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 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: 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 thapsigarginin, which were found to be responsible for the medicinal activity1. Even though, thapsigargin and thapsigarginin 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 reported2 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-workers3,4 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 reported5 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 suggested3,4 for the carbon framework cis-1,2,6,8,9-hexamethylbicyclo[4.3.0]nonane 15 present in these compounds. Structures of all the thapsanes isolated so far are given in Chart I. The absolute configuration of the thapsanes was deduced from the analysis of the CD spectra of the compounds 16 containing the cyclohexanone part structure, which were obtained by degradation of the 3- and 5-acyloxythapsanes6 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 targets7. 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 described7h,m the first enantiospecific synthesis of the hemiacetalic thapsane 14, which also established the absolute configuration of thapsanes. In continuation, herein is described the details26 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-1,2,6-tetramethylbicyclo[4.3.0]nonane containing...
three contiguous quaternary 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.

To begin, synthesis of the ester 21 was carried out as described in earlier literature (Scheme II). Carvone 17 has been converted into the trimethylcarvone 22 via sequential kinetic alkylation followed by alkyllative 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. 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 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. Regioselective hydrogenation using 5% palladium on
carbon as the catalyst in ethyl acetate at one atmospheric pressure of hydrogen (balloon) transformed the enone \( \text{26} \) into the saturated ketone \( \text{27} \). Hydrolysis of the keto ester \( \text{27} \) 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 \( \text{28} \) in 70% yield. Treatment of the hydroxy ester \( \text{28} \) with \( \text{tert}-\text{butyl}-\text{dimethylsilyl chloride} \) and DMAP in DMF generated the TBDMS ether \( \text{21} \) in 95% yield.

Conversion of the ester \( \text{21} \) into the tricyclic \( \beta \)-keto ester \( \text{18} \) was then addressed (Scheme III). Thus, reduction of the ester \( \text{21} \) with LAH at RT furnished the alcohol \( \text{29} \), 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 \( \text{20} \) in 90% yield. Reaction of the aldehyde \( \text{20} \) with ethyl diazoacetate in methylene chloride in the presence of a catalytic amount of stannous chloride\(^\text{12} \) furnished the \( \beta \)-keto ester \( \text{19} \) in 92% yield. Diazo transfer reaction with tosyl azide and triethylamine in acetonitrile converted the \( \beta \)-keto ester \( \text{19} \) into the \( \alpha \)-diazo-\( \beta \)-keto ester \( \text{30} \) in 90% yield. Rhodium acetate catalyzed decomposition\(^\text{13} \) of the diazo compound \( \text{30} \) in benzene at RT furnished an ~5:1 mixture of the tricyclic \( \beta \)-keto ester \( \text{18} \) and the by-product \( \text{31} \), in 54% yield, which were separated by column chromatography over silica gel. The structure of the tricyclic keto ester \( \text{18} \) rests secured from its spectral data. The structure of the by-product \( \text{31} \) 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 \( \text{31} \) is isomeric with the tricyclic compound \( \text{18} \). Presence of an absorption band 891 cm\(^{-1} \) in the IR spectrum, two singlets at \( \delta \) 5.06 and 5.00 in the \( ^1\text{H} \) NMR spectrum, and a quaternary carbon at \( \delta \)
157.8 and a methylene at $\delta$ 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 $\delta$ 4.72 in the $^1$H NMR spectrum and an up-field methine carbon at $\delta$ 89.2 in the $^{13}$C NMR spectrum due to the enol ether group and presence of a quaternary carbon at $\delta$ 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 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 $\alpha$-diazo-$\beta$-keto esters, recently a few examples of similar kind of insertion reaction with $\alpha$-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. Anhydrous copper sulfate-copper catalyzed decomposition of the $\alpha$-diazo-$\beta$-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 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 $\alpha,\beta$-unsaturated esters to primary alcohols.16
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 1H and 13C 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 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_{3}O_{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 1H and 13C NMR spectra revealed the formation of the trifluoroacetate 42. In the 1H 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 13C 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 methane 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 (J_{CF} = 42 Hz) due to the carbonyl carbon of the trifluoroacetate and a quartet at δ 114.5 (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
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-protect as the acetal-esterification of the secondary alcohol and hydrolysis of the acetal sequence was conceived. Accordingly, treatment of the hydroxy lactone (+)-41 with DIBAL-H 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 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 Criege fragmentation sequence has been employed for the enantiomeric 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-[(1R,2R)-2-(tert-Butyldimethylsiloxy)-1,5,5-trimethyl-6-methylenecyclohexyl]ethanol 29. To a magnetically stirred, cold (0°C) solution of the ester 21 (500 mg, 1.47 mmole) in anhydrous ether (3 mL) was added LiAlH4 (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 LiAlH4. 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. Na2SO4). 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 29 (420 mg, 91.5%) as a white solid, which was recrystallised from hexanes.

\[ R_{	ext{D}}^2: -10.9^\circ \quad \text{(c 1.1, CHCl}_3) \]

IR (thin film): 3304, 2954, 2857, 1624, 1463, 1362, 1254, 1130, 1085, 994, 938, 898, 836, 772, 672 cm\(^{-1}\); H NMR (300 MHz, CDCl3+CCl4): \( \delta \) 5.05 (1 H, s) and 4.87 (1 H, s) [C=CH2], 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-CH3], 0.89 [9 H, s, C(CH3)3], 0.06 (3 H, s) and 0.02 (3 H, s) [Si(CH3)2]; \( ^{13} \)C NMR (75 MHz, CDCl3+CCl4): \( \delta \) 202.9 (CH, CHO), 159.4 (C, C-6'), 110.8 (CH2, C=CH2), 74.9 (CH, C-2'), 50.8 (CH2, C-2'), 44.9 (C, C-1'), 36.7 (CH3, C-4'), 36.0 (C, C-5'), 31.8 (CH3), 31.5 (CH3), 27.2 (CH2, C-3'), 26.0 [3 C, CH3, C(CH3)3], 24.8 (CH3), 18.2 [C, C(CH3)3], -3.7 (CH3) and -4.7 (CH3) [Si(CH3)2].

Ethyl 4-[(1R,2R)-2-(tert-butylidimethylsiloxy)-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 CH2Cl2 (1 mL) was added SnCl2.H2O (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 \( \beta \)-keto ester 19 (299 mg, 92%) as oil. \([\alpha]_D^{26}: -34.0^\circ \quad \text{(C 1.0, CHCl}_3) \]

IR (neat): 3100, 2954, 1747, 1720, 1625, 1471, 1361, 1253, 1101, 1083, 1007, 887, 837, 774, 676 cm\(^{-1}\); 1H NMR (300 MHz, CDCl3+CCl4): \( \delta \) 9.68 (1 H, br s, CHO), 5.09 (1 H, s) and 4.88 (1 H, s) [C=CH2], 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-CH3], 0.89 [9 H, s, C(CH3)3], 0.06 (3 H, s) and 0.02 (3 H, s) [Si(CH3)2]; \( ^{13} \)C NMR (75 MHz, CDCl3+CCl4): \( \delta \) 202.9 (CH, CHO), 159.4 (C, C-6'), 110.8 (CH2, C=CH2), 74.9 (CH, C-2'), 50.8 (CH2, C-2'), 44.9 (C, C-1'), 36.7 (CH3, C-4'), 36.0 (C, C-5'), 31.8 (CH3), 31.5 (CH3), 27.2 (CH2, C-3'), 26.0 [3 C, CH3, C(CH3)3], 24.8 (CH3), 18.2 [C, C(CH3)3], -3.7 (CH3) and -4.7 (CH3) [Si(CH3)2].
Et 2-diazo-4-[(1R,2R)-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 2 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 (1:10) furnished the tricyclic keto ester 30 (270 mg, 90.5%) as oil.

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 mmolos) 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%).

Ethyl (1R,3R,6R,7R)-7-(tert-butyldimethylsilyloxy)-6,10,10-trimethyl-4-oxo 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 Rh2(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. [α]D25: +31.7° (c 1.2, CHCl3); IR (neat): 2954, 2856, 2131, 1718, 1700, 1662, 1624, 1464, 1373, 1298, 1252, 1209, 1100, 1073, 1034, 957, 886, 836, 814, 774, 743, 677 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 5.06 (1 H, s) and 5.00 (1 H, s) [C=CH2], 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, OCH2CH3), 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, OCH2CH3), 1.30 (3 H, s), 1.15 (3 H, s) and 1.11 (3 H, s) [3 × tert-CH3], 0.88 [9 H, s, C(CH3)3], 0.25 (3 H, s) and 0.10 (3 H, s) [Si(CH3)3]. [13C] NMR (75 MHz, CDCl3): δ 168.8 (C, OC=O), 165.2 (C, C-8′), 157.8 (C, C-2′), 112.6 (C, C-6′), 110.1 (CH2, C=CH2), 89.2 (CH, C-2), 58.9 (CH2, OCH2CH3), 50.2 (C, C-1′), 45.9 (CH2, C-9′), 35.4 (C, C-3′), 35.2 (CH2, C-4′), 31.3 (CH3), 30.1 [2 C, CH3 and CH2 (C-5′)], 25.9 [3 C, CH3, C(CH3)], 25.5 (CH3), 18.1 [C, C(CH3)], 14.6 (CH3, OCH2CH3), -2.9 (CH3) and -3.8 (CH3) [Si(CH3)]; MS: m/z (%) (C22H38O4Si) 379 (M-Me, 9), 337 (38), 265 (14), 186 (12), 123 (11), 87 (18), 85 (100), 83 (100).
(1 mL). The resulting blue coloured solution was stirred for 10 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 (anhdy. Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5) as eluent, first furnished the decalin ester 34 (45 mg, 45%) as oil. [α]D<sup>22</sup> = -38.2° (c 1.3, CHCl₃); 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, CDCl₃+CCl₄): δ 12.11 (1 H, s, OH), 4.22 (2 H, q, J = 6.9 Hz, OCH₂CH₃), 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, OCH₂CH₃), 1.14 (1 H, dd, J = 12.3 and 5.1 Hz), 0.95 (3 H, s), 0.92 (3 H, s) and 0.90 (3 H, s) [3 × tert-CH₃], 0.89 [9 H, s, C(CH₃)₃], 0.07 (3 H, s) and 0.05 (3 H, s) [Si(CH₃)₄]; ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 174, 1105, 1069, 1007, 913, 885, 836, 774, 670 cm⁻¹; 1716, 1659, 1618, 1462, 1366, 1290, 1252, 1223, 47.6 (CH, C-1), 46.0 (CH₂, C-5), 40.3 (CH₂, C-2), 39.1 [C, C-6], 32.9 (CH₂), 32.7 (C, C-10), 28.1 (CH₃, C-9), 26.1 [3 C, CH₃, C(CH₃)₂], 21.8 (CH₃), 20.8 (CH₂, C-8), 18.2 [C, C(CH₃)₂], 14.6 (CH₂, OCH₂CH₃), 13.3 (CH₃), -3.6 (CH₃) and -4.6 (CH₃) [Si(CH₃)₄]; MS: m/z (%) 354 (M⁺, 1), 298 (24), 297 (100, M⁺-H₂O), 181 (100), 163 (33), 340 (25), 339 (100), 293 (12), 219 (23), 191 (20), 163 (28), 135 (28). Anal. For C₃₂H₆₀O₄Si: 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 bicyclo ketone alcohol 35 (5 mg, 5%) as a white solid, which was recrystallised from hexanes. m.p. 86-88°C; [α]D<sup>20</sup> = -38.0° (c 1.0, CHCl₃); IR (thin film): 3448, 2952, 2855, 1705, 1464, 1462, 1389, 1367, 1253, 1108, 1051, 1008, 881, 837, 774 cm⁻¹; ¹H NMR (300 MHz, CDCl₃+CCl₄): δ 3.62 (2 H, d, J = 5.1 Hz, CH₂OH), 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(CH₃)₉]; 0.93 (3 H, s), 0.82 (3 H, s) and 0.79 (3 H, s) [3 × tert-CH₃], 0.01 (3 H, s) and -0.01 (3 H, s) [Si(CH₃)₄]; ¹³C NMR (75 MHz, CDCl₃+CCl₄): δ 213.2 (C, C=O), 79.6 (CH, C-10), 62.4 (CH₂, CH₂OH), 56.0 (CH₂, C-2), 52.0 (CH) and 51.0 (CH) [C-4 and C-6], 44.7 (C, C-1), 40.0 (CH₂), 33.1 (C, C-7), 33.0 (CH₃), 28.2 (CH₂), 26.3 (CH₃), 25.9 [3 C, CH₃, C(CH₃)₂], 21.5 (CH₃), 18.1 [C, C(CH₃)₂], 13.6 (CH₃), -3.8 (CH₃) and -4.7 (CH₃) [Si(CH₃)₄]; MS: m/z (%) 354 (M⁺, 1), 298 (24), 297 (100, M⁺-Bu), 279 (15), 227 (13), 209 (11), 145 (85). Anal. For C₃₂H₆₀O₄Si: Calcd: C, 67.74; H, 10.80. Found: C, 67.84; H, 10.68%.

**Ethyl (1R,2R,6R,7R)-2-(tert-butylidimethylsilyloxy)-1,5,5,6-tetramethyl-8-methylenecyclo[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 methyltriphenylphosphorane 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 NH₄Cl solution (5 mL) was added and extracted with ether (3 × 5 mL). The ether extract was washed with brine and dried (anhdy. Na₂SO₄). Evaporation of the solvent and purification of the product over a silica gel column using hexane as eluent furnished the methyleneated compound 37
(41.6 mg, 83.6%) as oil. \([\alpha]_D^{24} = +20.5^\circ\) (c 4.0, CHCl₃); IR (neat): 2954, 1745, 1717, 1653, 1462, 1374, 1333, 1255, 1147, 1099, 1056, 1005, 883, 836, 772 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃+CCL₄): \(\delta\) 4.91 (1 H, s) and 4.83 (1 H, s) [C=CH₂], 4.22-4.02 (2 H, m, OCH₂CH₃), 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, OCH₂CH₃), 1.12 (3 H, s), 1.00 (3 H, s), 0.98 (3 H, s) and 0.81 (3 H, s) [4 × tert-CH₃], 0.88 [9 H, s, (CH₃)₃], 0.02 [6 H, s, Si(CH₃)₂]. \(^{13}\)C NMR (75 MHz, CDCl₃+CCL₄): \(\delta\) 173.4 (C, OC=O), 148.9 (C, C-8), 108.5 (CH₂, C-CH₂), 72.9 (CH, C-2), 59.9 (CH₂, OCH₂CH₃), 54.7 (CH, C-7), 54.3 (C, C-6), 49.9 (C, C-1), 44.0 (CH₂, C-9), 36.7 (CH₂, C-4), 36.2 (C, C-5), 28.6 (CH₃), 27.9 (CH₂, C-3), 26.1 [3 C, CH₃, C(CH₃)₃], 25.3 (CH₃), 18.2 [2 C, C(CH₃)₂], 15.5 (CH₃), 14.9 (CH₃), 14.5 (CH₃), -3.6 (CH₃) and -4.7 (CH₃) [Si(CH₃)₂]; MS: m/z (%) \((C₂H₅)₂O_Si) 394 (M⁺, 3), 337 (48, M⁻Bu), 267 (16), 189 (47), 133 (22), 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 material 33 (8 mg, 16%).

Ethyl \((1R,2R,6R,7S)-2-(\text{tert-butylidemethylsilyloxy})-1,5,5,6-tetramethylbicyclo[4.3.0]nonane-[8.2.2]\)-spirooxirane-7-carboxylates 38. To a magnetically stirred solution of the ene ester 37 (18 mg, 0.046 mmole) in CH₂Cl₂ (0.5 mL) was added \(m\)-CPBA [assay 50%, 45 mg, 0.13 mmole, washed twice with saturated NaHCO₃ solution (10 mL) followed by pH 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 CH₂Cl₂ (3 × 3 mL). The combined CH₂Cl₂ extract was washed with saturated NaHCO₃ solution and brine, and dried (anhyd. Na₂SO₄). 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. \([\alpha]_D^{25} = +11.7^\circ\) (c 0.6, CHCl₃); IR (neat): 2955, 2857, 1737, 1461, 1376, 1337, 1254, 1173, 1170, 1139, 1100, 1067, 1033, 889, 873, 837, 774 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃+CCL₄): \(\delta\) 4.05 (2 H, q, J = 6.9 Hz, OCH₂CH₃), 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, OCH₂CH₃), 1.18 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s) and 0.81 (3 H, s) [4 × tert-CH₃], 0.88 [9 H, s, (CH₃)₃], 0.09 [6 H, s, Si(CH₃)₂]; \(^{13}\)C NMR (75 MHz, CDCl₃+CCL₄): \(\delta\) 173.0 (C, OC=O), 73.0 (CH, C-2), 64.2 (C, C-8), 60.0 (CH₂, OCH₂CH₃), 55.5 (C, C-6), 54.6 (CH, C-7), 50.9 (CH₂, C-3'), 50.7 (C, C-1), 43.6 (CH₂, C-9), 36.6 (CH₂, C-4), 36.4 (C, C-5), 28.6 (CH₃), 28.0 (CH₂, C-3), 26.1 [3 C, CH₃, C(CH₃)₂], 25.4 (CH₃), 18.3 [C, C(CH₃)₂], 15.8 (CH₃), 15.4 (CH₃), 14.3 (CH₃, OCH₂CH₃), -3.6 (CH₃) and -4.6 (CH₃) [Si(CH₃)₂]; MS: m/z (\%) \((C₂H₅)₂O_Si) 365 (M-OEt, 6), 354 (20), 353 (76, M⁻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. \([\alpha]_D^{25} = +4.2^\circ\) (c 1.2, CHCl₃); IR (neat): 2955, 2888, 1753, 1465, 1462, 1376, 1338, 1256, 1155, 1106, 1066, 1034, 889, 837, 774 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃+CCL₄): \(\delta\) 4.13-3.93 (2 H, m, OCH₂CH₃), 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, OCH₂CH₃), 1.34 (3 H, s), 1.04 (3 H, s), 0.99 (3 H, s) and 0.77 (3 H, s) [4 × tert-CH₃], 0.87 [9 H, s, (CH₃)₃], 0.05 (3 H, s) and 0.03 (3 H, s) [Si(CH₃)₂]; \(^{13}\)C NMR (75 MHz, CDCl₃+CCL₄): \(\delta\) 169.3 (C, OC=O), 73.8 (CH, C-2), 60.3 (C, C-8), 59.9 (CH₂, OCH₂CH₃), 53.8 (C, C-6), 52.2 (CH₂, C-7), 51.4 (CH₂, C-3'), 50.6 (C, C-1), 42.5 (CH₂, C-9), 36.5 (CH₂, C-4), 36.1 (C, C-5), 29.0 (CH₃), 27.9 (CH₂, C-3), 26.0 [3 C, CH₃, C(CH₃)₂], 25.1 (CH₃), 18.3 [C, C(CH₃)₂], 15.7 (CH₃), 14.8 (CH₃), 14.4 (CH₃), -3.4 (CH₃) and -4.8 (CH₃) [Si(CH₃)₂]; MS: m/z (\%) \((C₂H₅)₂O_Si) 365 (M-OEt, 5), 353 (19, M⁻Bu), 307 (20), 267 (20), 187 (38), 145 (20), 131 (19), 119 (21), 107 (19), 105 (26), 85 (44).
(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 CH2Cl2 (5 mL) with 3 drops of BF3·Et2O, as described above, furnished the acetal 39 (5 mg, 25%) and hydroxy acetal 40 (5 mg, 35%).

Spectral data for the TBDMS ether 39: [α]D25: -40.0° (c 0.6, CHCl3); IR (neat): 2955, 2857, 1772 (γ-lactone), 1461, 1378, 1353, 1252, 1160, 1120, 1074, 963, 890, 836, 774 cm⁻¹; 1H NMR (300 MHz, CDCl3): 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) [OCH2CH3], 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, OCH2CH3), 1.07 (3 H, s), 0.97 (3 H, s) and 0.94 (3 H, s) [4 × tert-CH3]; MS: m/z 39 (M-H2O), 35 (M-H3O), 27 (M-H5O), 24 (M-H6O), 21 (M-H7O), 16 (M-H8O), 15 (M-H9O), 14 (M-H10O), 13 (M-H11O), 12 (M-H12O), 11 (M-H13O), 10 (M-H14O), 9 (M-H15O), 8 (M-H16O), 7 (M-H17O), 6 (M-H18O), 5 (M-H19O), 4 (M-H20O), 3 (M-H21O), 2 (M-H22O), 1 (M-H23O).

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; [α]D25: +34.3° (c 1.4, CHCl3); IR (neat): 2963, 1776 (γ-lactone and OOCF3), 1482, 1461, 1384, 1354, 1216, 1158, 1075, 1023, 960, 926, 875, 776, 727 cm⁻¹; 1H NMR (300 MHz, CDCl3): 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-CH3]; 13C NMR (75 MHz, CDCl3): δ 176.8 (C, OC=O), 157.5 (C, q, CF3CO2), 114.5 (CF3, q, JCF = 284 Hz), 80.3 (CH, C-9), 72.7 (CH2, C-5), 54.4 (C) and 52.6 (C) [C-1 and C-8], 50.7 (CH, C-2), 43.8 (CH2, C-7), 36.3 (CH2, C-11), 35.9 (C, C-12), 35.6 (CH2, C-6), 30.2 (CH3), 24.5 (CH3), 23.6 (CH2, C-10), 16.0 (CH3), 15.1 (CH3); MS: m/z (%) (C13H23F3O4) 348 (M⁺, 6), 234 (22, M-CF3CO2H), 219 (19), 165 (32), 153 (32), 121 (34), 119 (32), 107 (38), 105 (31), 96 (33), 93 (53), 91 (35), 85 (75).
acetate-hexane as eluent (1:2) furnished the hydroxy lactone 41 (11 mg, 95%) as a white solid, which was recrystallized from hexane. m.p. 177-79°C (lit.4 184-186°C); \([\alpha]_D^{23}: +40.0^\circ (c 0.9, \text{CHCl}_3) [\text{lit.}^4 \text{for } (-)-41: -71.6^\circ (c 0.85, \text{CHCl}_3)]; IR (thin film): 3385, 2968, 2912, 1764 (\gamma\text{-lactone), 1476, 1454, 1397, 1378, 1252, 1177, 1076, 1016, 1000 cm}^{-1}; 1^H \text{NMR (300 MHz, CDCl}_3): \delta 4.45 (1 \text{H, t, } J = 9.0 \text{ Hz}) and 3.96 (1 \text{H, dd, } J = 9.0 \text{ and } 5.4 \text{ Hz}) [\text{H}-5], 3.49 (1 \text{H, m, H-9}), 3.25-3.05 (2 \text{H, m, H-2 and H-6}), 2.38 (1 \text{H, dd, } J = 13.0 \text{ and } 8.0 \text{ Hz, H-7A}), 1.70-1.30 (6 \text{H, m}), 1.11 (3 \text{H, s}, 1.05 (3 \text{H, s}), 1.01 (3 \text{H, s}) and 0.99 (3 \text{H, s}) [4 \times \text{tert-CH}_3]; 13^C \text{NMR (75 MHz, CDCl}_3): \delta 177.7 (C, \text{OC=O}), 73.4 (\text{CH}_2, C-5), 72.8 (\text{CH, C-9}), 53.84 (C) [C-1 and C-8], 51.2 (\text{CH, C-2}), 43.8 (\text{CH}_3, \text{C-7}), 38.0 (\text{CH, C-6}), 36.5 (\text{CH}_2, C-11), 35.9 (\text{CH}, C-12), 28.0 (\text{CH}_2), 27.6 (\text{CH}_2, C-10), 24.6 (\text{CH}_3), 14.7 (\text{CH}_3), 13.4 (\text{CH}_3); MS: m/z (%) (C\text{_{18}H_{28}O_{3}}) 237 (M^-), 153 (7), 139 (7), 109 (20), 108 (21), 93 (19), 85 (63), 83 (100).

\[(1R,2R,3S,6R,8R,9R,9S)-3-Methoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodec-9-yl-3\text{-methylbut-2-enoate 45.}\] 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-enolic 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 \(\text{CH}_2\text{Cl}_2\) (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 (1:1) as eluent furnished a ~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\text{3} solution (5 mL) and extracted with \(\text{CH}_2\text{Cl}_2\) (3 × 3 mL). The combined \(\text{CH}_2\text{Cl}_2\) extract was washed with brine and dried (anhyd. Na\text{2}SO\text{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 \(\sim 1:1\) epimeric mixture of the lactones 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}.

\[\alpha]_D^{23}: +48.5^\circ (c 1.3, \text{CHCl}_3) [\text{lit.}^4 \text{for } (-)-45: -37.0^\circ (c 1.0, \text{CHCl}_3)]; IR (neat): 2941, 1714, 1651, 1452, 1378, 1228, 1144, 1105, 1072, 1009, 990, 950, 851 cm}^{-1}; 1^H \text{NMR (300 MHz, CDCl}_3): \delta 5.67 (1 \text{H, s, H-2}), 4.97 (1 \text{H, dd, } J = 11.1 \text{ and } 4.5 \text{ Hz, H-9}), 4.79 (1 \text{H, s, H-3}), 3.92 (1 \text{H, t, } J = 8.0 \text{ Hz}) and 3.58 (1 \text{H, d, } J = 8.0 \text{ Hz}) [\text{H}-5], 3.26 (3 \text{H, s, OCH}_3), 3.00-2.80 (2 \text{H, m, H-2' and H-6'}), 2.17 (3 \text{H, s}) and 1.89 (3 \text{H, s}) [2 \times \text{olefinic CH}_3], 1.85-1.50 (4 \text{H, m}) 1.35-1.20 (2 \text{H, m}), 1.04 (3 \text{H, s}), 0.98 (3 \text{H, s}) and 0.90 (6 \text{H, s}) [4 \times \text{tert-CH}_3]; 13^C \text{NMR (75 MHz, CDCl}_3): \delta 166.6 (C, \text{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, C-5'), 57.6 (CH, C-2'), 54.3 (CH, 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-1'), 35.8 (C, C-12'), 27.6 (CH_2), 27.3 (CH_2, C-10'), 24.6 (CH_3), 14.7 (CH_3), 13.4 (CH_3); MS: m/z (%) (C\text{_{18}H_{28}O_{3}}) 237 (M^-), 153 (7), 139 (7), 109 (20), 108 (21), 93 (19), 85 (63), 83 (100).

\[(1R,2R,3S,6R,8R,9R,9S)-3-Methoxy-1,8,12,12-tetramethyl-4-oxatricyclo[6.4.0.0^{2,6}]dodec-9-yl-3-methylbut-2-enoate 45.\] 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-enolic 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 (1:1) 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 \(\text{CH}_2\text{Cl}_2\) (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 (1:1) as eluent furnished the senecioate ester 46 (6.5 mg, 99.5%).
diluted with water (10 mL) and extracted with CH₂Cl₂ stirred for 50 min at RT. The reaction-mixture was (75 MHz, CDCl₃): (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 = 11.4 and 4.5 Hz, H-10').

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References and Notes


6 We were given to understand that the structures of all the thaspanes in the papers published by Professor Grande were wrongly depicted, indicating the opposite absolute configuration14. Incidentally, this is same as that proposed by Rasmussen and coworkers2. Grande M, Personal Communication.


