Enantiospecific synthesis of sesquiterpenes from \((R)\)-carvone.

Synthesis of 3-thapsenol

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Enantiospecific synthesis of 3-thapsenol, comprising 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 utilizing the isopropenyl group as a masked hydroxy group. A combination of alkylation, orthoester Claisen rearrangement and intramolecular diazo ketone cyclopropanation reactions has been employed for the creation of the three requisite contiguous quaternary carbon atoms.

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Thapsanes 1-14 (Figure 1) are a small group of sesquiterpenes isolated from Thapsia villosa¹. 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 5 and 6 (ref. 2). 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 targets¹. In continuation of our interest in thapsanes, enantiospecific synthesis of a thapsane has been initiated starting from the readily and abundantly available monoterpene \((R)\)-carvone 17. Herein, we describe the details³ of the enantiospecific synthesis of a thapsane containing an oxygen substituent at the C-3 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 methodology was developed⁴ earlier in our laboratory for the annulation of a cyclopentanone with two vicinal ring junction quaternary carbon atoms starting from a 2,3-disubstituted cycloalk-2-enols on the basis of a combination of a Claisen rearrangement, an intramolecular diazo ketone cyclopropanation reaction and regioselective reductive cyclopropane ring cleavage reactions. Based on which, retrosynthesis for the construction of a thapsane containing an oxygen functionality at the C-3 position with the \(\gamma,\delta\)-unsaturated acid 18 as the key intermediate and the isopropenyl group as a masked hydroxy group, is conceived (Scheme I). It was contemplated that intramolecular cyclopropanation of the diazo ketone 19, derived from the acid 18, could generate the tricyclic ketone 20, which could be further elaborated into a thapsan-3-ol via regiospecific cleavage of the cyclopropane ring, introduction of one carbon each at the C-8 and C-9 positions and degradation of the isopropenyl group. The acid 18, being a \(\gamma,\delta\)-unsaturated acid, could be obtained from the allylic alcohol 21 by a Claisen rearrangement. The allyl alcohol 21, containing the first quaternary carbon atom, could be obtained from carvone 17 via 3,4,4-trimethylcarvone 22.

Accordingly, the synthetic sequence has been initiated with \((R)\)-carvone 17 as the starting material, and to begin with, synthesis of the allyl alcohol 21 was addressed (Scheme II). The quaternary carbon atom was created by sequential kinetic alkylation⁵. Thus, regiospecific generation of the kinetic dienolate with lithium diisopropylamide (LDA) at -15 to -10°C and alkylation with methyl iodide transformed carvone into a 3:2 epimeric mixture of 6-methylcarvone, which on second alkylation with LDA and methyl iodide furnished 6,6-dimethylcarvone 23. For the conversion of dimethylcarvone 23 into 3,4,4-trimethylcarvone 22, a 1,3-enone transposition methodology⁶ was employed. Regioselective 1,2-addition of
Figure 1

Scheme I
methyl lithium to dimethyl carvone 23 followed by oxidation of the resulting allylic tertiary alcohol 24 with a mixture of pyridinium chlorochromate (PCC) and silica gel in methylene chloride generated 3,4,4-trimethyl carvone 22 in 70% yield. Reduction of trimethyl carvone 22 with lithium aluminum hydride (LAH) furnished the allyl alcohol 21, in a highly regio- and stereo-selective manner, in 93% yield. The syn stereochemistry of the hydroxy group in the allyl alcohol 21 was assigned on the basis of the preferential axial approach of the hydride, and in analogy to the reduction of carvone 17 and its derivatives. Next, attention was focused on the creation of the second quaternary carbon atom. An orthoester variant of the Claisen rearrangement developed by Johnson and co-workers, was opted for the generation of the key intermediate of the sequence, the acid 18. Thermal activation of the syn allylic alcohol 21 at 180 °C with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube furnished the γ,δ-unsaturated ester 25 in 34% yield, whose structure was deduced from its spectral data. For the annulation of the five-membered ring as well as the creation of the third quaternary carbon atom, an intramolecular cyclopropanation reaction of the diazo ketone 19 was contemplated. Thus, refluxing a solution of the ester 25 in methanolic potassium hydroxide led to the hydrolysis of the ester moiety to furnish the acid 18, m.p. 83-86 °C (sublimed), in 88% yield. Reaction of the acid 18 with oxalyl chloride in benzene at room temperature followed by treatment of the resultant acid chloride with an excess of ethereal diazomethane furnished the diazo ketone 19 (ν_max/cm⁻¹ 2100 and 1635). Anhydrous copper sulfate and copper catalyzed decomposition of the diazo ketone 19 in refluxing cyclohexane, under irradiation with a tungsten lamp, led to the insertion of the resulting keto carbenoid into the ring olefin moiety to furnish the tricyclic ketone 20, in 56% yield (from the acid 18), in a regio- and stereo-specific manner, whose structure was established from its spectral data. The stereochemistry of the tricyclic ketone 20 was a consequence of the insertion of the intermediate carbenoid from syn face of the olefin due to steric reasons.

Attention was then turned towards the conversion of the tricyclic ketone 20 into a thapsenol, which requires regiospecific cleavage of the C-2 C-9 cyclopropane bond, introduction of one carbon each at the C-7 and C-8 positions of the tricyclic ketone 20 and degradation of the isopropenyl group. For the introduction of the carbons at C-7 and C-8 positions, kinetic alkylation and Wittig reactions were contemplated. Since the alkylation after the cleavage of the cyclopropane ring will lead to regiochemical problems, alkylation was carried out prior to the cyclopropane ring cleavage. Thus, alkylation of the tricyclic ketone 20 with potassium hydride and methyl iodide furnished the alkylated product 26, in 59% yield, along with a small amount of the enol ether 27. The structure of the methylated product 26 was delineated from its spectral data in comparison with that of the starting material 20. Stereochemistry of the secondary methyl group in the tricyclic ketone 26 was assigned on the basis of the preferential approach of the electrophile from the sterically less crowded exo face of the molecule. Hydrolysis of the enol ether 27 with p-TSA in moist methylene chloride furnished the tricyclic ketone 26, confirming the structure of the enol ether 27. For the regiospecific cleavage of the C-2 C-9 cyclopropane
bond in 26, reduction using alkali metal in liquid ammonia was considered. It is well established that in the reductive cleavage of cyclopropyl ketones using lithium-liquid ammonia conditions, of the two cyclopropane bonds, the one which has better overlap with the carbonyl π-orbital will be cleaved. In the tricyclic ketone 26, from the Drieding models, it is clear that the π-orbital of the carbonyl group will have better overlap with the C-2 C-9 bond than the C-1 C-9 bond of the cyclopropane ring. Thus, reaction of the tricyclic ketone 26 with lithium in liquid ammonia and THF for 5 min furnished a 2:1 mixture of the bicyclic ketone 28 and the alcohol 29 in 95% yield, which were separated by column chromatography on silica gel. Oxidation of the alcohol 29 with PCC and silica gel in methylene chloride at room temperature furnished the ketone 30. For the degradation of the isopropenyl group in the bicyclic ketone 28, a one pot ozonation, followed by Criegee rearrangement sequence was conceived. Ozonolysis of the bicyclic ketone 28 in methanol-methylene chloride followed by treatment with acetic anhydride, triethylamine and DMAP in refluxing benzene transformed the tricyclic ketone 26 into a 3:2 mixture of the keto acetate 32 and the simple ozonolysis product the dione 33, in 64% yield, which were separated by column chromatography on silica gel. The structures of the keto acetate 32 and the dione 33 rest secured from their spectral data.

To overcome the unexpected failure of the Criegee rearrangement, degradation of the isopropenyl group was explored prior to the cleavage of the cyclopropane bond in the tricyclic ketone 26. Thus, ozonolysis in methanol-methylene chloride followed by Criegee rearrangement of the resultant methoxyhydroperoxide with acetic anhydride, triethylamine and DMAP in refluxing benzene transformed the tricyclic ketone 26 into a 3:2 mixture of the keto acetate 32 and the simple ozonolysis product the dione 33, in 64% yield, which were separated by column chromatography on silica gel. The structures of the keto acetate 32 and the dione 33 rest secured from their spectral data.

Reaction of the acetoxy ketone 32 with lithium in liquid ammonia at \(-33^\circ\text{C}\) for 3 min furnished the bicyclic keto acetate 30 along with varying amounts of the hydroxy ketone 34, which were separated by column chromatography on silica gel. Acetylation of the hydroxy ketone 34 with acetic anhydride and DMAP in pyridine at room temperature furnished the keto acetate 30. Next, to complete the synthesis of the carbon framework of thapsane, a Wittig reaction was opted for the introduction of the fifteenth carbon atom. Thus, reaction of the keto acetate 34 with methylenetriphenylphosphorane in benzene at room temperature furnished a 5:1 mixture of the thapsenyl
acetate 35 and the thapsenol 36 in 72% yield, which were separated by column chromatography on silica gel. Cleavage of the ester group in thapsenyl acetate 35 using LAH in ether at room temperature furnished the thapsenol 36 in 90% yield. The structure of the thapsenol 36 was established from its spectral data. In the $^1$H NMR spectrum, presence of two singlets at $\delta$ 4.78 and 4.73 due to the olefinic protons, a multiplet at 3.60-3.45 due to the H-3, a doublet at 1.05 due to the secondary methyl group and four singlets at 1.08, 1.05, 0.90 and 0.78 ppm due to four tertiary methyl groups established the structure of the thapsenol 36. In the $^{13}$C NMR spectrum, presence of a quaternary carbon at $\delta$ 156.8 and a methylene at 105.4 due to the olefinic carbons, a methane at 78.4 due to the hydroxy bearing carbon atom, three quaternary carbons at 49.2, 42.5 and 40.2, a methane at 43.6, three methylenes at 49.4, 29.8 and 26.2 and five methyl carbons at 26.2, 25.0, 23.4, 18.1 and 14.2 ppm further confirmed the structure of the thapsenol 36. Generation of the thapsenol 36 and thapsenyl acetate 35, thus, completed the enantiospecific first total synthesis of a thapsane containing an oxygen functionality at the C-3 position.

In conclusion, we have accomplished the enantiospecific total synthesis of the thapsenes 35 and 36 containing oxygen functionality at the C-3 position. The isopropenyl group of carvone has been exploited as a source of chirality as well as a masked hydroxy group. A combination of alkylation, orthoester Claisen rearrangement, intramolecular diazo ketone cyclopropanation and regiospecific ring cleavage of cyclopropane were employed for the stereo-specific generation of the three requisite contiguous quaternary carbon atoms.

Experimental Section

(+)-(5S)-5-Isopropenyl-2,3,4,4-tetramethylcyclohex-2-enone 22. To a cold (0°C), magnetically stirred solution of 6,6-dimethylcarvone 5 23 (1 g, 5.62 mmoles) in ether (2 mL) was slowly added a solution of lithium (1.1 M in ether, 6.1 mL, 6.7 mmoles) over a period of 20 min. The reaction mixture was slowly warmed up to RT and stirred for 1 hr. It was then poured into a cold saturated aqueous NH$_4$Cl solution and extracted with ether (2 × 10 mL). The combined ether extract was washed with brine and dried (Na$_2$SO$_4$). Evaporation of the solvent furnished the tertiary alcohol 24. A mixture of PCC (1.8 g, 8.4 mmoles) and silica gel (1.8 g) was added to a solution of the tertiary alcohol 24, obtained above, in 5 mL of CH$_2$Cl$_2$ and stirred for 12 hr at RT. The reaction mixture was filtered through a small silica gel column and the column was eluted with more CH$_2$Cl$_2$. Evaporation of the solvent and purification of the product on a silica gel column using EtOAc-hexane (1:50 to 1:20) as eluent furnished the trimethylcarvone 22 (750 mg, 70%) as oil, which was distilled under vacuum, b.p. 150-55 °C / 0.5 mm; $\left[\alpha\right]_D^{24} +88.0$ (c 4.3, CHCl$_3$); IR (neat): 1665, 1613, 896 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$ + CCl$_4$): $\delta$ [4.86 (1 H, s), 4.69 (1 H, s), C=CH$_2$], 2.55-2.45 (3 H, m), [1.83 (3 H, s), 1.70 (3 H, s), 1.66 (3 H, s), 3 × olefinic CH$_3$], [1.13 (3 H, s), 1.02 (3 H, s), 2 × tert-CH$_3$]; $^{13}$C NMR (75 MHz, CDCl$_3$ + CCl$_4$): $\delta$ 197.3 (C, C=O), 160.4 (C, C-3), 145.4 (C, C=CH$_2$), 130.4 (C, C-2), 115.2 (CH$_2$, C=CH$_2$), 51.7 (CH, C-5), 39.5 (2 C, C and CH$_2$, C-4 and C-6), 26.9 (CH$_3$), 23.1 (CH$_3$), 21.8 (CH$_3$), 16.4 (CH$_3$), 11.6 (CH$_3$).

(+)-(1S,5S)-5-Isopropenyl-2,3,4,4-tetramethylcyclohex-2-enol 21. To a magnetically stirred, cold
extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-hexane (1:10 to 1:5) as eluent furnished the allyl alcohol 21 (1.7 g, 93%) as a white solid, which was recrystallized from hexane, m.p. 89-91 °C; [α]D₂⁰ +59.2 (c 1.3, CHCl₃); IR (thin film): 3283, 1636, 893 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ [4.93 (1 H, s), 4.70 (1 H, s), C=CH₂], 4.09 (1 H, t, J = 7.8 Hz, H-1), 2.12 (1 H, dd, J = 13.2 and 2.1 Hz), 1.95 (1 H, ddd, J = 12.3, 6.3 and 2.4 Hz), 1.80-1.70 (1 H, m), [1.77 (3 H, s), 1.69 (3 H, s), 1.60 (3 H, s), 3 × olefinic CH₃], 1.57 (1 H, br s, OH), [1.00 (3 H, s), 0.96 (3 H, s), 2 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 146.7 (C, C=CH₂), 137.4 (C, C-3), 128.3 (C, C-2), 114.3 (CH₂, C=CH₂), 71.6 (CH, C-1), 50.0 (CH, C-5), 39.1 (C, C-4), 34.7 (CH₂, C-6), 26.5 (CH₃), 22.9 (CH₃), 22.0 (CH₃), 15.1 (CH₃), 14.3 (CH₃); Mass: m/z 176 (M-H₂O, 2%), 149 (17), 135 (55), 111 (45), 97 (33), 96 (29), 91 (20), 83 (37); Anal. Caled for C₁₃H₂₃O₃: C, 80.35; H, 11.41. Found: C, 80.46; H, 11.50%.

(-)-Ethyl 2-[(1S,5S)-5-isopropenyl-1,2,6,6-tetramethylcyclohex-2-enyl]acetate 25. A solution of the allyl alcohol 21 (500 mg, 2.58 mmoles), triethyl orthoacetate (2.5 mL, 13.7 mmoles) and a catalytic amount of propionic acid was placed in a sealed tube and heated to 180 °C for 4 days in an oil bath. The reaction mixture was then cooled, diluted with CH₂Cl₂ (5 mL), washed with 3 N aqueous HCl (5 mL) followed by saturated NaHCO₃ solution (5 mL) and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-hexane (1:50) as eluent furnished the ester 25 (234 mg, 34%) as oil, [α]D₂⁰ -17.86 (c 1.4, CHCl₃); IR (neat): 1733, 1638, 892 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 5.38 (1 H, br d, J = 5.1 Hz, H-3), 4.90 (1 H, s), 4.73 (1 H, s), C=CH₂], 4.08, 4.07 (2 H, q of AB q, J = 11.1 and 6.9 Hz, OCH₂CH₃), 2.45-2.30 (1 H, m), 2.38, 2.32 (2 H, AB q, J = 14.4 Hz, H-2), 2.12 (1 H, m of t, J = 15.0 Hz), 1.80-1.70 (1 H, m), [1.79 (3 H, s), 1.71 (3 H, s), 2 × olefinic CH₃], 1.25 (3 H, t, J = 6.9 Hz, OCH₂CH₃), [1.18 (3 H, s), 0.90 (3 H, s), 0.83 (3 H, s), 3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 172.9 (C, OC=O), 147.3 (C, C=CH₂), 138.7 (C, C-2'), 122.8 (CH, C-3'), 113.3 (CH₂, C=CH₂), 59.9 (CH₂, OCH₂CH₃), 46.2 (C, C-1'), 45.7 (CH, C-5'), 39.5 (C, C-6'), 39.2 (CH₂, C-2'), 29.2 (CH₂, C-4'), 25.8 (CH₃), 22.8 (CH₃), 21.9 (CH₃), 20.8 (CH₃), 17.5 (CH₃), 14.2 (CH₃, OCH₂CH₃); Mass (C₁₇H₂₃O₂): m/z 264 (M⁺, 3%), 168 (38), 140 (20), 135 (22), 122 (49), 121 (24), 107 (22), 96 (100), 95 (38).

(-)-2-[(1S,5S)-5-Isopropenyl-1,2,6,6-tetramethylcyclohex-2-enyl]acetic acid 18. A magnetically stirred solution of the ester 25 (470 mg, 1.78 mmoles) and 20% KOH in methanol (5 mL) was refluxed in an oil-bath for 24 hr. The reaction mixture was cooled, acidified with 3 N aqueous HCl (25 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 18 (370 mg, 88%) as a solid, which was recrystallized from hexane, m.p. 83-86 °C (sublimed); [α]D₂⁰ -20.0 (c 1.0, CHCl₃); IR (thin film): 3600-2500, 1703, 1638, 892 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 5.38 (1 H, d, J = 4.5 Hz, H-3'), [4.90 (1 H, s), 4.73 (1 H, s), C=CH₂], 2.43, 2.37 (2 H, AB q, J = 14.7 Hz, H-2), 2.40-2.35 (1 H, m), 2.11 (1 H, t, J = 12.3 Hz), 1.85-1.75 (1 H, m), [1.79 (3 H, s), 1.72 (3 H, s), 2 × olefinic CH₃], [1.20 (3 H, s), 0.93 (3 H, s), 0.87 (3 H, s), 3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 180.0 (C, OC=O), 147.2 (C, C=CH₂), 138.4 (C, C-2'), 123.0 (CH, C-3'), 113.5 (CH₃, C=CH₂), 46.3 (C, C-1'), 45.6 (CH, C-5'), 39.6 (C, C-6'), 39.2 (CH₂, C-2'), 29.2 (CH₂, C-4'), 25.8 (CH₃), 22.9 (CH₃), 20.8 (CH₃), 17.5 (CH₃), Mass (C₁₈H₂₄O₂): m/z 236 (M⁺, 0.5%), 140 (14), 125 (15), 121 (15), 107 (16), 97 (17), 96 (100), 95 (20), 91 (17), 83 (24), 81 (41).

(-)-(1R,2R,4S,6R,9S)-4-Isopropenyl-1,5,5,6-tetramethyltricyclo[4.3.0.0²,9]nonan-8-one 20. To a magnetically stirred solution of the acid 18 (545 mg, 2.3 mmoles) in dry benzene was added oxalyl chloride (1 mL, 11.6 mmoles) and stirred for 2.5 hr at RT. Evaporation of the excess oxalyl chloride and the solvent under reduced pressure afforded the acid chloride, which was taken in dry ether (3 mL) and added dropwise to a cold, magnetically stirred ethereal solution of diazomethane (excess, prepared from 3 g of N-nitroso-N-methylurea and 15 mL of 60% aqueous KOH solution and 15 mL of ether) and the reaction mixture was stirred at RT for 1.5 hr.
Careful evaporation of the excess diazomethane and the solvent on water-bath and purification of the residue over a silica gel column using EtOAc-hexane (1:10) as eluent furnished the diazo ketone \(19\) (550 mg) as yellow oil. IR (neat): \(\nu_{\text{max}}\) 2100, 1635, 890 cm\(^{-1}\). To a magnetically stirred refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (1.5 g, 23.6 mmol) and anhydrous copper sulfate (1.1 g, 6.89 mmol) in dry cyclohexane (70 mL) was added dropwise, a solution of the diazo ketone \(19\) in dry cyclohexane (20 mL) over a period of 30 min and the reaction mixture was refluxed for 5 hr. 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 EtOAc-hexane (1:25 to 1:20) as eluent furnished the tricyclic ketone \(20\) (300 mg, 56% from the acid \(18\)) as a solid, which was recrystallized from hexane, m.p. 94-95°C; \([\alpha]_D^{25} +145.0\) (c 1.0, CHCl$_3$); IR (thin film): 1708, 1635, 897 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl$_3$ + CCl$_4$): \(\delta\) [4.85 (1 H, s), 4.70 (1 H, s), C=CH$_2$], 2.25 (1 H, dd, \(J = 13.8\) and 4.8 Hz), 2.21, 1.90 (2 H, 2 \( \times \) d, \(J = 19.2\) Hz, H-7), 2.02-1.90 (1 H, d, \(J = 14.4\), 9.0 and 4.5 Hz), 1.74 (3 H, s, olefinic CH$_3$), 1.80-1.65 (1 H, m), 1.61 (1 H, d, \(J = 9.3\) Hz), 1.37 (1 H, d of t, \(J = 14.2\) and 6.5 Hz), [1.32 (3 H, s), 1.22 (3 H, s), 1.10 (3 H, s), 0.78 (3 H, s), 4 \( \times \) tert-CH$_3$]; \(^{13}\)C NMR (75 MHz, CDCl$_3$ + CCl$_4$): \(\delta\) 211.0 (C, C=O), 146.6 (C, C=CH$_2$), 113.7 (CH$_2$, C=CH$_3$), 53.8 (CH, C-4), 52.8 (CH$_2$, C-7), 43.4 (C, C-6), 42.6 (CH, C-9), 38.1 (C, C-5), 35.1 (C, C-1), 29.6 (CH, C-2), 29.1 (CH$_3$), 24.2 (CH$_2$, C-3), 23.5 (CH$_3$), 22.9 (CH$_3$), 22.7 (CH$_3$), 20.4 (CH$_3$); Mass: m/z 232 (M$^+$, 1.5%), 123 (33), 122 (22), 121 (24), 107 (22), 105 (28), 96 (100), 95 (30), 94 (40), 93 (49), 91 (55); Anal. Calcd for C$_{16}$H$_{26}$O: C 82.70, H 10.41. Found: C, 82.90; H, 10.73%.

\(\text{(+)-(1R,2R,4S,6R,7S,9S)-4-Isopropenyl-1,5,5,6,7-pentamethyltricyclo[4.3.0.0^{2,9}]nonan-8-one 26}\). To a magnetically stirred, ice-cold suspension of KH (30% dispersion in oil, 345 mg, 2.58 mmol) washed with dry hexane) in anhydrous THF (1 mL) was added the tricyclic ketone \(20\) (400 mg, 1.72 mmol) in anhydrous THF (1 mL) slowly over 5 min and stirred for 2 hr at the same temperature. Methyl iodide (0.2 mL, 3.21 mmol) was added to the reaction mixture and stirred for 22 hr at RT. The reaction mixture was quenched with saturated NH$_4$Cl solution (10 mL) and 3 N aqueous HCl (10 mL), and extracted with CH$_2$Cl$_2$ (3 \( \times \) 5 mL). The combined CH$_2$Cl$_2$ extract was washed with brine and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished the enol ether \(27\) (33 mg, 7.4%) as oil, IR (neat): 1689, 1638, 890 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl$_3$ + CCl$_4$): \(\delta\) [4.78 (1 H, m), 4.63 (1 H, m), C=CH$_2$], 3.58 (3 H, s, OCH$_3$), 1.97 (1 H, dd, \(J = 13.5\) and 3.9 Hz, H-4), 1.65-1.20 (4 H, m), [1.68 (3 H, s), 1.55 (3 H, s), 2 \( \times \) olefinic CH$_3$], [1.20 (3 H, s), 1.12 (3 H, s), 0.96 (3 H, s), 0.76 (3 H, s), 4 \( \times \) tert-CH$_3$]. Further elution of the column with EtOAc-hexane (1:50) as eluent furnished the methylated tricyclic ketone \(26\) (251 mg, 59%) as oil, \([\alpha]_D^{25} +90.0\) (c 1.0, CHCl$_3$); IR (neat): 1716, 1636, 892 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl$_3$ + CCl$_4$): \(\delta\) [4.85 (1 H, s), 4.71 (1 H, s), C=CH$_2$], 2.28 (1 H, dd, \(J = 14.2\) and 5.0 Hz), 2.03 (1 H, q, \(J = 7.2\) Hz, H-7), 1.97 (1 H, d, \(J = 14.7\), 9.1 and 5.1 Hz), 1.82-1.64 (1 H, m), 1.72 (3 H, s, olefinic CH$_3$), 1.58 (1 H, d, \(J = 9.2\) Hz), 1.46 (1 H, d of t, \(J = 14.4\) and 6.0 Hz), [1.29 (3 H, s), 1.08 (3 H, s), 1.06 (3 H, s) and 0.80 (3 H, s), 4 \( \times \) tert-CH$_3$], 0.99 (3 H, d, \(J = 7.2\) Hz, sec-CH$_3$); \(^{13}\)C NMR (75 MHz, CDCl$_3$ + CCl$_4$): \(\delta\) 213.3 (C, C=O), 146.6 (C, C=CH$_2$), 113.5 (CH$_2$, C=CH$_3$), 54.0 (CH, C-7), 51.1 (CH, C-4), 45.6 (C, C-6), 41.3 (CH, C-9), 39.2 (C, C-5), 33.9 (C, C-1), 29.5 (CH, C-2), 29.0 (CH$_3$), 24.1 (CH$_2$, C-3), 22.5 (2 C, CH$_3$), 21.1 (CH$_3$), 17.1 (CH$_3$), 12.6 (CH$_3$, sec-CH$_3$); Mass (C$_{17}$H$_{26}$O): m/z 246 (M$^+$, 0.6%), 150 (9), 137 (10), 135 (7), 107 (14), 105 (7), 97 (11), 96 (100), 91 (13), 81 (36). Further elution of the column with EtOAc-hexane (1:25 to 1:20) as eluent furnished the unreacted starting material \(20\) (86 mg, 21.5%).

**Hydrolysis of the enol ether 27.** To a magnetically stirred solution of the enol ether \(27\) (50 mg, 0.192 mmol) in CH$_2$Cl$_2$ (2 mL) was added a catalytic amount of p-TSA and stirred for 1 hr at RT. The reaction mixture was then diluted with CH$_2$Cl$_2$ (5 mL) and washed with saturated aqueous NaHCO$_3$ solution (5 mL) and brine, and dried (Na$_2$SO$_4$). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-hexane (1:50) as eluent furnished the tricyclic ketone \(26\) (32 mg, 67.6%) as oil, whose TLC and spectral data (IR and \(^1\)H NMR) were identical with those of the sample obtained in the previous experiment.

\((S,3S,6R,9S)-3-Isopropenyl-1,2,2,6,9-pentamethylbicyclo[4.3.0]nonan-8-one 28\). To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (20 mL) in a two necked flask,
equipped with Dewar condenser, was added freshly cut lithium (5 mg, 0.72 mmole) followed by the tricyclic ketone 26 (25 mg, 0.1 mmole) in anhydrous THF (1 mL). The resulting blue coloured solution was stirred for 5 min 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 × 3 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 EtOAc-hexane (1:50) as eluent furnished the ketone 28 (16 mg, 63.5%) as oil, IR (neat): 1736, 1637, 891 cm⁻¹; ¹H NMR (300 MHz, CDCl3 + CCl4): δ [4.90 (1 H, s), 4.68 (1 H, s, C=CH2)], 2.67 (1 H, d, J = 18.9 Hz, H-7a), 2.47 (1 H, q, J = 7.8 Hz, H-9), 2.27 (1 H, m of d, J = 12.0 Hz), 1.85-1.35 (5 H, m), 1.79 (3 H, s, olefinic CH3), 1.14 (3 H, d, J = 7.8 Hz, sec-CH2), [1.05 (3 H, s), 1.01 (3 H, s), 0.97 (3 H, s), 0.81 (3 H, s), 4 × tert-CH3]; ¹³C NMR (75 MHz, CDCl3 + CCl4): δ 221.8 (C, C=O), 147.6 (C, C=CH2), 114.0 (CH2, C=CH2), 51.3 (CH2, C-7), 49.1 (CH, C-9), 49.0 (C, C=1), 48.8 (CH, C-3), 42.0 (C), 41.4 (C), 34.7 (CH2, C-5), 31.0 (CH3), 27.7 (CH3), 25.6 (CH2), 24.9 (CH2, C-4), 21.2 (CH3), 15.6 (CH3), 15.0 (CH3). Further elution of the column with EtOAc-hexane (1:10 to 1:5) as eluent furnished the alcohol 29 (8 mg, 31.5%) as oil, IR (neat): 3340, 1640, 890 cm⁻¹; ¹H NMR (300 MHz, CDCl3 + CCl4): δ [4.87 (1 H, s), 4.71 (1 H, s, C=CH2)], 3.85 (1 H, q, J = 8.1 Hz), 2.22 (1 H, dd, J = 12.3 and 5.7 Hz), 2.04 (1 H, quintet, J = 7.2 Hz), 1.77 (3 H, s, olefinic CH3), 1.76-1.30 (7 H, m), 1.05 (3 H, d, J = 7.2 Hz, sec-CH2), [1.10 (3 H, s), 0.97 (3 H, s), 0.83 (3 H, s), 0.78 (3 H, s), 4 × tert-CH3].

**Oxidation of the alcohol 29.** To a magnetically stirred solution of the bicyclic alcohol 29 (13 mg, 0.052 mmole) in 1 mL of CH2Cl2 was added a mixture of PCC (25 mg, 0.116 mmole) and silica gel (25 mg). The reaction mixture was stirred for 3 hr at RT, filtered through a small silica gel column and eluted the column with more CH2Cl2. Evaporation of the solvent and purification of the product on a silica gel column using EtOAc-hexane (1:50) as eluent furnished the ketone 31 (15 mg, 86%) as oil, which was contaminated with trace amount of the Criegee rearrangement product, the bicyclic keto acetate 30, IR (neat): 1733, 1707 cm⁻¹; ¹H NMR (300 MHz, CDCl3 + CCl4): δ 3.50-3.40 (1 H, m, H-9), 2.80-2.71 (1 H, m, H-3), 2.17 (3 H, s, COCH3), 2.00-1.60 (6 H, m), 1.07 (3 H, d, J = 7.5 Hz, sec-CH3), [1.20 (3 H, s), 1.09 (3 H, s), 1.03 (3 H, s), 0.88 (3 H, s), 4 × tert-CH3].

(-)-(1R,2R,4R,6S,7S,9S)-4-Acetoxy-1,5,5,6,7-pentamethyltricyclo[4.3.0.0²,⁹]nonan-8-one 32 and (-)-(1R,2R,4R,6R,7S,9S)-4-acetyl-1,5,5,6,7-pentamethyltricyclo[4.3.0.0²,⁹]nonan-8-one 33. Pre-cooled dry ozone in oxygen gas was passed through a cold (-70 °C) suspension of the tricyclic ketone 26 (120 mg, 0.49 mmole) and NaHCO3 (10 mg) in 1:2 MeOH-CH2Cl2 (3 mL) till pale permanent blue colour appeared. Excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue was dissolved in dry benzene (1 mL). Ac2O (0.5 mL, 5.3 mmole), NEt3 (0.2 mL, 1.43 mmole) and a catalytic amount of DMAP (10 mg) were added to the reaction mixture, stirred at RT for 15 min and then refluxed for 6 hr. Work-up of the reaction as described in the previous experiment, and purification of the product on a silica gel column using EtOAc-hexane (1:10 to 1:5) as eluent furnished the ketone 32 (49 mg, 38%) as oil, [α]D²⁵ -24.6 (c 1.14, CHCl3); IR (neat): 1738, 1715 cm⁻¹; ¹H NMR (300 MHz, CDCl3 + CCl4): δ 4.64 (1 H, dd, J = 7.2 and 3.0 Hz, H-4), 2.60 (1 H, q, J = 7.3 Hz, H-7), 2.53 (1 H, t of d, J = 16.5 and 7.4 Hz), 1.97 (3 H, s, COCH3), 1.76 (1 H, d, J = 16.5 Hz), 1.65 (1 H, d, J = 10.2 Hz), 1.60-1.40 (1 H, m), 1.09 (3 H, d, J = 7.0 Hz, sec-CH3), [1.29 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s), 0.87 (3 H, s), 4 × tert-CH3].
and 6.3 Hz, H-4), 2.20 (3 H, s, COCH 3), 2.20-2.00 (2 H, m), 1.64 (1 H, d, J = 7.5 Hz, sec-CH$_3$); 13C NMR (75 MHz, CDCl$_3$ + CCl$_4$): δ 221.0 (C, C=O), 77.7 (CH, C-3), 53.6 (CH$_2$, C-7), 50.9 (CH, C-9), 47.7 (C, C-1), 40.2 (C), 39.5 (C), 30.8 (CH$_2$, C-5), 26.3 (CH$_3$), 25.0 (CH$_3$), 23.4 (CH$_3$), 14.7 (CH$_3$), 13.0 (CH$_3$); Mass: m/z 207 (M-OH, 11%), 137 (56), 135 (20), 125 (24), 124 (77), 123 (36), 121 (22), 109 (37), 97 (27), 95 (25).

Acetylation of the hydroxy ketone 34. To a magnetically stirred solution of the hydroxy ketone 34 (8 mg, 0.036 mmole) in pyridine (0.04 mL, 0.5 mmole) were added acetic anhydride (0.04 mL, 0.424 mmole) and a catalytic amount of DMAP and stirred for 24 hr at RT. The reaction mixture was diluted with water (5 mL) and extracted with CH$_2$Cl$_2$ (2 × 3 mL). The combined CH$_2$Cl$_2$ extract was washed with 3 N aqueous HCl (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 EtOAc-hexane (1:20) as eluent furnished the hydroxy ketone 34 (7.5 mg, 7.7%) as a solid, [α]$_D^{25}$ +46.7 (c 1.2, CHCl$_3$); IR (neat): 3481, 1730 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$ + CCl$_4$): δ 3.57 (1 H, s, H-3), 3.50 (1 H, q, J = 6.9 Hz, H-2), 2.92, 1.95 (2 H, 2 × d, J = 18.3 Hz, H-7), 2.06-1.96 (2 H, m), 1.65-1.50 (1 H, m), 1.30-1.10 (2 H, m), 1.05 (3 H, d, J = 6.9 Hz, sec-CH$_3$), [1.22 (3 H, s), 1.06 (3 H, s), 0.97 (3 H, s), 0.85 (3 H, s), 4 × tert-CH$_3$]; 13C NMR (75 MHz, CDCl$_3$ + CCl$_4$): δ 221.0 (C, C=O), 77.7 (CH, C-3), 53.6 (CH$_2$, C-7), 50.9 (CH, C-9), 47.7 (C, C-1), 40.2 (C), 39.5 (C), 30.8 (CH$_2$, C-5), 26.3 (CH$_3$), 25.0 (CH$_3$), 23.4 (CH$_3$), 14.7 (CH$_3$), 13.0 (CH$_3$); Mass: m/z 207 (M-OH, 11%), 137 (56), 135 (20), 125 (24), 124 (77), 123 (36), 121 (22), 109 (37), 97 (27), 95 (25).

Acetylation of the hydroxy ketone 34. To a magnetically stirred solution of the hydroxy ketone 34 (8 mg, 0.036 mmole) in pyridine (0.04 mL, 0.5 mmole) were added acetic anhydride (0.04 mL, 0.424 mmole) and a catalytic amount of DMAP and stirred for 24 hr at RT. The reaction mixture was diluted with water (5 mL) and extracted with CH$_2$Cl$_2$ (2 × 3 mL). The combined CH$_2$Cl$_2$ extract was washed with 3 N aqueous HCl (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 EtOAc-hexane (1:20) as eluent furnished the keto acetate 30 (8 mg, 84%), which exhibited TLC and spectral data (IR and 1H NMR) identical with the sample obtained in the previous experiment.

(-)-(IS,3R,6R,9R)-1,2,2,6,9-Pentamethyl-8-methylenebicyclo[4.3.0]nonan-3-yl acetate [Thaps-8(11)-
en-3-y1 acetate 35). To a magnetically stirred solution of freshly prepared K'fAmO' [prepared from the reaction of potassium (74 mg, 1.89 mmoles) and tert-amyl alcohol (1.9 mL) followed by evaporation of the excess tert-amyl alcohol under vacuum] in dry benzene (0.5 mL) was added methyltrityphenylphosphonium iodide (840 mg, 2.08 mmoles), and the resulting yellow colour solution was stirred for 30 min at RT. To the dark yellow coloured solution of methyltri-phenylphosphorane was added the bicyclic keto acetate 30 (50 mg, 0.19 mmoles) in dry benzene (0.2 mL) and stirred for 3 hr at RT. Saturated aqueous NH4Cl solution (5 mL) and stirred for 3 hr at RT. EtOAc (1 mL) and evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-hexane (1:20) as eluent furnished the thapsenol 35 (3 mg, 60%) as oil, [α]D21 -8.1 (c 1.36, CHCl3); IR (neat): 1740, 1651, 874 cm-1; 1H NMR (300 MHz, CDCl3 + CCl4): δ 4.81 (1 H, s), 4.78 (1 H, s), C=CH2], 3.60-3.45 (2 H, m), 2.42 (1 H, q of d, J = 6.9 Hz, sec-CH3), [1.09 (3 H, s), 1.056 (3 H, s), 0.90 (3 H, s), 0.78 (3 H, s), 4 × tert-CH3]; 13C NMR (75 MHz, CDCl3 + CCl4): δ 156.8 (C, C-8), 105.4 (CH3, C=C-CH2), 78.4 (CH, C-3), 49.4 (CH2, C-7), 49.2 (C, C-1), 43.6 (CH, C-9), 42.5 (C, C-2), 40.2 (C, C-6), 29.8 (CH3, C-5), 26.2 (2 C, CH3 and CH2), 25.0 (CH3), 23.4 (CH3), 18.1 (CH3), 14.2 (CH3); Mass: m/z 204 (M-H2O, 7%), 189 (21), 148 (25), 147 (43), 133 (45), 123 (25), 122 (25), 121 (100), 107 (22), 105 (22), 91 (31); Anal. Calcd for C15H26O: C, 81.02; H, 11.79. Found: C, 81.24; H, 12.02%.

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References and Notes

1 For the details on isolation and other aspects of thapsanes, see Srikrishna A & Ramachary D B, Indian J Chem, 44B, 2005, 751.
2 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 (see: Teresa J P, Moran J R & Grande M, Chem Lett, 1985, 865 and Teresa J P, Moran J R, Fernandez A & Grande M, Phytochemistry, 25, 1986, 703, 1171). Incidentally, this is same as that proposed by Rasmussen and coworkers (see: Lemmich E, Jensen B & Rasmussen U, Phytochemistry, 23, 1984, 809). Grande M, (Personal Communication).

(b) Burke S D & Greico P A, *Org React*, 26, **1979**, 361.
