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Enantiospecific total synthesis of *ent*-5-senecioyloxy-10,11-epoxythapsan-10-ol

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Enantiospecific total synthesis of optical antipode of the sesquiterpene 5-senecioyloxy-10,11-epoxythapsan-10-ol has been described. (*R*)-Carvone has been employed as the chiral starting material and a combination of intramolecular alkyation 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: *Thapsia*, thapsane, sesquiterpene, enantiospecific

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]. As a part of ongoing interest in the synthesis of sesquiterpenes, enantiospecific approaches to thapsanes have been initiated starting from the readily and abundantly available monoterpene (*R*)-carvone **17**. Earlier, we have described[7h,m] the first enantiospecific synthesis of the hemiacetalic thapsane **14**, which also established the absolute configuration of thapsanes. In continuation, herein is described the details[7i] of the first total synthesis of the optical antipode of 5-senecioyloxy-10,11-epoxythapsan-10-ol **6**.

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

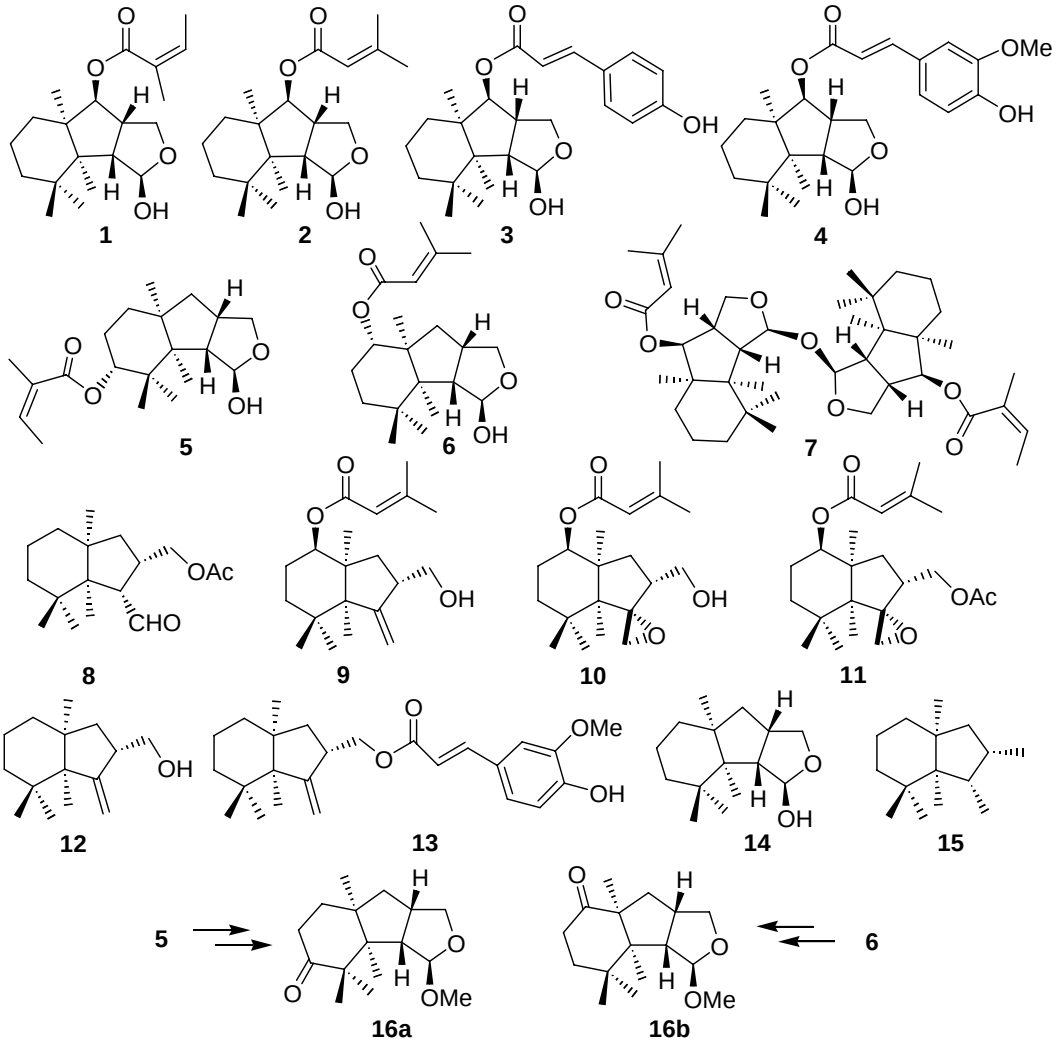
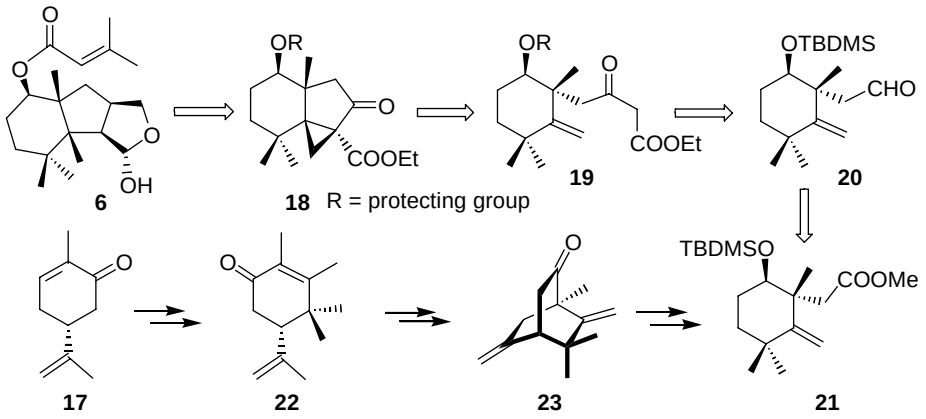


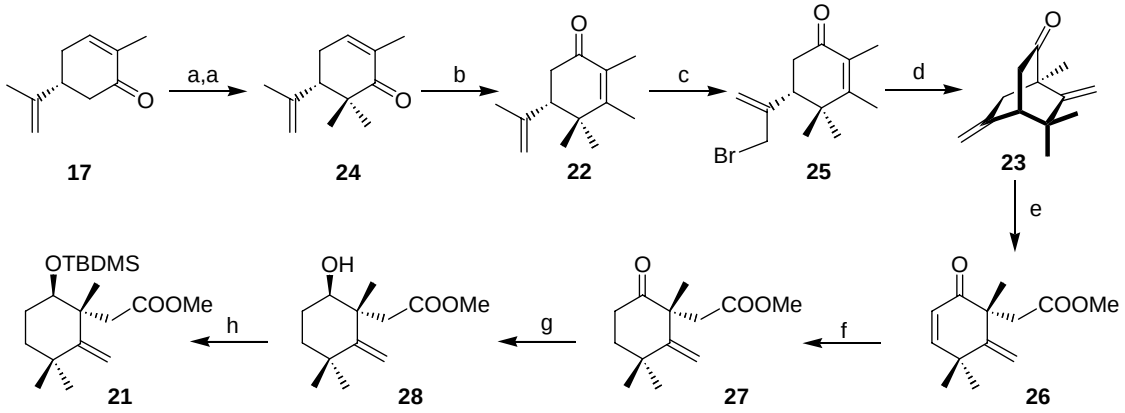
Chart I

three contiguous quarternary carbon atoms (C-1, C-2 and C-6). The retrosynthesis of thapsane **6** (**Scheme I**) identified the tricyclic keto ester **18** as the key intermediate. It was anticipated that intramolecular 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 thapsane **6**. It was contemplated that the aldehyde **20**, which could be obtained from the ester **21**, would serve as an ideal precursor for the enantiospecific generation of the β-keto ester **19**. Synthesis of the ester **21** from (*R*)-carvone **17**, *via* the trimethylcarvone **22** and bicyclo[2.2.2]octanone **23**, has already been reported earlier[7l].

To begin, synthesis of the ester **21** was carried out as described in earlier literature[7l] (**Scheme II**). Carvone **17** has been converted[8] into the trimethylcarvone **22** *via* sequential kinetic alkylation followed by alkylative 1,3-enone transposition of 6,6-dimethylcarvone **24**. Reaction of trimethylcarvone **22** with *N*-bromosuccinimide (NBS) in methanol-methylene chloride medium furnished the allyl bromide **25** in 90% yield in a highly regioselective manner[9]. Generation of the thermodynamic dienolate of the bromoenone **25** 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 **23**. Controlled ozonolysis of the bicyclic ketone **23** 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 **26** *via* the Criegee fragmentation[11]. Regioselective hydrogenation using 5% palladium on



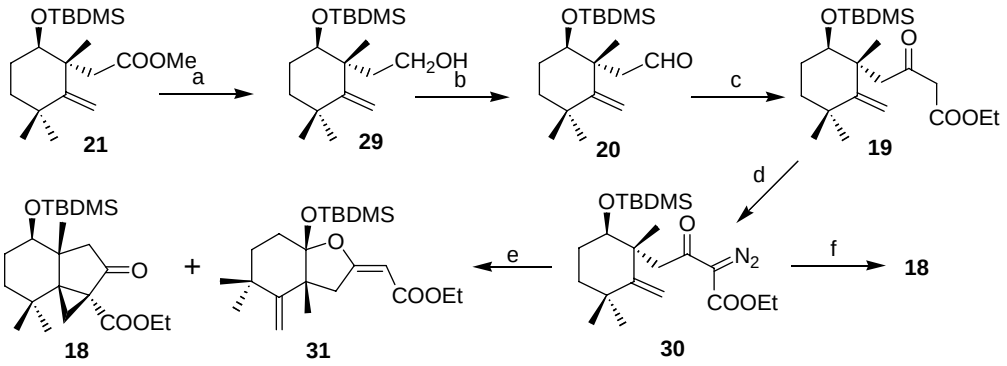
Scheme I



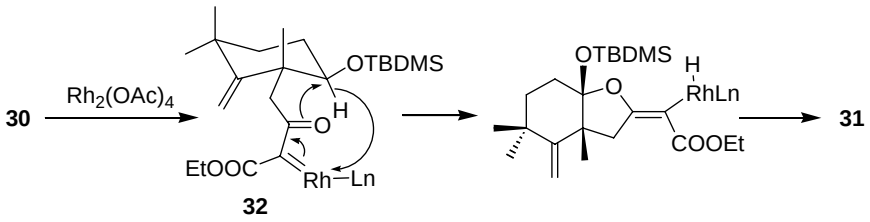
Scheme II — (a) LDA, THF, MeI; (b) i. MeLi, Et_2O; ii. PCC, silica gel, CH_2Cl_2; (c) NBS, CH_2Cl_2, MeOH; (d) KO^tBu, ^tBuOH, THF; (e) i. O_3, CH_2Cl_2, MeOH; ii. Ac_2O, Et_3N, DMAP, C_6H_6; (f) H_2, 5% Pd/C, EtOAc; (g) i. NaOH, MeOH, H_2O; ii. $NaBH_4$, THF; iii. CH_2N_2, Et_2O; (h) TBDMSCl, DMAP, DMF.

carbon as the catalyst in ethyl acetate at one atmospheric pressure of hydrogen (balloon) transformed the enone **26** into the saturated ketone **27**. Hydrolysis of the keto ester **27** with 5% sodium hydroxide in refluxing aqueous methanol followed by treatment of the resultant keto acid with sodium borohydride in THF generated hydroxy ester, which on esterification furnished the hydroxy ester **28** in 70% yield. Treatment of the hydroxy ester **28** with *tert*-butyldimethylsilyl chloride and DMAP in DMF generated the TBDMS ether **21** in 95% yield.

Conversion of the ester **21** into the tricyclic β-keto ester **18** was then addressed (**Scheme III**). Thus, reduction of the ester **21** with LAH at RT furnished the alcohol **29**, m.p. 68-70°C, in 91% yield, which on oxidation with PCC and silica gel in methylene chloride at RT for 3 hr furnished the aldehyde **20** in 90% yield. Reaction of the aldehyde **20** with ethyl diazoacetate in methylene chloride in the presence of a catalytic amount of stannous chloride[12] furnished the β-keto ester **19** in 92% yield. Diazo transfer reaction with tosyl azide and triethylamine in acetonitrile converted the β-keto ester **19** into the α-diazo-β-keto ester **30** in 90% yield. Rhodium acetate catalyzed decomposition[13] of the diazo compound **30** in benzene at RT furnished an ~5:1 mixture of the tricyclic β-keto ester **18** and the by-product **31**, in 54% yield, which were separated by column chromatography over silica gel. The structure of the tricyclic keto ester **18** rests secured from its spectral data. The structure of the by-product **31** was deduced from its spectral data. Presence of a fragment ion at *m/z* 379 (M-Me) in the mass spectrum indicated that the by-product **31** is isomeric with the tricyclic compound **18**. Presence of an absorption band 891 cm^{-1} in the IR spectrum, two singlets at δ 5.06 and 5.00 in the ^1H NMR spectrum, and a quaternary carbon at δ



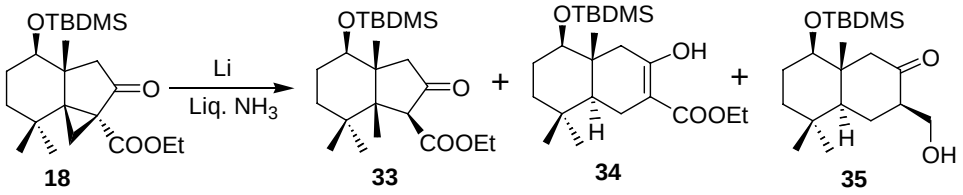
Scheme III — (a) LAH, Et_2O; (b) PCC, silica gel, CH_2Cl_2; (c) $N_2CHCOOEt$, $SnCl_2$, CH_2Cl_2; (d) TsN_3, NEt_3, CH_3CN; (e) $Rh_2(OAc)_4$, C_6H_6; (f) Cu, $CuSO_4$, *c*-C_6H_{12}.



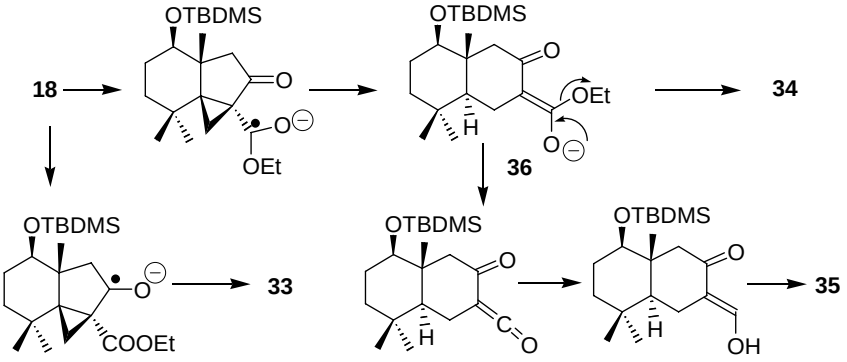
Scheme IV

157.8 and a methylene at δ 110.1 ppm in the ^{13}C NMR spectrum revealed that the exomethylene group is present in the molecule, and absence of the resonance due to the proton attached to the carbon bearing siloxy group indicated that the product might be derived from the insertion of the intermediate rhodium carbenoid into an aliphatic C-H bond. However, absence of a signal due to the ketone carbon in the ^{13}C NMR spectrum ruled out direct insertion of the rhodium carbenoid in any CH bond. Presence of an up-field olefinic proton at δ 4.72 in the ^1H NMR spectrum and an up-field methine carbon at δ 89.2 in the ^{13}C NMR spectrum due to the enol ether group and presence of a quaternary carbon at δ 112.6 due to a ketal carbon revealed the structure of the product **31**. The formation of the by-product **31** can be rationalized as depicted in **Scheme IV**. The rhodium carbenoid **32**, generated by the reaction of the diazo compound **30** with rhodium acetate, inserts into the δ C-H bond through the oxygen atom. Even though there is no precedence in the literature on the C-H insertion reaction of this type with α-diazo-β-keto esters, recently a few examples of similar kind of insertion reaction with α-diazo ketones appeared in the literature[14].

In order to suppress the formation of the by-product **31**, copper-copper sulfate mediated reaction was explored[13]. Anhydrous copper sulfate-copper catalyzed decomposition of the α-diazo-β-keto ester **30** in refluxing cyclohexane, under irradiation with tungsten light, resulted in the formation of the tricyclic keto ester **18** in a stereospecific manner, in 59% yield. Reductive cleavage[15] of the cyclopropane ring (**Scheme V)**, in the tricyclic keto ester **18** employing lithium in liquid ammonia at -33°C furnished a 3:4 mixture of the ester **33** and the bicyclic keto ester **34**, m.p. 85-87°C, in 78% yield, along with a small amount of the keto alcohol **35**, which were separated by column chromatography over silica gel. The structure of the bicyclic keto ester **33** rests secured from its spectral data. The structures of the ester **34** and the keto alcohol **35** were also established from their spectral data. The formation of esters **33** and **34** can be explained *via* transfer of the electron to ketone and ester carbonyl groups, respectively, followed by cleavage of the respective cyclopropane bond which has better overlap with the carbonyl group (**Scheme VI**, Ref 15). Formation of the keto alcohol **35** can be rationalized *via* elimination of the ethoxy group in the intermediate **36** followed by further reduction, analogous to the reduction of α,β-unsaturated esters to primary alcohols[16].

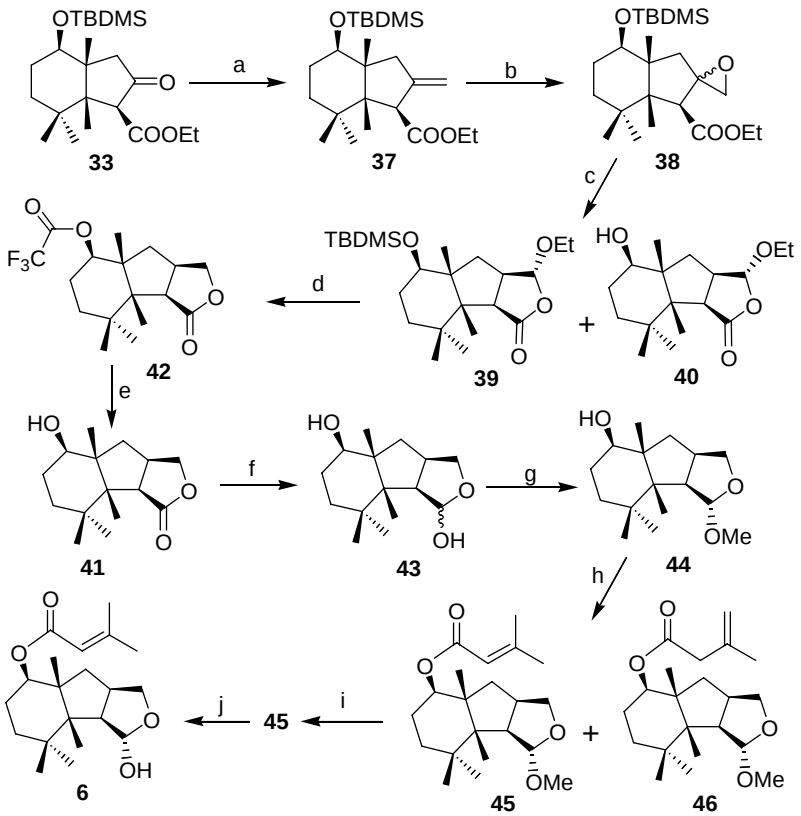


Scheme V



Scheme VI

Thereafter, attention was focused on the conversion of the keto ester **33** into the thapsane **6** (**Scheme VII**). Accordingly, Wittig olefination of the keto ester **33** with methylenetriphenylphosphorane in refluxing benzene for 12 hr furnished the ene ester **37** in 99% yield. Reaction of the ene ester **37** with MCPBA in methylene chloride at RT for 24 hr furnished a 2:1 epimeric mixture of the epoxide **38** in 80% yield, which were separated by silica gel column chromatography. The structures of the epoxides **38** were established from their spectral data. The ^{1}H and ^{13}C NMR spectra of the two epoxides **38** were very similar, confirming their epimeric nature. Treatment of either isomer of the epoxide **38** with a catalytic amount of boron trifluoride etherate in methylene chloride at RT furnished a 5:4 mixture of the acetal **39** and the desilylated acetal **40** in 70% yield, which were separated by column chromatography over silica gel. The ionic hydrogenation[17] of the acetal **39** with a combination of trifluoroacetic acid (TFA) and triethylsilane, contrary to the expected hydroxy lactone **41**, furnished the trifluoroacetate **42**, m.p. 100-102°C, in 67% yield. In a similar manner, reaction of the hydroxy acetal **40** with triethylsilane in refluxing TFA also generated the trifluoroacetate **42** in 71% yield. Presence of the molecular ion at *m/z* 348 ($C_{17}H_{23}F_3O_4$) in the mass spectrum and presence of absorption band at 1776 cm^{-1} due to the γ-lactone moiety and $OCOCF_3$ group, and absence of absorption due to a hydroxy group in the IR spectrum and absence of resonances due to the TBDMS and ethoxy groups in the ^{1}H and ^{13}C NMR spectra revealed the formation of the trifluoroacetate **42**. In the ^{1}H NMR spectrum presence of a doublet of doublet at δ 4.99 due to the proton attached to the carbon bearing the trifluoroacetoxy group, a triplet at 4.44 and a doublet of doublet at 3.96 due to the C-5 methylene protons and four singlets at δ 1.17, 1.15, 1.05 and 1.04 due to four tertiary methyl groups established the structure of the trifluoroacetate **42**. The ^{13}C NMR spectrum exhibited a quaternary carbon at δ 176.8 due to the γ-lactone carbonyl carbon, a methine at 80.3 due to the carbon bearing the trifluoroacetoxy group, a methylene at 72.7 (C-5), three quaternary carbons at δ 54.4, 52.6 and 35.9, two methines at 50.7 and 35.6, three methylenes at 43.8, 36.3 and 23.6, four methyl carbons at 30.2, 24.5, 16.0 and 15.1, and in particular a quartet at 157.5 ($^{2}J_{CF}$ = 42 Hz) due to the carbonyl carbon of the trifluoroacetate and a quartet at δ 114.5 ($^{1}J_{CF}$ = 284 Hz) due to the CF_3 group, confirming the structure of the trifluoroacetate **42**. Formation of the trifluoroacetate **42** from the acetal **39** can be explained by the hydrolysis of the TBDMS group followed by esterification of the secondary alcohol group in **41** with trifluoroacetic acid under the reaction conditions. Hydrolysis of the



Scheme VII — (a) $Ph_3P{=}CH_2$, C_6H_6; (b) *m*-CPBA, CH_2Cl_2; (c) $BF_3.Et_2O$, CH_2Cl_2; (d) Et_3SiH, CF_3CO_2H; (e) K_2CO_3, MeOH; (f) DIBAL-H, PhMe; (g) MeOH, *p*-TSA, CH_2Cl_2; (h) DCC, DMAP, $Me_2C{=}CHCO_2H$, PhMe; (i) DBU, CH_2Cl_2; (j) HCl, aq. THF.

trifluoroacetate moiety in **42** with potassium carbonate in methanol at RT furnished the hydroxy lactone **41**, m.p. 177-79°C (lit. 184-86°C), in 95% yield. For the conversion of the hydroxy lactone **41** into the thapsane **6**, reduction of the lactone to the lactol and esterification of the secondary alcohol group with senecioic acid needs to be carried out. To overcome the regiochemical problems, reduction of the lactone-protection as the acetal-esterification of the secondary alcohol and hydrolysis of the acetal sequence was conceived. Accordingly, treatment of the hydroxy lactone (+)-**41** with DIBALH in toluene generated an ~1:1 epimeric mixture of the lactols **43** in 89% yield, which on treatment with a catalytic amount of *p*-TSA in methanol at RT, as expected, resulted in the formation of a single epimer of the methyl acetal **44**, m.p. 110-12°C (lit.[4] 112-14°C), in 84% yield, whose structure was delineated from its spectral data. For the esterification of the secondary alcohol group in the methyl acetal **44** a *N*,*N*′-dicyclohexylcarbodiimide (DCC) mediated coupling with senecioic acid was explored. Treatment of the hydroxy acetal **44** with 3-methylbut-2-enoic acid and DCC in the presence of a catalytic amount of DMAP furnished a 5:1 mixture of the ester **45** and the deconjugated ester **46**, which on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride at RT furnished the senecioate ester **45** in quantitative yield. Finally, the acetal moiety in the methyl acetal **45** was hydrolyzed with 3 *N* aqueous HCl and THF at RT to furnish the thapsane (+)-**6**, $[\alpha]_D^{23}$ +37.3° (c 1.1, $CHCl_3$) [lit.[4] for (-)-**6** -35.7° (c 4.7, $CHCl_3$)], in 96% yield, whose structure was established from its spectral data. It was confirmed by comparison of the ^{1}H NMR spectral data of the synthetic thapsane (+)-**6** with that of the natural product (-)-**6**. The IR spectra of the compounds hydroxy lactone **43**, hydroxy methyl acetal **44**, methyl acetal **45** and thapsane **6** were found to be identical with those of the authentic samples. The sign of the optical rotation of the synthetic thapsane (+)-**6** was opposite to that of the natural thapsane (-)-**6**, establishing the absolute configuration of the natural thapsane.

In conclusion, the first enantiospecific total synthesis of the optical antipode of the natural

hemiacetalic thapsane **6** has been accomplished. An intramolecular alkylation and regioselective Criegee fragmentation sequence has been employed for the enatiospecific transfer of the chiral 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

2-[(1*R*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]ethanol 29. To a magnetically stirred, cold (0°C) solution of the ester **21** (500 mg, 1.47 mmoles) in anhydrous ether (3 mL) was added $LiAlH_4$ (80 mg, 2.11 mmoles) and the reaction-mixture was stirred at RT for 2 hr. Ethyl acetate (1 mL) was added to the reaction-mixture to consume the excess $LiAlH_4$. The reaction was then quenched with water (4 mL) and extracted with ether (3 × 5 mL). The combined ether extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the product over a silica gel column using ethyl acetate-hexane (1:6) as eluent furnished the alcohol **29** (420 mg, 91.5%) as a white solid, which was recrystallised from hexanes. m.p. 68-70°C; $[\alpha]_D^{26}$: -10.9° (*c* 1.1, $CHCl_3$); IR (thin film): 3304, 2954, 2857, 1624, 1463, 1362, 1254, 1130, 1085, 1052, 1017, 994, 938, 898, 836, 772, 672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.05 (1 H, s) and 4.87 (1 H, s) [C=CH_2], 3.70-3.54 (2 H, m, C*H*$_2$OH), 3.51 (1 H, dd, *J* = 6.4 and 2.7 Hz, H-2'), 2.05-1.85 (2 H, m), 1.80-1.50 (3 H, m), 1.35-1.15 (2 H, m), 1.14 (3 H, s), 1.13 (3 H, s) and 1.10 (3 H, s) [3 × *tert*-CH_3], 0.88 [9 H, s, C$(CH_3)_3$], 0.04 [6 H, s, Si$(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 159.1 (C, C-6'), 110.1 (CH_2, C=*C*H_2), 75.9 (CH, C-2'), 59.9 (CH_2, CH_2OH), 44.5 (C, C-1'), 40.7 (CH_2, C-2), 36.0 (C, C-5'), 35.7 (CH_2, C-4'), 32.6 (CH_3), 31.3 (CH_3), 26.7 (CH_2, C-3'), 26.0 [3 C, CH_3, C(*C*H_3)$_3$], 25.6 (CH_3), 18.3 [C, *C*$(CH_3)_3$], -3.8 (CH_3) and -4.7 (CH_3) [Si$(CH_3)_2$]; MS: *m/z* (%) 312 (M^+, 1), 295 (4), 171 (31), 163 (51), 137 (27), 135 (34), 121 (49), 107 (79), 105 (29), 95 (29), 93 (32). Anal. For $C_{18}H_{36}O_2Si$, Calcd: C, 69.17; H, 11.61. Found: C, 69.60; H, 11.83%.

2-[(1*R*,2*R*)-2-(*tert*-Butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]acetaldehyde 20. To a magnetically stirred solution of the alcohol **29** (285 mg, 0.91 mmoles) in 2 mL of CH_2Cl_2 was added a mixture of PCC (400 mg, 1.86 mmoles) and silica gel (400 mg). The reaction-mixture was stirred at RT for 3 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 over a silica gel column using ethyl acetate-hexane (1:30) as eluent furnished the aldehyde **20** (255 mg, 90%) as oil. $[\alpha]_D^{24}$: -8.5° (*c* 4.0, $CHCl_3$); IR (neat): 3100, 2954, 2857, 2737, 1720, 1624, 1471, 1361, 1253, 1101, 1083, 1007, 887, 837, 774, 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.68 (1 H, br s, CHO), 5.09 (1 H, s) and 4.88 (1 H, s) [C=CH_2], 3.70 (1 H, t, *J* = 6.6 Hz, H-2'), 2.65 (1 H, dd, *J* = 16.5 and 2.1 Hz) and 2.47 (1 H, dd, *J* = 16.5 and 3.0 Hz) [H-2], 1.82-1.72 (2 H, m), 1.61 (1 H, dt, *J* = 13.5 and 5.4 Hz), 1.35 (1 H, dt, *J* = 13.5 and 6.9 Hz), 1.20 (3 H, s), 1.16 (3 H, s) and 1.13 (3 H, s) [3 × *tert*-CH_3], 0.89 [9 H, s, C$(CH_3)_3$], 0.06 (3 H, s) and 0.02 (3 H, s) [Si$(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.9 (CH, CHO), 159.4 (C, C-6'), 110.8 (CH_2, C=*C*H_2), 74.9 (CH, C-2'), 50.8 (CH_2, C-2), 44.9 (C, C-1'), 36.7 (CH_2, C-4'), 36.0 (C, C-5'), 31.8 (CH_3), 31.5 (CH_3), 27.2 (CH_2, C-3'), 26.0 [3 C, CH_3, C$(CH_3)_3$], 24.8 (CH_3), 18.2 [C, *C*$(CH_3)_3$], -3.7 (CH_3) and -4.7 (CH_3) [Si$(CH_3)_2$].

Ethyl 4-[(1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]-3-oxobutanoate 19. To a magnetically stirred solution of the aldehyde **20** (255 mg, 0.82 mmole) and ethyl diazoacetate (0.13 mL, 1.23 mmole) in CH_2Cl_2 (1 mL) was added $SnCl_2.2H_2O$ (20 mg, 0.089 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) as eluent to furnish the β-keto ester **19** (299 mg, 92%) as oil. $[\alpha]_D^{26}$: -34.0° (*c* 1.0, $CHCl_3$); IR (neat): 2954, 1747, 1720, 1625, 1468, 1365, 1307, 1253, 1161, 1098, 1074, 889, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.92 (1 H, s) and 4.72 (1 H, s) [C=CH_2], 4.22-4.10 (3 H, m, H-2' and OC*H*$_2$CH$_3$), 3.32 (2 H, s, H-2), 2.94 and 2.81 (2 H, AB q, *J* = 18.2 Hz, H-4), 1.80-1.60 (2 H, m), 1.51-1.45 (2 H, m), 1.28 (3 H, t, *J* = 7.4 Hz, OCH$_2$C*H*$_3$), 1.13 (3 H, s), 1.12 (3 H, s) and 1.09 (3 H, s) [3 × *tert*-CH_3], 0.88 [9 H, s, C$(CH_3)_3$], 0.04 (3 H, s) and -0.02 (3H, s) [Si$(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 200.6 (C, C=O), 167.0 (C, OC=O), 160.3 (C, C-6'), 108.1 (CH_2, C=*C*H_2), 73.3 (CH, C-2'), 61.1 (CH_2, O*C*H$_2$CH$_3$), 51.0 (CH_2, C-2), 50.3 (CH_2, C-4), 45.4 (C, C-1'), 36.7 (CH_2, C-4'), 35.8 (C, C-5'),

32.1 (CH_3), 32.0 (CH_3), 27.3 (CH_2, C-3'), 26.0 [3 C, CH_3, C(CH_3)$_3$], 25.0 (CH_3), 18.2 [C, $C(CH_3)_3$], 14.2 (CH_3, OCH_2CH_3), -3.8 (CH_3) and -4.9 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) ($C_{22}H_{40}O_4Si$) 398 (M^++2, 13), 380 (28), 340 (100), 267 (68), 248 (62), 187 (69), 173 (97), 171 (28), 159 (49), 75 (46), 73 (42).

Ethyl 2-diazo-4-[(1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]-3-oxobutanoate 30. To a magnetically stirred solution of the β-keto ester **19** (280 mg, 0.706 mmole) in dry acetonitrile (1 mL) was added tosyl azide (0.11 mL, 0.72 mmole), followed by triethylamine (0.1 mL, 0.72 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 (1:30) as eluent furnished the α-diazo-β-keto ester **30** (270 mg, 90.5%) as oil. IR (neat): 2955, 2131, 1718, 1662, 1624, 1464, 1373, 1298, 1252, 1209, 1100, 1073, 1034, 957, 886, 836, 814, 774, 743, 676 cm^{-1}.

Ethyl (1*R*,3*R*,6*R*,7*R*)-7-(*tert*-butyldimethylsilyloxy)-6,10,10-trimethyl-4-oxotricyclo[4.4.0.0^{1,3}]decane-3-carboxylate 18. Method 1: To a magnetically stirred solution of the diazo ketone **30** (68 mg, 0.16 mmole) in dry benzene (17 mL) was added a catalytic amount of $Rh_2(OAc)_4$ (~3 mg) and the reaction-mixture was stirred for 24 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 (1:25) as eluent furnished the by-product **31** (6 mg, 9.4%) as oil. $[\alpha]_D^{25}$: +31.7° (*c* 1.2, $CHCl_3$); IR (neat): 2955, 1718, 1700, 1663, 1360, 1269, 1214, 1165, 1132, 1091, 1043, 958, 891, 872, 840, 835, 782, 677 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 5.06 (1 H, s) and 5.00 (1 H, s) [C=CH_2], 4.72 (1 H, d, *J* = 1.1 Hz, C=CH), 4.14 and 4.06 (2 H, q of AB q, *J* = 10.6 and 7.0 Hz, OCH_2CH_3), 2.95 (1 H, d, *J* = 16.2 Hz) and 2.76 (1 H, dd, *J* = 16.2 Hz and 1.6 Hz) [H-9'], 2.15 (1 H, dt, *J* = 14.3 and 4.0 Hz), 1.98 (1 H, td, *J* = 14.0 and 4.0 Hz), 1.63 (1 H, td, *J* = 13.2 and 4.0 Hz), 1.36 (1 H, dt, *J* = 14.0 and 4.0 Hz), 1.24 (3 H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.30 (3 H, s), 1.15 (3 H, s) and 1.11 (3 H, s) [3 × *tert*-CH_3], 0.88 [9 H, s, C(CH_3)$_3$], 0.25 (3 H, s) and 0.10 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 168.8 (C, OC=O), 165.2 (C, C-8'), 157.8 (C, C-2'), 112.6 (C, C-6'), 110.1 (CH_2, C=CH_2), 89.2 (CH, C-2), 58.9 (CH_2, OCH_2CH_3), 50.2 (C, C-1'), 45.9 (CH_2, C-9'), 35.4 (C, C-3'), 35.2 (CH_2, C-4'), 31.3 (CH_3), 30.1 [2 C, CH_3 and CH_2 (C-5')], 25.9 [3 C, CH_3, C(CH_3)$_3$], 25.5 (CH_3), 18.1 [C, $C(CH_3)_3$], 14.6 (CH_3, OCH_2CH_3), -2.9 (CH_3) and -3.8 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) ($C_{22}H_{38}O_4Si$) 379 (M-Me, 9), 337 (38), 265 (14), 186 (12), 123 (11), 87 (18), 85 (100), 83 (100).

Further elution of the column with ethyl acetate-hexane (1:10) as eluent furnished the tricyclic keto ester **18** (29 mg, 45%) as oil.

Method 2: To a magnetically stirred refluxing (by placing two 100 W tungsten lamps near the reaction flask) suspension of copper powder (260 mg, 4.09 mmole) and anhydrous copper sulfate (320 mg, 2.0 mmoles) in dry cyclohexane (40 mL) was added, drop wise a solution of the α-diazo-β-keto ester **30** (170 mg, 0.40 mmole) in dry cyclohexane (10 mL) over a period of 25 min and the reaction-mixture was refluxed for 24 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 ethyl acetate-hexane (1:10) as eluent furnished the tricyclic keto ester **18** (94 mg, 59%). $[\alpha]_D^{25}$: -27.9° (*c* 1.4, $CHCl_3$); IR (neat): 2954, 2856, 1742, 1722, 1472, 1368, 1340, 1253, 1238, 1206, 1181, 1111, 1078, 1052, 1007, 878, 836, 775, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.17 (2 H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.35 (1 H, dd, *J* = 11.1 and 4.2 Hz, H-7), 2.22 and 1.83 (2 H, 2 × d, *J* = 18.0 Hz, H-5), 1.85-1.50 (4 H, m), 1.46 (1 H, dt, *J* = 13.5 and 3.6 Hz), 1.33-1.26 (1 H, m), 1.28 (3 H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.13 (3 H, s), 1.11 (3 H, s) and 0.60 (3 H, s) [3 × *tert*-CH_3], 0.85 [9 H, s, C(CH_3)$_3$], 0.05 [6 H, s, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 207.0 (C, C-4), 167.9 (C, OC=O), 76.5 (CH, C-7), 61.2 (CH_2, OCH_2CH_3), 53.5 (C, C-3), 49.0 (C, C-1), 45.3 (CH_2, C-5), 44.8 (C, C-6), 37.0 (CH_2, C-9), 33.0 (C, C-10), 28.2 (CH_3), 27.5 (CH_2, C-8), 27.0 (CH_3), 25.8 [3 C, CH_3, C(CH_3)$_3$], 18.05 (CH_3), 18.0 [C, $C(CH_3)_3$], 17.6 (CH_2, C-2), 14.0 (CH_3, OCH_2CH_3), -3.7 (CH_3) and -5.0 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) ($C_{22}H_{38}O_4Si$) 394 (M^+, 1), 337 (85, M-^{t}Bu), 209 (35), 199 (99), 171 (86), 121 (28), 75 (85), 73 (100).

Ethyl (1*R*,2*R*,6*R*,7*S*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5,6-tetramethyl-8-oxobicyclo[4.3.0]nonane-7-carboxylate 33. To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (100 mL) in a two necked flask, equipped with Dewar condenser, was added freshly cut lithium (6 mg, 0.86 mmole) followed by the tricyclic keto ester **18** (100 mg, 0.25 mmole) in anhydrous THF

(1 mL). The resulting blue coloured solution was stirred for 10 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 (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50) as eluent, first furnished the decalin ester **34** (45 mg, 45%) as oil. $[\alpha]_D^{22}$: -38.2° (*c* 1.3, $CHCl_3$); IR (neat): 2952, 2856, 1716, 1659, 1618, 1462, 1366, 1290, 1252, 1223, 1174, 1105, 1069, 1007, 913, 885, 836, 774, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 12.11 (1 H, s, OH), 4.22 (2 H, q, *J* = 6.9 Hz, OCH_2CH_3), 3.25 (1 H, dd, *J* = 10.8 and 4.0 Hz, H-7), 2.36-2.26 (1 H, m), 2.23 and 1.96 (2 H, 2 × d, *J* = 17.7 Hz, H-5), 2.10-1.95 (1 H, m), 1.70-1.20 (4 H, m), 1.34 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3), 1.14 (1 H, dd, *J* = 12.3 and 5.1 Hz), 0.93 (3 H, s), 0.92 (3 H, s) and 0.90 (3 H, s) [3 × *tert*-CH_3], 0.89 [9 H, s, $C(CH_3)_3$], 0.07 (3 H, s) and 0.05 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 172.3 (C, C-4), 170.9 (C, OC=O), 96.1 (C, C-3), 80.6 (CH, C-7), 60.1 (CH_2, OCH_2CH_3), 47.6 (CH, C-1), 46.0 (CH_2, C-5), 40.3 (CH_2, C-2), 39.1 (C, C-6), 32.9 (CH_3), 32.7 (C, C-10), 28.1 (CH_2, C-9), 26.1 [3 C, CH_3, $C(CH_3)_3$], 21.8 (CH_3), 20.8 (CH_2, C-8), 18.2 [C, $C(CH_3)_3$], 14.6 (CH_3, OCH_2CH_3), 13.3 (CH_3), -3.6 (CH_3) and -4.6 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) ($C_{22}H_{40}O_4Si$) 396 (M^+, 2), 340 (11), 339 (47, M-^{t}Bu), 321 (10), 293 (33), 149 (12), 123 (11), 91 (12), 81 (15), 75 (100).

Further elution of the column with ethyl acetate-hexane (1:20) as eluent furnished the bicyclic keto ester **33** (33 mg, 33%) as a white solid, which was recrystallised from hexanes. m.p. 85-87°C; $[\alpha]_D^{22}$: +67.5° (*c* 1.17, $CHCl_3$); IR (thin film): 2954, 2858, 1756 (OC=O), 1731 (C=O), 1464, 1462, 1368, 1323, 1253, 1182, 1144, 1102, 1059, 1033, 882, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.19 and 4.13 (2 H, q of AB q, *J* = 10.1 and 7.2 Hz, OCH_2CH_3), 3.59 (1 H, s, H-7), 3.44 (1 H, dd, *J* = 10.2 and 4.2 Hz, H-2), 2.45 and 2.18 (2 H, 2 × d, *J* = 18.9 Hz, H-9), 1.77-1.50 (3 H, m), 1.40-1.35 (1 H, m), 1.27 (3 H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.22 (3 H, s), 1.13 (3 H, s), 1.05 (3 H, s) and 0.83 (3 H, s) [4 × *tert*-CH_3], 0.87 [9 H, s, $C(CH_3)_3$], 0.04 (3 H, s) and 0.02 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 211.0 (C, C=O), 169.6 (C, OC=O), 74.0 (CH, C-2), 61.9 (CH, C-7), 60.8 (CH_2, OCH_2CH_3), 53.1 (C, C-6), 49.5 (CH_2, C-9), 47.3 (C, C-1), 36.4 (CH_2, C-4), 36.3 (C, C-5), 28.7 (CH_3), 27.8 (CH_2, C-3), 26.0 [3 C, CH_3, $C(CH_3)_3$], 25.5 (CH_3), 18.1 [C, $C(CH_3)_3$], 15.7 (CH_3), 15.3 (CH_3), 14.2 (CH_3, OCH_2CH_3), -3.5 (CH_3) and -4.8 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 397 (M^++1, 1), 340 (25), 339 (100), 293 (12), 219 (23), 191 (20), 163 (28), 135 (28). Anal. For $C_{22}H_{40}O_4Si$, Calcd: C, 66.62; H, 10.16. Found: C, 66.84; H, 10.33%.

Further elution of the column with ethyl acetate-hexane (1:5) as eluent furnished the bicyclic keto alcohol **35** (5 mg, 5%) as a white solid, which was recrystallised from hexanes. m.p. 86-88°C; $[\alpha]_D^{26}$: -38.0° (*c* 1.0, $CHCl_3$); IR (thin film): 3448, 2952, 2855, 1705, 1464, 1462, 1389, 1367, 1253, 1108, 1051, 1008, 881, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 3.62 (2 H, d, *J* = 5.1 Hz, CH_2OH), 3.31 (1 H, dd, *J* = 10.8 and 3.9 Hz, H-10), 2.42-2.34 (1 H, m), 2.36 and 1.93 (2 H, 2 × d, *J* = 12.6 Hz, H-2), 1.91-1.85 (1 H, m), 1.70-1.10 (7 H, m), 0.85 [9 H, s, $C(CH_3)_3$], 0.93 (3 H, s), 0.82 (3 H, s) and 0.79 (3 H, s) [3 × *tert*-CH_3], 0.01 (3 H, s) and -0.01 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.2 (C, C=O), 79.6 (CH, C-10), 62.4 (CH_2, CH_2OH), 56.0 (CH_2, C-2), 52.0 (CH) and 51.0 (CH) [C-4 and C-6], 44.7 (C, C-1), 40.0 (CH_2), 33.1 (C, C-7), 33.0 (CH_3), 28.2 (CH_2), 26.3 (CH_2), 25.9 [3 C, CH_3, $C(CH_3)_3$], 21.5 (CH_3), 18.1 [C, $C(CH_3)_3$], 13.6 (CH_3), -3.8 (CH_3) and -4.7 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) 354 (M^+, 1), 298 (24), 297 (100, M-^{t}Bu), 279 (15), 227 (13), 209 (11), 145 (85). Anal. For $C_{20}H_{38}O_3Si$, Calcd: C, 67.74; H, 10.80. Found: C, 67.84; H, 10.68%.

Ethyl (1*R*,2*R*,6*R*,7*R*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5,6-tetramethyl-8-methylenebicyclo[4.3.0]-nonane-7-carboxylate 37. To a magnetically stirred suspension of methyltriphenylphosphonium bromide (200 mg, 0.56 mmole) in dry benzene (0.4 mL) was added 1 *M* solution of potassium *tert*-amylate in *tert*-amyl alcohol (0.38 mL, 0.38 mmole) and the resulting yellow colour solution was stirred for 30 min at RT. To this solution of methylenetriphenylphosphorane was added a solution of the bicyclic keto ester **33** (50 mg, 0.126 mmole) in dry benzene (0.8 mL) and refluxed for 12 hr. The reaction-mixture was cooled, saturated aqueous NH_4Cl solution (5 mL) was added and extracted with ether (3 × 5 mL). The ether extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the product over a silica gel column using hexane as eluent furnished the methylenated compound **37**

(41.6 mg, 83.6%) as oil. $[\alpha]_D^{24}$: +20.5° (*c* 4.0, $CHCl_3$); IR (neat): 2954, 1745, 1717, 1653, 1462, 1374, 1333, 1255, 1147, 1099, 1056, 1005, 883, 836, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.91 (1 H, s) and 4.83 (1 H, s) [C=CH_2], 4.22-4.02 (2 H, m, OC*H*$_2$CH$_3$), 3.63 (1 H, br s, H-7), 3.41 (1 H, dd, *J* = 10.5 and 4.2 Hz, H-2), 2.44 and 2.28 (2 H, 2 × d, *J* = 16.2 Hz, H-9), 1.75-1.35 (4 H, m), 1.27 (3 H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$), 1.12 (3 H, s), 1.00 (3 H, s), 0.98 (3 H, s) and 0.81 (3 H, s) [4 × *tert*-CH_3], 0.88 [9 H, s, C(C*H*$_3$)$_3$], 0.02 [6 H, s, Si(C*H*$_3$)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 173.4 (C, OC=O), 148.9 (C, C-8), 108.5 (CH_2, C=*C*H$_2$), 72.9 (CH, C-2), 59.9 (CH_2, O*C*H$_2$CH$_3$), 54.7 (CH, C-7), 54.3 (C, C-6), 49.9 (C, C-1), 44.0 (CH_2, C-9), 36.7 (CH_2, C-4), 36.2 (C, C-5), 28.6 (CH_3), 27.9 (CH_2, C-3), 26.1 [3 C, CH_3, C(*C*H$_3$)$_3$], 25.3 (CH_3), 18.2 [C, *C*(CH$_3$)$_3$], 15.5 (CH_3), 14.9 (CH_3), 14.5 (CH_3), -3.6 (CH_3) and -4.7 (CH_3) [Si(CH$_3$)$_2$]; MS: *m/z* (%) ($C_{23}H_{42}O_3Si$) 394 (M^+, 3), 337 (48, M-^{t}Bu), 267 (16), 189 (47), 133 (32), 119 (21), 107 (16), 85 (61), 83 (100).

Further elution of the column with ethyl acetate-hexane (1:20) as eluent furnished the unreacted starting matetial **33** (8 mg, 16%).

Ethyl (1*R*,2*R*,6*R*,7*S*)-2-(*tert*-butyldimethylsilyloxy)-1,5,5,6-tetramethylbicyclo[4.3.0]nonane-[8.2']-spirooxirane-7-carboxylates 38. To a magnetically stirred solution of the ene ester **37** (18 mg, 0.046 mmole) in CH_2Cl_2 (0.5 mL) was added *m*-CPBA [assay 50%, 45 mg, 0.13 mmole, washed twice with saturated $NaHCO_3$ solution (10 mL) followed by *p*H 7.4 phosphate buffer solution] and stirred at RT for 24 hr. Saturated sodium sulfite solution (5 mL) was added to the reaction-mixture and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with saturated $NaHCO_3$ solution and brine, and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:50) as eluent furnished, first the less polar isomer of the epoxide **38** (10 mg, 53%) as oil. $[\alpha]_D^{25}$: +11.7° (*c* 0.6, $CHCl_3$); IR (neat): 2955, 2857, 1737, 1461, 1376, 1337, 1254, 1173, 1170, 1139, 1100, 1067, 1033, 889, 873, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.05 (2 H, q, *J* = 6.9 Hz, OC*H*$_2$CH$_3$), 3.89 (1 H, dd, *J* = 11.0 and 4.5 Hz, H-2), 3.31 (1 H, s, H-7), 2.65 and 2.55 (2 H, 2 × d, *J* = 4.2 Hz, H-3'), 2.08 and 1.77 (2 H, 2 × d, *J* = 14.7 Hz, H-9), 1.85-1.25 (4 H, m), 1.23 (3 H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$), 1.18 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s) and 0.81 (3 H, s) [4 × *tert*-CH_3], 0.88 [9 H, s, C(C*H*$_3$)$_3$], 0.09 [6 H, s, Si(CH$_3$)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 173.0 (C, OC=O), 73.0 (CH, C-2), 64.2 (C, C-8), 60.0 (CH_2, O*C*H$_2$CH$_3$), 55.5 (C, C-6), 54.6 (CH, C-7), 50.9 (CH_2, C-3'), 50.7 (C, C-1), 43.6 (CH_2, C-9), 36.6 (CH_2, C-4), 36.4 (C, C-5), 28.6 (CH_3), 28.0 (CH_2, C-3), 26.1 [3 C, CH_3, C(*C*H$_3$)$_3$], 25.4 (CH_3), 18.3 [C, *C*(CH$_3$)$_3$], 15.8 (CH_3), 15.4 (CH_3), 14.3 (CH_3, OCH$_2$*C*H$_3$), -3.6 (CH_3) and -4.6 (CH_3) [Si(CH$_3$)$_2$]; MS: *m/z* (%) ($C_{23}H_{42}O_4Si$) 365 (M-OEt, 6), 354 (20), 353 (76, M-^{t}Bu), 283 (20), 187 (24), 171 (26), 103 (21), 85 (63), 83 (100).

Further elution of the column with the same solvent furnished the polar isomer of the epoxide **38** (5 mg, 27%) as oil. $[\alpha]_D^{25}$: +4.2° (*c* 1.2, $CHCl_3$); IR (neat): 2955, 2858, 1753, 1465, 1462, 1376, 1338, 1256, 1155, 1106, 1066, 1034, 889, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 4.13-3.93 (2 H, m, OC*H*$_2$CH$_3$), 3.63 (1 H, dd, *J* = 10.0 and 4.6 Hz, H-2), 3.41 (1 H, s, H-7), 2.75 and 2.66 (2 H, 2 × d, *J* = 5.4 Hz, H-3'), 2.02 and 1.86 (2 H, 2 × d, *J* = 14.1 Hz, H-9), 1.73-1.13 (4 H, m), 1.21 (3 H, t, *J* = 6.9 Hz, OCH$_2$C*H*$_3$), 1.34 (3 H, s), 1.04 (3 H, s), 0.99 (3 H, s) and 0.77 (3 H, s) [4 × *tert*-CH_3], 0.87 [9 H, s, C(C*H*$_3$)$_3$], 0.05 (3 H, s) and 0.03 (3 H, s) [Si(CH$_3$)$_2$]; ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 169.3 (C, OC=O), 73.8 (CH, C-2), 60.3 (C, C-8), 59.9 (CH_2, O*C*H$_2$CH$_3$), 53.8 (C, C-6), 52.2 (CH, C-7), 51.4 (CH_2, C-3'), 50.6 (C, C-1), 42.5 (CH_2, C-9), 36.5 (CH_2, C-4), 36.1 (C, C-5), 29.0 (CH_3), 27.9 (CH_2, C-3), 26.0 [3 C, CH_3, C(*C*H$_3$)$_3$], 25.1 (CH_3), 18.3 [C, *C*(CH$_3$)$_3$], 15.7 (CH_3), 14.8 (CH_3), 14.4 (CH_3), -3.4 (CH_3) and -4.8 (CH_3) [Si(CH$_3$)$_2$]; MS: *m/z* (%) ($C_{23}H_{42}O_4Si$) 365 (M-OEt, 5), 353 (19, M-^{t}Bu), 307 (20), 267 (20), 187 (38), 145 (20), 131 (19), 119 (21), 107 (19), 105 (26), 85 (44).

(1*R*,2*R*,5*S*,6*R*,8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-5-ethoxy-1,8,12,12-tetramethyl-4-oxatricyclo-[6.4.0.0^{2,6}]dodecan-3-one 39 and (1*R*,2*R*,5*S*,6*R*,8*R*,9*R*)-5-ethoxy-9-hydroxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-one 40. To a magnetically stirred solution of the less polar isomer of the epoxide **38** (9 mg, 0.022 mmole) in dry CH_2Cl_2 (5 mL) was added 1 drop of $BF_3.Et_2O$, and stirred at RT for 15 min. 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 (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane

(1:20) as eluent furnished the acetal **39** (3.5 mg, 39%) as oil. Further elution of the column with ethyl acetate-hexane (1:3) as eluent furnished the hydroxy acetal **40** (2 mg, 31%) as oil.

Reaction of the polar isomer of the epoxide **38** (20 mg, 0.048 mmole) in dry CH_2Cl_2 (5 mL) with 3 drops of $BF_3.Et_2O$, as described above, furnished the acetal **39** (5 mg, 25%) and hydroxy acetal **40** (5 mg, 35%).

Spectral data for the TBDMS ether **39**: $[\alpha]_D^{25}$: -40.0° (*c* 0.6, $CHCl_3$); IR (neat): 2955, 2857, 1772 (γ-lactone), 1461, 1378, 1353, 1252, 1160, 1120, 1074, 963, 890, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.14 (1 H, s, H-5), 3.87 (1 H, dq, *J* = 9.3 and 6.9 Hz) and 3.56 (1 H, dq, *J* = 9.3 and 6.9 Hz) [OCH_2CH_3], 3.39 (1 H, dd, *J* = 10.8 and 3.6 Hz, H-9), 3.30 (1 H, d, *J* = 11.1 Hz, H-2), 2.75 (1 H, q, *J* = 9.9 Hz, H-6), 2.23 (1 H, dd, *J* = 12.9 and 9.3 Hz, H-7A), 1.70-1.20 (5 H, m), 1.23 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3), 1.07 (3 H, s), 1.01 (3 H, s), 0.97 (3 H, s) and 0.94 (3 H, s) [4 × *tert*-CH_3], 0.89 [9 H, s, $C(CH_3)_3$], 0.06 (3 H, s) and 0.055 (3 H, s) [$Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6 (C, OC=O), 107.9 (CH, C-5), 73.0 (CH, C-9), 64.9 (CH_2, OCH_2CH_3), 53.8 (C) and 53.3 (C) [C-1 and C-8], 51.6 (CH, C-2), 44.2 (CH, C-6), 40.3 (CH_2, C-7), 36.9 (CH_2, C-11), 35.7 (C, C-12), 30.3 (CH_3), 27.6 (CH_2, C-10), 25.8 [3 C, CH_3, $C(CH_3)_3$], 24.5 (CH_3), 18.0 [C, $C(CH_3)_3$], 15.8 (CH_3), 15.3 (CH_3), 14.9 (CH_3), -3.7 (CH_3) and -4.9 (CH_3) [$Si(CH_3)_2$]; MS: *m/z* (%) ($C_{23}H_{42}O_4Si$) 353 (M-^{t}Bu, 11), 302 (7), 187 (9), 87 (10), 85 (65), 83 (100).

Spectral data for the hydroxy acetal **40**: $[\alpha]_D^{23}$: -59.4° (*c* 1.6, $CHCl_3$); IR (neat): 3461 (OH), 2932, 1769 (γ-lactone), 1459, 1379, 1353, 1165, 1120, 1030, 958 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.16 (1 H, s, H-5), 3.86 (1 H, dq, *J* = 9.3 and 7.2 Hz) and 3.56 (1 H, dq, *J* = 9.3 and 7.2 Hz) [OCH_2CH_3], 3.44 (1 H, dd, *J* = 9.0 and 6.6 Hz, H-9), 3.30 (1 H, d, *J* = 11.1 Hz, H-2), 2.86 (1 H, q, *J* = 9.9 Hz, H-6), 2.35 (1 H, dd, *J* = 12.9 and 9.3 Hz, H-7A), 1.75-1.10 (6 H, m), 1.22 (3 H, t, *J* = 6.9 Hz, OCH_2CH_3), 1.09 (3 H, s), 1.03 (3 H, s), 0.97 (3 H, s) and 0.96 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5 (C, OC=O), 107.9 (CH, C-5), 72.4 (CH, C-9), 65.0 (CH_2, OCH_2CH_3), 53.5 (C) and 53.0 (C) [C-1 and C-8], 51.5 (CH, C-2), 44.1 (CH, C-6), 40.1 (CH_2, C-7), 36.9 (CH_2, C-10), 35.9 (C, C-12), 30.2 (CH_3), 27.5 (CH_2, C-11), 24.5 (CH_3), 15.2 (CH_3), 15.1 (CH_3), 14.9 (CH_3); MS: *m/z* (%) ($C_{17}H_{28}O_4$) 251 (M-OEt, 1), 197 (3), 153 (5), 151 (3), 137 (3), 123 (4), 107 (6), 95 (5), 87 (10), 85 (62), 83 (100).

(1*R*,2*R*,6*R*,8*R*,9*R*)-1,8,12,12-Tetramethyl-9-trifluoroacetoxy-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-one 42. From the silyloxy acetal **39**: To a magnetically stirred solution of the acetal **39** (3.5 mg, 0.0085 mmole) in TFA (0.6 mL) was added triethylsilane (0.02 mL, 0.13 mmole) and refluxed for 4 hr. TFA 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 (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the trifluoroacetate **42** (2 mg, 67%) as a white solid, which was recrystallised from hexane.

From the hydroxy acetal **40**: Reaction of the hydroxy acetal **40** (6 mg, 0.02 mmole) in TFA (1 mL) with triethylsilane (0.02 mL, 0.127 mmole), as described above, furnished the trifluoroacetate **42** (5 mg, 71%). m.p. 100-102°C; $[\alpha]_D^{23}$: +34.3° (*c* 1.4, $CHCl_3$); IR (neat): 2963, 1776 (γ-lactone and $OCOCF_3$), 1482, 1461, 1384, 1354, 1216, 1158, 1075, 1023, 960, 926, 875, 776, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (1 H, dd, *J* = 12.2 and 4.4 Hz, H-9), 4.44 (1 H, t, *J* = 9.2 Hz) and 3.96 (1 H, dd, *J* = 9.6 and 3.9 Hz) [H-5], 3.30-3.10 (2 H, m, H-2 and H-6), 2.00-1.40 (6 H, m), 1.17 (3 H, s), 1.15 (3 H, s), 1.05 (3 H, s) and 1.04 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (C, OC=O, C-3), 157.5 (C, q, CF_3COO, $^2J_{CF}$ = 42 Hz), 114.5 (CF_3, q, $^1J_{CF}$ = 284 Hz), 80.3 (CH, C-9), 72.7 (CH_2, C-5), 54.4 (C) and 52.6 (C) [C-1 and C-8], 50.7 (CH, C-2), 43.8 (CH_2, C-7), 36.3 (CH_2, C-11), 35.9 (C, C-12), 35.6 (CH, C-6), 30.2 (CH_3), 24.5 (CH_3), 23.6 (CH_2, C-10), 16.0 (CH_3), 15.1 (CH_3); MS: *m/z* (%) ($C_{17}H_{23}F_3O_4$) 348 (M^+, 6), 234 (22, M-CF_3CO_2H), 219 (19), 165 (32), 153 (32), 121 (34), 119 (32), 107 (38), 105 (31), 96 (33), 93 (53), 91 (35), 85 (75).

(1*R*,2*R*,6*R*,8*R*,9*R*)-9-Hydroxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-3-one 41. To a magnetically stirred solution of the trifluoroacetate **42** (16 mg, 0.046 mmole) in methanol (2 mL) was added K_2CO_3 (20-30 mg) and stirred at RT for 6 hr. Water (5 mL) was added to the reaction-mixture and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl

acetate-hexane as eluent (1:2) furnished the hydroxy lactone **41** (11 mg, 95%) as a white solid, which was recrystallised from hexane. m.p. 177-79°C (lit.[4] 184-186°C); $[\alpha]_D^{23}$: +40.0° (*c* 0.9, $CHCl_3$) [lit.[4] for (-)-**41**: -71.6° (*c* 0.85, $CHCl_3$)]; IR (thin film): 3385, 2968, 2912, 1764 (γ-lactone), 1476, 1454, 1397, 1378, 1252, 1177, 1076, 1016, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (1 H, t, *J* = 9.0 Hz) and 3.96 (1 H, dd, *J* = 9.0 and 5.4 Hz) [H-5], 3.49 (1 H, m, H-9), 3.25-3.05 (2 H, m, H-2 and H-6), 2.38 (1 H, dd, *J* = 13.0 and 8.0 Hz, H-7A), 1.70-1.30 (6 H, m), 1.11 (3 H, s), 1.05 (3 H, s), 1.01 (3 H, s) and 0.99 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7 (C, OC=O), 73.4 (CH_2, C-5), 72.8 (CH, C-9), 53.84 (C) and 53.77 (C) [C-1 and C-8], 51.2 (CH, C-2), 43.8 (CH_2, C-7), 37.0 (CH_2, C-10), 36.0 (C, C-12), 35.9 (CH, C-6), 30.4 (CH_3), 27.7 (CH_2, C-11), 24.5 (CH_3), 15.3 (CH_3), 15.1 (CH_3); MS: *m/z* (%) ($C_{15}H_{24}O_3$) 252 (M^+, 5), 219 (7), 183 (39), 165 (10), 153 (100), 152 (25), 107 (31), 93 (62), 85 (44), 83 (57).

(1*R*,2*R*,3*S*,6*R*,8*R*,9*R*)-3-Methoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-9-ol 44. To a cold (-70°C, alcohol-liquid N_2 bath) magnetically stirred solution of the lactone **41** (5 mg, 0.02 mmole) in toluene (1 mL) was added a solution of DIBALH (1.0 M in toluene, 0.05 mL, 0.05 mmole) and stirred for 1 hr 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 (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:1) as eluent furnished an ~1:1 epimeric mixture of the lactols **43** (4.5 mg, 89%) as oil. IR (neat): 3414, 2951, 1456, 1395, 1377, 1263, 1174, 1102, 1058, 984, 980, 936, 932, 737 cm^{-1}.

To a magnetically stirred solution of an epimeric mixture of the lactol **43** (4.5 mg, 0.018 mmole) in methanol (2 mL) was added a catalytic amount of *p*-TSA and stirred for 10 min. The reaction-mixture was then quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:3) as eluent furnished the methyl acetal (+)-**44** (4 mg, 84%) as a solid, which was recrystallised from hexane. m.p. 110-12°C (lit.[4] 112-14°C); $[\alpha]_D^{24}$: +64.3° (*c* 0.7, $CHCl_3$) [lit.[4] for (-)-**44**: -67.5° (*c* 2.4, $CHCl_3$)]; IR (neat): 3461, 2941, 2876, 1454, 1395, 1376, 1190, 1105, 1069, 1028, 986, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.79 (1 H, s, H-3), 3.96 (1 H, t, *J* = 7.8 Hz) and 3.63 (1 H, d, *J* = 7.8 Hz) [H-5], 3.64-3.58 (1 H, m, H-9), 3.27 (3 H, s, OCH_3), 2.85-2.74 (2 H, m, H-2 and H-6), 2.25-2.10 (1 H, m, H-7a), 1.80-1.50 (4 H, m), 1.35-1.20 (2 H, m), 0.96 (6 H, s) and 0.88 (6 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.3 (CH, C-3), 72.5 (CH_2, C-5), 72.4 (CH, C-9), 57.7 (CH, C-2), 54.3 (CH_3, OCH_3), 53.4 (C, C-1), 50.1 (C, C-8), 43.4 (CH_2, C-7), 38.0 (CH, C-6), 36.5 (CH_2, C-11), 35.8 (C, C-12), 28.0 (CH_3), 27.6 (CH_2, C-10), 24.6 (CH_3), 14.7 (CH_3), 13.4 (CH_3); MS: *m/z* (%) ($C_{16}H_{28}O_3$) 237 (M-OMe, 3), 153 (7), 139 (7), 109 (20), 108 (21), 93 (19), 85 (63), 83 (100).

(1*R*,2*R*,3*S*,6*R*,8*R*,9*R*)-3-Methoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-9-yl 3-methylbut-2-enoate 45. To a cold (0°C) magnetically stirred solution of the hydroxy acetal **44** (5 mg, 0.0186 mmole) in toluene (0.5 mL) were added 3-methylbut-2-enoic acid (10 mg, 0.1 mmole), DCC (20 mg, 0.097 mmole) and a catalytic amount of DMAP, and warmed up to RT and stirred for 24 hr. The reaction-mixture was purified over a silica gel column using ethyl acetate-hexane (1:10) as eluent to furnish a 5:1 mixture of the two esters **45** and **46** (6.5 mg, 99.5%).

A solution of a mixture of the two esters **45** and **46** (6.5 mg, 0.019 mmole), obtained above, and one drop of DBU in CH_2Cl_2 (2 mL) was magnetically stirred for 9 hr at RT. Evaporation of the solvent under vacuum and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the senecioate ester **45** (6.5 mg, 100%) as a solid. $[\alpha]_D^{24}$: +48.5° (*c* 1.3, $CHCl_3$) [lit.[4] for (-)-**45**: -37.0° (*c* 1.0, $CHCl_3$)]; IR (neat): 2941, 1714, 1651, 1452, 1378, 1228, 1144, 1105, 1072, 1009, 990, 950, 930, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (1 H, s, H-2), 4.97 (1 H, dd, *J* = 11.1 and 4.5 Hz, H-9'), 4.79 (1 H, s, H-3'), 3.92 (1 H, t, *J* = 8.0 Hz) and 3.58 (1 H, d, *J* = 8.0 Hz) [H-5'], 3.26 (3 H, s, OCH_3), 3.00-2.80 (2 H, m, H-2' and H-6'), 2.17 (3 H, s) and 1.89 (3 H, s) [2 × olefinic CH_3], 1.85-1.50 (4 H, m) 1.35-1.20 (2 H, m), 1.04 (3 H, s), 0.98 (3 H, s) and 0.90 (6 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (C, OC=O), 156.2 (C, C-3), 116.5 (CH, C-2), 107.2 (CH, C-3'), 73.5 (CH, C-9'), 72.2 (CH_2, C-5'), 57.6 (CH, C-2'), 54.3 (CH_3, OCH_3), 52.2 (C, C-1'), 50.5 (C, C-8'), 43.5 (CH_2, C-7'), 38.1 (CH, C-6'), 36.2 (CH_2, C-11'), 35.8 (C, C-12'), 27.9 (CH_3), 27.4 (CH_3), 24.6 (CH_3), 24.3 (CH_2, C-10'), 20.2 (CH_3), 16.0 (CH_3), 13.2 (CH_3);

MS: *m/z* (%) ($C_{21}H_{34}O_4$) 319 (M-OMe, 3), 190 (18), 175 (10), 134 (13), 119 (14), 85 (11), 83 (100).

(1*R*,2*R*,3*S*,6*R*,8*R*,9*R*)-3-Hydroxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodecan-9-yl 3-methylbut-2-enoate (5-Senecioyloxy-10,11-epoxythapsan-10-ol 6). To a magnetically stirred solution of the methyl acetal **45** (6.5 mg, 0.0186 mmole) in THF (6 mL) was added 3 *N* aqueous HCl (1.5 mL) and stirred for 50 min at RT. The reaction-mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 extract was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:10) as eluent, first furnished the unreacted starting material **45** (0.5 mg, 8%). Further elution of the column with ethyl acetate-hexane (1:4 to 1:3) as eluent furnished the thapsane **6** (5.5 mg, 88%) as oil. $[\alpha]_D^{23}$: +37.3° (*c* 1.1, $CHCl_3$) [lit.[4] for (-)-**6**: -35.7 (c 4.7, $CHCl_3$)]; IR (neat): 3408, 2954, 2876, 1714, 1650, 1452, 1378, 1229, 1144, 1076, 1045, 993, 930, 851 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 (1 H, s, H-2), 5.36 (1 H, s, H-3'), 4.99 (1 H, dd, *J* = 11.4 and 4.5 Hz, H-9'), 4.14 (1 H, t, *J* = 8.0 Hz) and 3.62 (1 H, d, *J* = 8.0 Hz) [H-5'], 3.05-2.85 (2 H, m, H-2' and H-6'), 2.21 (1 H, br s, OH), 2.17 (3 H, s) and 1.89 (3 H, s) [2 × olefinic CH_3], 1.95-1.50 (4 H, m) 1.35-1.20 (2 H, m), 1.05 (3 H, s), 0.99 (3 H, s), 0.94 (3 H, s) and 0.89 (3 H, s) [4 × *tert*-CH_3]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6 (C, OC=O), 156.3 (C, C-3), 116.4 (CH, C-2), 100.7 (CH, C-3'), 73.5 (CH, C-9'), 72.8 (CH_2, C-5'), 58.3 (CH, C-2'), 52.3 (C, C-1'), 50.6 (C, C-8'), 43.5 (CH_2, C-7'), 38.0 (CH, C-6'), 36.2 (CH_2, C-11'), 35.8 (C, C-12'), 28.1 (CH_3), 27.4 (CH_3), 24.6 (CH_3), 24.3 (CH_2, C-10'), 20.2 (CH_3), 16.0 (CH_3), 13.2 (CH_3); MS: *m/z* (%) ($C_{20}H_{32}O_4$) 319 (M-OH, 7), 190 (31), 175 (17), 134 (20), 121 (16), 119 (19), 107 (15), 83 (100).

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