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Enantiospecific synthesis of thaps-8-en-5-ol *via* stereospecific intramolecular chirality transfer

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Enantiospecific synthesis of thaps-8-en-5-ol, comprising of the carbon framework of a small group of sesquiterpenes containing three contiguous quaternary carbon atoms has been described. (*R*)-Carvone has been employed as the chiral starting material and a combination of intramolecular alkyation and Criegee fragmentation have been employed for intramolecular stereospecific transfer of the chirality. An intramolecular diazoketone cyclopropanation and regioselective cyclopropane ring cleavage reactions have been employed for the creation of the three requisite contiguous quaternary carbon atoms.

Keywords: Enantiospecific synthesis, thaps-8-en-5-ol, sesquiterpenes, (*R*)-Carvone, Criegee fragmentation

The medicinal properties of the plants belonging to the umbelliferous genus *Thapsia*, mostly distributed in the Mediterranean region and in the Iberian peninsula, were recognized as early as 300 B.C. For centuries, preparations containing resin from the root of *Thapsia garganica* L. have been used in Arabian and European medicine for the treatment of pulmonary diseases, catarrh and as counter-irritants for the relief of rheumatic pains. Phytochemical investigations of *Thapsia garganica* led to the isolation of two major active principles, sesquiterpene lactones (guaianolides) thapsigargin and thapsi-gargicin, which were found to be responsible for the medicinal activity[1]. Even though, thapsigargin and thapsigargicin were absent in *Thapsia villosa*, it contains a large number of sesquiterpenes belonging to guaianolides, germacranes, cadinenes and caryophyllenes, and in addition a new group of sesquiterpenes named as Thapsanes, which are unique to *Thapsia villosa*. In 1984, Rasmussen and co-workers reported[2] isolation of the first member of this new group of sesquiterpenes, from the ethanolic extract of the roots of *Thapsia villosa* L, whose structure was established as the ester **1** from its spectral data and confirmed by single crystal X-ray analysis. Simultaneously (1985), Grande and co-workers[3,4] reported the isolation of the corresponding senecioate ester **2** from the benzene extract of the roots of *Thapsia villosa* L. var. *minor* (Hoff. and Link) Cout., along with five other hemiacetalic **3-7** and four nonacetalic **8-11** minor components, having the same carbon framework. In 1990, Christensen and co-workers have reported[5] the isolation of three more thapsanes, two nonacetalic **12** and **13**, and one hemiacetalic **14** from *Thapsia villosa* var. *minor* collected near Capo Espichel. The trivial name "*thapsane*" was suggested[3,4] for the carbon framework *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane **15** present in these compounds. Structures of all the thapsanes isolated so far are given in **Chart I**. The absolute configuration of the thapsanes was deduced from the analysis of the CD spectra of the compounds **15** and **16** containing the cyclohexanone part structure, which were obtained by degradation of the 3- and 5-acyloxythapsanes[6] **5** and **6**. Presence of the unique, sterically crowded structure containing six one carbon substituents on a hydrindane framework, three contiguous quaternary carbon atoms and five to six chiral centers made thapsanes attractive synthetic targets[7]. In continuation of our interest in thapsanes, enantiospecific synthesis of thapsanes has been initiated starting from the readily and abundantly available monoterpene (*R*)-carvone **17**. Herein, we describe the details[7e] of the enantiospecific synthesis of a thapsane containing an oxygen substituent at the C-5 position.

A cursory look at the molecular architecture of thapsanes revealed that the most important task for

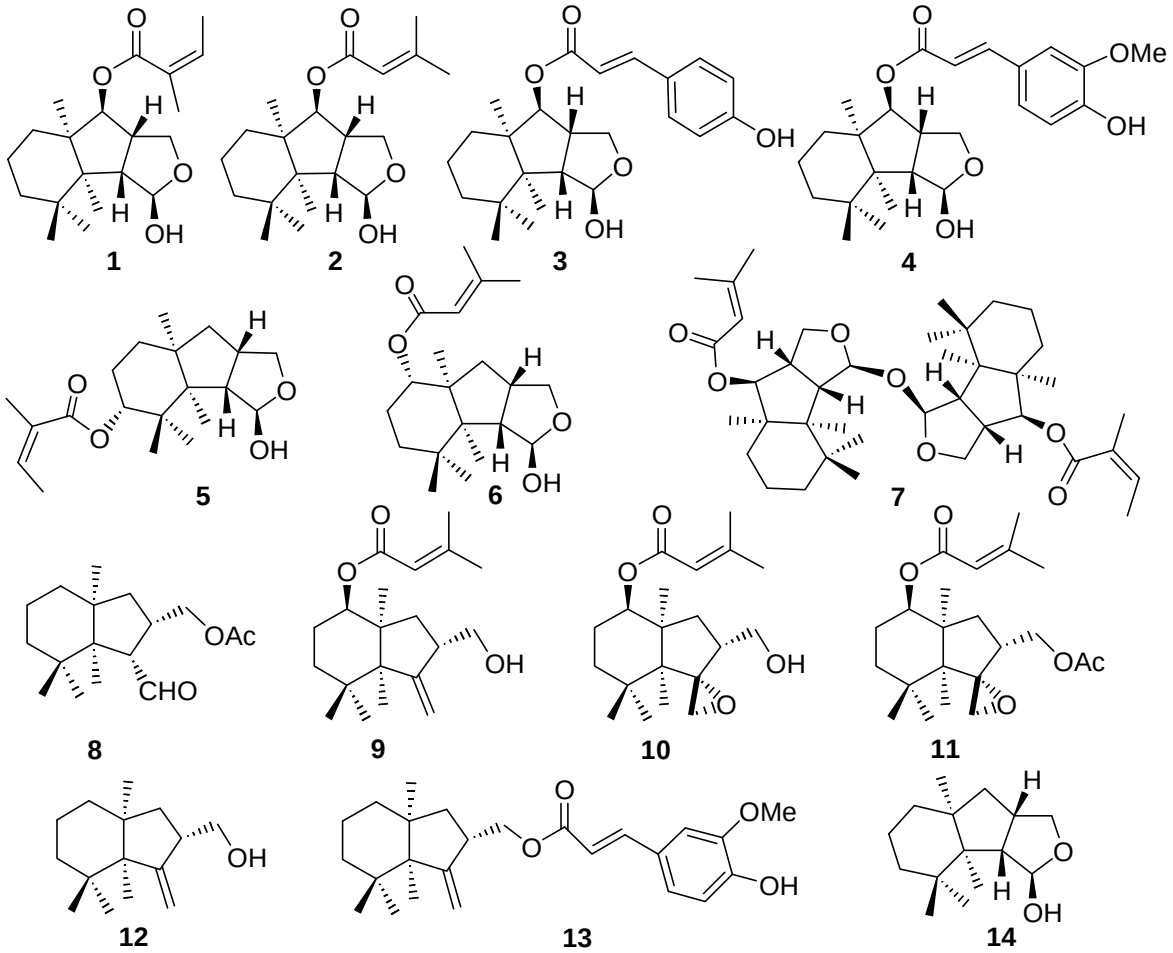
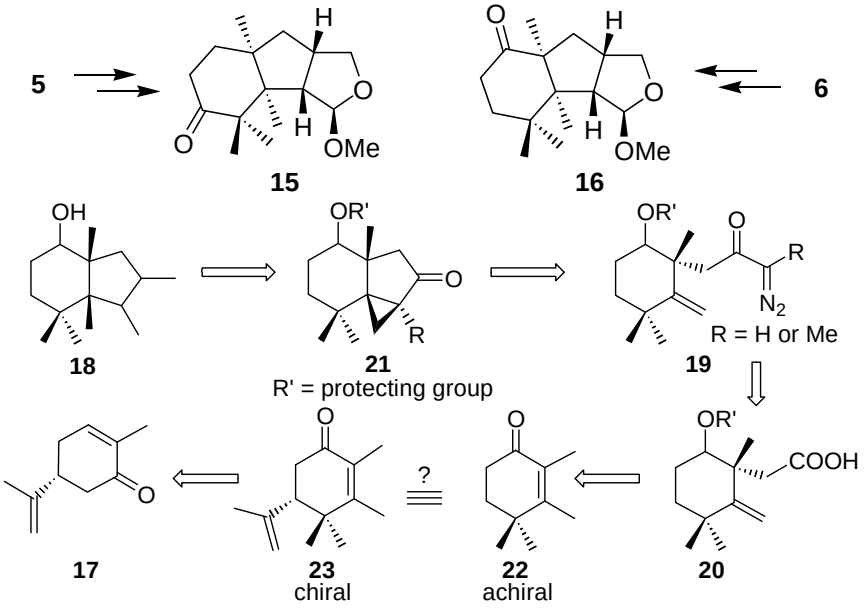


Chart I

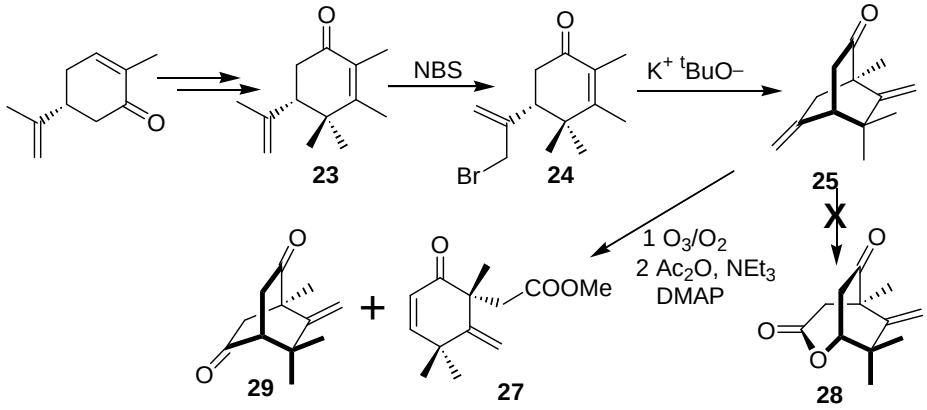
the synthesis of thapsanes is the construction of a suitably functionalized *cis*-1,2,2,6-tetramethylbicyclo-[4.3.0]nonane containing three contiguous quaternary carbon atoms (C-1, C-2 and C-6). A perusal of the structures of the thapsanes isolated so far revealed that an oxygen functionality is present at the C-3 or C-5 or C-7 positions besides the C-10 and C-11 positions of thapsanes. Attention was focused on the enantiospecific synthesis of a thapsane containing oxygen functionality at the C-5 position. Retrosynthetic analysis depicted in **Scheme I** was conceived for the synthesis of the thapsane **18**. It was anticipated that intramolecular cyclopropanation of the diazoketone **19**, derived from the acid **20**, would generate the tricyclic ketone **21**, which could be further elaborated into thapsane **18**. Alkylation at the α-position of the enone **22** with an equivalent of CH_2COOH suggested the enone **22** as the appropriate precursor for the acid **20**. As the cyclohexenone **21** is achiral, identifying the isopropenyl group as a disposable group, trimethylcarvone **23** was chosen as the chiral equivalent of **21**, whose synthesis from (*R*)-carvone **17** has already been reported[7k,8].

Conceptually it is not appealing to remove three carbons (isopropenyl group) and introduce two carbons separately. Hence, instead of the degradation of the iso-propenyl group and introduction of a side chain at the C-2 position in the trimethylcarvone **23**, a regio-, stereo- and enantiospecific translocation of the isopropenyl group from the C-5 position of trimethylcarvone **23** to the C-2 position as the acetate side chain was envisaged. For the translocation of the isopropenyl group, it was conceived that first joining the C-2 carbon of trimethylcarvone **23** with the isopropenyl carbon, and subsequent cleavage of the bond connecting the C-5 position with the isopropenyl group, which will also result in the total control of regio- and stereoselectivity, **Scheme II**.

Reaction of the trimethylcarvone **23** with *N*-bromo-succinimide (NBS) in methanol-methylene chloride medium furnished the allyl bromide **24** in 90% yield in a highly regioselective manner[9]. Generation of the



Scheme I



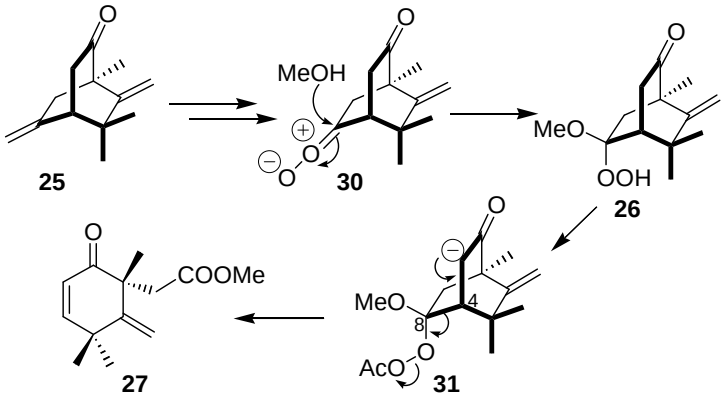
Scheme II

thermodynamic dienolate of the bromoenone **24** with potassium tertiary butoxide in tertiary butyl alcohol and THF resulted in the regioselective intramolecular alkylation[8,10] to furnish the bicyclo[2.2.2]octanone **25**, thus creating the second quaternary carbon atom required for the thapsanes. The steric hindrance of the C-6 exomethylene group was exploited for the regioselective cleavage of the C-8 exomethylene group in the bicyclo[2.2.2]octanone **25**, employing an ozonolysis followed by Criegee rearrangement sequence[11]. Thus, controlled ozonolysis of the bicyclic ketone **25** in a mixture of methanol-methylene chloride followed by treatment of the intermediate methoxyhydroperoxide **26** with a mixture of acetic anhydride, triethylamine and a catalytic amount of DMAP in refluxing benzene furnished the keto ester **27** *via* the Criegee fragmentation, instead of the expected lactone **28** (*via* Criegee rearrangement)[11] along with varying amounts of simple ozonolysis product, the dione **29**. Facile formation of the ester **27** can be rationalized as depicted in **Scheme III**. Ozonolysis of **25** followed by cleavage of the secondary ozonide furnishes the sterically biased carbonyl oxide **30**. Preferential addition of methanol to the carbonyl oxide **30** from the less hindered face of the molecule furnishes the methoxyhydroperoxide **26**, which on acetylation generates the peroxy acetate **31**. The orientation of the acetate group in the peroxy acetate **31** is ideally suited for a facile elimination reaction under the basic conditions of the reaction to furnish the ester **27** *via* the cleavage of the C-4 C-8 bond.

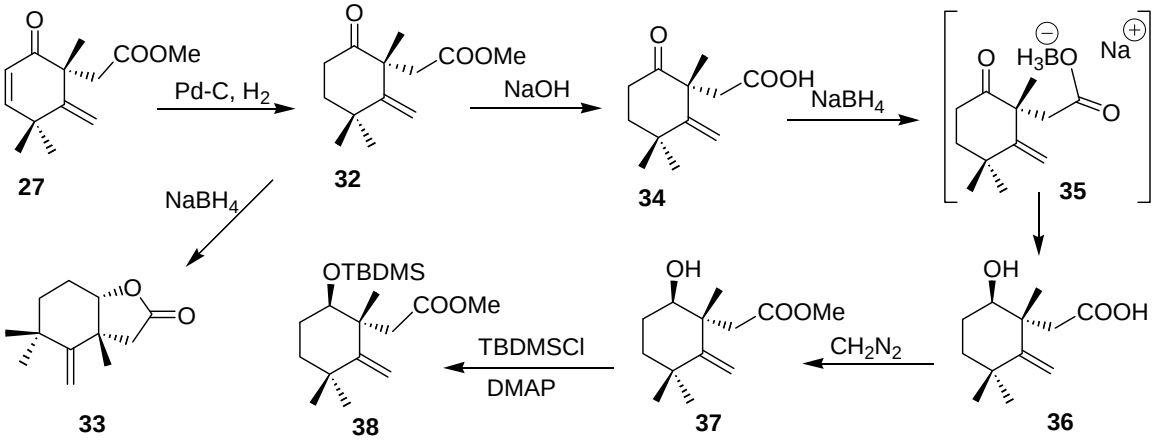
After successfully translocating the isopropenyl group from the C-5 position of trimethylcarvone **23** to

the C-2 position as an acetate side chain in a regio- and enantiospecific manner, conversion of the keto ester **27** into a bicyclo[4.3.0]nonane was addressed, **Scheme IV**. Regioselective hydrogenation using 5% palladium on carbon as the catalyst in ethyl acetate at one atmospheric pressure of hydrogen (balloon) transformed the enone **27** into the saturated ketone **32**. For further elaboration, it was considered that the ketone group could be blocked *via* conversion to the corresponding alcohol followed by protection. Reduction of the keto ester **32** with sodium borohydride in methanol, quite expectedly, generated the *cis*-lactone **33**, whose structure rests secured from its spectral data. It was conceived that the problem could be circumvented by carrying out the reduction of the ketone group in the keto ester **32** in an intramolecular fashion *via* a carboxyborohydride[12]. Consequently, hydrolysis of the keto ester **32** with 5% sodium hydroxide in refluxing aqueous methanol generated the keto acid **34**. Treatment of the keto acid **34** with sodium borohydride in THF delivered the hydride in an intramolecular fashion *via* the carboxyborohydride **35** and generated, as anticipated, the hydroxy acid **36**, which on esterification with diazomethane followed by purification on a silica gel column furnished the hydroxy ester **37** in 70% yield. Treatment of the hydroxy ester **37** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and DMAP in *N*,*N*-dimethylformamide (DMF) at RT for 2 days furnished the TBDMS ether **38** in 95% yield.

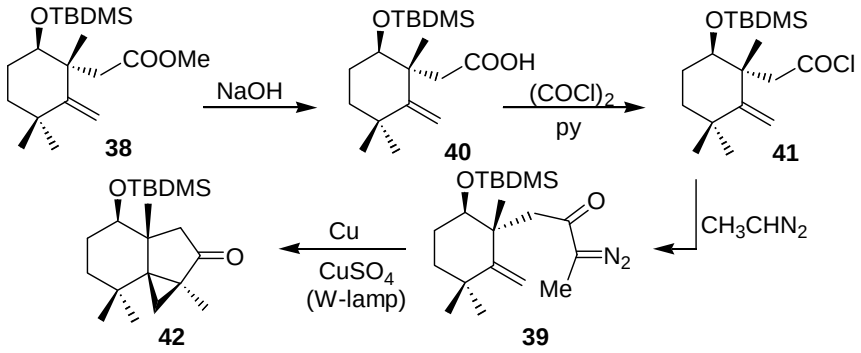
Next, for the creation of third quaternary carbon atom of thapsanes, an intramolecular cyclopropanation reaction[13] followed by regiospecific cyclopropane ring cleavage was considered, **Scheme V**. To overcome the regiochemical problem at a later stage, it was decided to introduce the fourteenth carbon during the cyclopropanation reaction itself by using the diazoketone **39**, which could be prepared from diazoethane and the corresponding acid chloride. Thus, refluxing a solution of the ester **38** and sodium hydroxide in aqueous methanol furnished the acid **40**, m.p. 69-71°C, in 94% yield. Reaction of the acid **40** with oxalyl chloride in benzene and pyridine at RT generated the acid chloride **41**, which on treatment



Scheme III



Scheme IV



Scheme V

with an excess of ethereal diazoethane, generated from *N*-nitroso-*N*-ethylurea, furnished the diazoketone **39**. Anhydrous copper sulfate-copper catalyzed decomposition of the diazoketone **39** in refluxing cyclohexane, under irradiation with a tungsten lamp, led to the stereospecific insertion of the intermediate keto-carbenoid into the exomethylene moiety to furnish the tricyclic ketone **42**, m.p. 73-75°C, containing four quaternary carbon atoms.

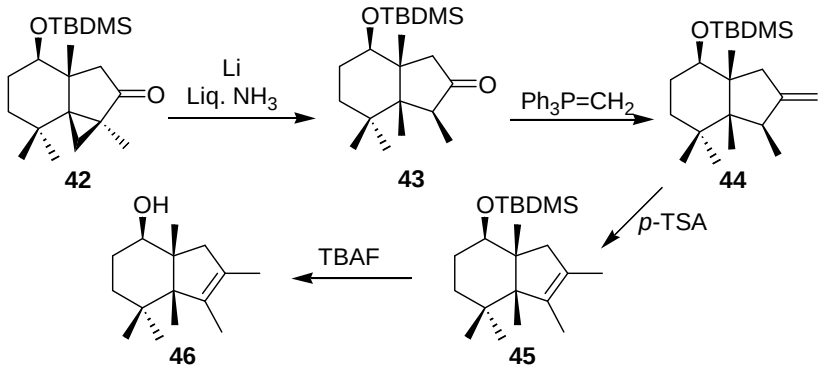
Regiospecific reductive cleavage of the cyclopropane ring employing lithium in liquid ammonia transformed the tricyclic ketone **42** into the bicyclic ketone **43**, m.p. 76-78°C, in a highly regio- and stereoselective manner, **Scheme VI**. The structure of the bicyclic ketone **43** rests secured from its spectral data. The regiospecificity[14] in the cyclopropane ring cleavage was a consequence of the better overlap of the C-2 C-3 bond of the cyclopropane with the π orbital of the carbonyl group in the tricyclic ketone **42**. The stereochemistry of the secondary methyl group was assigned on the basis of thermodynamic considerations. Molecular mechanics (PCMODEL) calculations indicated that the *exo* isomer **43** is ≈6.0 kcal/mole stable than the corresponding *endo* isomer. Wittig reaction of the ketone **43** with methylenetriphenylphosphorane, generated from potassium tertiary butoxide and methyltriphenylphosphonium iodide, in benzene at 70°C furnished the silyl ether of thaps-8(11)-en-5-ol **44**, whose structure was delineated from its spectral data. Isomerization of the double bond in 5-silyloxythaps-8(11)-ene **44** with a catalytic amount of *p*-TSA in methylene chloride furnished TBDMS ether of thaps-8-en-5-ol **45** in 69% yield. Finally, cleavage of the TBDMS ether in **45** with tetrabutylammonium fluoride (TBAF) in refluxing THF for 24 h furnished 5-hydroxythaps-8-ene **46**, m.p 77-79°C, in 91% yield.

In conclusion, we have accomplished the enantiospecific total synthesis of the thapsenes **44-46** containing oxygen functionality at the C-5 position. An intramolecular alkylation and regioselective Criegee fragmentation sequence has been employed for the enatiospecific transfer of the chirality centre. A combination of intramolecular diazoketone cyclopropanation and regiospecific cleavage of cyclopropane ring were employed for the stereospecific generation of the three requisite contiguous quaternary carbon atoms.

Experimental Section

(5*R*)-5-(3-Bromopropen-2-yl)-2,3,4,4-tetramethylcyclohex-2-enone 24. To an ice cold magnetically stirred solution of trimethylcarvone[7k] **23** (1 g, 5.2 mmoles) in a 3:2 mixture of CH_2Cl_2 and methanol (5 mL) was slowly added NBS (1.1 g, 6.2 mmoles) over a period of 20 min. The reaction mixture was stirred for 6 h at RT, diluted with water and extracted with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 extract was washed with 5% aq. NaOH 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 (1:20) as eluent furnished the allyl bromide **24** (1.27 g, 90%) as oil[8], which was distilled under vacuum. b.p.: 180-182°C/0.5 mm; $[\alpha]_D^{25}$: +14.8° (*c* 6.4, $CHCl_3$); IR (neat): 2973, 1662, 1612, 1470, 1441, 1374, 1323, 1209, 1075, 920 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 5.43 (1 H, s) and 5.02 (1 H, s) [C=CH_2], 3.95 and 3.90 (2 H, AB q, *J* = 10.0 Hz, CH_2Br), 2.74 (1 H, dd, *J* = 9.0 and 6.9 Hz), 2.53 (1 H, d, *J* = 6.9 Hz), 2.52 (1 H, d, *J* = 9.0 Hz), 1.88 (3 H, s, C_3-CH_3), 1.74 (3 H, s, C_2-CH_3), 1.14 (3 H, s) and 1.08 (3 H, s) [2 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 196.7 (C, C=O), 160.1 (C, C-3), 145.9 (C, C=CH_2), 130.6 (C, C-2), 118.9 (CH_2, C=CH_2), 47.5 (CH, C-5), 40.6 (CH_2), 39.8 (C, C-4), 38.6 (CH_2), 26.7 (CH_3), 21.5 (CH_3), 16.5 (CH_3), 11.7 (CH_3).

(1*R*,4*S*)-1,5,5-Trimethyl-6,8-bis(methylene)bicyclo[2.2.2]octan-2-one 25. To a cold (-5°C), magneti-



Scheme VI

cally stirred 1 M solution of potassium tert-butoxide [freshly prepared from potassium (87 mg, 2.2 mmoles) and ^{t}BuOH (2.2 mL)] in 2.5 mL of THF was added a solution of the bromoenone **24** (280 mg, 1.04 mmoles) in 2.5 mL of THF. The reaction mixture was slowly warmed up to RT and stirred for 12 h. It was then quenched with water and extracted with ether (2 × 5 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:50) as eluent furnished the bicyclic ketone **25** (150 mg, 76%) as oil[8], which was distilled under vacuum. b.p.: 100-105°C/0.5 mm; $[\alpha]_D^{24}$: -5.4° (*c* 7.9, $CHCl_3$); IR (neat): 2973, 1727, 1653, 1636, 1455, 1406, 1124, 1078, 996, 894 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 4.95 (2 H, s), 4.88 (1 H, s) and 4.74 (1 H, s) [2 × C=CH_2], 2.61 (1 H, dd, *J* = 18.9 and 2.6 Hz, H-3a), 2.45-2.30 (2 H, m), 2.30-2.20 (1 H, m), 2.20 (1 H, dd, *J* = 18.9 and 2.6 Hz, H-3b), 1.14 (3 H, s), 1.12 (3 H, s) and 1.09 (3 H, s) [3 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 210.8 (C, C=O), 156.5 (C, C-6), 145.7 (C, C-8), 108.9 (CH_2) and 108.7 (CH_2) [2 × C=CH_2], 52.7 (C, C-1), 50.6 (CH, C-4), 40.8 (CH_2, C-3), 38.6 (CH_2, C-7), 37.8 (C, C-5), 31.4 (CH_3), 28.6 (CH_3), 16.5 (CH_3).

Methyl 2-[(1*R*)-1,5,5-trimethyl-6-methylene-2-oxocyclohex-3-enyl]acetate 27 and (1*R*,4*R*)-1,8,8-trimethyl-7-methylenebicyclo[2.2.2]octane-2,5-dione 29. Pre-cooled dry ozone in oxygen gas was passed through a cold (-70°C) suspension of the bicyclic ketone **25** (200 mg, 1.05 mmoles) and $NaHCO_3$ (10 mg) in 1:4 MeOH-CH_2Cl_2 (5 mL) for 5 min. Excess ozone was flushed off with oxygen. The solvent was evaporated *in vacuo* and the residue was dissolved in dry benzene (2 mL). Acetic anhydride (1 mL, 10.5 mmoles), triethylamine (0.72 mL, 5.2 mmoles) and a catalytic amount of DMAP were added to the reaction mixture and stirred at RT for 15 min. It was then refluxed for 6 h, diluted with water and extracted with ether (3 × 10 mL). The ether extract was washed with 3 *N* aq. HCl, water and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50) as eluent furnished the unreacted starting material **25** (80 mg, 40%). Further elution of the column with ethyl acetate-hexane (1:20 to 1:10) as eluent furnished the ester **27** (93 mg, 40%) as oil. $[\alpha]_D^{25}$: +38.0° (*c* 1.08, $CHCl_3$). IR (neat): 2971, 1740, 1680, 1622, 1437, 1343, 1197, 1172, 1105, 1011, 902, 830 cm^{-1}. ^{1}H NMR ($CDCl_3$ + CCl_4): δ 6.52 (1 H, d, *J* = 10.2 Hz, H-4'), 5.98 (1 H, d, *J* = 10.2 Hz, H-3'), 5.15 (1 H, s) and 5.10 (1 H, s) [C=CH_2], 3.55 (3 H, s, OCH_3), 3.33 and 2.75 (2 H, 2 × d, *J* = 16.7 Hz, H-2), 1.38 (3 H, s), 1.34 (3 H, s) and 1.29 (3 H, s) [3 × tert-CH_3]. ^{13}C NMR ($CDCl_3$ + CCl_4): δ 199.9 (C, C=O), 171.1 (C, OC=O), 157.4 (C, C-6'), 155.6 (CH, C-4'), 124.0 (CH, C-3'), 110.4 (CH_2, C=CH_2), 51.3 (CH_3, OCH_3), 49.3 (C, C-1'), 42.8 (CH_2, C-2), 37.5 (C, C-5'), 33.1 (CH_3), 31.3 (CH_3), 30.9 (CH_3). MS: *m/z* (%) 222 (M^+, $C_{13}H_{18}O_3$, 16), 191 (51), 175 (64), 163 (33), 162 (30), 149 (73), 148 (37), 147 (74), 135 (31), 121 (100), 119 (55), 105 (55), 96 (40), 91 (44).

Further elution of the column with ethyl acetate-hexane (1:5) as eluent furnished the diketone **29** (18 mg, 9%) as oil. $[\alpha]_D^{24}$: +58.6° (*c* 2.2, $CHCl_3$); IR (neat): 2970, 1732, 1636, 1457, 1401, 1244, 1122, 1078, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$ + CCl_4): δ 5.15 (2 H, s, C=CH_2), 2.78 (1 H, dd, *J* = 20.1 and 3.3 Hz), 2.46 (1 H, dd, *J* = 20.1 and 2.4 Hz), 2.42 (1 H, s, H-4), 2.40-2.30 (2 H, m), 1.24 (3 H, s) and 1.21 (6 H, s) [3 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 209.4 (C, C=O), 207.4 (C, C=O), 153.9 (C, C-7), 110.5 (CH_2, C=CH_2), 56.7 (CH, C-4), 53.9 (C, C-1), 45.3 (CH_2), 37.7 (C, C-8), 36.3 (CH_2), 31.2 (CH_3), 27.9 (CH_3), 16.0 (CH_3); MS: *m/z* (%) 192 (M^+, $C_{12}H_{16}O_2$, 44), 177

(100), 149 (94), 121 (49), 107 (60), 96 (58), 93 (32), 91 (37), 83 (44).

Methyl 2-[(1*R*)-1,5,5-trimethyl-6-methylene-2-oxocyclohexyl]acetate 32. To a magnetically stirred solution of the enone **27** (200 mg, 0.90 mmole) in EtOAc (2 mL) was added 5% Pd-C (30 mg) and the reaction mixture was stirred at RT in hydrogen atmosphere, created by evacuative displacement of air (balloon), for 30 min. 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 ethyl acetate-hexane (1:10) as eluent furnished the ketone **32** (182 mg, 90%) as oil. $[\alpha]_D^{25}$: +20.8° (*c* 1.2, $CHCl_3$); IR (neat): 3092, 2967, 1740, 1713, 1627, 1436, 1344, 1200, 1154, 1012, 899 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 5.05 (1 H, s) and 4.94 (1 H, s) [$C=CH_2$], 3.57 (3 H, s, OCH_3), 3.23 and 2.71 (2 H, 2 × d, *J* = 16.5 Hz, H-2), 2.70–2.45 (2 H, m, H-3'), 1.90-1.75 (2 H, m, H-4'), 1.25 (3 H, s), 1.24 (3 H, s) and 1.21 (3 H, s) [3 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 212.8 (C, C=O), 171.4 (C, OC=O), 159.6 (C, C-6'), 108.6 (CH_2, $C=CH_2$), 51.4 (CH_3, OCH_3), 51.3 (C, C-1'), 44.1 (CH_2, C-2), 35.7 (C, C-5'), 35.5 (CH_2) and 34.5 (CH_2) [C-3' and C-4'], 31.5 (CH_3), 30.3 (2 C, CH_3); MS: *m/z* (%)224 (M^+, $C_{13}H_{20}O_3$, 83), 193 (44), 165 (85), 151 (26), 137 (37), 135 (30), 123 (42), 121 (30), 109 (100), 108 (34), 107 (59), 95 (42).

(1*R*,6*S*)-1,3,3-Trimethyl-2-methylene-7-oxabicyclo[4.3.0]nonan-8-one 33. To an ice cold, magnetically stirred solution of the keto ester **32** (7 mg, 0.031 mmole) in dry methanol (1 mL) was added $NaBH_4$ (5 mg, 0.13 mmole) and stirred for 30 min at the same temperature. The reaction was then quenched with water (3 mL) followed by 3 N aq. HCl (3 mL) and extracted with CH_2Cl_2 (2 × 3 mL). The combined CH_2Cl_2 extract 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 (1:10 to 1:6) furnished the cis-lactone **33** (5 mg, 82%), which was recrystallized from hexanes. m.p.: 39-41°C; $[\alpha]_D^{26}$: +6.15° (*c* 1.3, $CHCl_3$); IR (neat): 3096, 2935, 1785, 1626, 1458, 1360, 1274, 1213, 1172, 1107, 1038, 1000, 952, 902 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 5.17 (1 H, s) and 5.05 (1 H, s) [$C=CH_2$], 4.25 (1 H, t, *J* = 4.5 Hz, H-6), 2.87 and 2.31 (2 H, 2 × d, *J* = 17.1 Hz, H-9), 2.10-1.80 (2 H, m), 1.66 (1 H, ddd, *J* = 15.0, 12.0 and 4.0 Hz), 1.30 (1 H, dt, *J* = 13.6 and 5.0 Hz), 1.36 (3 H, s), 1.15 (3 H, s) and 1.13 (3 H, s) [3 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 175.3 (C, OC=O), 156.8 (C, C-2), 112.0 (CH_2, $C=CH_2$), 85.3 (CH, C-6), 45.2 (CH_2, C-9), 44.4 (C, C-1), 35.4 (C, C-3), 33.1 (CH_2, C-5), 31.6 (CH_3), 30.9 (CH_3), 28.4 (CH_3), 23.2 (CH_2, C-4); MS: *m/z* (%) 194 (M^+, 76), 152 (25), 138 (26), 137 (42), 134 (28), 133 (100), 124 (38), 123 (53), 119 (49), 110 (41), 109 (68), 107 (44), 99 (32), 95 (28); Anal.: For $C_{12}H_{18}O_2$, Calcd.: C, 74.19; H, 9.34%. Found: C, 73.82; H, 9.45%.

(1*R*)-1,5,5-Trimethyl-6-methylene-2-oxocyclohexylacetic acid 34. A magnetically stirred solution of the keto ester **32** (418 mg, 1.87 mmoles) in methanol (4 mL) and 10% aq. NaOH (4 mL, 10 mmoles) was refluxed in an oil bath for 12 h. The reaction mixture was cooled, acidified with 3 N aq. HCl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the keto acid **32** (370 mg, 94%) as sticky oil. $[\alpha]_D^{23}$: +21.1° (*c* 1.9, $CHCl_3$); IR (neat): 3100, 3094, 2967, 2870, 1710, 1627, 1452, 1429, 1368, 1261, 1230, 1155, 1107, 1018, 900, 801 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 5.06 (1 H, s) and 4.98 (1 H, s) [$C=CH_2$], 3.26 (1 H, d, *J* = 16.5 Hz) and 2.69 (1 H, d, *J* = 16.5 Hz) [H-2], 2.53 (2 H, br s), 1.80 (2 H, t, *J* = 6.3 Hz), 1.24 (6 H, s) and 1.18 (3 H, s) [3 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 212.2 (C, C=O), 176.7 (C, OC=O), 159.5 (C, C-6'), 108.9 (CH_2, $C=CH_2$), 51.1 (C, C-1'), 44.0 (CH_2, C-2), 35.7 (C, C-5'), 35.3 (CH_2, C-3'), 34.5 (CH_2, C-4'), 31.5 (CH_3), 30.32 (CH_3), 30.27 (CH_3); MS: *m/z* (%) 210 (M^+, $C_{12}H_{18}O_3$, 100), 165 (27), 137 (32), 123 (26), 109 (60), 107 (38), 95 (38).

Methyl 2-[(1*R*,2*R*)-2-hydroxy-1,5,5-trimethyl-6-methylenecyclohexyl]acetate 37. To an ice cold, magnetically stirred solution of the keto acid **34** (370 mg, 1.76 mmoles) in dry THF (8 mL) was added $NaBH_4$ (73 mg, 1.93 mmoles) in small portions over a period of 30 min. The reaction was allowed to come to RT and stirred for 3 h. It was then quenched very carefully with water (2 mL) followed by 3 N aq. HCl (5 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the hydroxy acid **36**. To a magnetically stirred, ice-cold solution of the hydroxy acid **36** in ether (2 mL) was added an ice-cold ethereal diazomethane solution (excess, prepared from 2 g of *N*-nitroso-*N*-methylurea and 25 mL of 60% KOH and 10 mL of ether) and stirred for 10 min at the same temperature. Careful evaporation of the excess diazomethane and the solvent, followed by purification of the residue over a

silica gel column using ethyl acetate-hexane (1:5) as eluent afforded the hydroxy ester **37** (280 mg, 70%) as oil. $[\alpha]_D^{26}$: -13.6° (*c* 0.88, $CHCl_3$); IR (neat): 3470, 2949, 1736, 1624, 1436, 1345, 1206, 1173, 1128, 1044, 1016, 899 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 5.02 (1 H, s) and 4.97 (1 H, s) [C=CH_2], 4.03 (1 H, dd, *J* = 9.0 and 4.8 Hz, H-2'), 3.62 (3 H, s, OCH_3), 2.71 and 2.57 (2 H, AB q, *J* = 15.0 Hz, H-2), 1.90-1.65 (3 H, m), 1.57 (1 H, ddd, *J* = 13.6, 6.3 and 4.4 Hz), 1.41 (1 H, ddd, *J* = 13.6, 9.9 and 4.7 Hz), 1.20 (3 H, s), 1.15 (3 H, s) and 1.12 (3 H, s) [3 × tert-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 172.5 (C, OC=O), 159.7 (C, C-6'), 109.6 (CH_2, C=CH_2), 73.2 (CH, C-2'), 51.2 (CH_3, OCH_3), 45.0 (C, C-1'), 43.1 (CH_2, C-2), 36.6 (CH_2, C-3'), 36.0 (C, C-5'), 32.0 (CH_3), 31.8 (CH_3), 26.9 (CH_2, C-4'), 23.8 (CH_3); MS: *m/z* (%) 227 (M^++1, $C_{13}H_{23}O_3$, 2), 208 (44), 152 (58), 137 (52), 135 (70), 133 (39), 119 (61), 109 (100), 107 (55), 95 (51), 93 (47).

Methyl 2-[(1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]acetate 38. To a magnetically stirred solution of the alcohol **37** (245 mg, 1.08 mmoles) in dry DMF (0.4 mL) were added TBDMSCl (165 mg, 1.1 mmoles) and a catalytic amount of DMAP and stirred at RT for 2 days. Water (10 mL) was then added to the reaction mixture and extracted with CH_2Cl_2 (2 × 5 mL). The combined CH_2Cl_2 extract 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 (1:50) as eluent furnished the TBDMS ether **38** (350 mg, 95%) as oil. $[\alpha]_D^{26}$: -41.8° (*c* 0.79, $CHCl_3$); IR (neat): 2952, 2857, 1741, 1625, 1464, 1435, 1341, 1252, 1171, 1129, 1100, 1075, 1016, 888, 837, 774 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 4.95 (1 H, s) and 4.88 (1 H, s) [C=CH_2], 4.23 (1 H, t, *J* = 7.2 Hz, H-2'), 3.59 (3 H, s, OCH_3), 2.64 and 2.53 (2 H, AB q, *J* = 15.9 Hz, H-2), 1.72 (2 H, m), 1.53 (1 H, dt, *J* = 13.2 and 5.1 Hz), 1.39 (1 H, dd, *J* = 13.5 and 6.9 Hz), 1.13 (3 H, s), 1.12 (3 H, s) and 1.11 (3 H, s) [3 × tert-CH_3], 0.88 [9 H, s, $C(CH_3)_3$], 0.06 (3 H, s) and 0.01 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 172.0 (C, OC=O), 160.4 (C, C-6'), 108.6 (CH_2, C=CH_2), 73.2 (CH, C-2'), 50.9 (CH_3, OCH_3), 45.3 (C, C-1'), 42.2 (CH_2, C-2), 36.7 (CH_2, C-4'), 35.9 (C, C-5'), 32.0 (2 C, CH_3), 27.3 (CH_2, C-3'), 26.1 [3 C, CH_3, $C(CH_3)_3$], 25.2 (CH_3), 18.2 [C, $C(CH_3)_3$], -3.9 (CH_3) and -4.9 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 283 (M-^{t}Bu, ($C_{15}H_{27}O_3Si$, 100), 266 (7), 251 (5), 223 (8), 209 (12), 177 (9), 171 (19), 159 (10), 149 (16), 135 (23), 131 (21), 121 (15), 107 (20), 93 (17), 91 (12), 89 (62).

Further elution of the column with ethyl acetate-hexane (1:5) as eluent afforded the unreacted starting material **37** (8 mg, 3%).

(1*R*,2*R*)-2-[2-(*tert*-Butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]acetic acid 40. A magnetically stirred solution of the ester **38** (420 mg, 1.23 mmoles) in methanol (3 mL) and 10% aq. NaOH (3 mL, 7.5 mmoles) was refluxed in an oil bath for 22 h. The reaction mixture was cooled, acidified with 3 N aq. HCl (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the acid **40** (380 mg, 94%), which was recrystallized from hexanes. m.p.: 69-71°C; $[\alpha]_D^{23}$: -37.8° (*c* 0.9, $CHCl_3$); IR (thin film): 3300-2700, 3090, 2929, 1708, 1624, 1469, 1427, 1372, 1251, 1226, 1101, 1072, 1005, 951, 887, 834, 771, 671 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 4.98 (1 H, s) and 4.94 (1 H, s) [C=CH_2], 4.20 (1 H, t, *J* = 6.9 Hz, H-2'), 2.70 and 2.55 (2 H, AB q, *J* = 16.2 Hz, H-2), 1.76-1.66 (2 H, m), 1.52 (1 H, dt, *J* = 13.5 and 4.8 Hz), 1.42 (1 H, dd, *J* = 13.5 and 7.2 Hz), 1.14 (6 H, s) and 1.11 (3 H, s) [3 × tert-CH_3], 0.83 [9 H, s, $C(CH_3)_3$], 0.06 (3 H, s) and 0.02 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 178.0 (C, OC=O), 160.2 (C, C-6'), 108.9 (CH_2, C=CH_2), 73.1 (CH, C-2'), 45.4 (C, C-1'), 42.3 (CH_2, C-2), 36.7 (CH_2, C-4'), 35.9 (C, C-5'), 32.0 (2 C, CH_3), 27.3 (CH_2, C-3'), 26.1 [3 C, CH_3, $C(CH_3)_3$], 25.2 (CH_3), 18.3 [C, $C(CH_3)_3$], -3.8 (CH_3) and -4.8 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 269 (M-^{t}Bu, $C_{14}H_{25}O_3Si$, 10), 177 (14), 149 (19), 135 (36), 133 (11), 121 (12), 107 (16), 93 (18), 83 (26), 75 (100).

(1*R*,3*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-3,6,10,10-tetramethyltricyclo[4.4.0.0^{1,3}]decan-4-one 42. A solution of the acid **40** (380 mg, 1.16 mmoles), oxalyl chloride (0.3 mL, 3.48 mmoles) and pyridine (0.2 mL, 2.48 mmoles) in dry benzene (4 mL) was magnetically stirred for 3 h at RT. Evaporation of the excess oxalyl chloride and solvent under reduced pressure afforded the acid chloride **41**. A solution of the acid chloride **41** in dry ether (5 mL) was added, drop wise, to a cold, magnetically stirred ethereal solution of diazoethane (excess, prepared from 3 g of *N*-nitroso-*N*-ethylurea and 20 mL of 60% aq. KOH solution and 10 mL of ether) and stirred at RT for 3 h. Careful evaporation of the excess diazoethane and solvent on water bath and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the diazoketone **39** as

yellow oil. [IR (neat): 2940, 2080, 1640, 1465, 1380, 1260, 1105, 1075, 890, 840, 780 cm^{-1}].

To a magnetically stirred, refluxing (by placing two 100 *W* tungsten lamps near the reaction flask) suspension of copper powder (740 mg, 11.65 mmoles) and anhydrous copper sulfate (280 mg, 1.75 mmoles) in dry cyclohexane (40 mL) was added, drop wise, a solution of the diazoketone **39** in dry cyclohexane (10 mL) over a period of 40 min and the reaction mixture was refluxed for 5 h. It was then cooled and copper and copper sulfate were filtered off using a sintered funnel. Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the tricyclic ketone **42** (145 mg, 37% from acid **40**), which was recrystallized from hexanes. m.p.: 73-75°C; $[\alpha]_D^{25}$: -25.0° (*c* 1.0, $CHCl_3$); IR (thin film): 2952, 2853, 1715, 1471, 1465, 1400, 1380, 1364, 1332, 1258, 1106, 1077, 1063, 1027, 1007, 960, 889, 872, 838, 777, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.15 (1 H, dd, *J* = 11.3 and 4.4 Hz, H-7), 2.12 and 1.74 (2 H, 2 × d, *J* = 18.0 Hz, H-5), 1.90-1.40 (5 H, m), 1.03 (1 H, d, *J* = 4.8 Hz), 1.37 (3 H, s), 1.15 (3 H, s), 1.11 (3 H, s) and 0.82 (3 H, s) [4 × tert-CH_3], 0.86 [9 H, s, $C(CH_3)_3$], 0.03 [6 H, s, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 213.2 (C, C=O), 76.9 (CH, C-7), 48.5 (C), 44.7 (CH_2, C-5), 44.2 (C), 41.4 (C), 38.3 (CH_2, C-9), 33.6 (C), 28.9 (CH_3), 28.6 (CH_3), 27.7 (CH_2, C-8), 25.8 [3 C, CH_3, $C(CH_3)_3$], 21.3 (CH_2, C-2), 18.5 (CH_3), 18.0 [C, $C(CH_3)_3$], 14.2 (CH_3), -3.7 (CH_3) and -5.0 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 321 (M-Me, 7), 279 (38), 223 (20), 209 (15), 195 (15), 171 (17), 159 (18), 141 (19), 135 (15), 121 (35), 119 (21), 115 (18), 109 (21), 105 (18), 75 (100). Anal.: For $C_{20}H_{36}O_2Si$, Calcd.: C, 71.37; H, 10.78%. Found: C, 71.30; H, 11.34%.

(1*R*,2*R*,6*R*,7*S*)-2-(*tert*-Butyldimethylsilyloxy)-1,5,5,6,7-pentamethylbicyclo[4.3.0]nonan-8-one 43. To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (50 mL) in a two necked flask, equipped with a Dewar condenser, was added freshly cut lithium (28 mg, 4 mmoles) followed by a solution of the tricyclic ketone **42** (135 mg, 0.4 mmole) in anhydrous THF (3 mL) and *tert*-butanol (0.04 mL, 0.4 mmole). The resulting blue colored solution was stirred for 2.5 h at -33 °C and then the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken in water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extract 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 (1:25) as eluent furnished the bicyclic ketone **43** (95 mg, 70%), which was recrystallized from hexanes. m.p.: 76-78°C; $[\alpha]_D^{25}$: +76.0° (*c* 1.0, $CHCl_3$); IR (thin film): 2950, 2835, 1730, 1471, 1412, 1393, 1375, 1253, 1113, 1093, 1069, 1032, 1006, 890, 859, 837, 773, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.40 (1 H, dd, *J* = 11.0 and 4.4 Hz, H-2), 2.50 (1 H, q, *J* = 7.0 Hz, H-7), 2.40 and 2.00 (2 H, AB q, *J* = 18.7 Hz, H-9), 1.75-1.20 (4 H, m), 1.07 (3 H, d, *J* = 7.0 Hz, sec-CH_3), 1.12 (3 H, s), 1.05 (3 H, s), 0.91 (3 H, s) and 0.88 (3 H, s) [4 × tert-CH_3], 0.87 [9 H, s, $C(CH_3)_3$], 0.03 (3 H, s) and 0.01 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 220.2 (C, C=O), 74.1 (CH, C-2), 50.0 (C, C-6), 49.5 (CH_2, C-9), 49.2 (CH, C-7), 46.6 (C, C-1), 36.9 (CH_2, C-4), 36.3 (C, C-5), 29.9 (CH_3), 27.9 (CH_2, C-3), 26.0 [3 C, CH_3, $C(CH_3)_3$], 25.7 (CH_3), 18.2 [C, $C(CH_3)_3$], 16.0 (CH_3), 14.2 (CH_3), 13.5 (CH_3), -3.6 (CH_3) and -4.9 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 281 (M-^{t}Bu, 100%), 189 (30), 137 (22), 133 (25), 75 (63), 73 (43); Anal.: For $C_{20}H_{38}O_2Si$, Calcd.: C, 70.94; H, 11.31; Found: C, 71.35; H, 11.63%.

Further elution with the same solvent as eluent furnished the unreacted starting material **42** (20 mg, 15%).

(1*R*,2*R*,6*R*,7*R*)-2-(*tert*-Butyldimethylsilyloxy)-1,5,5,6,7-pentamethyl-8-methylenebicyclo[4.3.0]nonane 44. To a magnetically stirred solution of K^+ $^tBuO^-$ [freshly prepared from potassium (48 mg, 1.23 mmoles) and ^{t}BuOH (1.3 mL) followed by removal of the excess ^{t}BuOH by distillation] in dry benzene (1.5 mL) was added methyltriphenylphosphonium iodide (595 mg, 1.47 mmoles) and the resulting yellow color solution was stirred for 30 min at RT. A solution of the bicyclic ketone **43** (83 mg, 0.245 mmole) in dry benzene (0.5 mL) was added to the dark yellow colored solution of methylenetriphenylphosphorane and the reaction mixture was refluxed for 4 h. Saturated aq. NH_4Cl solution (5 mL) was added to the reaction mixture and extracted with ether (2 × 5 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished the thapsenol TBDMS ether **44** (51 mg, 62%) as colourless oil. $[\alpha]_D^{25}$: +26.7° (*c* 1.2, $CHCl_3$); IR (neat): 2954, 2928, 2856, 1652, 1462, 1375, 1253, 1100, 1071, 888, 835,

773 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 4.84 (1 H, s) and 4.79 (1 H, s) [C=CH_2], 3.42 (1 H, dd, *J* = 11.2 and 4.4 Hz, H-2), 2.70 (1 H, m, H-7), 2.35 and 2.15 (2 H, AB q, *J* = 16.2 Hz, H-9), 1.70-1.55 (2 H, m), 1.50-1.15 (2 H, m), 1.07 (3 H, d, *J* = 7.0 Hz, sec-CH_3), 0.98 (3 H, s), 0.96 (3 H, s), 0.86 (3 H, s) and 0.82 (3 H, s) [4 × tert-CH_3], 0.88 [9 H, s, C(CH_3)$_3$], 0.02 [6 H, s, Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 156.5 (C, C-8), 106.3 (CH_2, C=CH_2), 73.0 (CH, C-2), 50.9 (C, C-6), 49.3 (C, C-1), 44.4 (CH_2, C-9), 42.6 (CH, C-7), 37.1 (CH_2, C-4), 36.2 (C, C-5), 29.9 (CH_3), 27.9 (CH_2, C-3), 26.1 [3 C, CH_3, C(CH_3)$_3$], 25.5 (CH_3), 18.5 (CH_3), 18.2 [C, C(CH_3)$_3$], 15.9 (CH_3), 13.8 (CH_3), -3.7 (CH_3) and -4.7 (CH_3) [Si(CH_3)$_2$]; MS: *m/z* (%) 336 (M^+, $C_{21}H_{40}OSi$, 3), 279 (20), 205 (10), 203 (12), 91 (16), 85 (13), 83 (22), 75 (100).

Further elution with ethyl acetate-hexane (1:20) as eluent furnished the unreacted starting material **43** (15 mg, 18%).

(1*R*,2*R*,6*S*)-1,5,5,6,7,8-Hexamethylbicyclo[4.3.0]-non-7-en-2-yl *tert*-butyldimethylsilyl ether 45. To a magnetically stirred solution of the thapsenol TBDMS ether **44** (45 mg, 0.13 mmole) in dry CH_2Cl_2 (3 mL) was added a catalytic amount of PTSA and stirred for 12 h at RT. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed with saturated aq. $NaHCO_3$ solution (3 mL) and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished the thapsenol TBDMS ether **45** (31 mg, 69%) as colourless oil. $[\alpha]_D^{25}$: -13.6° (*c* 2.2, $CHCl_3$); IR (neat): 2927, 2855, 1461, 1375, 1363, 1252, 1069, 1044, 1003, 984, 836, 771, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 3.62 (1 H, dd, *J* = 4.9 and 2.2 Hz, H-2), 2.21 (1 H, d, *J* = 15 Hz, H-9a), 1.85-1.65 (2 H, m), 1.62 (1 H, br s), 1.57 (3 H, s) and 1.55 (3 H, s) [2 × olefinic CH_3], 1.50-1.35 (2 H, m), 0.96 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s) and 0.80 (3 H, s) [4 × tert-CH_3], 0.91 [9 H, s, C(CH_3)$_3$], 0.03 [6 H, s, Si(CH_3)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 137.6 (C, C-7), 128.9 (C, C-8), 74.1 (CH, C-2), 55.4 (C, C-6), 49.9 (CH_2, C-9), 49.2 (C, C-1), 37.2 (C, C-5), 33.1 (CH_2, C-4), 30.6 (CH_3), 27.9 (CH_3), 27.0 (CH_2, C-3), 26.1 [3 C, CH_3, C(CH_3)$_3$], 18.3 [C, C(CH_3)$_3$], 16.7 (2 C, CH_3), 14.4 (CH_3), 13.2 (CH_3), -4.1 (CH_3) and -4.7 (CH_3) [Si(CH_3)$_2$]; MS: *m/z* (%) 336 (M^+, $C_{21}H_{40}OSi$, 10), 267 (36), 215 (100), 135 (25), 122 (50), 101 (38).

(1*R*,2*R*,6*S*)-1,5,5,6,7,8-Hexamethylbicyclo[4.3.0]-non-7-en-2-ol (Thaps-8-en-5-ol 46). To a magnetically stirred solution of the TBDMS ether of thapsenol **45** (10 mg, 0.03 mmole) in dry THF (0.5 mL) was added tetrabutylammonium fluoride (47 mg, 0.15 mmole) and refluxed for 24 h. The reaction mixture was then diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract 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 (1:20) as eluent furnished thapsenol **46** (6 mg, 91%), which was recrystallized from hexanes. m.p.: 77-79°C; $[\alpha]_D^{26}$: -15.2° (*c* 1.12, $CHCl_3$); IR (thin film): 3408, 2929, 1453, 1380, 1378, 1370, 1091, 1031, 997, 963, 893 cm^{-1}; ^1H NMR ($CDCl_3$ + CCl_4): δ 3.61 (1 H, dd, *J* = 5.4 and 3.3 Hz, H-2), 2.22 (1 H, d, *J* = 15.3 Hz, H-9a), 1.88-1.40 (5 H, m), 1.55 (6 H, s, 2 × olefinic CH_3), 1.24 (1 H, s), 0.98 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s) and 0.82 (3 H, s) [4 × tert-CH_3]; ^{13}C NMR ($CDCl_3$ + CCl_4): δ 137.6 (C, C-7), 129.0 (C, C-8), 73.4 (CH, C-2), 55.4 (C, C-6), 49.8 (CH_2, C-9), 48.4 (C, C-1), 37.0 (C, C-5), 33.3 (CH_2, C-3), 30.0 (CH_3), 27.6 (CH_3), 26.7 (CH_2, C-4), 16.8 (2 C, CH_3), 14.3 (CH_3), 13.2 (CH_3); MS: *m/z* (%) 222 (M^+, 10), 135 (14), 123 (42), 122 (100), 107 (30), 91 (11); Anal.: For $C_{15}H_{26}O$, calcd.: C, 81.02; H, 11.79%. Found: C, 80.98; H, 12.05%.

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