Tetrahedron: *Asymmetry* 21 (2010) 202–207

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective syntheses of diquinane and (*cis*, *anti*, *cis*)-linear triquinanes

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ARTICLE INFO

Article history:
Received 30 November 2009
Accepted 21 January 2010

ABSTRACT

The enantioselective syntheses of diquinane and *cis*, *anti*, *cis*-linear triquinanes, starting from the readily available (*S*)-campholenaldehyde, employing an intramolecular rhodium carbenoid CH insertion reaction, are described.

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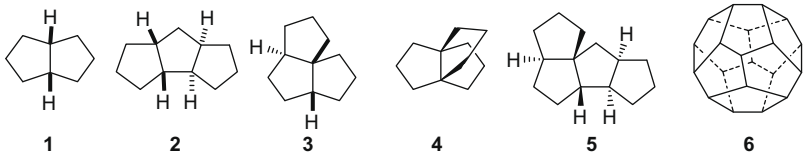
1. Introduction

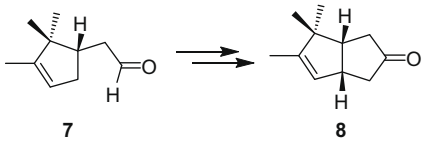
Over the last three decades polycondensed cyclopentane rings, commonly known as polyquinanes, have attracted the attention of synthetic chemists, both in the context of natural product synthesis[1] and aesthetically appealing molecules such as dodecahedrane.[2] Polyquinane natural products were revealed to chemists only in the second half of 20th century. The structure determination of the first 'authentic' polyquinane natural product, hirsutic acid-C[3] was accomplished in 1966. Despite this belated discovery, during the second half of the last century, several polyquinane natural products have been encountered among plant, marine, and microbial sources. So far, natural products containing up to four fused cyclopentanes, **1**–**5**, have been revealed, whereas the aesthetically appealing dodecahedrane **6** has 12 cyclopentanes.



1 **2** **3** **4** **5** **6**

The polyquinane natural products have attracted a great deal of interest amongst synthetic chemists over the last three decades.[1] Among the polyquinanes, triquinanes are the most commonly encountered in sesquiterpenes and are classified according to ring fusion as linear **2**, angular **3** or propellane **4**. The linear triquinanes bearing thermodynamically favored *cis*, *anti*, *cis*-tricyclo[6.3.0.0^{2,6}]undecane **2** moiety as the fundamental ring system are the most abundant among natural polyquinanes.

(*S*)-Campholenaldehyde **7**, readily available from α-pinene epoxide, is a commonly available cyclopentane-based chiral starting material, and has been employed in the synthesis of a variety of industrially (flavors and fragrance) important monocyclic compounds.[4] However, the use of campholenaldehyde **7** as a chiral starting material in the synthesis of polycyclic compounds in natural product synthesis is relatively unexplored.[5] In continuation of our interest[6] in the enantiospecific synthesis of polycyclic compounds starting from (*S*)-campholenaldehyde **7**, we have explored its utility in the enantioselective synthesis of diquinane and *cis*, *anti*, *cis*-triquinanes, which do not contain a *gem*-dimethyl grouping.



7 **8** (1)

Recently, we have reported an efficient route for the enantiospecific conversion of (*S*)-campholenaldehyde **7** into diquinane **8** (Eq. 1), which retains the *gem*-dimethyl grouping of campholenaldehyde.[6a] Of the three methyl groups in campholenaldehyde **7**, the olefinic methyl group can be easily functionalized, for example, via allylic oxidation. However, the remaining two tertiary methyl groups are difficult to functionalize, and to the best of our knowledge, there is no report in the literature on the utility of these methyl groups for further elaboration (other than as a dimethyl grouping in the targets). We conceived that it could be possible to utilize tertiary methyl carbon for ring construction via an intramolecular rhodium carbenoid γ-CH insertion reaction.[7] In this direction, it was contemplated that the olefinic methyl group could be linked to one of the tertiary methyl groups via an extra carbon

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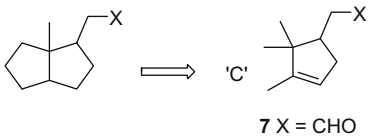
doi:10.1016/j.tetasy.2010.01.014

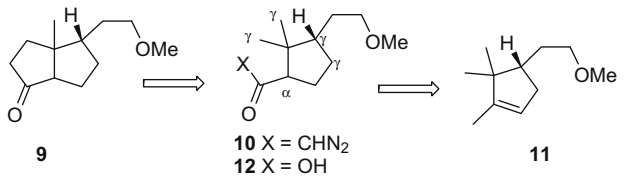
and a cyclopentannulation could be affected, with the product containing only one methyl group (Eq. 2). Based on this concept, we herein report the synthesis of diquinane and *cis, anti, cis*-linear triquinanes.



(2)

2. Results and discussion

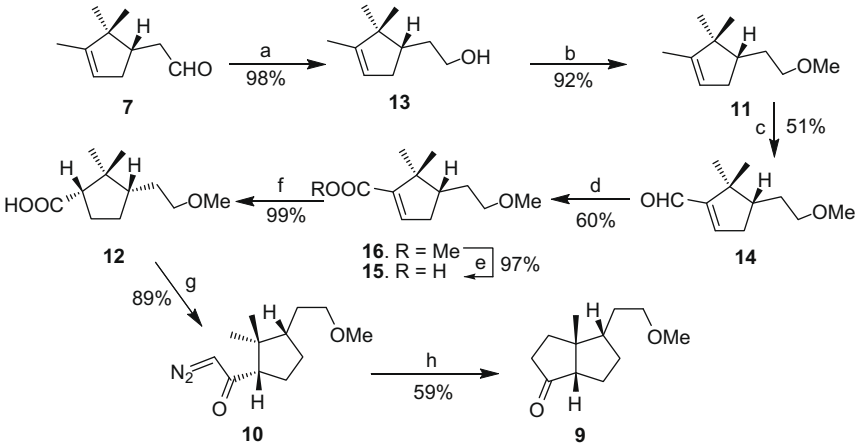
Initially, the synthesis of the diquinane **9** was investigated in order to test the feasibility of the concept. It was contemplated (Scheme 1) that the diquinane **9** could be obtained by intramolecular insertion of the rhodium carbenoid derived from the diazoketone **10** in the CH bond of one of the gem dimethyl groups, as the other two possible γ-CH bonds lead to strained bridged compounds. Allylic oxidation of the olefinic methyl group in the readily available campholenyl methyl ether[8] **11** was conceived for the generation of acid **12**.



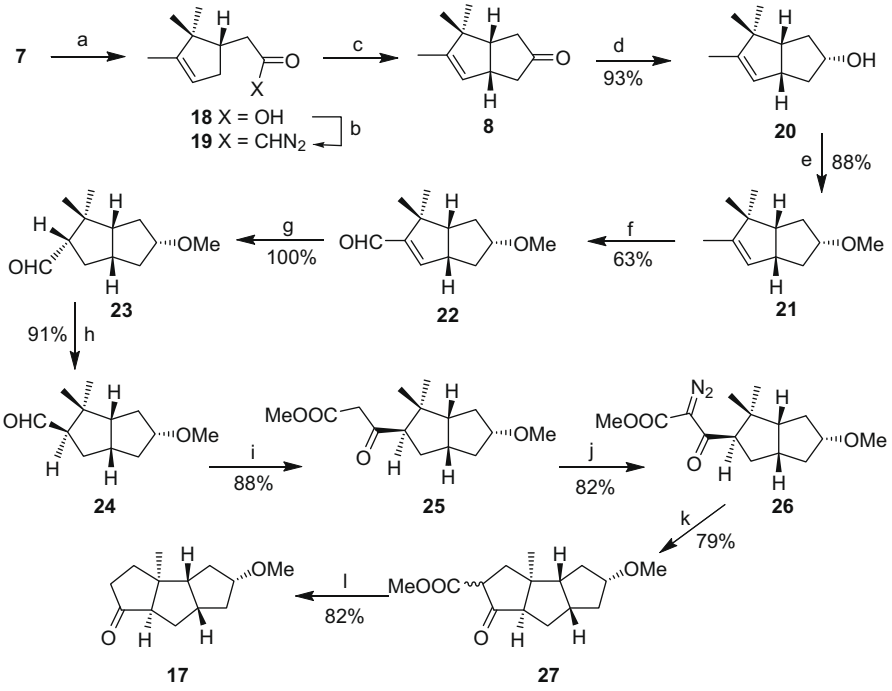
Scheme 1.

The synthetic sequence is depicted in Scheme 2. The reduction of campholenaldehyde **7** with sodium borohydride in methanol, followed by Williamson's etherification of the resultant alcohol **13** with sodium hydride and methyl iodide generated the requisite starting material **11**.[8] Allylic oxidation of the methyl ether **11** with selenium dioxide in refluxing aqueous dioxane furnished the unsaturated aldehyde **14** in a highly regioselective manner. Further oxidation of aldehyde **14** with sodium chlorite in tertiary butyl alcohol generated the acid **15**, which was purified as its methyl ester **16**. Since the rhodium carbenoid derived from the acid **15**, in principle, could insert into either of the two gem dimethyl groups leading to regioisomers, it was decided to saturate the olefin in **15**. Accordingly, the hydrolysis of the ester **16** with sodium hydroxide in aqueous methanol furnished the acid **15**, mp 106–09 °C. Hydrogenation of the olefin in the acid **15** in ethyl acetate with 10% palladium on carbon as the catalyst at one atmospheric pressure of hydrogen generated the acid **12** in a highly stereoselective manner via the addition of hydrogen from the opposite face of the methoxyethyl side chain.[6c] The reaction of acid **12** with oxalyl chloride followed by the treatment of the resultant acid chloride with an excess of ether diazomethane furnished diazoketone **10** in 89% yield. The reaction of the diazoketone **10** with a catalytic amount of rhodium acetate in refluxing methylene chloride furnished diquinane **9** in 59% yield, via regio- and stereospecific insertion[7] of the intermediate rhodium carbenoid in the CH bond of the *cis*-methyl group. The structure of the diquinane **9** was established from its spectroscopic data, in particular, the presence of a carbonyl absorption band at 1737 cm^{-1} in the IR spectrum, the presence of only one tertiary methyl group at δ 1.34 in the ^1H NMR spectrum, and the presence of a typical cyclopentanone ketone carbon resonance at δ 221.5 ppm in the ^{13}C NMR spectrum.

After successfully accomplishing the synthesis of diquinane **9**, the synthesis of a *cis*, *anti*, *cis*-triquinane **17** was investigated starting from the diquinane **8** (Scheme 3). The diquinane **8** was prepared as described earlier.[6a] Thus, the oxidation of campholenaldehyde **7** with Jones' reagent generated acid **18**, which was converted into the diazoketone **19** via the corresponding acid chloride. The reaction of diazoketone **19** with a catalytic amount of rhodium acetate in refluxing methylene chloride furnished diquinane **8**, via regio- and stereospecific insertion of the intermediate rhodium carbenoid in the allylic CH bond. In order to avoid regiochemical problems at a later stage, the ketone in diquinane **8** was masked. Reduction of the ketone in **8** with sodium borohydride in methanol furnished alcohol **20** in a highly stereoselective manner, which on etherification with sodium hydride and methyl iodide furnished the methyl ether **21**. Oxidation of diquinane **21** with selenium dioxide in refluxing aqueous dioxane furnished aldehyde **22**. Hydrogenation of the olefin in **22** in ethyl acetate at one atmospheric pressure of hydrogen using 10% palladium over carbon as the catalyst furnished the saturated *endo*-aldehyde **23** in a stereoselective manner via the delivery of the hydrogen from the *exo* face of the molecule. It was obvious that for the generation of the *cis*, *anti*, *cis*-triquinane, the carboxyl group needed to be in the *exo* orientation, for which the aldehyde group in **23** needs to be isomerized. The treatment of aldehyde **23** with diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride furnished *exo*-aldehyde **24**. For the construction of the third ring, an intramolecular rhodium carbenoid insertion of an α-diazo-β-keto ester was chosen. Accordingly, the treatment of aldehyde **24** with methyl diazoacetate in the presence



Scheme 2. Reagents: (a) $NaBH_4$, MeOH; (b) NaH, MeI, TBAI, THF; (c) SeO_2, dioxane–H_2O; (d) (i) $NaClO_2$, ^tBuOH, $CH_2{=}CMe_2$, NaH_2PO_4, (ii) CH_2N_2, Et_2O; (e) NaOH, MeOH–H_2O; (f) H_2, 10% Pd/C, EtOAc; (g) (i) $(COCl)_2$, C_6H_6, (ii) CH_2N_2, Et_2O; (h) $Rh_2(OAc)_4$, CH_2Cl_2.



Scheme 3. Reagents: (a) Jones' reagent, acetone; (b) (i) $(COCl)_2$, C_6H_6, (ii) CH_2N_2, Et_2O; (c) $Rh_2(OAc)_4$, CH_2Cl_2; (d) $NaBH_4$, MeOH; (e) NaH, MeI, TBAI, THF; (f) SeO_2, dioxane–H_2O; (g) H_2, 10% Pd/C, EtOAc; (h) DBU, CH_2Cl_2; (i) $N_2CHCOOMe$, $SnCl_2{\cdot}2H_2O$, CH_2Cl_2; (j) TsN_3, Et_3N, MeCN; (k) $Rh_2(OCOCF_3)_4$, CH_2Cl_2; (l) LiCl, DMSO-H_2O.

of a catalytic amount of stannous chloride generated the β-keto ester **25**.[9] The diazo transfer reaction of the β-keto ester **25** with toluenesulfonyl azide and triethylamine in acetonitrile furnished the α-diazo-β-keto ester **26**. The rhodium carbenoid reaction of **26** was found to be inefficient with rhodium acetate, hence it was carried out with rhodium trifluoroacetate. Thus, the treatment of the diazo ester **26** with a catalytic amount of rhodium trifluoroacetate in refluxing methylene chloride furnished an epimeric mixture of the triquinane **27** in 79% yield. Finally, Krapcho decarboxylation[10] of the β-keto ester **27** in DMSO and lithium chloride in the presence of water furnished the triquinane ketone **17**, whose structure was deduced from its spectroscopic data.

3. Conclusion

In conclusion, we have accomplished enantioselective synthesis of diquinane **9** and *cis*, *anti*, *cis*-linear triquinane **17**, starting from (*S*)-campholenaldehyde **7**, employing an intramolecular rhodium carbenoid insertion reaction in an iterative manner. An extension of the methodology for the enantioselective synthesis of tri- and tetraquinane based natural products is currently under investigation.

4. Experimental

Melting points are recorded using a Buchi melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Jasco FTIR 410 and Perkin–Elmer FTIR spectrophotometers. ^1H (300 and 400 MHz) and ^{13}C (75 and 100 MHz) NMR spectra were recorded on JNM λ-300 and Brucker AMX 400 spectrometers using either $CDCl_3$ or a 1:1 mixture of $CDCl_3$ and CCl_4 as a solvent. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and a Jasco P-1020 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical thin-layer chromatography (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 and hexane were used as an eluent. Visualization of spots was accomplished by exposure to iodine vapor. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product).

4.1. (4*S*)-4-(2-Methoxyethyl)-5,5-dimethylcyclopent-1-ene-1-carboxaldehyde 14

To a magnetically stirred solution of the methyl ether[8] **11** (500 mg, 2.97 mmol) in dioxane–H_2O (4:1) (5 mL) was added SeO_2 (660 mg, 5.95 mmol) and the reaction mixture was refluxed for 1 h. The reaction mixture was then cooled and filtered. Aqueous ammonium chloride (5 mL) was added to the filtrate and extracted with ether (10 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 (1:19) as an eluent furnished the aldehyde **14** (280 mg, 51%) as an oil. $[\alpha]_D^{27} = -3.6$ (*c* 9.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3040, 2932, 2869, 2829, 2709, 1683, 1610, 1459, 1433, 1388, 1362, 1342, 1326, 1212, 1146, 1118, 994, 975, 914, 834, 805, 732; ^1H NMR (300 MHz): δ 9.65 (1H, s, HC=O), 6.68 (1H, dd, *J* 6.0 and 3.0 Hz, H-2), 3.50–3.33 (2H, m, OCH_2), 3.31 (3H, s, OCH_3), 2.62 (1H, dq, *J* 18.6 and 3.3 Hz), 2.20–1.90 (2H, m), 1.85–1.70 (1H, m), 1.55–1.35 (1H, m), 1.37 (3H, s) and 1.24 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz): δ 189.3 (CH, CHO), 154.8 (CH, C-2), 151.2 (C, C-3), 71.9 (CH_2, C-2′), 58.5 (CH_3, OCH_3), 48.0 (CH, C-4), 45.5 (C, C-5), 36.9 (CH_2), 29.0 (CH_2), 25.6 (CH_3), 20.1 (CH_3); HRMS: *m/z* calcd for $C_{11}H_{18}O_2Na$ (M+Na): 205.1204; found: 205.1203.

4.2. Methyl (4*S*)-4-(2-methoxyethyl)-5,5-dimethylpent-1-ene-1-carboxylate 16

To a magnetically stirred solution of the aldehyde **14** (500 mg, 2.75 mmol) in *tert*-butyl alcohol (10 mL) and 2-methyl-2-butene (10 mL) was added a solution of sodium chlorite (994 mg, 11.0 mmol) and sodium dihydrogen phosphate (2.1 g, 13.7 mmol) in water (10 mL). The reaction mixture was stirred at rt for 24 h. The volatile components were removed in vacuo, and the residue was dissolved in water (10 mL) and then extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with brine (8 mL), dried (Na_2SO_4), and concentrated to give the acid **15** (510 mg, 94%). To an ice cold solution of the acid **15** (500 mg, 2.5 mmol) in ether was added an ethereal solution of diazomethane [prepared from 1.5 g of *N*-nitroso-*N*-methylurea, 60% aq KOH solution (30 mL), and ether (20 mL)] and stirred at the same temperature for 10 min. 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 (1:20) as an eluent furnished the ester **16** (350 mg, 65%) as an oil. $[\alpha]_D^{26} = -10.0$ (*c* 1.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2931, 2868, 1719, 1620, 1456, 1435, 1325, 1259, 1242, 1198, 1119, 1062, 759; ^{1}H NMR (400 MHz): δ 6.66 (1H, t, *J* 2.2 Hz, H-2), 3.69 (3H, s, $COOCH_3$), 3.50–3.30 (2H, m, H-2′), 3.31 (3H, s, OCH_3), 2.48 (1H, ddd, *J* 17.2, 7.2 and 3.2 Hz), 2.06–1.55 (3H, m), 1.53–1.42 (1H, m), 1.21 (3H, s) and 0.96 (3H, s) [$2 \times$ *tert*-CH_3]; ^{13}C NMR (100 MHz): δ 165.0 (C, OC=O), 144.2 (C, C-1), 141.8 (CH, C-2), 72.0 (CH_2, C-2′), 58.4 (CH_3), 50.8 (CH_3), 47.0 (CH, C-4), 46.2 (C, C-5), 36.0 (CH_2), 29.2 (CH_2), 25.9 (CH_3), 20.3 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{20}O_3Na$ (M+Na): 235.1310; found: 235.1308.

4.3. (4*S*)-4-(2-Methoxyethyl)-5,5-dimethylcyclopent-1-ene-1-carboxylic acid 15

To a magnetically stirred solution of the ester **16** (100 mg, 0.47 mmol) was added 5% aq methanolic NaOH solution (5 mL) and refluxed for 4 h. The reaction mixture was cooled, neutralized with 10% HCl, and extracted with CH_2Cl_2 (3×5 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and concentrated to give acid **15** (90 mg, 97%), which was recrystallized from hexane. Mp 106–109 °C; IR (KBr): ν_{max}/cm^{-1} 2933 (br), 1674, 1614, 1420, 1263, 1114, 1048, 974, 942; ^{1}H NMR (400 MHz): δ 6.85 (1H, s, H-2), 3.65–3.35 (2H, m, H-2′), 3.30 (3H, s, OCH_3), 2.53 (1H, dd, *J* 17.0 and 5.8 Hz), 2.20–1.65 (3H, m), 1.65–1.38 (1H, m), 1.24 (3H, s) and 0.98 (3H, s) [$2 \times$ *tert*-CH_3]; ^{13}C NMR (100 MHz): δ 170.2 (C, OC=O), 144.8 (C, C-1), 144.0 (CH, C-2), 72.0 (CH_2, C-2′), 58.5 (CH_3, OCH_3), 47.1 (CH, C-4), 46.0 (C, C-5), 36.1 (CH_2), 29.2 (CH_2), 25.8 (CH_3), 20.2 (CH_3); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.92; H, 8.87.

4.4. (1*S*,3*S*)-3-(2-Methoxyethyl)-2,2-dimethylcyclopentane-1-carboxylic acid 12

To a solution of the acid **15** (90 mg, 0.45 mmol) in ethyl acetate (1.5 mL) was added activated 10% Pd/C (20 mg) and the reaction mixture was stirred at 1 atm. pressure of hydrogen, created by evacuative displacement of air (balloon), for 3 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. Evaporation of the solvent furnished the acid **12** (90 mg, 99%) as an oil. $[\alpha]_D^{26} = -5.2$ (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3000 (br), 2962, 2873, 2743, 1702, 1464, 1456, 1418, 1390, 1371, 1239, 1177, 1122; ^{1}H NMR (400 MHz): δ 3.50–3.35 (2H, m, H-2′), 3.31 (3H, s, OCH_3), 2.49 (1H, t, *J* 9.4 Hz, H-1), 2.20–1.20 (7H, m), 1.14 (3H, s) and 0.70 (3H, s) [$2 \times$ *tert*-CH_3]; ^{13}C NMR (100 MHz): δ 180.1 (C, OC=O), 72.0 (CH_2, C-2′), 58.4 (CH_3, OCH_3), 55.2 (CH, C-1), 47.8 (CH, C-3), 44.5 (C, C-2), 29.6 (CH_2), 28.0 (CH_2), 26.4 (CH_3), 23.8 (CH_2), 16.4 (CH_3); HRMS: *m/z* calcd for $C_{11}H_{20}O_3Na$ (M+Na): 223.1310; found: 233.1318.

4.5. (1*S*,5*R*,6*S*)-6-(2-Methoxyethyl)-5-methylbicyclo[3.3.0]-octan-2-one 9

To a magnetically stirred solution of the acid **12** (135 mg, 0.67 mmol) in dry benzene (2 mL) was added oxalyl chloride (0.2 mL, 2.0 mmol) and stirred for 4 h. Evaporation of the excess oxalyl chloride and solvent under reduced pressure gave the acid chloride, which was taken in dry ether (3 mL), and added to a cold (0 °C), magnetically stirred ethereal solution of diazomethane [excess, prepared from *N*-nitroso-*N*-methylurea (300 mg), 60% aq KOH solution (15 mL), and ether (5 mL)] and the reaction mixture was stirred 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 (1:9) as an eluent furnished diazoketone **10** (125 mg, 89%) as an oil. IR (neat): ν_{max}/cm^{-1} 3089, 2962, 2934, 2872, 2102, 1729, 1639, 1466, 1370, 1323, 1156, 1121.

To a magnetically stirred refluxing solution of rhodium acetate (2 mg) in dry CH_2Cl_2 (5 mL) was added a solution of the diazoketone **10** (125 mg, 0.56 mmol) in CH_2Cl_2 (25 mL) dropwise over a period of 30 min and refluxed for 3.5 h. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as an eluent furnished the diquinane ketone **9** (64 mg, 59%) as an oil. $[\alpha]_D^{26} = +1.4$ (*c* 13.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2950, 2870, 1737 (C=O), 1455, 1414, 1387, 1275, 1180, 1120, 935; ^{1}H NMR (400 MHz): δ 3.50–3.30 (2H, m, H-2′), 3.27 (3H, s, OCH_3), 2.40–2.25 (1H, m, H-1), 2.25–2.10 (2H, m), 1.95–1.24 (9H, m), 1.34 (3H, s, *tert*-CH_3); ^{13}C NMR (100 MHz): δ 221.5 (C, C=O), 72.0 (CH_2, C-2′), 59.2 (CH, C-1), 58.4 (CH_3, OCH_3), 49.7 (C, C-5), 47.7 (CH, C-6), 38.0 (CH_2, C-3), 31.0 (CH_2, C-4), 28.7 (CH_2), 28.4 (CH_2), 27.5 (CH_2), 25.6 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{20}O_2Na$ (M+Na): 219.1361; found: 219.1361.

4.6. (1*R*,3*R*,5*R*)-7,8,8-Trimethylbicyclo[3.3.0]oct-6-en-3-ol 20

To a cold (0 °C), magnetically stirred solution of the ketone[6a] **8** (400 mg, 2.44 mmol) in methanol (2 mL) was added $NaBH_4$ (278 mg, 7.32 mmol) in batches and stirred for 10 min at the same temperature. Methanol was evaporated under reduced pressure. Water (2 mL) followed by 3 N HCl (3 mL) was added to the reaction mixture and extracted with ether (3×5 mL). The combined ether extract was washed with brine (5 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate/hexane (1:9) as an eluent furnished alcohol **20** (376 mg, 93%) as a colorless oil. $[\alpha]_D^{22} = -23.3$ (*c* 5.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3345, 3028, 2954, 2868, 1439, 1360, 1346, 1115, 1090, 1065, 1012, 827; ^{1}H NMR (300 MHz): δ 5.16 (1H, br s, H-6), 4.07 (1H, quintet, *J* 6.3 Hz, H-3), 3.10–2.90 (1H, m, H-5), 2.26 (1H, q, *J* 8.4 Hz), 2.00 (1H, dt, *J* 12.9 and 7.8 Hz), 1.85–1.70 (1H, m), 1.65–1.45 (2H, m), 1.56 (3H, s, olefinic-CH_3), 1.39 (1H, dt, *J* 12.9 and 5.4 Hz), 0.98 (6H, s, $2 \times$ *tert*-CH_3); ^{13}C NMR (75 MHz): δ 146.0 (C, C-7), 128.5 (CH, C-6), 74.9 (CH, C-3), 52.3 (CH, C-1), 47.7 (C, C-8), 45.0 (CH, C-5), 40.6 (CH_2), 37.7 (CH_2), 29.2 (CH_3), 22.6 (CH_3), 12.5 (CH_3); HRMS: *m/z* calcd for $C_{11}H_{19}O$ (M+H): 167.1436; found: 167.1442.

4.7. (1*R*,5*R*,7*R*)-7-Methoxy-3,4,4-trimethylbicyclo[3.3.0]oct-2-ene 21

To an ice cold magnetically stirred suspension of NaH (60% dispersion in oil, 350 mg, 8.77 mmol, washed with dry hexane) and TBAI (8 mg, catalytic) in THF (2 mL) was added a solution of the alcohol **20** (485 mg, 2.92 mmol) in THF (5 mL) and stirred for

30 min at rt. To the alkoxide thus formed was added methyl iodide (0.60 mL, 9.64 mmol) and the reaction mixture was stirred for 12 h at rt. Water (3 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 hexane as an eluent furnished the methyl ether **21** (455 mg, 88%) as an oil. $[\alpha]_D^{23} = -20.3$ (*c* 10.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2954, 2924, 2871, 2854, 1668, 1653, 1464, 1365, 1109; ^1H NMR (300 MHz): δ 5.11 (1H, br s, H-2), 3.79–3.60 (1H, m, H-7), 3.28 (3H, s, OCH_3), 3.00–2.85 (1H, m, H-1), 2.28–2.12 (2H, m), 1.87 (1H, dt, *J* 11.7 and 6.3 Hz), 1.57 (3H, s, olefinic-CH_3), 1.38 (2H, q, *J* 11.4 Hz), 1.30–1.15 (2H, m), 0.99 (3H, s) and 0.97 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz): δ 144.5 (C, C-3), 127.9 (CH, C-2), 83.1 (CH, C-7), 57.1 (CH_3, OCH_3), 51.9 (CH, C-5), 47.2 (C, C-4), 43.4 (CH, C-1), 36.7 (CH_2), 33.8 (CH_2), 28.7 (CH_3), 22.0 (CH_3), 12.4 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{20}ONa$ (M+Na): 203.1413; found: 203.1406.

4.8. (1*R*,5*R*,7*R*)-7-Methoxy-4,4-dimethylbicyclo[3.3.0]oct-2-ene-3-carboxaldehyde 22

To a solution of methyl ether **21** (317 mg, 1.79 mmol) in dioxane and water (4:1) was added SeO_2 (596 mg, 5.37 mmol) and refluxed for 3 h. The reaction mixture was cooled, filtered, and the residue was washed with ether (5 mL). Aq NH_4Cl solution (3 mL) was added to the filtrate and extracted with ether (3 × 5 mL). The combined organic phase was washed with brine (4 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 an eluent furnished the aldehyde **22** (217 mg, 63%) as an oil. $[\alpha]_D^{20} = -33.8$ (*c* 4.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2958, 2927, 2862, 2824, 2706, 1682, 1608, 1458, 1365, 1111, 1032; ^1H NMR (300 MHz): δ 9.70 (1H, s, HC=O), 6.55 (1H, s, H-2), 3.78–3.64 (1H, m, H-7), 3.28 (3H, s, OCH_3), 3.30–3.15 (1H, m, H-1), 2.38–2.21 (2H, m), 2.05–1.88 (1H, m), 1.54–1.40 (2H, m), 1.26 (3H, s) and 1.17 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz): δ 190.0 (CH, CHO), 155.8 (CH, C-2), 151.1 (C, C-3), 82.4 (CH, C-7), 57.1 (CH_3, OCH_3), 53.5 (CH, C-5), 45.9 (C, C-4), 45.4 (CH, C-1), 35.5 (CH_2), 33.7 (CH_2), 29.1 (CH_3) and 21.8 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{18}O_2Na$ (M+Na): 217.1204; found: 217.1204.

4.9. (1*R*,3*S*,5*S*,7*R*)-7-Methoxy-2,2-dimethylbicyclo[3.3.0]octane-3-carboxaldehyde 23

To a solution of the unsaturated aldehyde **22** (261 mg, 1.35 mmol) in ethyl acetate (2 mL) was added activated 10% Pd/C (60 mg) and the reaction mixture was stirred at 1 atm pressure of hydrogen atmosphere, created by evacuative displacement of air (balloon), for 2 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 on a silica gel column using ethyl acetate/hexane (1:19) as an eluent furnished a ~10:1 epimeric mixture of the aldehydes **23** and **24** (263 mg, 100%) as an oil. IR (neat): ν_{max}/cm^{-1} 2956, 2868, 2822, 2714, 1719, 1464, 1370, 1243, 1222, 1188, 1120; ^1H NMR (300 MHz): δ (peaks due to **23**) 9.70 (1H, d, *J* 2.7 Hz, HC=O), 3.66 (1H, tt, *J* 8.7 and 6.3 Hz, H-7), 3.23 (3H, s, OCH_3), 2.50–2.25 (2H, m), 2.25–1.70 (4H, m), 1.35–1.12 (3H, m), 1.12 (3H, s) and 0.93 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz): δ (peaks due to **23**) 203.9 (CH, C=O), 84.0 (CH, C-7), 64.1 (CH, C-3), 56.9 (CH_3, OCH_3), 53.0 (CH, C-1), 44.3 (C, C-2), 39.1 (CH, C-5), 38.8 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.1 (CH_3), 21.2 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{20}O_2Na$ (M+Na): 219.1362; found: 219.1357.

4.10. (1*R*,3*R*,5*S*,7*R*)-7-Methoxy-2,2-dimethylbicyclo[3.3.0]-octane-3-carboxaldehyde 24

To a magnetically stirred solution of a ~10:1 epimeric mixture of the aldehydes **23** and **24** (263 mg, 1.33 mmol) in dry CH_2Cl_2 (2 mL) was added DBU (0.04 mL, 0.27 mmol) and stirred for 10 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (15 mL), washed with 3 M HCl solution (3 mL) and brine (4 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 an eluent furnished the *exo* aldehyde **24** (239 mg, 91%) as an oil. $[\alpha]_D^{21} = -21.2$ (*c* 9.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2956, 2872, 2822, 2713, 1718, 1463, 1387, 1370, 1264, 1190, 1120, 1095, 1001, 965; ^1H NMR (300 MHz): δ 9.76 (1H, d, *J* 2.1 Hz, H-C=O), 3.64–3.52 (1H, m, H-7), 3.30 (3H, s, OCH_3), 2.69–1.90 (6H, m), 1.50 (1H, ddd, *J* 13.5, 8.4 and 2.1 Hz), 1.33–1.12 (2H, m), 1.17 (3H, s) and 0.92 (3H, s) [2 × *tert*-CH_3]; ^{13}C NMR (75 MHz): δ 204.7 (CH, C=O), 82.2 (CH, C-7), 57.9 (CH, C-3), 57.1 (CH_3, OCH_3), 54.2 (CH, C-1), 44.9 (C, C-2), 40.2 (CH_2), 36.6 (CH, C-5), 34.5 (CH_2), 32.3 (CH_2), 24.7 (CH_3), 24.3 (CH_3); HRMS: *m/z* calcd for $C_{12}H_{20}O_2Na$ (M+Na): 219.1362; found: 219.1366.

4.11. Methyl 3-[(1*R*,3*R*,5*S*,7*R*)-7-methoxy-2,2-dimethylbicyclo-[3.3.0]oct-3-yl]-3-oxopropanoate 25

To a magnetically stirred solution of the aldehyde **24** (203 mg, 1.06 mmol) and methyl diazoacetate (0.34 mL, 3.17 mmol) in dry CH_2Cl_2 (2 mL) was added $SnCl_2{\cdot}2H_2O$ (24 mg, 0.11 mmol) in batches over a period of 30 min and stirred for 2.5 h at rt. The solvent was evaporated under reduced pressure and the residue was purified over a silica gel column using ethyl acetate/hexane (1:9) as an eluent to furnish the β-keto ester **25** (229 mg, 88%) as oil, which was found to exist as a mixture of keto and enol forms. $[\alpha]_D^{22} = -21.5$ (*c* 3.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2955, 2824, 1751, 1710, 1646, 1622, 1447, 1406, 1370, 1316, 1242, 1225, 1155, 1118, 1095, 1024; ^1H NMR (300 MHz): δ (peaks due to the keto form) 3.71 (3H, s, CO_2CH_3), 3.55–3.40 (1H, m, H-7′), 3.28 (3H, s, OCH_3), 2.91 (2H, dd, *J* 11.7 and 7.5 Hz, H-2), 2.50–1.70 (6H, m), 1.55–1.51 (1H, m), 1.30–1.07 (2H, m), 1.13 (3H, s) and 0.85 (3H, s) [2 × *tert*-CH_3]; (select peaks due to the enol form) 12.11 (1H, s, enolic-OH), 4.91 (1H, s, H-2), 3.69 (3H, s, CO_2CH_3), 3.41 (3H, s, OCH_3), 1.01 (3H, s) and 0.83 (3H, s) [2 × *tert*-CH_3]. ^{13}C NMR (75 MHz): δ (peaks due to the keto form) 203.9 (C, C=O), 167.4 (C, OC=O), 82.1 (CH, C-7′), 57.6 (CH, C-3′), 57.2 (CH_3), 54.2 (CH_3), 52.2 (CH, C-1′), 50.5 (CH_2, C-2), 44.8 (C, C-2′), 40.2 (CH_2, C-4′), 35.8 (CH, C-5′), 35.0 (CH_2), 34.7 (CH_2), 24.8 (2 C, CH_3); (peaks due to the enol form) 179.0 (C, C-1), 167.4 (C, OC=O), 89.7 (CH, C-2), 82.0 (CH, C-7′), 57.2 (CH_3), 53.0 (CH_3), 51.0 (CH, C-1′), 50.6 (CH), 44.7 (C, C-2′), 40.2 (CH_2, C-4′), 35.6 (CH, C-5′), 34.8 (CH_2), 34.2 (CH_2), 24.9 (CH_3), 24.2 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{24}O_4Na$ (M+Na): 291.1573; found: 291.1570.

4.12. Methyl 3-[(1*R*,3*R*,5*S*,7*R*)-7-methoxy-2,2-dimethylbicyclo-[3.3.0]oct-3-yl]-2-diazo-3-oxopropanoate 26

To a magnetically stirred solution of the β-keto ester **25** (360 mg, 1.43 mmol) in acetonitrile (2 mL) were added tosyl azide (283 mg, 1.71 mmol) and NEt_3 (0.4 mL, 2.86 mmol), and stirred at rt for 5 h. The solvent was then evaporated under reduced pressure and the residue was purified on a silica gel column using ethyl acetate/hexane (1:19) as an eluent to furnish the α-diazo-β-keto ester **26** (326 mg, 82%) as an oil. IR (neat): ν_{max}/cm^{-1} 2956, 2823, 2137 (N=N), 1724 (OC=O), 1649 (C=O), 1463, 1438, 1372, 1307, 1208, 1119, 840, 777, 768, 741.

4.13. Methyl (1*R*,2*S*,6*R*,8*S*,10*R*)-10-methoxy-2-methyl-5-oxotricyclo[6.3.0.0^{2,6}]undecane-4-carboxylate (27)

To a magnetically stirred, refluxing solution of $Rh_2(OCOCF_3)_4$ (8 mg) in anhydrous CH_2Cl_2 (20 mL) was added a solution of the α-diazo-β-keto ester **26** (352 mg, 1.27 mmol) in dry CH_2Cl_2 (15 mL, 0.01 M) over a period of 30 min and refluxed for 3.5 h. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate/hexane (1:19) as an eluent furnished an epimeric mixture of the triquinane **27** (250 mg, 79%) as an oil. $[\alpha]_D^{24} = -40.0$ (*c* 1.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2953, 2874, 2824, 1751, 1728, 1662, 1623, 1446, 1365, 1287, 1264, 1235, 1198, 1142, 1114; ^{1}H NMR (300 MHz): δ (peaks due to the major isomer) 3.90–3.60 (1H, m), 3.75 (3H, s), 3.50–3.30 (1H, m), 3.30 (3H, s), 2.80–2.50 (2H, m), 2.45–1.90 (5H, m), 1.87–1.70 (1H, m), 1.50–1.20 (3H, m), 1.12 (3H, s); ^{13}C NMR (75 MHz): δ (peaks due to the major isomer) 212.0 (C, C=O), 170.0 (C, OC=O), 82.8 (CH, C-10), 58.5 (CH), 57.0 (CH_3), 54.1 (CH_3), 52.8 (CH), 52.4 (CH), 49.5 (C, C-2), 40.5 (CH), 39.1 (CH_2), 38.6 (CH_2), 35.7 (CH_2), 34.8 (CH_2), 22.1 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{22}O_4Na$ (M+Na): 289.1417; found: 289.1406.

4.14. (1*R*,2*S*,6*R*,8*S*,10*R*)-10-Methoxy-2-methyltricyclo[6.3.0.0^{2,6}]-undecan-5-one 17

A solution of the keto ester **27** (34 mg, 0.14 mmol) and LiCl (23 mg, 0.54 mmol) in DMSO (0.5 mL) and water (0.01 mL) was placed in a Carius tube and heated to 180 °C for 10 h. The reaction mixture was cooled to rt, diluted with ether (3 mL), washed with water (2 mL) and brine, 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 an eluent furnished the ketone **17** (23 mg, 82%) as an oil. $[\alpha]_D^{25} = -45.5$ (*c* 1.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2950, 2872, 2822, 1738 (C=O), 1456, 1365, 1262, 1195, 1114; ^{1}H NMR (400 MHz): δ 3.67 (1H, quintet, *J* 7.2 Hz, H-10), 3.29 (3H, s, OCH_3), 2.60–2.45 (1H, m), 2.40–2.25 (3H, m), 2.25–2.20 (2H, m), 2.05–1.85 (2H, m), 1.81–1.70 (3H, m), 1.50–1.20 (2H, m), 1.11 (3H, s, *tert*-CH_3); ^{13}C NMR (100 MHz): δ 221.2 (C, C=O), 83.0 (CH, C-10), 59.1 (CH, C-6), 57.0 (CH_3, OCH_3), 52.5 (CH, C-1), 51.1 (C, C-2), 40.8 (CH, C-8), 39.1 (CH_2), 36.6 (CH_2), 36.3 (CH_2), 34.7 (CH_2), 34.6 (CH_2), 22.3 (CH_3); HRMS: *m/z* calcd for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361; found: 231.1351.

Acknowledgments

We thank the Department of Science and Technology, New Delhi, for the financial support, Council of Scientific and Industrial Research, New Delhi, and University Grants Commission, New Delhi, for the award of research fellowships to V.G. and G.N., respectively. We are grateful to M/s Organica Aromatics (Bangalore) Pvt. Ltd, for the generous gift of campholenaldehyde.

References

1. (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41; (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141; (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1; (d) Ramaiah, M. *Synthesis* **1984**, 529; (e) Paquette, L. A.; Doherty, A. M. *Recent Synthetic Developments in Polyquinane Chemistry*; Springer: New York, 1987; (f) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467; (g) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671; (h) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647.
2. (a) Paquette, L. A. *Chem. Rev.* **1989**, *89*, 1051; (b) Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189.
3. Corner, F. W.; Trotter, J. *J. Chem. Soc. B* **1966**, 11.
4. Bajgrowicz, J. A.; Frank, I.; Frater, G.; Hennig, M. *Helv. Chim. Acta* **1998**, *81*, 1349; Castro, J. M.; Linares-Palomino, P. J.; Salido, S.; Altarejos, J.; Nogueras, M.; Sanchez, A. *Tetrahedron* **2005**, *61*, 11192.
5. For a few examples, see: Mehta, G.; Nandakumar, J. *Tetrahedron Lett.* **2001**, *42*, 7667; Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113; Liu, H. J.; Chan, W. H. *Can. J. Chem.* **1979**, *57*, 708; Chan, W. H. *Can. J. Chem.* **1982**, *60*, 1081; Sakurai, K.; Kitahara, T.; Mori, K. *Tetrahedron* **1988**, *44*, 6581.
6. (a) Srikrishna, A.; Beeraiah, B.; Satyanarayana, G. *Tetrahedron: Asymmetry* **2006**, *17*, 1544; (b) Srikrishna, A.; Beeraiah, B. *Tetrahedron: Asymmetry* **2007**, *18*, 2587; (c) Srikrishna, A.; Beeraiah, B.; Babu, R. R. *Tetrahedron: Asymmetry* **2008**, *19*, 624; (d) Srikrishna, A.; Beeraiah, B. *Tetrahedron: Asymmetry* **2008**, *19*, 884; (e) Srikrishna, A.; Beeraiah, B.; Gowri, V. *Tetrahedron* **2009**, *65*, 2647.
7. Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091; Doyle, M. P.. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12,. Chapter 5.2 Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; John Wiley and Sons: New York, 1998. Chapter 3.
8. Anhalt, K.; Sprung, I.; Schulze, K. *Monatsh. Chem.* **2003**, *134*, 1593.
9. Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
10. Krapcho, A. P. *Synthesis* **1982**, 893.