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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[1]. Even though, thapsigargin and thapsigargicin were absent in *Thapsia villosa*, it contains a large number of sesquiterpenes belonging to guaianolides, germacranes, cadinenes and caryophyllenes, and in addition a new group of sesquiterpenes named as thapsanes, which are unique to *Thapsia villosa*. In 1984, Rasmussen and co-workers reported[2] isolation of the first member of this new group of sesquiterpenes, from the ethanolic extract of the roots of *Thapsia villosa* L, whose structure was established as the ester **1** from its spectral data and confirmed by single crystal X-ray analysis. Simultaneously (1985), Grande and co-workers[3,4] reported the isolation of the corresponding senecioate ester **2** from the benzene extract of the roots of *Thapsia villosa* L. var. *minor* (Hoff. and Link) Cout., along with five other hemiacetalic **3-7** and four nonacetalic **8-11** minor components, having the same carbon framework. In 1990, Christensen and co-workers have reported[5] the isolation of three more thapsanes, two nonacetalic **12** and **13**, and one hemiacetalic **14** from *Thapsia villosa* var. *minor* collected near Capo Espichel. The trivial name "*thapsane*" was suggested[3,4] for the carbon framework *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane **15** present in these compounds. Structures of all the thapsanes isolated so far are given in **Chart I**. The absolute configuration of the thapsanes was deduced from the analysis of the CD spectra of the compounds **16** containing the cyclohexanone part structure, which were obtained by degradation of the 3- and 5-acyloxythapsanes[6] **5** and **6**. Presence of a unique, sterically crowded structure containing 4-oxatricyclo[6.4.0.0^{2,6}]dodecane incorporating three contiguous quaternary carbon atoms and five to six chiral centers made thapsanes attractive synthetic targets[7]. 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[7h] 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

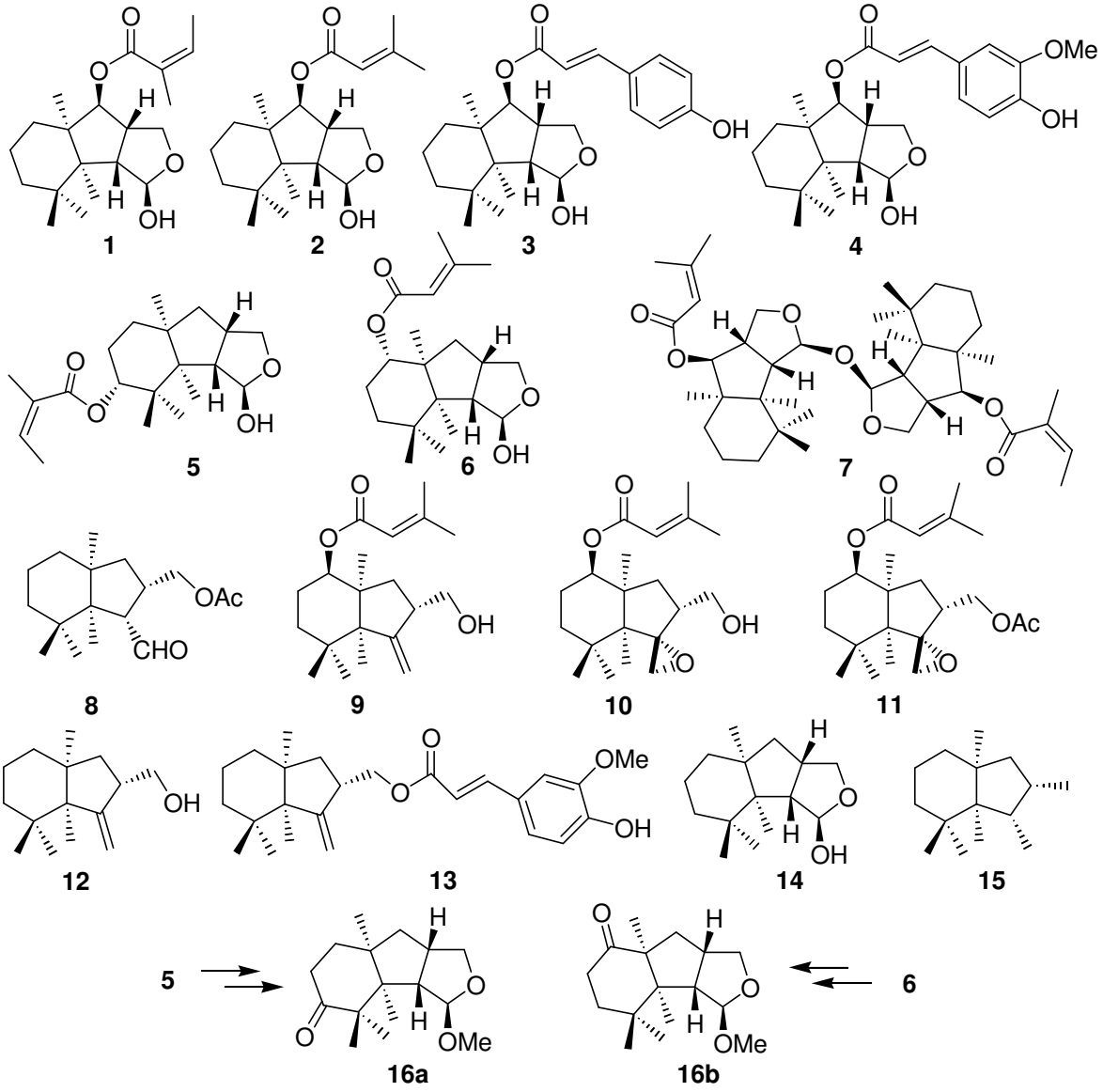
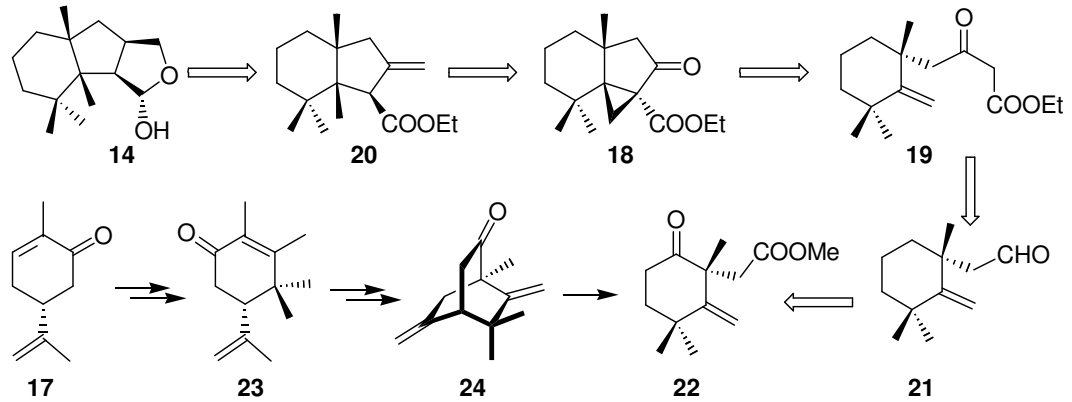


Chart I

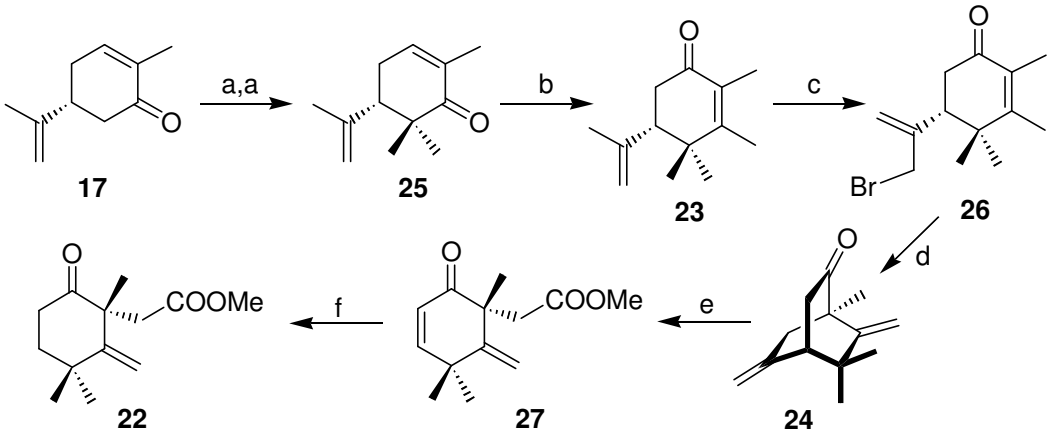


Scheme I

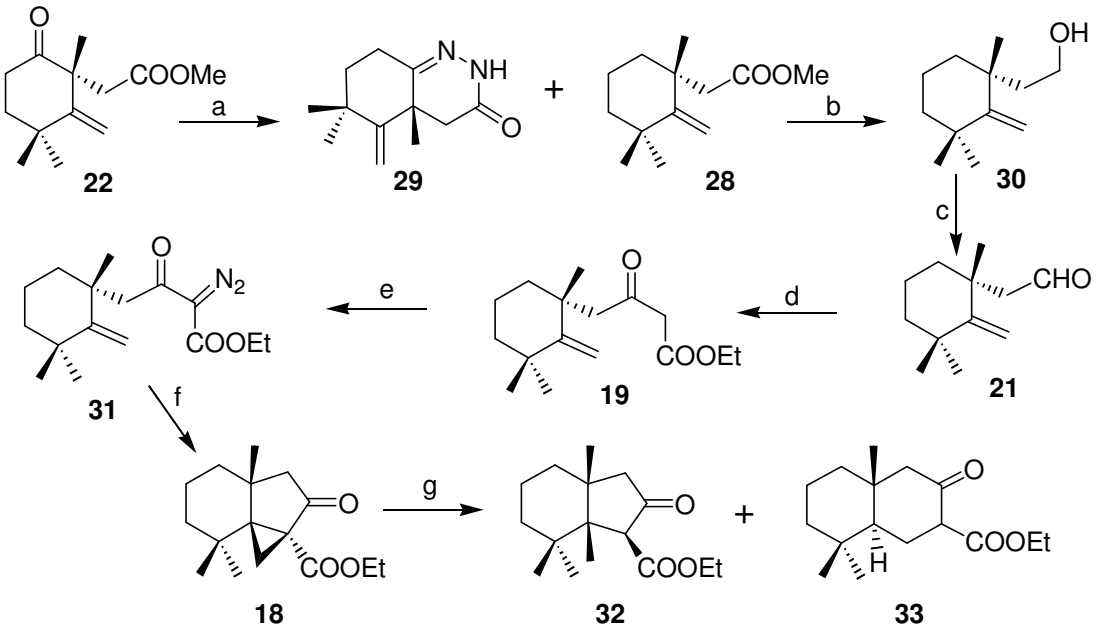
molecular cyclopropanation of the α-diazo-β-keto ester derived from the β-keto ester **19** could generate the tricyclic keto ester **18**, which could be further elaborated into the thapsane **14** *via* the thapsene ester **20**. It was contemplated that the aldehyde **21**, which could be obtained 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[7l].

To begin synthesis of the keto ester **22** was carried out as described in earlier literature[7l] (**Scheme II**). Carvone **17** has been converted[8] 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 manner[9]. Generation of the thermodynamic dienolate of the bromoenone **26** 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 **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**.

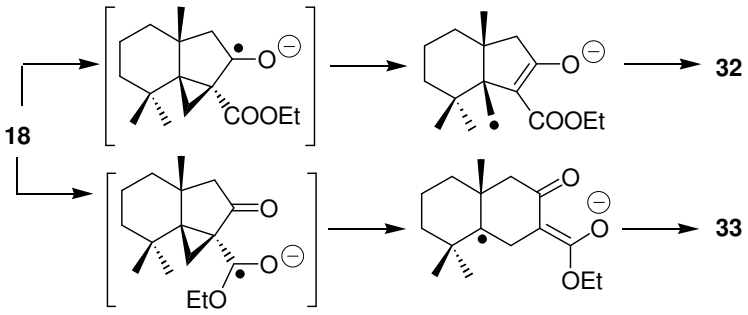
For the reductive deoxygenation of the keto ester **22**, Huang-Minlon modified Wolff-Kishner reduction was explored, **Scheme III**. Reaction of the keto ester **22** with hydrazine hydrate and potassium hydroxide in diethylene glycol at 180°C, followed by esterification of the resultant acid with diazomethane furnished the ester **28**, in 53% yield, along with varying amounts of the hexahydrocinnolinone **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 diazoacetate[12] 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 reaction[13] of the diazo compound **31** in benzene at RT furnished the tricyclic β-keto ester **18**, in 69% yield. Reductive cyclopropane ring cleavage[14] employing lithium in liquid ammonia at -33°C for 5 min, transformed the tricyclic keto ester **18** into a 3:5 mixture of the hydrindanone **32** and the decalinone **33**, in 86% yield, which were separated by column chromatography on



Scheme II — (a) LDA, THF, MeI; (b) i. MeLi, Et_2O; ii. PCC, silica gel, CH_2Cl_2; (c) NBS, CH_2Cl_2, MeOH; (d) KO^{t}Bu, ^{t}BuOH, THF; (e) i. O_3, CH_2Cl_2, MeOH; ii. Ac_2O, Et_3N, DMAP, C_6H_6; (f) H_2, 5% Pd/C, EtOAc



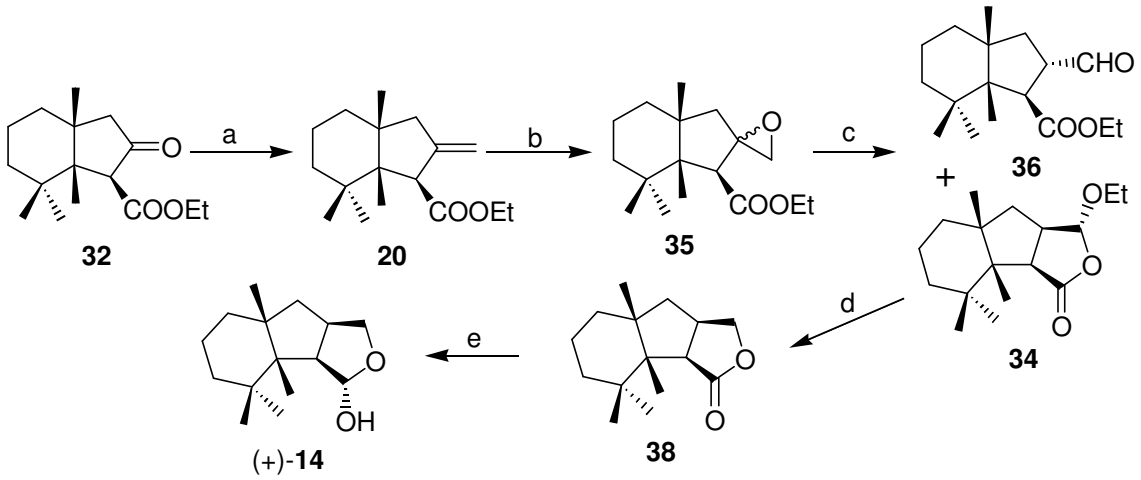
Scheme III — (a) i. $NH_2NH_2.H_2O$, KOH, digol; ii. CH_2N_2, Et_2O; (b) LAH, Et_2O; (c) PCC, silica gel, CH_2Cl_2; (d) $N_2CHCOOEt$, $SnCl_2.2H_2O$, CH_2Cl_2; (e) TsN_3, NEt_3, CH_3CN; (f) $Rh_2(OAc)_4$, C_6H_6; (g) Li, liq. NH_3, THF



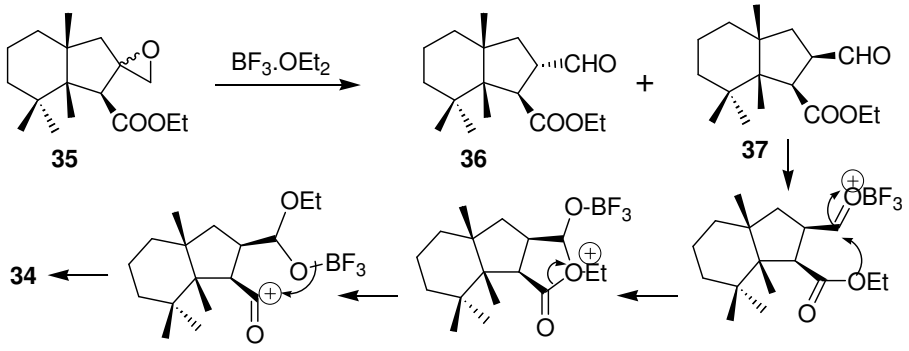
Scheme IV

silica gel. The formation of the two esters **32** and **33** can be explained[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[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[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



Scheme V — (a) $Ph_3P{=}CH_2$, C_6H_6; (b) MMPPA, EtOH; (c) $BF_3.Et_2O$, CH_2Cl_2; (d) Et_3SiH, CF_3COOH; (e) DIBALH, hexane



Scheme VI

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[16] of the ethoxy lactone **34** using a combination of trifluoroacetic acid and triethylsilane furnished the lactone **38**, m.p. 120-23°C (lit.[4] 123-25°C), $[\alpha]_D^{25}$: +43.3 (*c* 1, $CHCl_3$) [lit.[4] for (-)-**38**: -41 (*c* 1.4, $CHCl_3$)], a degradation product of a number of thapsanes, in 74% yield. The lactone **38** exhibited ^1H 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. 85-87°C (lit.[5] 85.5-87°C), $[\alpha]_D^{25}$: +40 (*c* 0.5, $CHCl_3$) [lit.[5] for (-)-**14**: -47 (*c* 0.16, $CHCl_3$)] in 87% yield, which exhibited the ^1H 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-[(1*R*)-1,3,3-trimethyl-2-methylenecyclohexyl]acetate 28 and (6*R*)-6,8,8-trimethyl-7-methylene-2,3-diazabicyclo[4.4.0]dec-1-en-4-one 29

A solution of the keto ester[71] **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 CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished a residue, which was esterified without further purification. An ice-cold ethereal diazomethane solution (excess, prepared from *N*-nitroso-*N*-methylurea, 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%), $[\alpha]_D^{26}$: -3.7° (*c* 3, $CHCl_3$); IR (neat): 2927, 1739 (OC=O), 1624 (C=C), 1463, 1436, 1323, 1202, 1133, 1014, 902 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 4.99 (1 H, s) and 4.89 (1 H, s) [C=CH_2], 3.61 (3 H, s, OCH_3), 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*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 172.1 (C, OC=O), 160.7 (C, C-2'), 108.7 (CH_2, C=*C*H_2), 51.0 (CH_3, OCH_3), 46.0 (CH_2, C-2), 40.8 (CH_2, C-6'), 38.91 (CH_2, C-4'), 38.86 (C, C-1'), 36.4 (C, C-3'), 32.5 (CH_3), 31.2 (CH_3), 29.7 (CH_3), 18.6 (CH_2, C-5'); MS: *m/z* (%) ($C_{13}H_{22}O_2$) 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, hexahydrocinnolinone **29** (102 mg, 22.2%) as a white solid, which was recrystallized from a mixture of CH_2Cl_2 and hexane. m.p.: 119-21°C; $[\alpha]_D^{23}$: -85.5° (*c* 2.0, $CHCl_3$); IR (thin film): 3225 (N-H), 2966, 1685 (HNC=O), 1619 (C=C), 1464, 1357, 1077, 920, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 8.59 (1 H, br s, NH), 5.10 (1 H, s) and 4.95 (1 H, s) [C=CH_2], 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*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 166.9 (C, C=O), 159.4 (C) and 158.2 (C) [C-1 and C-7], 109.1 (CH_2, C=*C*H_2), 41.2 (CH_2, C-5), 39.8 (C, C-6), 35.8 (C, C-8), 35.2 (CH_2, C-9), 26.9 (CH_2, C-10), 30.9 (CH_3), 30.1 (CH_3), 25.3 (CH_3); MS: *m/z* (%) 207 (M + 1, 30%), 206 (M^+, 100), 191 (72), 163 (60), 149 (43), 148 (46), 135 (36), 123 (29), 107 (44), 93 (39), 91 (39); Anal. Calcd. for $C_{12}H_{18}N_2O$. C, 69.87; H, 8.80; N, 13.58. Found: C, 70.22; H, 9.01; N, 13.90%.

2-[(1*R*)-1,3,3-Trimethyl-2-methylenecyclohexyl]-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 $LiAlH_4$ (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 $LiAlH_4$. 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 (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10 to 1:6 v/v) as eluent furnished the alcohol **30** (395 mg, 91%) as oil. $[\alpha]_D^{26}$: +32.5° (*c* 2.4, $CHCl_3$); IR (neat): 3333 (OH), 2926, 1623 (C=C), 1463, 1379, 1108, 1035, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.00 (1 H, s) and 4.85 (1 H, s) [C=CH_2], 3.70-3.50 (2 H, m, CH_2OH), 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*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 160.6 (C, C-2'), 108.8 (CH_2, C=CH_2), 60.4 (CH_2, C-1), 42.7 (CH_2), 41.5 (CH_2), 41.1 (CH_2), 38.6 (C, C-1'), 36.6 (C, C-3'), 32.7 (CH_3), 30.1 (2 C, CH_3), 18.6 (CH_2, C-5'); MS: *m/z* (%) ($C_{12}H_{22}O$) 182 (M^+, 8%), 181 (80), 179 (55), 138 (20), 123 (51), 121 (22), 109 (23), 95 (36), 85 (54), 83 (100), 81 (34).

2-[(1*R*)-1,3,3-Trimethyl-2-methylenecyclohexyl]-acetaldehyde 21

To a magnetically stirred solution of the alcohol **30** (450 mg, 2.47 mmole) in 3 mL of CH_2Cl_2 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 the column with more CH_2Cl_2. 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[7b]. $[\alpha]_D^{23}$: +3.75° (*c* 4.0, $CHCl_3$); IR (neat): 3101, 2928, 2735 (OC-H), 1720 (C=O), 1624 (C=C), 1466, 1381, 1103, 904 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 9.65 (1 H, t, *J* = 3.0 Hz, CHO), 5.09 (1 H, s) and 4.90 (1 H, s) [C=CH_2], 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*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 202.9 (CH, CHO), 159.4 (C, C-2'), 109.8 (CH_2, C=*C*H_2), 53.0 (CH_2, C-2), 41.0 (CH_2, C-6'), 40.3 (CH_2, C-4'), 38.6 (C, C-1'), 36.5 (C, C-3'), 32.4 (CH_3), 30.7 (CH_3), 30.3 (CH_3), 18.6 (CH_2, C-5').

Ethyl 4-[(1*R*)-1,3,3-trimethyl-2-methylenecyclohexyl]-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 CH_2Cl_2 (2 mL) was added $SnCl_2.2H_2O$ (50 mg, 0.22 mmole) portion wise over a period of 6 hr. After nitrogen evolution 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[7b]. $[\alpha]_D^{25}$: -10.0° (*c* 5.2, $CHCl_3$); 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, $CDCl_3$ + CCl_4): δ 5.00 (1 H, s) and 4.86 (1 H, s) [C=CH_2], 4.16 (2 H, q, *J* = 6.9 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 1.23 (3 H, s), 1.15 (3 H, s) and 1.14 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 200.8 (C, C-3), 166.8 (C, OC=O), 160.4 (C, C-2'), 108.8 (CH_2, C=*C*H_2), 61.0 (CH_2, O*C*H$_2$CH$_3$), 53.2 (CH_2, C-2), 51.3 (CH_2, C-4), 40.7 (CH_2, C-6'), 39.1 (C, C-1'), 38.7 (CH_2, C-4'), 36.3 (C, C-3'), 32.6 (CH_3), 31.3 (CH_3), 29.7 (CH_3), 18.5 (CH_2, C-5'), 14.3 (CH_3, OCH$_2$*C*H$_3$).

Ethyl 2-diazo-4-[(1*R*)-1,3,3-trimethyl-2-methylenecyclohexyl]-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=N), 1717 (OC=O), 1650 (C=O), 1464, 1372, 1299, 1200, 1170, 1117, 1088, 1030, 900, 813, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 4.98 (1 H, s) and 4.90 (1 H, s) [C=CH_2], 4.27 (2 H, q, *J* = 6.9 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 1.25 (3 H, s), 1.14 (3 H, s) and 1.13 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 190.8 (C, C-3), 161.2 (C) and 161.0 (C) [OC=O and C-2'], 108.4 (CH_2, C=*C*H_2), 61.0 (CH_2, O*C*H$_2$CH$_3$), 48.8 (CH_2, C-4), 40.6 (CH_2, C-6'), 39.8 (C, C-1'), 38.5 (CH_2, C-4'), 36.3 (C, C-3'), 32.6 (CH_3), 31.0 (CH_3), 29.6 (CH_3), 18.5 (CH_2, C-5'), 14.4 (CH_3, OCH$_2$*C*H$_3$).

Ethyl (1*R*,3*R*,6*R*)-6,10,10-trimethyl-4-oxotricyclo-[4.4.0.0^{1,3}]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 $Rh_2(OAc)_4$ 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 keto ester **18** (244 mg, 69%)[7b]. $[\alpha]_D^{24}$: -37.5° (*c* 1.2, $CHCl_3$); IR (thin film): 2931, 1720 (C=O), 1466, 1380, 1337, 1323, 1241, 1210, 1178, 1118, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 4.19 (2 H, q, *J* = 7.2 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 1.22 (3 H, s), 1.17 (3 H, s) and 0.64 (3 H, s) [3 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 206.8 (C, C=O), 168.0 (C, OC=O), 61.2 (CH_2, O*C*H$_2$CH$_3$), 54.4 (C, C-3), 49.9 (CH_2, C-5), 49.4 (C, C-1), 39.5 (CH_2) and 39.2 (CH_2) [C-7 and C-9], 38.7 (C, C-6), 33.6 (C, C-10), 28.3 (CH_3), 27.5 (CH_3), 23.2 (CH_3), 18.7 (CH_2) and 18.3 (CH_2) [C-2 and C-8], 14.2 (CH_3, OCH$_2$*C*H$_3$).

Ethyl (1*R*,6*R*,7*S*)-1,5,5,6-tetramethyl-8-oxobicyclo-[4.3.0]nonane-7-carboxylate 32 and ethyl (1*S*,6*R*)-

4-hydroxy-6,10,10-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 NH_4Cl. After evaporation of ammonia, the residue was taken in water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50 v/v) as eluent furnished the ester **33** (25 mg, 55%) as oil. $[\alpha]_D^{24}$: -51.6° (*c* 2.5, $CHCl_3$); IR (neat): 2927, 1716, 1656, 1617, 1466, 1401, 1365, 1292, 1261, 1235, 1225, 1172, 1069, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 12.05 (1 H, s, OH), 4.20 (2 H, q, *J* = 6.9 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 0.91 (9 H, s, 3 × *tert*-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 172.4 (C) and 170.7 (C) [C-4 and OC=O], 96.5 (C, C-3), 60.0 (CH_2, O*C*H$_2$CH$_3$), 48.9 (CH_2, C-5), 48.6 (CH, C-1), 42.8 (CH_2, C-2), 41.6 (CH_2, C-7), 33.2 (2 C, CH_3 and C), 33.0 (C, C-10), 21.7 (CH_3), 20.7 (CH_2, C-9), 19.6 (CH_3), 18.8 (CH_2, C-8), 14.6 (CH_3, OCH$_2$*C*H$_3$); MS: *m/z* (%) ($C_{16}H_{26}O_3$) 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]. $[\alpha]_D^{24}$: +70.0° (*c* 1.4, $CHCl_3$); 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, $CDCl_3$ + CCl_4): δ 4.17 and 4.13 (2 H, 2 × dq, *J* = 10.5 and 7.5 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 1.24 (3 H, s), 1.21 (3 H, s), 1.07 (3 H, s) and 0.86 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 210.8 (C, C=O), 169.6 (C, OC=O), 61.6 (CH, C-7), 60.6 (CH_2, O*C*H$_2$CH$_3$), 53.6 (CH_2, C-9), 51.2 (C, C-6), 40.5 (C, C-1), 37.4 (CH_2) and 37.2 (CH_2) [C-2 and C-4], 36.4 (C, C-5), 28.8 (CH_3), 25.4 (CH_3), 22.8 (CH_3), 18.6 (CH_2, C-3), 14.5 (CH_3), 14.2 (CH_3, OCH$_2$*C*H$_3$).

Ethyl (1*R*,6*R*,7*R*)-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 NH_4Cl solution (5 mL) was added and extracted with ether (3 × 5 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using hexane as eluent furnished the thapsene ester **20** (28 mg, 47%) as oil[7b]. $[\alpha]_D^{25}$: +23.6° (*c* 2.8, $CHCl_3$); 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, $CDCl_3$ + CCl_4): δ 4.83 (1 H, s) and 4.75 (1 H, s) [C=C*H*$_2$], 4.10 and 4.02 (2 H, 2 × dq, *J* = 11.1 and 7.0 Hz, OC*H*$_2$CH$_3$), 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, OCH$_2$C*H*$_3$), 1.03 (6 H, s), 0.92 (3 H, s) and 0.76 (3 H, s) [4 × *tert*-CH_3]. 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 (1*R*,6*R*,7*S*)-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 CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent furnished a 1:2 mixture of the epoxides **35** (22.5 mg, 83%) as oil[7b]. IR (neat): 2930, 2867, 1750 and 1736 (OC=O), 1458, 1379, 1336, 1172, 1097, 1035, 973 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4, 2:1 mixture of diastereomers): δ 4.05-3.90 (2 H, m, OC*H*$_2$CH$_3$), 3.36

(s) and 3.50 (s) [1 H, H-7], 2.55 and 2.48 (2 × d, *J* = 4.2 Hz) and, 2.70 and 2.61 (2 × d, *J* = 5.4 Hz) [2 H, H-3'], 2.26 (d, *J* = 14.1 Hz) and 2.06 (d, *J* = 14.1 Hz) [1 H, H-9A], 1.85 (td, *J* = 13.2 and 4.2 Hz) and 1.65 (td, *J* = 12.6 and 3.9 Hz) [1 H], 1.60-1.30 (6 H, m), 1.20-1.10 (3 H, m, OCH_2CH_3), 1.26 (s), 1.08 (s), 1.05 (s), 0.94 (s), 0.76 (s) and 0.73 (s) [12 H, 4 × CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4, 2:1 mixture of diastereomers): δ 173.0 and 169.4 (C, OC=O), 64.0 and 60.4 (C, C-8), 59.9 and 59.7 (CH_2, OCH_2CH_3), 54.3 and 51.7 (CH, C-7), 53.7 and 52.0 (C, C-6), 51.0 and 51.5 (CH_2, C-3'), 48.6 and 47.9 (CH_2, C-9), 44.0 and 43.6 (C, C-1), 37.9 and 37.7 (CH_2, C-2), 36.4 and 37.3 (CH_2, C-4), 36.5 and 36.2 (C, C-5), 28.7 and 29.2 (CH_3), 25.4 and 25.0 (CH_3), 22.9 (CH_3), 18.8 (CH_2, C-3), 14.7 and 14.4 (CH_3), 14.3 and 14.1 (CH_3).

(1*R*,2*R*,5*R*,6*R*,8*R*)-5-Ethoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-one 34 and ethyl (1*R*,6*R*,7*R*,8*S*)-8-formyl-1,5,5,6-tetramethylbicyclo[4.3.0]nonane-7-carboxylate 36

To a magnetically stirred solution of the epoxide **35** (22 mg, 0.08 mmole) in dry CH_2Cl_2 (4 mL) was added 3 drops of $BF_3.Et_2O$, and stirred for 2 hr at RT. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent furnished the acetal **34** (8.3 mg, 38%)[7b]. $[\alpha]_D^{25}$: -71.7° (*c* 1.66, $CHCl_3$); IR (neat): 2917, 2863, 1765 (γ-lactone), 1455, 1397, 1379, 1353, 1263, 1160, 1118, 1033, 966, 925, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.05 (1 H, s, H-5), 3.84 and 3.50 (2 H, 2 × dq, *J* = 9.0 and 7.0 Hz, OCH_2CH_3), 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, OCH_2CH_3), 1.08 (6 H, s), 0.97 (3 H, s) and 0.91 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 176.1 (C, OC=O), 107.5 (CH, C-5), 64.7 (CH_2, OCH_2CH_3), 52.1 (C, C-1), 51.3 (CH, C-2), 47.1 (C, C-8), 45.7 (CH_2, C-7), 44.4 (CH, C-6), 38.7 (CH_2, C-9), 36.6 (CH_2, C-11), 36.0 (C, C-12), 30.6 (CH_3), 24.8 (CH_3), 23.0 (CH_3), 18.7 (CH_2, C-10), 15.2 (CH_3), 15.0 (CH_3). 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. $[\alpha]_D^{25}$: +8.6° (*c* 1.4, $CHCl_3$); IR (neat): 2931, 2870, 2714 (OC-H), 1728 (C=O), 1460, 1397, 1379, 1348, 1174, 1096, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 9.68 (1 H, s, CHO), 4.15-3.95 (2 H, m, OCH_2CH_3), 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, OCH_2CH_3), 1.09 (6 H, s), 0.96 (3 H, s) and 0.86 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 200.5 (CH, CHO), 174.6 (C, OC=O), 60.0 (CH_2, OCH_2CH_3), 53.4 (C, C-6), 52.8 (CH, C-7), 48.5 (CH, C-8), 45.2 (C, C-1), 40.1 (CH_2, C-9), 37.5 (CH_2, C-2), 36.5 (CH_2, C-4), 36.2 (C, C-5), 28.6 (CH_3), 25.2 (CH_3), 23.0 (CH_3), 19.0 (CH_2, C-3), 14.0 (CH_3), 13.8 (CH_3).

(1*R*,2*R*,6*R*,8*R*)-1,8,12,12-Tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-one 38

To a magnetically stirred solution of the acetal **34** (8.3 mg, 0.03 mmole) in trifluoroacetic acid (1 mL) was added triethylsilane (0.01 mL, 0.06 mmole) and refluxed for 5 hr. Trifluoroacetic acid was removed under reduced pressure, the residue was taken in water (5 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 v/v) as eluent furnished the lactone **38** (5.2 mg, 74.3%) as a white solid, which was recrystallized from hexane. m.p.: 120-23°C (lit[4]. 123-25°C); $[\alpha]_D^{25}$: +43.3° (*c* 1, $CHCl_3$) [lit[4]. for (-)-**38**: -41° (*c* 1.4, $CHCl_3$)]; IR (thin film): 2984, 2906, 1764 (γ-lactone), 1478, 1453, 1398, 1379, 1178, 1101, 1080, 1021, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 4.39 (1 H, t, *J* = 9.0 Hz) and 3.90 (1 H, dd, *J* = 9.0 and 5.1 Hz) [H-5], 3.25 (1 H, d, *J* = 11.7 Hz, H-2), 3.20-3.00 (1 H, m, H-6), 1.75-1.20 (8 H, m), 1.09 (6 H, s), 0.98 (3 H, s) and 0.97 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 176.9 (C, C-3), 72.7 (CH_2, C-5), 52.2 (C, C-1), 50.8 (CH, C-2), 49.4 (CH_2, C-7), 47.8 (C, C-8), 38.7 (CH_2, C-9), 36.9 (CH_2, C-11), 36.1 (CH, C-6), 35.9 (C, C-12), 30.6 (CH_3), 24.6 (CH_3), 22.8 (CH_3), 18.6 (CH_2, C-10), 15.0 (CH_3).

(1*R*,2*R*,3*S*,6*R*,8*R*)-3-Hydroxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecane (10,11-epoxythapsan-10-ol 14)

To a cold (-70°C, alcohol-liquid N_2 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) and stirred for 1 hr and 15 min at -70°C. The reaction-mixture was warmed to RT, quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ether (3 × 3 mL). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 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[5]. 85.5-87°C); $[\alpha]_D^{24}$: +40.0° (*c* 0.5, $CHCl_3$) [lit[5]. for (-)-**14**: -47.0° (*c* 0.16, $CHCl_3$)]; IR (thin film): 3307 (OH), 2931, 2869, 1453, 1394, 1376, 1218, 1126, 1094, 1090, 1044, 982, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 5.31 (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*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ 101.1 (CH, C-3), 73.0 (CH_2, C-5), 58.2 (CH, C-2), 49.0 (CH_2, C-7), 48.5 (C) and 47.5 (C) [C-1 and C-8], 38.4 (CH, C-6), 38.0 (CH_2, C-9), 36.3 (CH_2, C-11), 36.0 (C, C-12), 28.5 (CH_3), 24.8 (CH_3), 22.8 (CH_3), 18.9 (CH_2, C-10), 13.2 (CH_3); MS: *m/z* (%) ($C_{15}H_{26}O_2$) 221 (M - OH, 35), 121 (31), 109 (59), 108 (100), 107 (60), 93 (48), 91 (31).

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