Enantiospecific total synthesis of ent-10,11-thapsan-10-ol

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First enantiospecific total synthesis of optical antipode of the sesquiterpene 10,11-epoxythapsan-10-ol has been described. (R)-Carvone has been employed as the chiral starting material and a combination of intramolecular alkylation and Criegee fragmentation are 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, Thapsia garganica, thapsane, Thapsia villosa

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 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 the 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-1,2,2,6,8,9-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 16 containing the cyclohexanone part structure, which were obtained by degradation of the 3- and 5-acyloxythapsanes 5 and 6. Presence of a unique, sterically crowded structure containing 4-oxatricyclo[6.4.0.02,6]dodecane incorporating three contiguous quaternary carbon atoms and five to six chiral centers made thapsanes attractive synthetic targets. In continuation of our interest in the synthesis of thapsanes, enantiospecific approaches to thapsanes have been initiated starting from the readily and abundantly available monoterpene (R)-carvone 17. Herein, we describe the details of the first enantiospecific synthesis of the hemiacetalic thapsane 14, which also confirmed the absolute configuration of thapsanes.

For the synthesis of thapsanes, the most important task 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). The retrosynthesis of thapsane 14 (Scheme I) identified the tricyclic keto ester 18 as the key intermediate. It was anticipated that intra
molecular cyclopropanation of the α-diazo-β-keto ester derived from the β-keto ester 19 could generate the tricyclic keto ester 18, which could be further elaborated into the thapsane 14 via the thapsene ester 20. It was contemplated that the aldehyde 21, which could be obtained from the keto ester 22 in optically active form, would serve as an ideal precursor for the enantiospecific generation of the β-keto ester 19. Synthesis of the keto ester 22 from (R)-carvone 17, via the trimethylcarvone 23 and bicycle[2.2.2]-octanone 24, has already been reported earlier.71

To begin synthesis of the keto ester 22 was carried out as described in earlier literature71 (Scheme II). Carvone 17 has been converted8 into the trimethylcarvone 23 via sequential kinetic alkylation followed by alkylative 1,3-enone transposition of 6,6-dimethylcarvone 25. Reaction of trimethylcarvone 23 with N-bromosuccinimide (NBS) in methanol-methylene chloride medium furnished the allyl bromide 26 in 90% yield in a highly regioselective manner9. Generation of the thermodynamic dienolate of the bromoenone 26 with potassium tertiary butoxide in tertiary butyl alcohol and THF resulted in the regioselective intramolecular alkylation10-12 to furnish the bicyclo[2.2.2]octanone 24. Controlled ozonolysis of the bicyclic ketone 24 in a mixture of methanol-methylene chloride followed by reaction 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 (via Criegee rearrangement)11. 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 22.

For the reductive deoxygenation of the keto ester 22, Huang-Minlon modified Wolff-Kishner reduction was explored, Scheme III. Reaction of the keto ester 22 with hydrazine hydrate and potassium hydroxide in diethylene glycol at 180°C, followed by esterification of the resultant acid with diazomethane furnished the ester 28, in 53% yield, along with varying amounts of the hexahydrocinnolinolone 29, m.p. 119-21°C. Reduction of the ester 28 with LAH in ether at RT furnished the alcohol 30, which on oxidation with a mixture of PCC and silica gel in methylene chloride furnished the aldehyde 21 in 75% yield, whose structure was established from its spectral data. For the conversion of the aldehyde 21 into the β-keto ester 19, a methodology based on the acid catalyzed coupling of an aldehyde and diazoacetate12 was employed. Thus, treatment of the aldehyde 21 with ethyl diazoacetate in methylene chloride in the presence of a catalytic amount of stannous chloride furnished the β-keto ester 19, in 88% yield. The β-keto ester 19 was then converted into the key intermediate of the sequence, tricyclic β-keto ester 18 via the α-diazo-β-keto ester 31. Diazo transfer reaction with tosyl azide in the presence of triethylamine in acetonitrile converted the β-keto ester 19 into the α-diazo-β-keto ester 31 in 89% yield. Rhodium acetate catalyzed stereospecific intramolecular cyclopropanation reaction13 of the diazo compound 31 in benzene at RT furnished the tricyclic β-keto ester 18, in 69% yield. Reductive cyclopropane ring cleavage14 employing lithium in liquid ammonia at -33°C for 5 min, transformed the tricyclic keto ester 18 into a 3:5 mixture of the hydridanone 32 and the decalinone 33, in 86% yield, which were separated by column chromatography on

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**Scheme II** — (a) LDA, THF, MeI; (b) i. MeLi, Et₂O; ii. PCC, silica gel, CH₂Cl₂; (c) NBS, CH₂Cl₂, MeOH; (d) KO'Bu, BuOH, THF; (e) i. O₃, CH₂Cl₂, MeOH; ii. Ac₂O, Et₃N, DMAP, C₆H₆; (f) H₂, 5% Pd/C, EtOAc
silica gel. The formation of the two esters 32 and 33 can be explained\textsuperscript{14} by the selective cleavage of either C-1 C-3 bond or C-2 C-3 bond of the cyclopropane in the tricyclic keto ester 18. It is well established in the reduction of cyclopropyl ketones with lithium in liquid ammonia, the cyclopropane bond which has better overlap with the π-orbital of the carbonyl carbon will be cleaved. Accordingly, in the keto ester 18 (Scheme IV) transfer of electron to the ketone carbonyl results in the cleavage of the C-2 C-3 bond leading to the formation of the bicyclic keto ester 32. On the other hand, transfer of electron to the ester carbonyl results in the cleavage of C-1 C-3 bond, because in the sterically less hindered conformation, as visualized by Drieding models, the C-1 C-3 bond has better overlap with the π-orbital of the ester carbonyl leading to the decalinone 33. The trans ring junction in the decalinone 33 was assigned based on the analogy of octalone reductions\textsuperscript{15}.

The β-keto ester 32 was elaborated to the thapsane (10,11-epoxythapsan-10-ol) 14 employing the same sequence as that used in racemic synthesis\textsuperscript{7b} via the ene ester 20 and the lactone 34, Scheme V. Thus, Wittig olefination of the β-keto ester 32 with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide and potassium tertiary amylate, in refluxing benzene for 12 hr furnished the ene ester 20 in 98% yield. Epoxidation of the exomethylene in the ester 20 with magnesium monoperoxyphthalate (MMPPA) in ethanol for 36 hr furnished a 1:2 epimeric mixture of the epoxides 35 in 83% yield. Treatment of the epimeric mixture of the

\[\text{Scheme III} \quad \rightarrow \begin{cases} \text{(a) i. NH}_2\text{NH}_2\cdot\text{H}_2\text{O, KOH, digol; ii. CH}_2\text{N}_2, \text{Et}_2\text{O; (b) LAH, Et}_2\text{O; (c) PCC, silica gel, CH}_2\text{Cl}_2; (d) N}_2\text{CHCOOEt, SnCl}_2\cdot2\text{H}_2\text{O, CH}_2\text{Cl}_2; (e) TsN}_3, \text{NEt}_3, \text{CH}_2\text{CN; (f) Rh}_2(\text{OAc})_4, \text{C}_6\text{H}_6; (g) Li, liq. NH}_3, \text{THF} \end{cases} \]
epoxides 35 with a catalytic amount of boron trifluoride etherate in methylene chloride furnished a 6:5 mixture of the ethoxy lactone 34 and the aldehyde ester 36, in 70% yield, which was separated by column chromatography on silica gel. The structures of 34 and 36 were established from spectral data. Formation of the ethoxy lactone 34 could be rationalized as depicted in Scheme VI.

Boron trifluoride etherate catalyzed rearrangement of the epoxide 35 generates a mixture of cis-and trans-isomers of the aldehyde ester 36. Boron trifluoride etherate mediated intramolecular trans-acetalization of the cis-isomer leads to the ethoxy lactone 34. The stereochemistry of the ethoxy group in the ethoxy lactone 34 was assigned based on the weak coupling of the acetal proton with the C-6 proton.

The ionic hydrogenation\(^\text{16}\) of the ethoxy lactone 34 using a combination of trifluoroacetic acid and triethylsilane furnished the lactone 38, m.p. 120-23°C (lit.\(^\text{4}\) 123-25°C), \([\alpha]_D^{25}: +43.3\) (c 1, CHCl\(_3\)) [lit.\(^\text{4}\) for (-)-38: -41 (c 1.4, CHCl\(_3\))], a degradation product of a number of thapsanes, in 74% yield. The lactone 38 exhibited \(^1\)H and \(^13\)C NMR spectral data identical to that of the sample derived from the natural thapsanes. Finally, reduction of the lactone 38 with diisobutylaluminum hydride in hexane furnished the thapsane (+)-14, m.p. 85.5-87°C (lit.\(^\text{5}\) 85.5-87°C), \([\alpha]_D^{25}: +40\) (c 0.5, CHCl\(_3\)) [lit.\(^\text{5}\) for (-)-14: -47 (c 0.16, CHCl\(_3\))] in 87% yield, which exhibited the \(^1\)H and \(^13\)C NMR spectral data identical to those of the natural thapsane.

In conclusion, we have accomplished the first enantiospecific total synthesis of the optical antipode of the natural hemiacetalic thapsane 14, which also confirmed the absolute configuration of thapsanes. 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 regioselective cleavage of cyclopropane ring were employed for the stereospecific generation of the three requisite contiguous quaternary carbon atoms.

**Experimental Section**

**Methyl 2-[(1R)-1,3,3-trimethyl-2-methylene-cyclohexyl]acetate 28 and (6R)-6,8,8-trimethyl-7-methylene-2,3-diazabicyclo[4.4.0]dec-1-en-4-one 29**

A solution of the keto ester 22 (500 mg, 2.23 mmole), potassium hydroxide (1.3 g, 23.3 mmole) and hydrazine hydrate (2.2 mL, 45.3 mmole) in diethylene glycol (3.5 mL) was taken in a sealed tube and heated to 180°C for 12 hr. The reaction-mixture was cooled, acidified with 3 N aqueous HCl (15 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The combined CH₂Cl₂ extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished a residue, which was esterified without further purification. An ice-cold ethereal diazomethane solution (excess, prepared from N-nitroso-N-methyleurea, 60% aqueous KOH and ether) was added to a magnetically stirred ice-cold solution of the mixture, obtained above, in ether (2 mL) 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 (1:50 v/v) as eluent, first furnished the ester 28 (250 mg, 53%), [α]D<sup>26</sup> -3.7° (c 3, CHCl₃); IR (neat): 2927, 1739 (OC=O), 1624 (C=O), 1463, 1436, 1323, 1202, 1133, 1014, 902 cm<sup>-1</sup>; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 4.99 (1 H, s) and 4.89 (1 H, s) [C=CH₂], 3.61 (3 H, s, OCH₃), 2.53 and 2.48 (2 H, 2 × d, J = 13.5 Hz, H-2), 1.76-1.25 (6 H, m), 1.25 (3 H, s), 1.14 (3 H, s) and 1.13 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 172.1 (C, OC=O), 160.7 (C, C-2'), 108.7 (CH₂, C=CH₂), 51.0 (CH₂, OCH₃), 46.0 (CH₂, C-2), 40.8 (CH₂, C-6'), 38.91 (CH₂, C=4'), 38.86 (C, C-1'), 36.4 (C, C-3'), 32.5 (CH₃), 31.2 (CH₃), 29.7 (CH₃), 18.6 (CH₃, C-5'); MS: m/z (%) (C₁₃H₂₀O₂) 211 (M + 1, 13%), 210 (9), 195 (20), 154 (34), 137 (40), 136 (40), 123 (25), 121 (100), 109 (46), 107 (33), 96 (36), 95 (78), 93 (39), 91 (30). Further elution of the column with ethyl acetate-hexane (2:3 v/v) as eluent furnished the by-product, hexahydrocinnolmine 29 (102 mg, 22.2%) as a white solid, which was recrystallized from a mixture of CH₂Cl₂ and hexane. m.p.: 119-21°C; [α]D<sup>25</sup> -85.5° (c 2.0, CHCl₃); IR (thin film): 3225 (N-H), 2966, 1685 (HNC=O), 1619 (C=O), 1464, 1357, 1077, 970, 742 cm<sup>-1</sup>; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 8.59 (1 H, br s, NH), 5.10 (1 H, s) and 4.95 (1 H, s) [C=CH₂], 2.65-2.45 (2 H, m), 2.59 and 2.40 (2 H, 2 × d, J = 16.2 Hz, H-5), 1.77 (1 H, ddd, J = 14.0, 8.7 and 6.0 Hz), 1.61 (1 H, dt, J = 13.5 and 6.3 Hz), 1.33 (3 H, s), 1.24 (3 H, s) and 1.17 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 166.9 (C, C=O), 159.4 (C) and 158.2 (C) [C-1 and C-7], 109.1 (CH₂, C=CH₂), 41.2 (CH₂, C-5), 39.8 (C, C-6), 35.8 (C-8), 35.2 (CH₂, C-9), 26.9 (CH₂, C-10), 30.9 (CH₃), 30.1 (CH₃), 25.3 (CH₃); MS: m/z (%) 207 (M + 1, 30%), 206 (M<sup>+</sup>), 191 (72), 163 (60), 149 (43), 148 (46), 135 (36), 123 (29), 107 (44), 93 (39), 91 (39); Anal. Calcd. for C₁₂H₁₈N₂O. C, 69.87; H, 8.80; N, 13.58. Found: C, 70.22; H, 9.01; N, 13.90%.

2-[(1R)-1,3,3-Trimethyl-2-methylene cyclohexyl]ethanol 30

To a magnetically stirred, cold (0°C) solution of the ester 28 (500 mg, 2.38 mmole) in anhydrous ether (5 mL) was added LiAlH₄ (180 mg, 4.75 mmole) and the reaction-mixture was stirred at RT for 2.5 hr. Ethyl acetate (3 mL) was added to the reaction-mixture to consume the excess LiAlH₄. The reaction was then quenched with water (10 mL) and extracted with ether (3 × 5 mL). The combined ether 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 (1:10 to 1:6 v/v) as eluent furnished the alcohol 30 (395 mg, 91%) as oil. [α]D<sup>25</sup> +32.5° (c 2.4, CHCl₃); IR (neat): 3333 (OH), 2926, 1623 (C=C), 1463, 1379, 1108, 1035, 900 cm<sup>-1</sup>; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 5.00 (1 H, s) and 4.85 (1 H, s) [C=CH₂], 3.70-3.50 (2 H, m, CH₂OH), 2.08 (1 H, ddd, J = 14.1, 8.7 and 6.0 Hz), 1.85-1.65 (1 H, m), 1.60-1.20 (7 H, m), 1.15 (3 H, s) and 1.12 (6 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 160.6 (C, C-2'), 108.8 (CH₂, C=CH₂), 60.4 (CH₂, C-1), 42.7 (CH₂), 41.5 (CH₂), 41.1 (CH₂), 38.6 (C, C-1'), 36.6 (C, C-3'), 32.7 (CH₂), 30.1 (2 C, CH₃), 18.6 (CH₂, C-5'); MS: m/z (%) (C₁₃H₂₂O) 182 (M<sup>+</sup>, 8%), 181 (80), 179 (55), 138 (20), 123 (51), 121 (22), 109 (23), 95 (36), 85 (54), 83 (100), 81 (34).

2-[(1R)-1,3,3-Trimethyl-2-methylene cyclohexyl]-acetaldehyde 21

To a magnetically stirred solution of the alcohol 30 (450 mg, 2.47 mmole) in 3 mL of CH₂Cl₂ was added a mixture of PCC (1 g, 4.65 mmole) and silica gel
(1 g). The reaction-mixture was stirred at RT for 1 hr, filtered through a small silica gel column, and eluted with more CH₂Cl₂. Evaporation of the solvent and purification of the product on a silica gel column using ethyl acetate-hexane (1:25 v/v) as eluent furnished the aldehyde 21 (370 mg, 83%) as oil. [α]D<sup>25</sup>: +3.75° (c 4.0, CHCl₃); IR (neat): 3101, 2928, 2735 (OC-H), 1720 (C=O), 1624 (C=C), 1466, 1381, 1103, 904 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 9.65 (1 H, t, J = 3.0 Hz, CHO), 5.09 (1 H, s) and 4.90 (1 H, s) [C=CH₂], 2.63 (1 H, dd, J = 15.0 and 2.7 Hz) and 2.29 (1 H, dd, J = 15.0 and 3.3 Hz) [H-2], 1.80-1.52 (3 H, m), 1.50-1.30 (3 H, m), 1.27 (3 H, s) and 1.17 (6 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 202.9 (CH, CHO), 159.4 (C, C-2'), 109.8 (CH₂, C=CH₂), 53.0 (CH₂, C-2), 41.0 (CH₂, C-6), 40.3 (CH₂, C-4), 38.6 (C, C-1'), 36.5 (C, C-3'), 32.4 (CH₃), 30.7 (CH₂), 30.3 (CH₃), 18.6 (CH₂, C-5').

Ethyl 4-[(1R)-1,3,3-trimethyl-2-methylencyclohexyl]-3-oxobutanoate 19

To a magnetically stirred solution of the aldehyde 21 (370 mg, 2.06 mmole) and ethyl diazoacetate (0.4 mL, 3.79 mmole) in CH₂Cl₂ (2 mL) was added SnCl₂·2H₂O (50 mg, 0.22 mmole) portion wise over a period of 6 hr. After nitrogen evacuation stopped, the solvent was evaporated and the residue was purified over a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent to furnish the β-keto ester 19 (481 mg, 88%) as oil. [α]D<sup>25</sup>: -10.0° (c 5.2, CHCl₃); IR (neat): 3102, 2963, 2928, 2870, 1747 (OC=O), 1718 (C=O), 1625, 1465, 1423, 1367, 1314, 1233, 1156, 1128, 1032, 902 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 5.00 (1 H, s) and 4.86 (1 H, s) [C=CH₂], 4.16 (2 H, q, J = 6.9 Hz, OCH₂CH₃), 3.34 (2 H, s, H-2), 2.74 (2 H, s, H-4). 1.90-1.20 (6 H, m), 1.28 (3 H, t, J = 6.9 Hz, OCH₂CH₃), 1.23 (3 H, s), 1.15 (3 H, s) and 1.14 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 200.8 (C, C-3), 166.8 (C, OC=O), 160.4 (C, C-2'), 108.8 (CH₂, C=CH₂), 61.0 (CH₂, OCH₂CH₃), 53.2 (CH₂, C-2), 51.3 (CH₃, C-4), 40.7 (CH₂, C-6'), 39.1 (C, C-1'), 38.7 (CH₂, C-4'), 36.3 (C, C-3'), 32.6 (CH₃), 31.3 (CH₃), 29.7 (CH₃), 18.5 (CH₂, C-5'), 14.3 (CH₃, OCH₂CH₃).

Ethyl 2-diazo-4-[(1R)-1,3,3-trimethyl-2-methylene-cyclohexyl]-3-oxobutanoate 31

To a magnetically stirred solution of the β-keto ester 19 (400 mg, 1.50 mmole) in dry acetonitrile (1.5 mL) was added tosyl azide (0.23 mL, 1.50 mmole), followed by triethylamine (0.2 mL, 1.5 mmole) and stirred for 12 hr at RT. Evaporation of the solvent and triethylamine under reduced pressure and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent furnished the α-diazo-β-keto ester 31 (390 mg, 89%) as yellow oil. IR (neat): 2927, 2130 (N=), 1717 (OC=O), 1650 (C=O), 1464, 1372, 1299, 1200, 1170, 1177, 1088, 1030, 900, 813, 745 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 4.98 (1 H, s) and 4.90 (1 H, s) [C=CH₂], 4.27 (2 H, q, J = 6.9 Hz, OCH₂CH₃), 3.15 and 3.08 (2 H, 2 × d, J = 15.6 Hz, H-4), 1.95-1.80 (1 H, m), 1.80-1.30 (5 H, m), 1.33 (3 H, t, J = 6.9 Hz, OCH₂CH₃), 1.25 (3 H, s), 1.14 (3 H, s) and 1.13 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 190.8 (C, C-3), 161.2 (C) and 161.0 (C) [OC=O and C-2'], 108.4 (CH₂, C=CH₂), 61.0 (CH₂, OCH₂CH₃), 48.8 (CH₂, C-4), 40.6 (CH₂, C-6'), 39.8 (C, C-1'), 38.5 (CH₂, C-4'), 36.3 (C, C-3'), 32.6 (CH₃), 31.0 (CH₃), 29.6 (CH₃), 18.5 (CH₂, C-5'), 14.4 (CH₃, OCH₂CH₃).

Ethyl (1R,3R,6R)-6,10-trimethyl-4-oxotricyclo[4.4.0.0<sup>13</sup>]<sub>3,10</sub>decane-3-carboxylate 18

To a magnetically stirred solution of the diazo ketone 31 (390 mg, 1.34 mmole) in dry benzene (135 mL) was added a catalytic amount of Rh₂(OAc)₄, and the reaction-mixture was stirred for 20 hr at RT. The catalyst was filtered off and the solvent was evaporated under reduced pressure. Purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:10 v/v) as eluent furnished the tricyclic ketone ester 18 (244 mg, 69%)<sup>7b</sup>; [α]D<sup>24</sup>: -37.5° (c 1.2, CHCl₃); IR (thin film): 2931, 1720 (C=O), 1466, 1380, 1337, 1323, 1241, 1210, 1178, 1118, 1041 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 4.19 (2 H, q, J = 7.2 Hz, OCH₂CH₃), 2.08 and 1.75 (2 H, 2 × d, J = 17.7 Hz, H-5), 1.82 (1 H, d, J = 5.7 Hz), 1.80-1.35 (7 H, m), 1.31 (3 H, t, J = 7.2 Hz, OCH₂CH₃), 1.22 (3 H, s), 1.17 (3 H, s) and 0.64 (3 H, s) [3 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 206.8 (C, C=O), 168.0 (C, OC=O), 61.2 (CH₂, OCH₂CH₃), 54.4 (C, C-3), 49.9 (CH₂, C-5), 49.4 (C, C-1), 39.5 (CH₂) and 39.2 (CH₃) [C-7 and C-9], 38.7 (C, C-6), 33.6 (C, C-10), 28.3 (CH₃), 27.5 (CH₃), 23.2 (CH₃), 18.7 (CH₃) and 18.3 (CH₂) [C-2 and C-8], 14.2 (CH₃, OCH₂CH₃).

Ethyl (1R,6R,7S)-1,5,5,6-tetramethyl-8-oxobicyclo[4.3.0]nonane-7-carboxylate 32 and ethyl (1S,6R)-
4-hydroxy-6,10,16-trimethylbicyclo[4.4.0]dec-3-ene-3-carboxylate 33

To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (30 mL) in a two necked flask, equipped with Dewar condenser, was added freshly cut lithium (4 mg, 0.57 mmole) followed by the tricyclic ketone 18 (45 mg, 0.17 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 × 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 (1:50 v/v) as eluent furnished the ester 33 (25 mg, 55%) as oil. [α]D25 24: -51.6° (c 2.5, CHCl3); IR (neat): 2986, 2931, 1753 (OC=O), 1726, 1653, 1649, 1594, 1531, 1389, 1333, 1258, 1230, 1147, 1107, 1037, 882 cm-1; 1H NMR (300 MHz, CDCl3 + CCl4): δ 12.05 (1 H, s, OH), 4.20 (2 H, q, J = 6.9 Hz, OCH2CH3), 2.30 (1 H, dd, J = 15.6 and 4.2 Hz, H-2a), 2.08 and 1.86 (2 H, 2 × d, J = 16.8 Hz, H-5), 2.00-1.85 (1 H, m), 1.60-1.00 (7 H, m), 1.32 (3 H, t, J = 6.9 Hz, OCH2CH3), 0.91 (9 H, s, 3 × tert-CH3); 13C NMR (75 MHz, CDCl3 + CCl4): δ 172.4 (C) and 170.7 (C) [C-4 and OC=O=], 96.5 (C, C-3), 60.0 (CH2, OCH2CH3), 48.9 (CH2, C-5), 48.6 (CH, C-1), 42.8 (CH2, C-2), 41.6 (CH2, C-7), 33.2 (C, CH3 and C), 33.0 (C, C-10), 21.7 (CH2), 20.7 (CH3, C-9), 19.6 (CH), 18.8 (CH3, C-8), 14.6 (CH3, OCH2CH3); MS: m/z (%) (C16H20O3) 266 (M+ 7%), 149 (15), 137 (13), 123 (26), 109 (64), 95 (28). Further elution of the column with ethyl acetate-hexane (1:20 v/v) as eluent furnished the bicyclic keto ester 32 (14 mg, 31%)7b. [α]D25 24: +70.0° (c 1.4, CHCl3); IR (neat): 2986, 2931, 1753 (OC=O), 1726 (C=O), 1460, 1406, 1380, 1365, 1324, 1172, 1136, 1094, 1024 cm-1; 1H NMR (300 MHz, CDCl3 + CCl4): δ 4.17 and 4.13 (2 H, 2 × dq, J = 10.5 and 7.5 Hz, OCH2CH3), 3.70 (1 H, s, H-7), 2.40 and 1.97 (2 H, 2 × d, J = 18.5 Hz, H-9), 1.75-1.35 (6 H, m), 1.27 (3 H, t, J = 7.5 Hz, OCH2CH3), 1.24 (3 H, s), 1.21 (3 H, s), 1.07 (3 H, s) and 0.86 (3 H, s) [4 × tert-CH3]; 13C NMR (75 MHz, CDCl3 + CCl4): δ 210.8 (C, C=O), 169.6 (C, OC=O), 61.6 (CH, C-7), 60.6 (CH2, OCH2CH3), 53.6 (CH2, C-9), 51.2 (C, C-6), 40.5 (C, C-1), 37.4 (CH2) and 37.2 (CH2) [C-2 and C-4], 36.4 (C, C-5), 28.8 (CH3), 25.4 (CH3), 22.8 (CH3), 18.6 (CH2, C-3), 14.5 (CH3), 14.2 (CH3, OCH2CH3).

Ethyl (IR,6R,7R)-1,5,5,6-tetramethyl-8-methylene-bicyclo[4.3.0]nonane-7-carboxylate 20

To a magnetically stirred suspension of methyltriphenylphosphonium bromide (270 mg, 0.76 mmole) in dry benzene (0.4 mL) was added 1 M solution of potassium tert-amylate in tert-amyl alcohol (0.4 mL, 0.4 mmole) and the resulting yellow colour solution was stirred for 30 min at RT. To this solution of methylenetriphenylphosphorane was added the bicyclic keto ester 32 (60 mg, 0.225 mmole) in dry benzene (0.8 mL) and stirred for 12 hr at reflux temperature. The reaction-mixture was cooled, saturated aqueous NH4Cl solution (5 mL) was added and extracted with ether (3 × 5 mL). The combined ether extract was washed with brine and dried (Na2SO4). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished the thapsene ester 20 (28 mg, 47%) as oil7b. [α]D25 25: +23.6° (c 2.8, CHCl3); IR (neat): 2927, 1745 (OC=O), 1714, 1653, 1460, 1396, 1379, 1333, 1259, 1230, 1147, 1097, 1037, 881, 798 cm-1; 1H NMR (300 MHz, CDCl3 + CCl4): δ 4.83 (1 H, s) and 4.75 (1 H, s) [C=CH2], 4.10 and 4.02 (2 H, 2 × dq, J = 11.1 and 7.0 Hz, OCH2CH3), 3.71 (1 H, br s, H-7), 2.47 (1 H, dq, J = 16.5 and 3.0 Hz) and 1.91 (1 H, d, J = 16.5 Hz) [H-9], 1.65-1.10 (6 H, m), 1.21 (3 H, t, J = 7.0 Hz, OCH2CH3), 1.03 (6 H, s), 0.92 (3 H, s) and 0.76 (3 H, s) [4 × tert-CH3]. Further elution of the column with ethyl acetate-hexane (1:20 v/v) as eluent furnished the unreacted starting material 32 (31 mg, 52%).

Ethyl (IR,6R,7S)-1,5,5,6-tetramethylbicyclo[4.3.0]-nonane-[8.2']-spirooxirane-7-carboxylates 35

To a magnetically stirred solution of the ene ester 20 (26 mg, 0.1 mmole) in absolute ethanol (1 mL) was added magnesium monoperoxyphthalate hexahydrate (100 mg, 0.2 mmole) and stirred at RT for 36 hr. The solvent was evaporated under reduced pressure. 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 on a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent furnished the diastereomers: δ 4.05-3.90 (2 H, m, OCH2CH3), 3.36
(1R,2R,5R,6R,8R)-5-Ethoxy-1,8,12,12-tetramethyl-4-oxtetacyclo[6.4.0.0²⁶]dodecan-3-one 34 and ethyl (1R,6R,7R,8S)-8-formyl-1,5,5,6-tetramethylbicyclo[4.3.0]nonane-7-carboxylic acid 36

To a magnetically stirred solution of the epoxide 35 (22 mg, 0.08 mmole) in dry CH₂Cl₂ (4 mL) was added 3 drops of BF₃·Et₂O, and stirred for 2 hr at RT. The reaction was quenched with saturated aqueous NaHCO₃ (3 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 ethyl acetate-hexane (1:20 v/v) as eluent furnished the acetal 38 (8.3 mg, 38%) [α]D²⁵: -71.7° (c 1.66, CHCl₃); IR (neat): 2917, 2863, 1765 (γ-lactone), 1455, 1397, 1379, 1353, 1236, 1160, 1118, 1033, 966, 925, 803 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, δ CCl₄): δ 5.05 (1 H, s, H-5), 3.84 and 3.50 (2 H, 2 × dq, J = 9.0 and 7.0 Hz, OCH₂CH₃), 3.33 (1 H, d, J = 10.8 Hz, H-2), 2.82 (1 H, q, J = 9.9 Hz, H-6), 1.80-1.10 (8 H, m), 1.21 (3 H, t, J = 6.9 Hz, OCH₂CH₃), 1.08 (6 H, s), 0.97 (3 H, s) and 0.91 (3 H, s) [4 × tert-CH₃]; ¹⁳C NMR (75 MHz, CDCl₃, δ CCl₄): δ 176.1 (C, OC=O), 107.5 (CH, C-5), 64.7 (CH₂, OCH₂CH₂), 52.1 (C, C-1), 51.3 (CH, C-2), 47.1 (C, C-8), 45.7 (CH₂, C-7), 44.4 (CH₂, C-6), 38.7 (CH₂, C-9), 36.6 (CH₂, C-11), 36.0 (C, C-12), 30.6 (CH₃), 24.8 (CH₃), 23.0 (CH₃), 18.7 (CH₂, C-10), 15.2 (CH₃), 15.0 (CH₃). Further elution of the column with ethyl acetate-hexane (1:10 v/v) as eluent furnished the aldehyde ester 36 (7 mg, 32%) as oil. [α]D²⁵: +8.6° (c 1.4, CHCl₃); IR (neat): 2931, 2870, 2714 (OC=H), 1728 (C=O), 1460, 1397, 1379, 1348, 1174, 1096, 1035 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 9.68 (1 H, s, CHO), 4.15-3.95 (2 H, m, OCH₂CH₃), 3.47 (1 H, d, J = 9.6 Hz, H-7), 2.96 (1 H, tm, J = 10.0 Hz), 1.97 (1 H, t, J = 12.6 Hz), 1.75-1.00 (7 H, m), 1.23 (3 H, t, J = 7.2 Hz, OCH₂CH₃), 1.09 (6 H, s), 0.96 (3 H, s) and 0.86 (3 H, s) [4 × tert-CH₃]; ¹⁳C NMR (75 MHz, CDCl₃ + CCl₄): δ 200.5 (CH, CHO), 174.6 (C, OC=O), 60.0 (CH₂, OCH₂CH₃), 53.4 (C, C-6), 52.8 (CH, C-7), 48.5 (CH, C-8), 45.2 (C, C-1), 40.1 (CH₂, C-9), 37.5 (CH₂, C-2), 36.5 (CH₂, C-4), 36.2 (C, C-5), 28.6 (CH₃), 25.2 (CH₃), 23.0 (CH₃), 19.0 (CH₂, C-3), 14.0 (CH₃), 13.8 (CH₃).

(1R,2R,3S,6R,8R)-3-Hydroxy-1,8,12,12-tetramethyl-4-oxtetacyclo[6.4.0.0²⁶]dodecane (10,11-epoxy-thapsan-10-ol 14)

To a cold (-70°C, alcohol-liquid N₂ bath) magnetically stirred solution of the lactone 38 (5.2 mg, 0.022 mmole) in dry hexane (1 mL) was added a solution of DIBALH (1.0 M in hexane, 0.02 mL, 0.02 mmole)
mmole) and stirred for 1 hr and 15 min at -70°C. The reaction-mixture was warmed to RT, quenched with saturated aqueous NH₄Cl (5 mL) and extracted with ether (3 × 3 mL). The combined ether 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 (1:2 v/v) as eluent furnished the unreacted starting material 38 (1.2 mg, 23%). Further elution of the column with ethyl acetate-hexane (1:10 v/v) as eluent furnished the thapsane 14 (3.5 mg, 67%) as a white solid, which was recrystallized from hexane. m.p.: 85-87°C (lit. 85.5-87°C); [α]D²⁴: +40.0° (c 0.5, CHCl₃) [lit. for (-)-14: -47.0° (c 0.16, CHCl₃); IR (thin film): 3307 (OH), 2931, 2869, 1453, 1394, 1376, 1218, 1126, 1094, 1090, 1044, 982, 931 cm⁻¹; ¹H NMR (300 MHz, CDCl₃ + CCl₄): δ 5.51 (1 H, s, H-3), 4.12 (1 H, t, J = 8.1 Hz) and 3.59 (1 H, d, J = 8.1 Hz) [H-5], 2.95-2.75 (2 H, m, H-2 and H-6), 2.03 (1 H, br s, OH), 1.70-1.10 (8 H, m), 1.02 (3 H, s), 0.96 (3 H, s), 0.91 (3 H, s) and 0.83 (3 H, s) [4 × tert-CH₃]; ¹³C NMR (75 MHz, CDCl₃ + CCl₄): δ 101.1 (CH, C-3), 73.0 (CH₂, C-5), 58.2 (CH, C-2), 49.0 (CH₂, C-7), 48.5 (C) and 47.5 (C [C-1 and C-8]), 38.4 (CH, C-6), 38.0 (CH₂, C-9), 36.3 (CH₂, C-11), 36.0 (C, C-12), 28.5 (CH₃), 24.8 (CH₃), 22.8 (CH₃), 18.9 (CH₂, C-10), 13.2 (CH₃); MS: m/z (%) (C₁₃H₂₅O₂) 221 (M - OH, 35), 121 (31), 109 (59), 108 (100), 107 (60), 93 (48), 91 (31).

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References and Notes

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. Incidentally, this is same as that proposed by Rasmussen and coworkers. Grande M, Personal Communication.
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