first generation catalyst in methylene chloride at room temperature furnished spiro alcohol **14** in 88% yield. Oxidation of homoallyl alcohol **14** with PCC and silica gel in methylene chloride generated ketone **15** in 95% yield, whose structure was established from its spectral data.[8]



Scheme 3. Reagents, conditions and yields: (a) (i) LAH, Et_2O, 0 °C, 2 h; (ii) PCC, silica gel, CH_2Cl_2, rt, 40 min; (b) $CH_2{=}CHMgBr$, THF, 0 °C, 0.5 h; (c) $Cl_2Ru(PCy_3)_2{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 10 min; (d) PCC, silica gel, CH_2Cl_2, rt, 3 h; (e) $CH_2{=}CHCH_2Br$, Zn, THF,))), 0.5 h; (f) $Cl_2Ru(PCy_3)_2{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 32 h.



Scheme 4. Reagents, conditions and yields: (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) hν, MeOH, 1 h; (d) (i) LAH, Et_2O, 0 °C, 2 h; (ii) PCC, NaOAc, CH_2Cl_2, rt, 40 min; (e) CH_2=CHMgBr, THF, 0 °C, 0.5 h; (f) Grubbs' II generation catalyst (5 mol %), CH_2Cl_2, rt, 5 h; (g) PCC, silica gel, CH_2Cl_2, rt, 3 h; (h) *i*-PrMgBr, THF, 0 °C, 0.5 h; (i) PCC, NaOAc, CH_2Cl_2, rt, 4 h.

Spirocyclohexannulation was also investigated via homologation of ester **8a** for the synthesis of a bisnorkomarovispirane, (Scheme 4). Thus, hydrolysis of ester **8a** with sodium hydroxide in aqueous methanol furnished acid **16**. The reaction of acid **16** with oxalyl chloride in benzene followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane furnished diazoketone **17**. Photochemical reaction of diazoketone **17** in methanol using a 450 W Hanovia medium pressure mercury vapor lamp furnished the homologated ester **18** in 86% yield. Ester **18** was then converted into aldehyde **19** in 84% yield by a reduction–oxidation protocol. Grignard reaction of aldehyde **19** with vinylmagnesium bromide in THF furnished hydroxydiene **20** in 96% yield. As the RCM reaction of hydroxydiene **20** with Grubbs' first generation catalyst was slow and inefficient, reaction was instead carried out with Grubbs' second generation catalyst. Thus, RCM of hydroxydiene **20** with 5 mol % of Grubbs' second generation catalyst in methylene chloride at room temperature for 5 h furnished the spiro alcohol **21** in 91% yield, which on oxidation with PCC and silica gel in methylene chloride gave spiroenone **22** in 94% yield.[8] An alkylative 1,3-enone transposition method[7] was employed for the conversion of spiroenone **22** into a bisnorkomarovispirane. The reaction of spiroenone **22** with isopropylmagnesium bromide in THF gave allyl alcohol **23**, which on oxidation with PCC and sodium acetate in methylene chloride furnished bisnorkomarovispirane **24** in 84% yield (over two steps).[8]

In conclusion, we have developed a convenient and efficient Claisen rearrangement–RCM reaction-based methodology for spirocyclopentane and spirocyclohexane annulation of bicyclic ketone **4** and applied it in the synthesis of a bisnorkomarovispirane. Extension of the strategy for the enantiospecific synthesis of a komarovispirane is currently under investigation.

Acknowledgement

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5. No attempt was made to separate and assign the structures of the *E* and *Z* isomers of **7** as both isomers lead to same product after Claisen rearrangement of the alcohol **6**.
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8. Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data ethyl 2-[(1*R*,3*R*,5*R*)-7,8,

8-trimethyl-3-vinylbicyclo[3.3.0]octa-6-en-3-yl]acetate **8a**: $[\alpha]_D^{26}$ −16.5 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1737, 1638, 912; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.97 (1H, dd, *J* 17.4 and 10.8 Hz), 5.06 (1H, br s), 4.95 (1H, dd, *J* 17.4 and 0.9 Hz), 4.90 (1H, dd, *J* 10.8 and 0.9 Hz), 4.08 (2H, q, *J* 7.2 Hz, OC H_2CH_3), 3.06–3.14 (1H, m), 2.34 (1H, t of d, *J* 12.0 and 7.2 Hz), 2.43 (2H, s), 2.01 (1H, ddd, *J* 12.6, 8.7 and 2.1 Hz), 1.72 (1H, ddd, *J* 12.6, 6.9 and 1.8 Hz), 1.56 (3H, s), 1.43 (1H, t, *J* 12.0 Hz), 1.35–1.25 (1H, m), 1.24 (3H, t, *J* 7.2 Hz), 1.02 (3H, s), 0.96 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 171.4 (C), 144.9 (CH), 144.6 (C), 127.4 (CH), 111.3 (CH_2), 59.7 (CH_2), 53.4 (CH), 49.3 (C), 46.8 (C), 45.0 (CH), 42.7 (CH_2), 42.1 (CH_2), 38.3 (CH_2), 29.4 (CH_3), 21.6 (CH_3), 14.4 (CH_3), 12.4 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830. Found: 285.1830. For ethyl 2-[(1*R*,3*S*,5*R*)-7,8,8-trimethyl-3-vinylbicyclo[3.3.0]octa-6-en-3-yl]acetate **8b**: $[\alpha]_D^{26}$ −7.4 (*c* 5.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1738, 1637, 912; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.76 (1H, dd, *J* 17.4 and 10.8 Hz), 5.06 (1H, br s), 5.02 (1H, d, *J* 10.8 Hz), 4.97 (1H, d, *J* 17.4 Hz), 4.06 (2H, q, *J* 7.2 Hz, OC H_2CH_3), 3.00–2.98 (1H, m), 2.41 and 2.33 (2H, 2 × d, *J* 13.8 Hz), 2.30–2.10 (2H, m), 1.68 (1H, ddd, *J* 12.3, 7.2 and 1.8 Hz), 1.54 (3H, s), 1.45–1.24 (2H, m), 1.22 (3H, t, *J* 7.2 Hz), 0.97 (3H, s), 0.94 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 171.4 (C), 144.7 (C), 144.0 (CH), 127.7 (CH), 112.7 (CH_2), 59.8 (CH_2), 53.5 (CH), 48.7 (C), 46.6 (C), 46.1 (CH_2), 45.5 (CH), 41.4 (CH_2), 40.0 (CH_2), 29.3 (CH_3), 21.7 (CH_3), 14.5 (CH_3), 12.5 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2Na$ (M+Na) 285.1830. Found: 285.1821. For (1*R*,3*R*,5*R*)-7,8,8-trimethylbicyclo[3.3.0]octanespiro[3.1′]cyclopentane-6,4′-dien-3′-one **12**: $[\alpha]_D^{26}$ −14.0 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1717, 1586; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.42 and 6.02 (2H, 2 × d, *J* 5.4 Hz), 5.01 (1H, br s), 3.25–3.05 (1H, m), 2.40–2.30 (1H, m), 2.19 (2H, s), 1.80–1.30 (4H, m), 1.58 (3H, s), 1.03 (3H, s), 0.96 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 208.4 (C), 171.3 (CH), 145.2 (C), 132.5 (CH), 127.1 (CH), 55.6 (CH), 53.8 (C), 49.1 (CH_2), 46.8 (C), 46.1 (CH), 44.6 (CH_2), 41.1 (CH_2), 29.2 (CH_3), 21.6 (CH_3), 12.4 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}ONa$ (M+Na): 239.1412. Found: 239.1413. For (1*R*,3*R*,5*R*)-7,8,8-trimethylbicyclo[3.3.0]octanespiro[3.1′]cyclohexane-6,5′-dien-3′-one **15**: $[\alpha]_D^{26}$ −19.4 (*c* 1.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1718; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.70–5.55 (2H, m), 4.98 (1H, br s), 3.20–3.05 (1H, m), 2.80 (2H, s), 2.50–2.35 (1H, m), 2.40 (2H, s), 1.81 (1H, dd, *J* 12.9 and 9.0 Hz), 1.56 (3H, s), 1.46 (2H, d, *J* 9.6 Hz), 1.30 (1H, dd, *J* 12.9 and 6.3 Hz), 1.00 (3H, s), 0.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 208.6 (C), 144.9 (C), 137.6 (CH), 127.4 (CH), 122.3 (CH), 53.9 (CH), 50.2 (CH_2), 49.9 (C), 46.8 (C), 45.5 (CH), 44.5 (CH_2), 41.3 (CH_2), 39.7 (CH_2), 29.2 (CH_3), 21.6 (CH_3), 12.5 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{22}OK$ (M+K): 269.1308. Found: 269.1327. For (1*R*,3*R*,5*R*)-7,8,8-trimethylbicyclo[3.3.0]octanespiro-[3.1′]cyclohexane-6,2′-dien-4′-one **22**: $[\alpha]_D^{26}$ −12.5 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1682; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.61 (1H, d, *J* 9.9 Hz), 5.82 (1H, d, *J* 9.9 Hz), 5.10 (1H, br s), 3.22–3.10 (1H, m), 2.46 (1H, dt, *J* 11.4 and 7.5 Hz), 2.45–2.30 (2H, m), 2.01 (1H, ddd, *J* 12.6, 8.7 and 1.8 Hz), 1.95–1.85 (2H, m), 1.58 (3H, t, *J* 1.8 Hz), 1.70–1.55 (1H, m), 1.49 (1H, t, *J* 12.0 Hz), 1.33 (1H, dd, *J* 13.2 and 6.0 Hz), 1.03 (3H, s), 0.97 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$):δ 199.2 (C), 159.0 (CH), 145.2 (C), 127.8 (CH), 127.3 (CH), 54.6 (CH), 46.9 (C), 45.9 (C), 45.8 (CH), 42.4 (CH_2), 40.3 (CH_2), 34.6 (CH_2), 32.6 (CH_2), 29.3 (CH_3), 21.6 (CH_3), 12.5 (CH_3). For (1*R*,3*R*,5*R*)-4′-isopropyl-7,8,8-trimethylbicyclo[3.3.0]octanespiro[3.1′]-cyclohexane-6,3′-dien-2′-one **24**: $[\alpha]_D^{26}$ −4.0 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1664, 1628; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.81 (1H, d, *J* 0.9 Hz), 5.09 (1H, br s), 3.15–3.00 (1H, m), 2.45–2.19 (5H, m), 1.90–1.68 (4H, m), 1.56 (3H, s), 1.52–1.39 (1H, m), 1.11 (6H, d, *J* 6.9 Hz), 1.00 (3H, s), 0.96 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 202.2 (C), 168.3 (C), 144.6 (C), 127.5 (CH), 123.9 (CH), 54.3 (CH), 53.6 (C), 46.9 (C), 45.3 (CH), 38.5 (CH_2), 35.6 (CH), 35.5 (CH_2), 32.1 (CH_2), 29.3 (CH_3), 24.9 (CH_2), 21.6 (CH_3), 20.9 (2 C, CH_3), 12.5 (CH_3); HRMS: *m*/*z* calcd for $C_{19}H_{29}O$ (M+H): 273.2218. Found: 273.2221.