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

A Srikrishna* & K Anebouselvy
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012
E mail: ask@orgchem.iisc.ernet.in

Received 13 June 2007; accepted 12 December 2007

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 alkylation 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 thapsigargicin, which were found to be responsible for the medicinal activity. Even though, thapsigargin and thapsigargicin were absent in *Thapsia villosa*, it contains a large number of sesquiterpenes belonging to guianolides, germacrines, 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 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 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 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 for the carbon framework cis-1,2,6,8,9-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. 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 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
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 CH₂COOH 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. 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-bromosuccinimide (NBS) in methanol-methylene chloride medium furnished the allyl bromide 24 in 90% yield in a highly regioselective manner. Generation of the
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 borohydr
dride 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 
way via a carboxyborohydride. 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 
(TBDMSCI) 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 cyclopropana-
tion reaction 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
with an excess of ethereal diazoethane, generated from N-nitroso-N-ethylurea, furnished the diazo-ketone 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 kcal/mole stable than the corresponding endo isomer. Wittig reaction of the ketone 43 with methylene-triphenylphosphorane, 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-en-5-ol 46, m.p 77-79°C, in 91% yield.

In conclusion, we have accomplished the enantio-specific 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 enantiospecific 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**

**(5R)-5-(3-Bromopropen-2-yl)-2,3,4,4-tetramethylcyclohex-2-enone 24.** To an ice cold magnetically stirred solution of trimethylcarvone 7k (1 g, 5.2 mmoles) in a 3:2 mixture of CH2Cl2 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 CH2Cl2 (2 × 10 mL). The combined CH2Cl2 extract was washed with 5% aq. NaOH and brine, and dried (Na2SO4). 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; [α]D25: +14.8° (c 6.4, CHCl3); IR (neat): 2973, 1662, 1612, 1470, 1441, 1374, 1323, 1209, 1075, 920 cm⁻¹; 1H NMR (CDCl3 + CCl4): δ 5.43 (1 H, s) and 5.02 (1 H, s) [C=CH2], 3.95 and 3.90 (2 H, AB q, J = 10.0 Hz, CH2Br), 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, C3-CH3), 1.74 (3 H, s, C2-CH3), 1.14 (3 H, s), and 1.08 (3 H, s) [2 × tert-CH3]; 13C NMR (CDCl3 + CCl4): δ 196.7 (C, C=O), 160.1 (C, C=CH2), 145.9 (C, C=CH2), 130.6 (C, C-2), 118.9 (CH2, C=CH2), 47.5 (CH, C-5), 40.6 (CH2), 39.8 (C, C-4), 38.6 (CH2), 26.7 (CH3), 21.5 (CH3), 16.5 (CH3), 11.7 (CH3).

**(1R,4S)-1,5,5-Trimethyl-6,8-bis(methylene)bicyclo[2.2.2]octan-2-one 25.** To a cold (-5°C), magneti-
cally stirred 1 M solution of potassium tert-butoxide [freshly prepared from potassium (87 mg, 2.2 mmoles) and tBuOH (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 (Na₂SO₄). 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, which was distilled under vacuum. b.p.: 100-105°C/0.5 mm; [α]D²⁴: -5.4° (c 7.9, CHCl₃); IR (neat): 2973, 1727, 1653, 1636, 1455, 1406, 1124, 1078, 996, 894 cm⁻¹; H NMR (CDCl₃ + CCl₄): δ 4.95 (2 H, s), 4.88 (1 H, s) and 4.74 (1 H, s) [2 × C=CH₂], 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-CH₃]; ¹³C NMR (CDCl₃ + CCl₄): δ 210.8 (C, C=O), 156.5 (C, C-6), 145.7 (C, C-8), 108.9 (CH₂) and 108.7 (CH₂) [2 × C=CH₂], 52.7 (C, C-1), 50.6 (CH, C-4), 40.8 (CH₂, C-3), 38.6 (CH₂, C-7), 37.8 (C, C-5), 31.4 (CH₃), 28.6 (CH₃), 16.5 (CH₃).

Methyl 2-[(1R)-1,5,5-trimethyl-6-methylene-2-oxocyclohex-3-enyl]acetate 27 and (1R,4R)-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 NaHCO₃ (10 mg) in 1:4 MeOH-CH₂Cl₂ (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 (Na₂SO₄). 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. [α]D²⁵: +38.0° (c 1.08, CHCl₃). IR (neat): 2971, 1740, 1680, 1622, 1437, 1343, 1197, 1172, 1105, 1011, 902, 830 cm⁻¹. H NMR (CDCl₃ + CCl₄): 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=CH₂], 3.55 (3 H, s, OCH₃), 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-CH₃]. ¹³C NMR (CDCl₃ + CCl₄): 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 (CH₂, C=CH₂), 51.3 (CH₃, OCH₃), 49.3 (C, C-1'), 42.8 (CH₂, C-2), 37.5 (C, C-5'), 33.1 (CH₃), 31.3 (CH₃), 30.9 (CH₃). MS: m/z (%) 222 (M⁺, C₁₃H₁₈O₃, 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. [α]D²⁴: +58.6° (c 2.2, CHCl₃); IR (neat): 2970, 1732, 1636, 1457, 1401, 1244, 1122, 1078, 905 cm⁻¹; H NMR (CDCl₃ + CCl₄): δ 5.15 (2 H, s, C=CH₂), 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-CH₃]; ¹³C NMR (CDCl₃ + CCl₄): δ 209.4 (C, C=O), 207.4 (C, C=O), 192.4 (C, C=O), 153.9 (C, C-7), 110.5 (CH₂, C=CH₂), 56.7 (CH, C-4), 53.9 (C, C-1), 45.3 (CH₂), 37.7 (C, C-8), 36.3 (CH₂), 31.2 (CH₃), 27.9 (CH₃), 16.0 (CH₃); MS: m/z (%) 192 (M⁺, C₁₃H₁₆O₂, 44), 177...
Methyl 2-[(1R)-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. \( [\alpha]_D^{25} +20.8^\circ \) (c 1.2, CHCl₃); IR (neat): 3092, 2967, 1740, 1713, 1627, 1436, 1344, 1200, 1154, 1012, 899 cm⁻¹; \( ^1H \) NMR (CDCl₃ + CCl₄): \( \delta \) 5.05 (1 H, s) and 4.94 (1 H, s) [C=CH₂], 3.57 (3 H, s, OCH₃), 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-CH₃]; \( ^13C \) NMR (CDCl₃ + CCl₄): \( \delta \) 121.8 (C, C=O), 171.4 (C, OC=O), 159.6 (C, C-6), 108.6 (CH₂, C=C=CH₂), 51.4 (CH₃, OCH₃), 51.3 (C, C-1'), 44.1 (CH₂, C-2), 35.7 (C, C-5'), 35.5 (CH₃) and 34.5 (CH₃) [C-3' and C-4'], 31.5 (CH₃), 30.3 (2 C, CH₂), MS: \( m/z \) 224 (M +, C₁₃H₂₀O₃, 83), 193 (44), 165 (85), 151 (26), 137 (37), 135 (30), 123 (42), 121 (30), 109 (100), 108 (34), 107 (39), 95 (42).

\( \text{(1R,6S)-1,3,3-Trimethyl-2-methylene-7-oxabicyclo[4.3.0]nonan-8-one 33.} \) To an ice cold, magnetically stirred solution of the keto ester 32 (7 mg, 0.031 mmole) in dry methanol (1 mL) was added NaBH₄ (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 CH₂Cl₂ (2 × 3 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished the cis-lactone 33 (5 mg, 82%), which was recrystallized from hexanes. m.p.: 39-41°C; \( [\alpha]_D^{26} +6.15^\circ \) (c 1.3, CHCl₃); IR (neat): 3096, 2935, 1785, 1626, 1458, 1360, 1274, 1213, 1172, 1107, 1038, 1000, 952, 902 cm⁻¹; \( ^1H \) NMR (CDCl₃ + CCl₄): \( \delta \) 5.17 (1 H, s) and 5.05 (1 H, s) [C=CH₂], 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-CH₃]; \( ^13C \) NMR (CDCl₃ + CCl₄): \( \delta \) 175.3 (C, OC=O), 156.8 (C, C-2), 112.0 (CH₂, C=CH₂), 85.3 (CH, C-6), 45.2 (CH₂, C-9), 44.4 (C, C-1), 35.4 (C, C-3), 33.1 (CH₂, C-5), 31.6 (CH₃), 30.9 (CH₃), 28.4 (CH₃), 23.2 (CH₂, C-4); MS: \( m/z \) (% 194 (M⁺, 100), 165 (94), 151 (59), 137 (42), 134 (28), 133 (100), 124 (38), 123 (53), 119 (49), 110 (41), 109 (68), 107 (44), 99 (32), 95 (28); Anal.: For C₁₂H₁₈O₃, Calcd.: C, 74.19; H, 9.34%. Found: C, 73.82; H, 9.45%.

\( \text{(1R)-1,5,5-Trimethyl-6-methylene-2-oxocyclohexylacetic acid 34.} \) 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 CH₂Cl₂ (3 × 10 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished the keto acid 32 (370 mg, 94%) as sticky oil. \( [\alpha]_D^{23} +21.1^\circ \) (c 1.9, CHCl₃); IR (neat): 3100, 3094, 2967, 2870, 1710, 1627, 1452, 1429, 1368, 1261, 1230, 1155, 1107, 1018, 900, 801 cm⁻¹; \( ^1H \) NMR (CDCl₃ + CCl₄): \( \delta \) 5.06 (1 H, s) and 4.98 (1 H, s) [C=CH₂], 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-CH₃]; \( ^13C \) NMR (CDCl₃ + CCl₄): \( \delta \) 212.2 (C, C=O), 176.7 (C, OC=O), 159.5 (C, C-6'), 108.9 (CH₃, C=CH₂), 51.1 (C, C-1'), 44.0 (CH₂, C-2), 35.7 (C, C-5'), 35.3 (CH₃, C-3'), 34.5 (CH₃, C-4'), 31.5 (CH₃), 30.32 (CH₃), 30.27 (CH₃); MS: \( m/z \) (% 210 (M⁺, C₁₂H₁₈O₃), 100), 165 (27), 137 (32), 123 (26), 109 (60), 107 (38), 95 (38).

Methyl 2-[(1R,2R)-2-hydroxy-1,5,5-trimethyl-6-methylenebicyclo[3.2.1]octyl]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 NaBH₄ (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 CH₂Cl₂ (3 × 8 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). 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
Methyl 2-[(1R,2R)-2-(tert-butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylene cyclohexyloxy]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 CH₂Cl₂ (2 × 5 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished the acid chloride 38 (350 mg, 95%) as oil. [α]D²⁶: -41.8° (c 0.79, CHCl₃); IR (neat): 3300-2700, 1718, 1624, 1469, 1427, 1372, 1251, 1173, 1128, 1100, 1072, 951, 887, 834, 771, 671 cm⁻¹; ¹H NMR (CDCl₃ + CCl₄): δ 4.95 (1 H, s) and 4.94 (1 H, s) [C=CH₂], 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-CH₃], 1.06 (3 H, s) [C(CH₃)₂]; ¹³C NMR (CDCl₃ + CCl₄): δ 178.0 (C, OC=O), 160.2 (C, C-6'), 108.9 (CH₂, C-2'), 73.1 (CH, C-2'), 45.4 (C, C-1'), 42.3 (CH₂, C-2'), 36.7 (CH₂, C-3'), 35.9 (C, C-5'), 32.0 (CH₂, CH₃), 31.8 (CH₃), 26.9 (CH₂, C-4'), 23.8 (CH₃); MS: m/z (%) 269 (M- tBu, (C₁₅H₂₇O₃Si, 100), 266 (7), 251 (11), 177 (14), 149 (19), 135 (36), 133 (131), 121 (12), 107 (16), 93 (18), 83 (26), 75 (100).

Further elution of the column with ethyl acetate-hexane (1:5) as eluent afforded 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 CH₂Cl₂ (3 × 5 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished the acid 40 (380 mg, 94%), which was recrystallized from hexanes. m.p.: 69-71°C; [α]D²³: -37.8° (c 0.9, CHCl₃); IR (thin film): 3300-2700, 2909, 2929, 1708, 1624, 1469, 1427, 1372, 1251, 1226, 1101, 1072, 1005, 981, 887, 834, 771, 671 cm⁻¹; ¹H NMR (CDCl₃ + CCl₄): δ 4.98 (1 H, s) and 4.94 (1 H, s) [C=CH₂], 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-CH₃], 0.83 [9 H, s, C(CH₃)₂], 0.06 (3 H, s) and 0.02 (3 H, s) [Si(CH₃)₃]; ¹³C NMR (CDCl₃ + CCl₄): δ 178.0 (C, OC=O), 160.2 (C, C-6'), 108.9 (CH₂, C-2'), 73.1 (CH, C-2'), 45.4 (C, C-1'), 42.3 (CH₂, C-2'), 36.7 (CH₂, C-3'), 35.9 (C, C-5'), 32.0 (2 C, CH₂), 27.3 (CH₂, C-3'), 26.1 [3 C, CH₃, C(CH₃)₂], 25.2 (CH₃), 18.3 [C, C(CH₃)₂], -3.8 (CH₃) and -4.8 (CH₃) [Si(CH₃)₃]; MS: m/z (%) 269 (M-Bu, C₁₅H₂₇O₃Si, 10), 177 (14), 149 (19), 135 (36), 133 (131), 121 (12), 107 (16), 93 (18), 83 (26), 75 (100).

(1R,3S,6R,7R)-7-(tert-Butyldimethylsilyloxy)-3,6,10,10-tetramethyltricyclo[4.4.0.0¹,3]decan-4-one 42. 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 mmol) and anhydrous copper sulfate (280 mg, 1.75 mmol) 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) afforded the unreacted starting material 40 (20 mg, 15%).

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

(1R,2R,6R,7R)-2-(tert-Butyldimethylsilyloxy)-1,5,5,6,7-pentamethyl-8-methylenebicyclo[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 mmol) followed by a solution of the tricyclic ketone 39 (135 mg, 0.4 mmol) in anhydrous THF (3 mL) and tert-butanol (0.04 mL, 0.4 mmol). The resulting blue colored solution was stirred for 2.5 h at -33 °C and then the reaction was quenched with solid NH₄Cl. After evaporation of ammonia, the residue was taken in water (5 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). 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; [α]D²⁵: +76.0° (c 1.0, CHCl₃); IR (thin film): 2950, 2835, 1730, 1471, 1393, 1375, 1253, 1113, 1093, 1069, 1032, 1006, 890, 859, 837, 773, 677 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): 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-CH₃), 1.12 (3 H, s), 1.05 (3 H, s), 0.91 (3 H, s) and 0.88 (3 H, s) [4 × tert-CH₃], 0.87 [9 H, s, C(CH₃)₃], 0.03 (3 H, s) and 0.01 (3 H, s) [Si(CH₃)₂]; ¹³C NMR (CDCl₃ + CCl₄): δ 220.2 (C, C=O), 74.1 (CH, C-2), 50.0 (C, C-6), 49.5 (CH₂, C-9), 49.2 (CH, C-7), 46.6 (C, C-1), 36.9 (CH₂, C-4), 36.3 (C, C-5), 29.9 (CH₃), 27.9 (CH₂, C-3), 26.0 [3 C, CH₃, C(CH₃)₃], 25.7 (CH₂), 18.2 [C, C(CH₃)₃], 16.0 (CH₃), 14.2 (CH₃), 13.5 (CH₃), -3.6 (CH₃) and -4.9 (CH₃) [Si(CH₃)₂]; MS: m/z (%) 281 (M-Bu, 100%), 189 (30), 137 (22), 133 (25), 75 (63), 73 (43); Anal.: For C₂₀H₃₆O₂Si, Calcd.: C, 70.94; H, 11.31; Found: C, 71.35; H, 11.63%.

(1R,2R,6R,7R)-2-(tert-Butyldimethylsilyloxy)-1,5,5,6,7-pentamethyl-8-methylenebicyclo[4.3.0]nonan-8-one 43. To a magnetically stirred, refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (740 mg, 11.65 mmol) and anhydrous copper sulfate (280 mg, 1.75 mmol) in dry cyclohexane (40 mL) was added, drop wise, a solution of the tricyclic ketone 39 (135 mg, 0.4 mmol) in dry benzene (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 bicyclic ketone 43 (95 mg, 70%), which was recrystallized from hexanes. m.p.: 76-78 °C; [α]D²⁵: +76.0° (c 1.0, CHCl₃); IR (thin film): 2950, 2835, 1730, 1471, 1393, 1375, 1253, 1113, 1093, 1069, 1032, 1006, 890, 859, 837, 773, 677 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): 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-CH₃), 1.12 (3 H, s), 1.05 (3 H, s), 0.91 (3 H, s) and 0.88 (3 H, s) [4 × tert-CH₃], 0.87 [9 H, s, C(CH₃)₃], 0.03 (3 H, s) and 0.01 (3 H, s) [Si(CH₃)₂]; ¹³C NMR (CDCl₃ + CCl₄): δ 220.2 (C, C=O), 74.1 (CH, C-2), 50.0 (C, C-6), 49.5 (CH₂, C-9), 49.2 (CH, C-7), 46.6 (C, C-1), 36.9 (CH₂, C-4), 36.3 (C, C-5), 29.9 (CH₃), 27.9 (CH₂, C-3), 26.0 [3 C, CH₃, C(CH₃)₃], 25.7 (CH₂), 18.2 [C, C(CH₃)₃], 16.0 (CH₃), 14.2 (CH₃), 13.5 (CH₃), -3.6 (CH₃) and -4.9 (CH₃) [Si(CH₃)₂]; MS: m/z (%) 281 (M-Bu, 100%), 189 (30), 137 (22), 133 (25), 75 (63), 73 (43); Anal.: For C₂₀H₃₆O₂Si, Calcd.: C, 70.94; H, 11.31; Found: C, 71.35; H, 11.63%.
Further elution with ethyl acetate-hexane (1:20) as eluent furnished the thapsenol TBDMS ether 46 (15 mg, 18%).

\((1R,2R,6S)-1,5,5,6,7,8-Hexamethylobicyclo[4.3.0]-non-7-en-2-yl tert-butylidimethylsilyl ether 45\). To a magnetically stirred solution of the thapsenol TBDMS ether 44 (45 mg, 0.13 mmole) in dry CH$_2$Cl$_2$ (3 mL) was added a catalytic amount of PTSA and stirred for 12 h at RT. The reaction mixture was then diluted with CH$_2$Cl$_2$ (5 mL) and washed with saturated aq. NaHCO$_3$ solution (3 mL) and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished thapsenol TBDMS ether 46 (6 mg, 91%), which was recrystallized from hexanes. m.p.: 77-79$^\circ$C; $[\alpha]_D^{25}$: -15.2$^\circ$ (c 1.12, CHCl$_3$); IR (thin film): 3408, 2929, 1453, 1380, 1378, 1370, 1091, 1031, 997, 963, 893 cm$^{-1}$; $^1$H NMR (CDCl$_3$ + CCl$_4$): $\delta$ 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 $\times$ 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) $[4 \times$ tert-CH$_3$]; $^{13}$C NMR (CDCl$_3$ + CCl$_4$): $\delta$ 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$_3$, C-3), 30.0 (CH$_3$), 27.6 (CH$_2$), 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%.

**Acknowledgements**

Authors thank Prof. Grande for exchanging the information and one of the authors (KA) is thankful to the CSIR, New Delhi for the award of a research fellowship.

**References**


6. We were given to understand that the structures of all the thapsanes in the papers published by Professor Grande were wrongly depicted, indicating the opposite absolute configuration$^{14}$. Incidentally, this is same as that proposed by Rasmussen and co-workers$^2$. Grande M, Personal Communication.

(b) Burke S D & Grieco P A, *Org React*, 26, 1979, 361;
(c) Mander L N, *Synlett*, 1991, 134 ;