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The first enantioselective total synthesis of cyclomyltaylane-5α-ol and determination of its absolute stereochemistry

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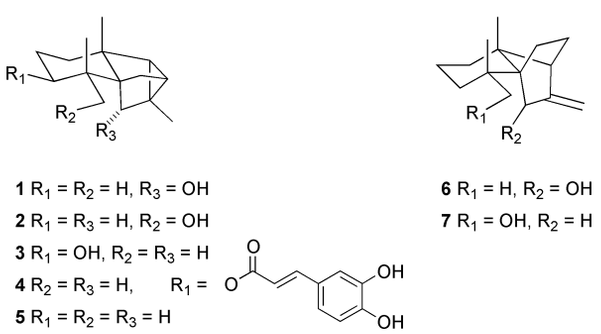
The tetracyclic sesquiterpenoid (+)-cyclomyltaylan-5α-ol **1** has been synthesized starting from (*S*)-(+)-Hajos–Wiechert ketone analogue **10** *via* stereoselective Claisen rearrangement followed by SmI_2-promoted reductive cyclisation. Thus, the absolute configuration has been established to be 2*R*,3*R*,4*R*,5*S*,6*R*,7*R* (cyclomyltaylane numbering) as depicted in structure **1**.

Natural products having diverse structures and important biological activities have been found from various natural sources by the efforts of many research groups.[1] Particularly, liverworts contain structurally as well as physiologically interesting organic molecules. Among them are cyclomyltaylane[2] and myltaylane[3] sesquiterpenoids which have unique tetracyclic and tricyclic carbon frameworks respectively. Since the isolation of cyclomyltaylenol[2a] (cyclomyltaylan-15-ol) **2** as the first cyclomyltaylane natural product from the Japanese *Mylia taylorii* (Hook.) S. Gray by Matsuo *et al.*, cyclomyltaylan-3-ol[2b] **3** along with cyclomyltaylyl 10α-caffeate[2b] **4** from the Japanese *Bazzania japonica* have been isolated by Asakawa *et al.* and subsequently cyclomyltaylane[2c] **5** and (+)-cyclomyltaylan-5α-ol[2d] **1** from the Taiwanese *Bazzania tridens* and *Reboulia hemisphaerica* by Wu *et al*. Their tricyclic congeners, (−)-myltaylenol [myltayl-4(12)-en-15-ol][3a] **6** and (−)-myltayl-4(12)-en-5-ol[3b] **7**, were also isolated by Matsuo *et al.* and Asakawa *et al.* from the *Mylia taylorii* and the French *Bazzania trilobata* respectively (Fig. 1).



1 $R_1 = R_2 = H$, $R_3 = OH$
2 $R_1 = R_3 = H$, $R_2 = OH$
3 $R_1 = OH$, $R_2 = R_3 = H$
4 $R_2 = R_3 = H$, R_1 =
5 $R_1 = R_2 = R_3 = H$

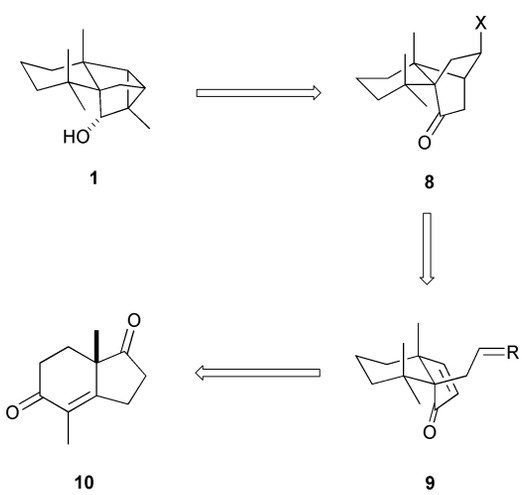
6 $R_1 = H$, $R_2 = OH$
7 $R_1 = OH$, $R_2 = H$

Fig. 1

Though biological activities of these sesquiterpenoids are underdeveloped, cyclomyltaylyl 3-caffeate **4** inhibited release of the superoxide anion from guinea-pig peritoneal macrophage induced by O_2^- stimulant FMLP (formyl-methionyl-leucyl-phenylalanine; 10^{-7} M) at ID_{50} 7.5 μg ml^{-1}.[2b] The relative stereochemistries of every cyclomyltaylane natural product have been determined by using modern NMR techniques, the absolute configurations have not been established yet except for compound **3** which was determined by the empirical CD octant rule. Intrigued by its novel carbon framework containing tetramethyltetracyclo[6.2.1.$0^{1,6}$.$0^{7,9}$]undecane ring with three contiguous quaternary carbon centers and an absence of successful total synthesis of cyclomyltaylane-type sesquiterpenoids, we set out on a synthetic study of cyclomyltaylane-5α-ol **1** and delineate herein the first enantioselective total synthesis of **1** thereby establishing its absolute stereochemistry.[4]

Results and discussion

Our retrosynthetic design is illustrated briefly in Scheme 1. Final



1 **8** **10** **9**

Scheme 1

ring closure to the cyclopropane ring of **1** could be accomplished by an intramolecular substitution of ketone **8** which could be derived by intramolecular reductive cyclisation of formyl-enone **9** (R = O). The enone **9** in turn could be obtained by stereoselective introduction of an allyl unit at the angular position of the Hajos–Wiechert ketone analogue **10**.

Though the absolute stereochemistry of the natural product **1** was unknown, we employed the optically active (*S*)-(+)-Hajos–Wiechert ketone analogue**10**[5] as a starting material which was prepared by amino acid mediated asymmetric intramolecular cyclisation of 2-methyl-2-(3-oxopentyl)cyclopentane-1,3-dione **11** (Scheme 2). The reaction conditions for cyclisation have already been developed by us in the

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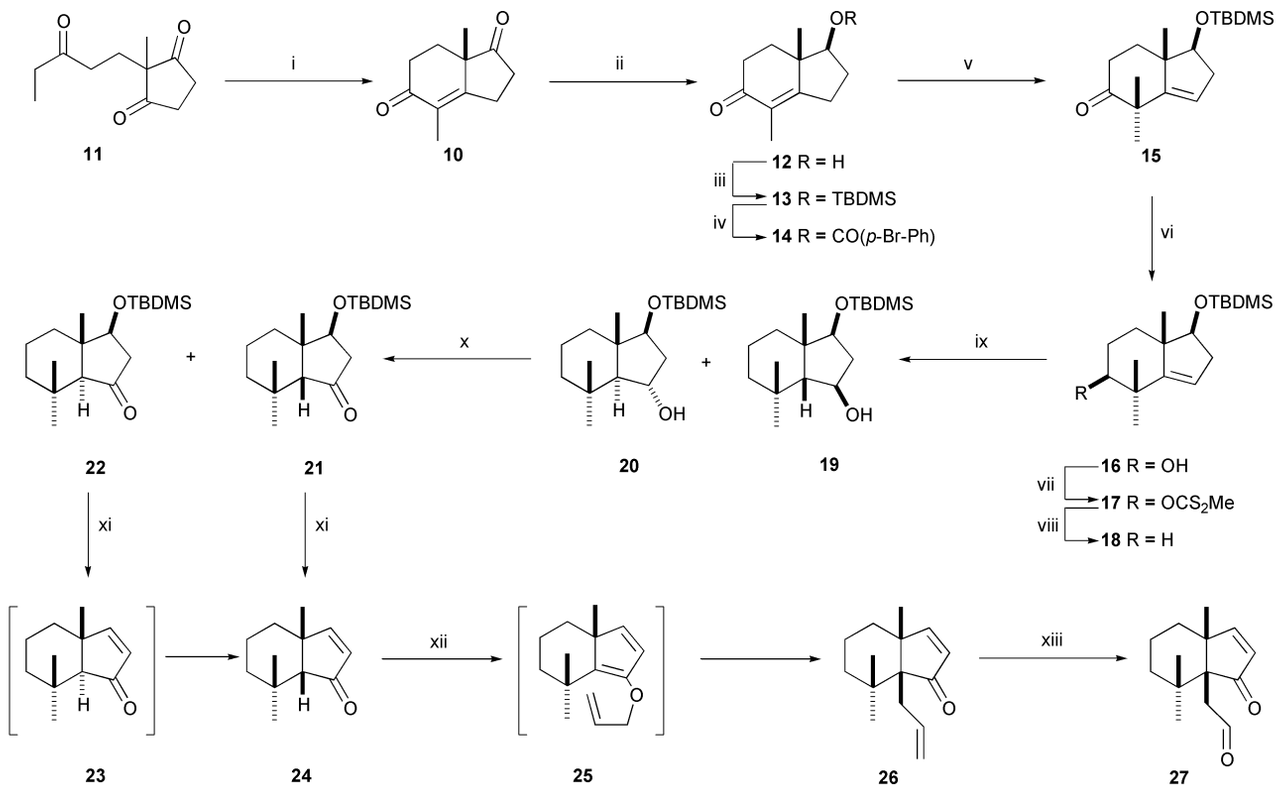
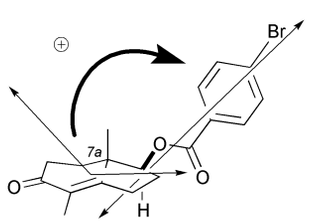


Scheme 2 *Reagent, conditions and yields*; i, L-β-phenylalanine, D-CSA, MeCN, 30–70 °C, 5 days, 99% (45% after recrystallizations); ii, $NaBH_4$, MeOH, −25 °C, 100%, iii, TBDMSCl, imidazole, DMAP, DMF, r.t., 98%; iv, *p*-Br–C_6H_4COCl, DMAP, pyridine, r.t., 99%; v, MeI, *t*-BuOK, *t*-BuOH, reflux, 65%; vi, LAH, Et_2O, −78 °C, 98%; vii, *n*-BuLi, CS_2, MeI, THF, 0 °C; viii, *n*-Bu_3SnH, AlBN, toluene, reflux, 8 min, 92% in two steps; ix, BH_3·THF, THF, r.t., 2.5 h, then NaOH, H_2O_2, r.t., overnight, 84%; x, PCC, 4 Å-MS, CH_2Cl_2, r.t., 9 h, 98% from **19**, 89% from **20**; xi, DBU, *t*-BuOH, reflux, overnight, 90% from **21**, 88% from **22**; xii, KH, allyl bromide, THF, 0 °C 2 h, r.t. 2 h, 45–50 °C 5 h, toluene, reflux 12 h, 96%; xiii, OsO_4, $NaIO_4$, *t*-BuOH, H_2O, r.t., 3 h, 81%.

preparation of optically active Wieland–Miescher ketone analogue[6] and successfully employed for the total syntheses of several terpenoids.[7] Thus treatment of **11** with L-phenylalanine and (+)-camphorsulfonic acid by gradual warming to 80 °C afforded (+)-enedione **10** ($[\alpha]_D$ +297) as crystals in 45% yield after recrystallisation. The enantiomeric excess of **10** was obtained by GLC analysis on a chiral stationary phase (column: cyclodextrine-β-236M-19) to be more than 98% ee. The absolute configuration of **10** was determined by applying the exciton chirality method as follows. The carbonyl group at C-1 in **10** was regio- and stereoselectively reduced with 0.26 equiv. of sodium borohydride in absolute EtOH at −20 °C to give quantitatively β-alcohol **12** as a sole product which was then treated with *p*-bromobenzoyl chloride in pyridine in the presence of DMAP to afford *p*-bromobenzoate **14** in 99% yield (Scheme 2).

The CD spectrum of the benzoate **14** showed an exciton type of positive first ($\Delta\varepsilon$ + 21.9 at 255 nm) and a negative second ($\Delta\varepsilon$ −37.4 at 203 nm) Cotton effect. This result clearly indicated that the chirality between the two long axes of transition moments of enone and benzoate chromophores was positive as shown in Fig. 2.[8]

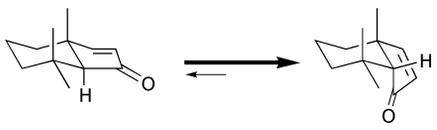
Thus, the absolute stereochemistry of the (+)-enedione **10** was unambiguously established as (7a*S*). Prior to the transformation of the cyclohexenone ring, the β-alcohol in **12** was protected with TBDMSCl to afford TBDMS ether **13**. Methylation with excess iodomethane (MeI) in the presence of *t*-BuOK in *t*-BuOH at reflux temperature[9] provided deconjugated ketone **15** in 65% yield along with the recovered **13** (11%) and a small amount of tetramethylindanone. Lithium aluminium hydride (LAH) reduction of **15** afforded β-alcohol **16** as a sole product in 98% yield. The stereochemistry of the resulting hydroxy group of **16** was determined to be β-equatorial orientation judging from coupling constants (9.2 and 7.4 Hz) of a proton at C_5.



14

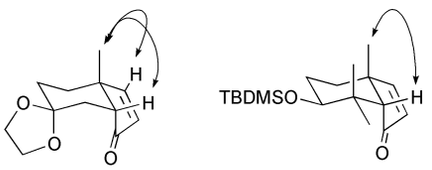
Fig. 2

The hydroxy group of the alcohol **16** was removed by Barton's radical protocol.[10] Treatment of the alcohol **16** with *n*-BuLi followed by successive addition of carbon disulfide and MeI afforded xanthate **17**. Then the xanthate **17** was subjected to reaction with *n*-Bu_3SnH in the presence of a catalytic amount of AIBN in toluene at reflux for 8 min to give olefin **18** in 92% yield from **16**. In order to arrange the cyclopentenone moiety, hydroboration of the olefin **18** was carried out to provide regioselectively β-**19** and α-alcohol **20** in 84% yield 1 : 1.9 ratio in favour of the latter indicating that the α-face of **18** was less sterically crowded. Independent PCC oxidation of **19** and **20** in the presence of molecular sieves powder afforded ketone **21** and **22** in 98 and 89% yield respectively. A slower rate of oxidation of **19** compared with **20** implies that the hydroxy group of **19** is sterically more hindered. Treatment of the ketones **21** and **22** with DBU in *t*-BuOH lead to the same cyclopentenone **24** in 90% and 88% yield, respectively. In benzene, the β-elimination required a longer reaction time and resulted in a lower yield. Concomitant facile isomerisation occurred from enone **23** to thermodynamically more stable **24** (Fig. 3), though the stereochemistry of **24** could not be assigned by NMR techniques. Deducing from the *cis*-stereochemistries of related compounds **28** and **29** determined by NOE (Fig. 4) and calculated heat of formation of **23** (−41.5 kcal mol^{-1}) and



23 **24**

Fig. 3

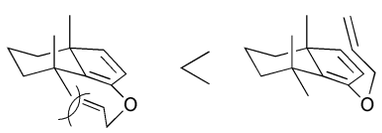


28 **29**

Fig. 4 Selected NOE of related compounds.

24 (−49.2 kcal mol^{-1}) by PM3 method, the enone **24** might have *cis*-stereochemistry as depicted in the structure **24**.

Introduction of the allyl unit was at first investigated by using enone **29**. D_2O quenching of the enolate of **29** generated by LDA at −78 °C incorporated deuterium in 93% yield at the angular position. However, attempts of angular allylation of the enolate of **29** generated by LDA with allyl bromide in the presence of HMPA resulted in complete recovery of **29**, probably due to steric hindrance imposed by bis-neopentyl position. On the other hand, treatment of the enone **24** with potassium hydride and allyl bromide furnished unstable *O*-allylated dienol ether **25**. After addition of toluene, the resulting solution was heated at reflux and the desired allylenone **26** was furnished by Claisen rearrangement as a single isomer in 96% yield in one pot operation. Unfortunately, the stereochemistry of **26** could not be determined by spectroscopic means. The stereoselective introduction of the allyl group from the β-face of the enone **24** was finally proved by transformation of **26** into the natural product **1**. Present stereoselective introduction of the allyl unit at angular position is explained by the fact that the Claisen rearrangement proceeded from the less sterically congested conformer **25B** by assuming a chair like transition state (Fig. 5).



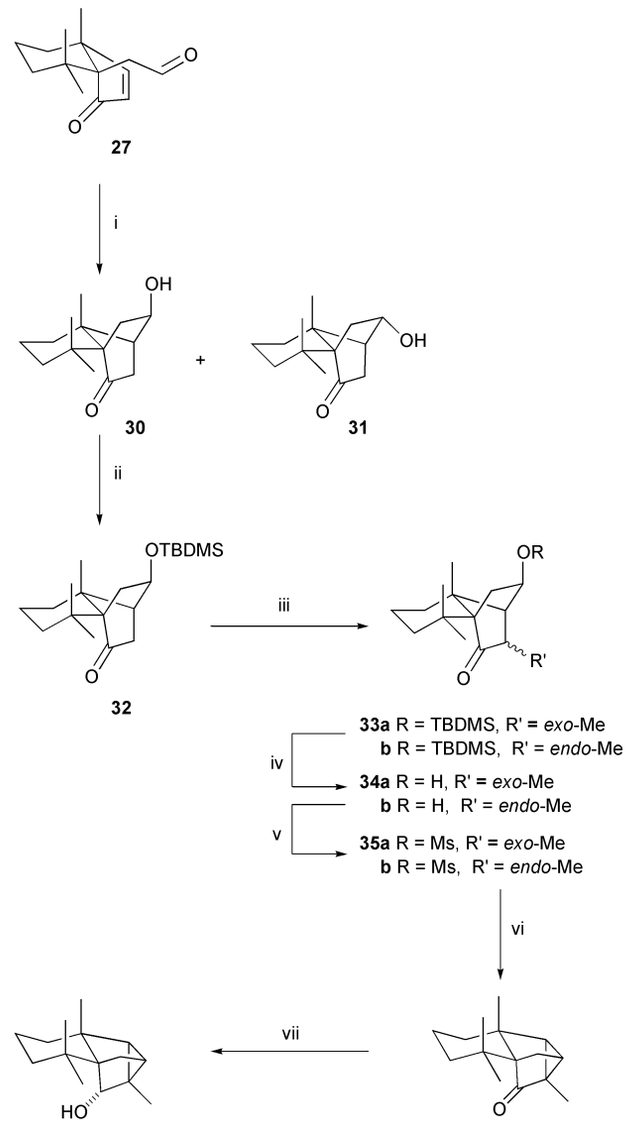
25A **25B**

Fig. 5

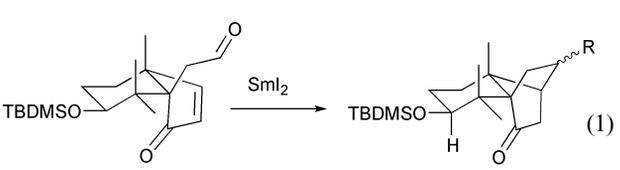
Then, construction of the tricyclo[5.2.2.0^{1,6}]undecane framework was investigated by intramolecular reductive cyclisation of formyl enone **27** (Scheme 3). Recently, efficiency of reductive cyclisation of alkyl or ketyl radical species generated by samarium(II) iodide (SmI_2) is well precedented.[11] Enholm *et al.* and other groups have reported SmI_2-mediated intramolecular reductive cyclisation of carbonyl groups with olefin or electron-deficient olefins[11,12] though these reactions proceeded only in *exo-trig* mode. We anticipated that such methodology would be applicable for our purpose, though a successful cyclisation between the cyclic enone moiety and formyl group has not been well precedented. To this end, the allyl group of olefin **26** was oxidatively cleaved with a catalytic amount of OsO_4 and excess $NaIO_4$ in *t*-BuOH–H_2O to furnish formylenone **27** in 81% yield.

According to the literature procedure,[13] SmI_2 was prepared as a 0.1 M solution in THF from excess metallic Sm and 1,2-diiodoethane in THF at room temperature. Optimised reaction conditions were investigated by using formyl-enone **37** alternatively prepared [Equation (1)].

In an initial attempt, treatment of **37** with 3.0 equiv. of SmI_2 gave the recovered aldehyde **37** (29%) and the enone **29** (18%)



Scheme 3 *Reagents conditions and yields*; i, SmI_2, *t*-BuOH, HMPA, −78 °C, 62%; ii, TBDMSCl, DMAP, imidazole, DMF, r.t., overnight, 94%; iii, LiHMDS, MeI, THF, 0 °C, 83% (mixture of **33a** and **33b**); iv, TBAF, THF, r.t., 90% (**34a** : **34b** = 1 : 2.3); v, MsCl, Et_3N, DCM, 94% (from **34b**), 76% (from **34a**); vi, NaOEt, r.t., 93% (from **35b**), 77% (from **35a**); vii, LAH, 0 °C, 81%.



37

40 (R = *endo*-OH)

41 (R = *exo*-OH)

after aqueous work up (Table 1, entry 1). With *t*- BuOH as a proton source and excess HMPA in order to enhance reducing ability of SmI_2,[14] the reaction of **37** with 1.8 equiv. of SmI_2 at room temperature for 0.5 h gave tricyclic hydroxyketone **40** and **41** in 5 and 18% yields respectively, along with the recovered aldehyde **37** (11%) after aqueous work up (Table 1, entry 2). From the TLC inspection of the aqueous layer, it was not possible to extract products **40** and **41** completely from the resulting aqueous layer. Thus direct isolation was carried out by silica gel column chromatography after quenching the reaction by addition of silica gel in entries 3 to 5. When the enone-aldehyde **37** was treated with SmI_2 and *t*-BuOH in the presence of excess HMPA at −78 °C for 10 min, hydroxyketone **40** and **41** were

Table 1

Entry	Substrate	Reagents	Conditions	Product and yield (%)
1	**37**	SmI_2 (3.0 equiv.)	r.t., 1.0 h	**37**, 29 **29**, 18
2	**37**	SmI_2 (1.8 equiv.) *t*-BuOH (1.2 equiv.) HMPA	r.t., 0.5 h	**41**, 18 **40**, 5 **37**, 11
3[a]	**37**	SmI_2 (3.0 equiv.) *t*-BuOH (1.2 equiv.)	r.t., 13 h	**41**, 1 **40**, 12 **29**, 44
4[a]	**37**	SmI_2 (3.0 equiv.) *t*-BuOH (1.2 equiv.) HMPA	−78 °C, 10 min	**41**, 52 **40**, 24
5[a]	**27**	SmI_2 (3.0 equiv.) *t*-BuOH (1.2 equiv.) HMPA	−78 °C, 15 min	**30**, 43 **31**, 19

[a] The products were isolated without aqueous work up.

obtained in 24 and 52% yield (Table 1, entry 4). In a similar manner, reaction of **27** provided the desired tricyclic product **30** and **31** in 43 and 19% yields respectively. The relative stereochemistry of the major hydroxyketone **41** was confirmed by NOE experiments as depicted in Fig. 6. In the minor hydroxyketone **40**, W-type long range coupling (1.2 Hz) between C_2–H (δ 4.71; dddd, *J* 9.6, 4.4, 4.4 and 1.2 Hz) and C_4–H_{exo} (δ 2.20; ddd, *J* 18.8, 4.4 and 1.2 Hz) established the orientation of the hydroxy group to be *endo* (Fig. 6). In a similar manner, W-type long range coupling was observed in the hydroxyketone **31**. The proton on a carbon with a hydroxy group in **30** appeared at a higher field (δ 4.04) than the corresponding proton of **31** (δ 4.67). These results also confirmed stereochemistries of the hydroxy groups of **30** and **31**. When the reaction was run without HMPA, reductive elimination of acetaldehyde predominated to give the enone **29** as a major product (Table 1, entry 3).

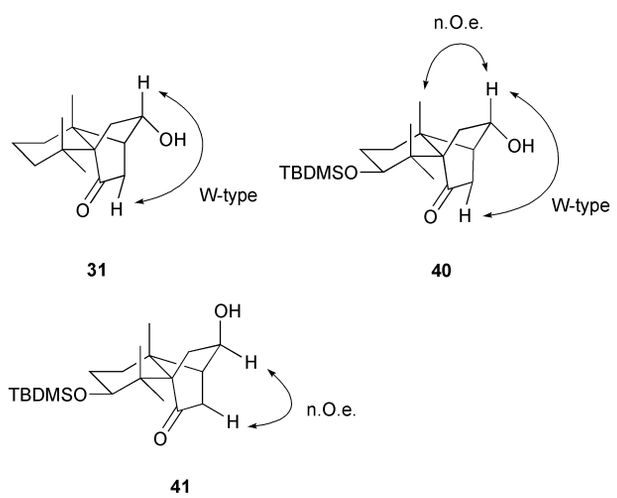


Fig. 6 Stereochemical assignments of pinacol products.

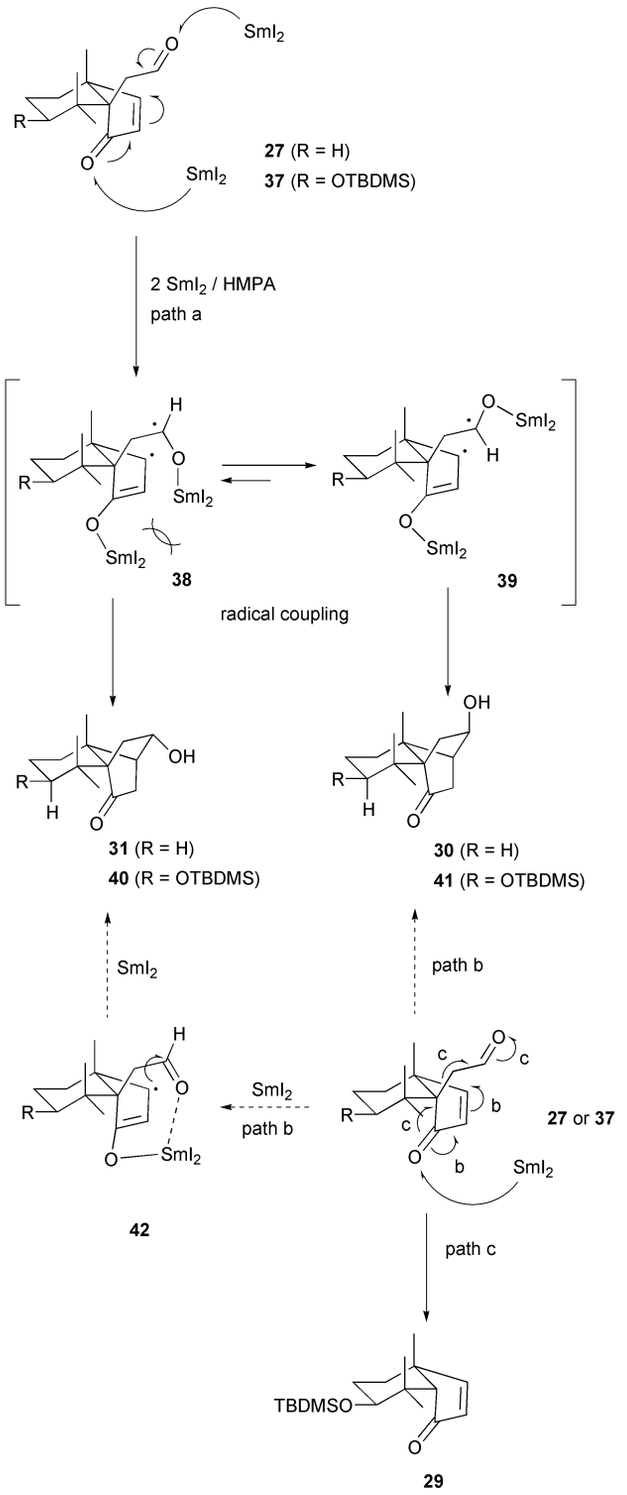
Plausible reaction pathway drawn from these results is described in Scheme 4. Since the reduction potential of cyclohexenone is lower (1.55 V *vs.* SCE) than propionaldehyde (1.8 V *vs.* SCE),[15] initially we anticipated that the reaction proceeded by chelation control through one-electron transfer to the cyclopentenone moiety followed by intramolecular trapping of the resulting radical by the formyl group in intermediate **42** (path b) to afford the *endo*-alcohol **31** or **40** as a major product. However, *exo*-hydroxyketone **30** or **41** was isolated as a major isomer with 3 equiv. of SmI_2. Judging from these results, the present reaction might proceed through the thermodynamically controlled 6-*endo*-*trig* mode vinylogous pinacol coupling pathway after two-electron transfer to **27** or **37** (path a). Steric interference between the two Sm atoms coordinated to the intermediary two alkoxy groups in the intermediate **38** equilibrated into more stable intermediate **39** and provided *exo*-alcohol **30** or **41** preferentially. In the absence of HMPA, the reaction became slow. An attempt at a higher reaction temperature resulted in reductive elimination of the acetaldehyde unit to give enone **29** (path c), [14a,16] During the course of our synthetic study, Tori and his co-workers also reported similar 6-*endo*-*trig* cyclisation of formylenone leading to hydrindanone.[17]

The final transformation to the natural product **1** to furnish the tetracyclic framework by intramolecular cyclisation was carried out as follows (Scheme 3). It was fortunate for our purpose that the *exo*-hydroxyketone **30** predominated by the reductive cyclisation. The hydroxyketone **30** was protected in 94% yield as the TBDMS ether **32** which was then methylated with LiHMDS and MeI in THF at 0 °C to afford **33** as a diastereomeric mixture. Without separation, subsequent deprotection of the TBDMS ether with TBAF provided alcohols **34a** and **34b** in a 1 : 2.3 ratio in 90% combined yield. These alcohols were separately subjected to conventional mesylation to yield mesylates **35a** and **35b** in 76 and 94% yield respectively. Intramolecular substitution of the mesylate **35a** or **35b** with NaOEt[18] provided cyclomyltaylan-5-one **36** in 77 or 93% yield respectively. Finally, stereoselective reduction of the ketone **36** with LAH furnished (+)-cyclomyltaylan-5α-ol **1** {$[a]_D^{20}$ +33 (*c* 0.3, $CHCl_3$)} in 81% yield. Spectral data of the synthetic **1** were completely identical with those of natural product **1** {$[a]_D$ +36 (*c* 0.2, $CHCl_3$)}[2d] thereby establishing the absolute stereochemistry of the natural product **1** as depicted in structure **1**.

In conclusion, we have achieved an enantioselective first total synthesis of (+)-cyclomyltaylan-5α-ol **1** starting from the optically active (*S*)-(+)-Hajos–Wiechert ketone analogue **10** *via* stereoselective Claisen rearrangement followed by SmI_2-mediated reductive coupling as key steps. The absolute configuration of the natural product **1** was thus established to be 2*R*,3*R*,4*R*,5*S*,6*R*,7*R* (cyclomyltaylane numbering) as shown in structure **1** in Fig. 1.

Experimental

Mps were determined with a Yanaco MP hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer in carbon tetrachloride unless otherwise indicated. ^{1}H-NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-Values are in Hz. ^{13}C-NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (50 MHz) and Unity 500plus (125 MHz) instruments. Mass spectral data were obtained with a Hitachi M-80B spectrometer. UV and CD spectra were obtained by a JASCO J-720W instrument. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for



Scheme 4

solutions in chloroform unless otherwise indicated and are given in 10^{-1} deg cm^2 g^{-1}. Medium-pressure liquid chromatographies (MPLC) were carried out on a JASCO PRC-50 instrument with a silica gel packed column. Microanalyses were carried out in the Instrumental Analysis Center for Chemistry, Tohoku University.

(7a*S*)-(+)-4,7a-Dimethyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5(6*H*)-dione 10

A solution of the triketone **11** (20.7 g, as a 100 mmol), L-β-phenylalanine (16.5 g, 100 mmol) and D-camphorsulfonic acid (11.6 g, 50 mmol) in acetonitrile (350 ml) was stirred at room temperature under a nitrogen atmosphere overnight. Then the mixture was heated at 30 °C for 24 h, and the temperature was raised in 10 °C intervals in every 24 h during 4 days. After the mixture was stirred at 70 °C for 19.5 h, the solvent was evaporated *in vacuo* and the residue was diluted with ethyl acetate. The organic layer was washed with water and brine. The aqueous layer was extracted with ethyl acetate six times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by flash column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 2) of the residue afforded diketone **10** (17.6 g, 99% for 2 steps) as a brown viscous oil which crystallised in *n*-hexane–diethyl ether at −78 °C. Recrystallization from diethyl ether at −30 °C gave pale yellow needles (7.97 g, 45%) which had mp 35.5–36.5 °C; $[a]_D^{25}$ +297 (*c* 1.03, benzene); ν_{max}/cm^{-1} ($CHCl_3$) 2955, 2932, 1748, 1659, 1449, 1354, 1117, 1082 and 1007; δ_H (200 MHz) 1.29 (s, 3H), 1.79 (s, 3H), 1.80 (dd, *J* 13.0, 7.0, 1H), 2.05 (dd, *J* 4.6, 2.8, 2H) and 2.35–3.10 (m, 6H).

An enantiomeric excess was obtained by GLC analysis on a chiral stationary phase (Cyclodextrine-β-236M-19).

(1*S*,7a*S*)-(+)-1-Hydroxy-4,7a-dimethyl-2,3,7,7a-tetrahydro-1*H*-indene-5(6*H*)-one 12

To a stirred solution of the diketone **10** (1.03 g, 5.76 mmol) in ethanol (20 ml) was added sodium borohydride (59 mg, 1.57 mmol) at −25 °C. After being stirred for 50 min at this temperature, the reaction was quenched by the addition of brine and the aqueous layer was extracted with ethyl acetate three times. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by flash column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 1) of the residue provided alcohol **12** (1.11 g, 100%) as a pale yellow viscous oil which had $[a]_D^{20}$ +58.2 (*c* 1.03); ν_{max}/cm^{-1} 3424, 2969, 1659, 1449, 1354, 1210, 1159, 1100, 1074, 1046 and 787; δ_H (200 MHz) 1.09 (s, 3H), 1.62 (s, 3H), 1.70–1.89 (m, 2H), 2.15–2.18 (m, 2H), 2.37–2.45 (m, 2H), 2.54–2.61 (m, 2H) and 3.82 (dd, *J* 10.6, 7.3, 1H).

(1*S*,7a*S*)-(+)-1-*p*-Bromobenzoyloxy-4,7a-dimethyl-2,3,7,7a-tetrahydro-1*H*-indene-5(6*H*)-one 14

A mixture of the alcohol **12** (76 mg, 0.421 mmol), *p*-bromobenzoyl chloride (228 mg, 1.26 mmol) and DMAP (27 mg, 0.224 mmol) in anhydrous pyridine (4 ml) was stirred at room temperature for 14.5 h under a nitrogen atmosphere. After addition of water, the resulting solution was extracted with ethyl acetate three times, and the combined organic layer was washed with water three times and brine twice and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 3) provided benzoate **14** (151 mg, 99%) which had UV (EtOH) λ_{max} 246.5 nm (ε 15,072); CD (EtOH) λ_{ext} 255 nm ($\Delta\varepsilon$ +21.9) and 203 (−37.4); ν_{max}/cm^{-1} 3042, 2944, 1721, 1657, 1591, 1485, 1271, 1119, 1017 and 851; δ_H (200 MHz) 1.30 (s, 3H), 1.71 (s, 3H), 1.85–2.15 (m, 3H), 2.35–2.81 (m, 5H), 5.04 (dd, *J* 10.2, 7.2, 1H), 7.60 (d, *J* 8.7, 2H) and 7.91 (d, *J* 8.7, 2H); δ_C (50 MHz) 10.86 (q), 16.98 (q), 25.81 (t), 26.63 (t), 33.08 (t), 34.10 (t), 44.79 (s), 81.99 (d), 128.28 (s), 128.85 (s), 129.41 (s), 131.03 (d × 2), 131.77 (d × 2), 165.26 (s), 165.33 (s), 198.16 (s).

(1*S*,7a*S*)-(+)-4,7a-Dimethyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)-2,3,7,7a-tetrahydro-1*H*-indene-5(6*H*)-one 13

To a stirred solution of the alcohol **12** (2.88 g, 16.0 mmol) in DMF (22 ml) was successively added imidazole (2.80 g, 41.1 mmol), DMAP (196.4 mg, 1.61 mmol) and TBDMSCl (4.84 g, 32.1 mmol) at 0 °C under a nitrogen atmosphere. After being stirred at room temperature overnight, the reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate three times. The organic layer was washed with water and brine and dried over

anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was purified by flash column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 30 then 1 : 10) and subsequent MPLC (eluent ethyl acetate–*n*-hexane = 1 : 10) provided ether **13** (4.12 g, 98%) as a pale yellow viscous oil which had $[\alpha]_D^{20}$ +32.8 (*c* 1.02); ν_{max}/cm^{-1} (neat) 2957, 1667, 1465, 1379, 1255, 1125, 1030 and 899; δ_H (200 MHz) 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.07 (s, 3H), 1.65 (s, 3H), 1.69–2.57 (m, 8H) and 3.72 (dd, *J* 10.3, 7.3, 1H); δ_C (50 MHz) −4.9 (q), −4.5 (q), 10.6 (q), 15.3 (q), 17.9 (s), 25.7 (q × 3 and t), 29.9 (t), 33.3 (t), 43.2 (t), 45.3 (s), 81.0 (d), 128.6 (s), 167.7 (s) and 198.6 (s) (Found: C, 69.08; H, 10.15%. Calc. for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.2%).

(1*S*,7a*S*)-(+)-4,4,7a-Trimethyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)-1,2,4,6,7,7a-hexahydro-5*H*-inden-5-one 15

To a stirred solution of the ether **13** (50 mg, 0.17 mmol) in absolute *tert*-butanol (2-methylpropan-2-ol) (*t*-BuOH) (2 ml) was added potassium *tert*-butoxide (*t*-BuOK) (95 mg, 0.85 mmol) at ambient temperature under a nitrogen atmosphere. The resulting solution was heated at reflux temperature for 30 min and then iodomethane (MeI) (106 µl, 1.7 mmol) was added. After being stirred for 1 h at the same temperature, additional MeI (53 µl, 0.85 mmol) was added and stirring was continued for 1 h. Removal of the solvent *in vacuo* followed by purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 10) afforded the recovered ether **13** (5 mg, 11%) and ketone **15** (34 mg, 65%) as a colorless oil which had $[\alpha]_D^{20}$ +48.5 (*c* 1.10); ν_{max}/cm^{-1} 3072, 2959, 1715, 1462, 1240, 1125, 1042 and 905; δ_H (200 MHz) 0.05 (s, 6H), 0.90 (s, 9H), 1.15 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 1.60–1.92 (m, 2H), 2.20–2.50 (m, 2H), 2.52–2.69 (ddd, *J* 15.2, 10.3, 5.5, 1H), 3.91 (dd, *J* 8.8, 7.6, 1H) and 5.40 (dd, *J* 3.3, 2.0, 1H); δ_C −4.9 (q), −4.4 (q), 17.6 (q), 18.0 (s), 23.7 (q), 25.8 (q × 3), 28.0 (q), 33.9 (t), 35.0 (t), 37.9 (t), 46.8 (s), 48.3 (s), 81.5 (d), 119.7 (d), 154.2 (s) and 215.1 (s) (Found: C, 70.14; H, 10.43%. Calc. for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.45%).

(1*S*,5*S*,7a*S*)-(−)-4,4,7a-Trimethyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)-1,2,4,6,7,7a-hexahydro-5*H*-inden-5-ol 16

To a stirred solution of the ketone **15** (1.84 g, 5.97 mmol) in diethyl ether (35 ml) was added LAH (228 mg, 6.02 mmol) at −78 °C under a nitrogen atmosphere. After being stirred for 30 min at −78 °C, the reaction was quenched by careful addition of aq. ammonium chloride. The resulting solution was passed through a short silica gel column with the aid of ethyl acetate. Evaporation of the solvent *in vacuo* gave alcohol **16** (1.83 g, 98%) as white needles which had mp 86.0–87.5 °C (from *n*-hexane); $[\alpha]_D^{20}$ −4.2 (*c* 0.996); ν_{max}/cm^{-1} 3505, 3072, 2959, 1552, 1471, 1360, 1250, 1121, 1067 and 1040; δ_H (200 MHz) 0.03 (s, 6H), 0.89 (s, 9H), 1.04 (s, 6H), 1.14 (s, 3H), 1.35–1.90 (m, 5H), 2.12 (ddd, *J* 14.9, 9.2, 1.7, 1H), 2.30 (ddd, *J* 14.9, 7.4, 3.3, 1H), 3.26 (dd, *J* 10.6, 4.4, 1H), 3.78 (dd, *J* 9.2, 7.4, 1H), 5.32 (dd, *J* 3.3, 1.7, 1H); δ_C −4.8 (q), −4.4 (q), 17.7 (q), 18.1 (s), 21.4 (q), 25.6 (q × 3), 25.9 (q), 27.9 (t), 37.3 (t), 38.2 (t), 39.5 (s), 47.0 (s), 78.0 (d), 83.8 (d), 118.5 (d) and 155.9 (s) (Found: C, 69.84; H, 11.04%. Calc. for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04%).

[(1*S*,5*S*,7a*S*)-4,4,7a-Trimethyl-1-(1,1,2,2-tetramethyl-1-silapropoxy)-1,2,4,6,7,7a-hexahydro-5*H*-inden-5-yl)oxy]methylthiomethane-1-thione 17

To a stirred solution of the alcohol **16** (156 mg, 0.514 mmol) in THF (4.5 ml) was added *n*-BuLi (700 µl, 1.06 mmol, 1.52 M solution in *n*-hexane) at 0 °C. After being stirred for 40 min, carbon disulfide (240 µl, 4.00 mmol) was added. The resulting solution was stirred for 1.5 h and then MeI (170 µl, 2.78 mmol) was added. After being stirred for 1.5 h, the reaction was quenched by addition of aq. ammonium chloride. The aqueous layer was extracted with ethyl acetate five times, and the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 20) of the residue provided xanthate **17** (236 mg) as a reddish oil which had ν_{max}/cm^{-1} ($CHCl_3$) 2996, 2857, 1462, 1258, 1123 and 1062; δ_H (200 MHz) 0.03 (s, 6H), 0.89 (s, 9H), 1.09 (s, 6H), 1.21 (s, 3H), 1.71–2.44 (m, 3H), 2.16 (ddd, *J* 15.0, 9.1, 1.7, 1H), 2.30 (ddd, *J* 15.0, 7.4, 3.3, 1H), 2.55 (s, 3H), 3.83 (dd, *J* 9.1, 7.4, 1H), 5.32 (dd, *J* 11.0, 4.8, 1H) and 5.40 (dd, *J* 3.3, 1.7, 1H); δ_C −4.8 (q), −4.4 (q), 17.7 (q), 18.1 (s), 18.7 (q), 23.4 (t), 23.5 (q), 25.5 (q), 25.8 (q × 3), 36.6 (t), 38.1 (t), 39.4 (s), 46.9 (s), 83.6 (d), 89.6 (d), 119.5 (d), 154.5 (s) and 215.6 (s) (Found: C, 59.84; H, 8.98%. Calc. for $C_{20}H_{36}O_2S_2Si$: C, 70.07; H, 10.45%).

[(1*S*,7a*S*)-(−)-4,4,7a-Trimethyl(2,4,5,6,7,7a-hexahydroindenyloxy)]-1,1,2,2-tetramethyl-1-silapropane 18

A solution of the xanthate **17** (234 mg, 0.514 mmol), tributyltin hydride (315 µl, 1.33 mmol) and AIBN (11 mg, 0.06 mmol) in toluene (4 ml) was heated at reflux for 8 min. After being cooled to room temperature, the resulting solution was passed through a silica gel column (eluent *n*-hexane involving a small amount of triethylamine). Evaporation of the solvent followed by MPLC (eluent *n*-hexane) of the residue provided olefin **18** (225.3 mg, 92%) as a colorless oil which had $[\alpha]_D^{20}$ −4.4 (*c* 0.318); ν_{max}/cm^{-1} (neat) 3075, 2959, 1462, 1363, 1256, 1121, 1038 and 885; δ_H (200 MHz) 0.03 (s, 6H), 0.89 (s, 9H), 1.02 (s, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.10–1.89 (m, 6H), 2.06 (ddd, *J* 14.5, 9.4, 1.8, 1H), 2.22 (ddd, *J* 14.5, 7.6, 3.3, 1H) and 5.23 (dd, *J* 3.3, 1.7, 1H); δ_C −4.7 (q), −4.4 (q), 17.6 (q), 18.2 (s), 19.2 (t), 25.9 (q × 3), 28.7 (q), 30.5 (q), 34.0 (s), 37.1 (t), 39.9 (t), 40.8 (t), 47.1 (s), 84.1 (d), 116.1 (d) and 156.5 (s) (Found: C, 73.35; H, 11.56%. Calc. for $C_{18}H_{34}OSi$: C, 73.40; H, 11.63%).

(1*S*,6*R*,7*R*,9*S*)-(+)-1,5,5-Trimethyl-9-(1,1,2,2-tetramethyl-1-silapropoxy)bicyclo[4.3.0]nonan-7-ol 19 and (1*S*,6*S*,7*S*,9*S*)-(+)-1,5,5-trimethyl-9-(1,1,2,2-tetramethyl-1-silapropoxy)bicyclo-[4.3.0]nonan-7-ol 20

To a stirred solution of the olefin **18** (1.22 g, 4.16 mmol) in THF (20 ml) was added borane–tetrahydrofuran complex (12.5 ml, 12.5 mmol, 1.0 M solution in THF) at room temperature under a nitrogen atmosphere. After being stirred for 2.5 h, the solution was heated at reflux for 5.5 h and 3 M aq. sodium hydroxide (28.0 ml, 84.0 mmol) and 30% H_2O_2 (9.4 ml, 83.1 mmol) were added at room temperature. After being stirred overnight, products were extracted with ethyl acetate twice and the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by flash column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 10) of the residue afforded the alcohols (1.08 g, 84%, **19**–**20** = 1 : 1.9). Analytical samples were obtained by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 7) to give *cis*-fused β-alcohol **19** as an oil and *trans*-fused α-alcohol **20** as white needles in the order of elution.

The β-alcohol **19** had $[\alpha]_D^{20}$ +18.8 (*c* 0.128); ν_{max}/cm^{-1} ($CHCl_3$) 3430, 2932, 1474, 1462, 1389, 1362, 1258, 1080 and 993; δ_H (200 MHz) 0.05 (s, 3H), 0.06 (s, 3H), 0.91 (s, 9H), 1.03 (s, 6H), 1.12 (s, 3H), 1.14–1.58 (m, 8H), 2.44 (ddd, *J* 15.3, 8.8, 4.5, 1H), 3.52 (d, *J* 4.5, 1H) and 4.12 (m, 1H); δ_C −4.9 (q), −4.4 (q), 18.1 (s), 18.4 (t), 23.8 (q), 25.9 (q × 3), 29.8 (q), 30.8 (q), 31.1 (s), 32.5 (t), 36.1 (t), 40.7 (s), 42.7 (t), 81.5 (d), 62.4 (d), 72.5 (d) and 83.1 (d) (Found: C, 69.10; H, 11.61%. Calc. for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61%).

The α-alcohol **20** had $[\alpha]_D^{20}$ +51.1 (*c* 0.558); mp 92.0–92.5 °C (from *n*-hexane); ν_{max}/cm^{-1} ($CHCl_3$) 3440, 2955, 1475, 1462, 1389, 1261, 1119, 1071 and 1028; δ_H (200 MHz) 0.002 (s, 6H), 0.80 (s, 3H), 0.86 (s, 9H), 0.97 (s, 3H), 1.01 (s, 3H), 1.72 (ddd,

J 13.9, 8.7, 3.2, 1H), 1.94 (m, 1H), 3.71 (dd, *J* 8.7, 8.7, 1H) and 4.23 (ddd, *J* 9.6, 9.6, 3.2, 1H); δ_C (50 MHz) −4.8 (q), −4.5 (q), 13.8 (q), 19.4 (t), 21.6 (q), 25.8 (q), 33.9 (q), 38.0 (t), 42.0 (t), 42.4 (t), 60.4 (d), 70.7 (d) and 79.5 (d) (Found: C, 69.24; H, 11.65%. Calc. for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61%).

(1*R*,6*R*,9*S*)-(+)-1,5,5-Trimethyl-9-(1,1,2,2-tetramethyl-1-silapropoxy)bicyclo[4.3.0]nonan-7-one 21

To a stirred mixture of the alcohol **19** (94 mg, 0.30 mmol) and 4 Å molecular sieves (100 mg) in DCM (4 ml) was added PCC (102 mg, 0.464 mmol) and the resulting slurry was stirred at room temperature for 9 h. The mixture was diluted with ethyl acetate and passed through a short silica gel column. The resulting organic layer was washed with water twice and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a short silica gel column to afford ketone **21** (92 mg, 98%) as white needles which had $[\alpha]_D^{20}$ +16.4 (*c* 0.554); mp 36.5–37.0 °C (from *n*-hexane); ν_{max}/cm^{-1} 2955, 1740, 1475, 1462, 1256, 1149, 1105 and 1009; δ_H (200 MHz) 0.02 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 0.88 (s, 3H), 0.93 (s, 3H), 1.03 (s, 3H), 1.04–1.79 (m, 6H), 1.80 (d, *J* 2.0, 1H), 2.18 (ddd, *J* 19.3, 7.7, 2.0, 1H), 2.55 (dd, *J* 19.3, 7.7, 1H) and 4.31 (dd, *J* 7.7, 7.7, 1H); δ_C (50 MHz) −5.0 (q), −4.5 (q), 18.0 (t and s), 24.7 (q), 24.9 (q), 25.8 (q × 3), 32.0 (t), 32.3 (q), 32.4 (s), 39.5 (t), 43.8 (s), 45.8 (t), 64.8 (d), 71.3 (d) and 218.3 (s) (Found: C, 69.65; H, 11.09%. Calc. for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04%).

(1*R*,6*S*,9*S*)-(+)-1,5,5-Trimethyl-9-(1,1,2,2-tetramethyl-1-silapropoxy)bicyclo[4.3.0]nonan-7-one 22

To a stirred mixture of the alcohol **20** (117 mg, 0.374 mmol) and 4 Å molecular sieves (125 mg) in DCM (4 ml) was added PCC (126 mg, 0.561 mmol) and stirring was continued for 4 h at room temperature. The mixture was diluted with ethyl acetate and passed through a short silica gel column. The organic layer was washed with water twice and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent *in vacuo*, the residue was chromatographed on a short silica gel column to afford ketone **22** (104 mg, 89%) as white needles which had $[\alpha]_D^{20}$ +120.9 (*c* 0.412); mp 83.5–84.5 °C (from *n*-hexane); ν_{max}/cm^{-1} 2951, 1743, 1475, 1462, 1387, 1258, 1140 and 1030; δ_H (200 MHz) 0.03 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 0.92 (s, 3H), 1.03 (s, 3H), 1.13 (s, 3H), 1.35–1.69 (m, 6H), 1.84 (ddd, *J* 12.4, 3.2, 3.2, 1H), 1.97 (dd, *J* 18.6, 8.2, 1H), 2.41 (ddd, *J* 18.6, 8.2, 1.0, 1H) and 3.83 (dd, *J* 8.2, 8.2, 1H); δ_C (50 MHz) −4.9 (q), −4.5 (q), 13.6 (q), 18.1 (s), 19.2 (t), 21.5 (q), 25.8 (q × 8), 32.1 (q), 32.3 (s), 37.6 (t), 41.9 (t), 44.1 (t), 44.2 (s), 66.2 (d), 76.8 (d) and 211.8 (s) (Found: C, 69.82; H, 11.10%. Calc. for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04%).

(3a*S*,7a*R*)-(−)-3a,7,7-Trimethyl-3a,4,5,6,7,7a-hexahydroinden-1-one 24

From the ketone 21. To a stirred solution of the ketone **21** (91 mg, 0.293 mmol) in absolute *t*-BuOH (4 ml) was added DBU (180 µl, 1.20 mmol) at room temperature under a nitrogen atmosphere. The resulting solution was heated at reflux temperature overnight and then passed through a short silica gel column. Evaporation of the solvent *in vacuo* followed by column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 5) of the residue gave enone **24** (47 mg, 90%) as white crystals which had $[\alpha]_D^{20}$ −85.2 (*c* 1.038); mp 30.5–32.0 °C (from *n*-hexane); ν_{max}/cm^{-1} 3081, 2967, 1712, 1597, 1465, 1377, 1265, 1147 and 953; δ_H (200 MHz) 0.94 (s, 3H), 1.20 (s, 6H), 1.22–1.48 (m, 2H), 1.50–1.75 (m, 4H), 1.80 (s, 1H), 6.00 (d, *J* 5.7, 1H) and 7.38 (d, *J* 5.7, 1H); δ_C (50 MHz) 17.4 (t), 24.7 (q), 29.0 (q), 31.6 (t), 32.8 (q), 35.9 (t), 61.8 (d), 131.6 (d) and 172.3 (d).

From the ketone 22. To a stirred solution of the ketone **22** (106 mg, 0.340 mmol) in absolute *t*-BuOH (4.5 ml) was added DBU (160 µl, 1.07 mmol) at room temperature under a nitrogen atmosphere. The resulting solution was heated at reflux temperature overnight and then passed through a short silica gel column. Evaporation of the solvent *in vacuo* followed by MPLC purification (eluent ethyl acetate–*n*-hexane = 1 : 5) of the residue afforded enone **24** (54 mg, 88%) as white crystals.

(3a*R*,7a*R*)-(−)-3a,7,7-Trimethyl-7a-prop-2-enyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one 26

To a suspension of potassium hydride (133 mg, 9.95 mmol, 30% in mineral oil, washed with *n*-hexane twice) in THF was added a solution of the enone **24** (585 mg, 3.28 mmol) in THF (3 ml) at 0 °C under a nitrogen atmosphere. After being stirred for 30 min, allyl bromide (1.75 ml, 20.1 mmol) was added to the reaction mixture which was stirred at 0 °C for 2 h, room temperature for 2 h and at 45–50 °C for 5 h. Then, toluene (40 ml) was added to the resulting mixture and stirring was continued at reflux temperature for 12 h. After evaporation of the solvent *in vacuo*, the residue was purified by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 7) to afford enone **26** (689 mg, 96%) as a colorless oil which had $[\alpha]_D^{20}$ −25.3 (*c* 0.198); ν_{max}/cm^{-1} 3081, 2944, 1712, 1638, 1601, 1462, 1392, 1163, 1117 and 993; δ_H (500 MHz) 1.10 (s, 6H), 1.24 (s, 3H), 1.38–1.59 (m, 4H), 1.65–1.92 (m, 2H), 2.60 (m, 2H), 4.90–5.05 (m, 2H), 5.77 (dddd, *J* 17.0, 10.0, 7.1, 7.1, 1H), 5.97 (d, *J* 5.7, 1H) and 7.20 (d, *J* 5.7, 1H); δ_C (50 MHz) 17.31 (t), 25.32 (q), 27.74 (q), 28.95 (q), 35.35 (t), 35.87 (t), 36.38 (t), 36.64 (s), 49.14 (s), 58.58 (s), 116.61 (t), 131.19 (d), 136.85 (d), 170.59 (d) and 213.83 (s) (Found: C, 82.25; H, 10.22%. Calc. for $C_{15}H_{22}O$: C, 82.52; H, 10.16%).

2-[(3a*R*,7a*R*)-(−)-3a,7,7-Trimethyl-1-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-inden-7a-yl]ethanal 27

To a stirred solution of the enone **26** (731 mg, 3.35 mmol) in *t*-BuOH (100 ml) and water (50 ml) was successively added osmium tetraoxide (14 mg, 0.0537 mmol) and sodium periodate (3.58 g, 16.7 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was poured into water. The resulting mixture was extracted with ethyl acetate twice. The organic layer was washed with aq. sodium hydrogencarbonate, water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification (eluent ethyl acetate–*n*-hexane = 1 : 5) of the residue afforded aldehyde **27** (599 mg, 81%) as a viscous oil which had $[\alpha]_D^{20}$ −10.7 (*c* 1.238); ν_{max}/cm^{-1} 2946, 2743, 1721, 1709, 1599, 1470, 1391, 1369, 1230, 1159, 1071 and 908; δ_H (200 MHz) 1.03 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.20–2.05 (m, 6H), 2.67 (dd, *J* 16.6, 3.3, 1H), 2.78 (dd, *J* 16.6, 2.0, 1H), 6.14 (d, *J* 5.8, 1H), 7.38 (d, *J* 5.8, 1H) and 9.73 (dd, *J* 3.3, 2.0, 1H).

(1*R*,6*R*,7*S*,11*S*)-(−)-11-Hydroxy-2,2,6-trimethyltricyclo-[5.2.2.0^{1,6}]undecan-9-one 30 and (1*R*,6*R*,7*S*,11*R*)-(−)-11-hydroxy-2,2,6-trimethyltricyclo[5.2.2.0^{1,6}]undecan-9-one 31

To a stirred solution of the aldehyde **27** (230 mg, 1.04 mmol), absolute *t*-BuOH (121 µl, 1.25 mmol) and HMPA (4.0 ml) in THF (40 ml) was added SmI_2 (31.3 ml, 3.13 mmol, 0.1 M solution in THF) at −78 °C under a nitrogen atmosphere. After being stirred for 15 min, the reaction was quenched by addition of *N,N′*-dimethylaminoethanol (4 ml) and silica gel, and stirring was continued for 1 h at room temperature. The reaction mixture was passed through a short silica gel column. Evaporation of the solvent *in vacuo* followed by MPLC (eluent ethyl acetate–*n*-hexane = 3 : 2) purification of the residue afforded tricyclic alcohol **31** (44 mg, 19%) as white needles and isomeric tricyclic alcohol **30** (101 mg, 43%) as white needles in the order of elution.

The alcohol **31** had mp 111–113 °C; $[\alpha]_D^{20}$ −32.2 (*c* 0.460); ν_{max}/cm^{-1} 3630, 3465, 2947, 2870, 1744, 1468, 1227, 1080, 1029 and 995; δ_H (500 MHz) 0.90 (s, 3H), 1.14 (s, 3H), 1.20 (s, 3H),

1.05–1.20 (m, 2H), 1.29–1.39 (m, 2H), 1.46 (m, 1H), 1.57–1.71 (m, 3H), 2.04 (dd, *J* 4.5, 4.5, 1H), 2.20 (dddd, *J* 18.5, 4.9, 0.8, 0.8, 1H), 2.39 (dd, *J* 14.0, 10.0, 1H), 2.58 (d, *J* 18.5, 1H) and 4.67 (m, 1H); δ_C (50 MHz) 18.4, 21.4, 24.2, 26.2, 30.6, 32.8, 32.9, 34.9, 35.8, 48.6, 49.2, 64.1, 70.2 and 218.7 (Found: C, 75.44; H, 10.10%. Calc. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%).

The alcohol **30** had mp 117–120 °C; $[\alpha]_D^{20}$ −28.3 (*c* 0.512); ν_{max}/cm^{-1} 3627, 3011, 2870, 1744, 1433, 1073, 1040 and 970; δ_H (500 MHz) 0.97 (s, 3H), 1.20 (s, 3H), 1.10–1.25 (m, 3H), 1.35 (s, 3H), 1.43 (br d, *J* 13.5, 1H), 1.48 (br d, *J* 13.5, 1H), 1.54 (d, *J* 18.5, 1H), 1.70 (m, 1H), 1.82 (dd, *J* 14.0, 7.2, 1H), 1.87 (dd, *J* 14.0, 3.5, 1H), 2.01 (br d, *J* 5.1, 1H), 2.24 (br s, 1H), 2.35 (ddd, *J* 18.5, 5.1, 0.9, 1H) and 4.01 (dd, *J* 7.2, 3.5, 1H); δ_C (50 MHz) 18.4, 21.9, 24.7, 26.4, 31.3, 32.4, 33.2, 35.8, 40.2, 48.1, 49.8, 64.1, 75.7 and 218.8 (Found: C, 75.49; H, 10.06%. Calc. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%).

(1*R*,6*R*,7*S*,11*R*)-2,2,6-Trimethyl-11-(1,1,2,2-tetramethyl-1-silapropoxy)tricyclo[5.2.2.0^{1,6}]undecan-9-one 32

To a stirred solution of the alcohol **30** (26 mg, 0.116 mmol) in DMF (2 ml) was successively added imidazole (16 mg, 0.239 mmol), a catalytic amount of DMAP and TBDMSCl (54 mg, 0.359 mmol) at room temperature under a nitrogen atmosphere. After being stirred overnight, the reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 10) of the residue provided TBDMS ether **32** (37 mg, 94%) as a colorless oil which had $[\alpha]_D^{20}$ +3.2 (*c* 1.046); ν_{max}/cm^{-1} 2960, 2861, 1734, 1460, 1260, 1159 and 1015; δ_H (200 MHz) 0.05 (s, 6H), 0.89 (s, 9H), 0.97 (s, 3H), 1.20 (s, 3H), 1.34 (s, 3H), 1.10–1.96 (m, 10H), 2.34 (dd, *J* 18.4, 5.3, 1H) and 3.87 (dd, *J* 6.4, 4.2, 1H); *m*/*z* 336 (M$^+$, 26%), 279 (100), 251 (11), 211 (14), 187 (13), 161 (23), 123 (12), 75 (52) and 41 (15) (Found: M$^+$, 336.2533. Calc. for $C_{20}H_{36}O_2Si$: M$^+$, 336.2484).

(1*R*,6*R*,7*S*,8*RS*,11*R*)-2,2,6,8-Tetramethyl-11-(1,1,2,2-tetramethyl-1-silapropoxy)tricyclo[5.2.2.0^{1,6}]undecan-9-one 33

To a stirred solution of hexamethyldisilazane (118 µl, 0.562 mmol) in THF (1.5 ml) was added a solution of *n*-BuLi (317 µl, 0.499 mmol, 1.58 M solution in *n*-hexane) at 0 °C under a nitrogen atmosphere. After being stirred for 20 min, a solution of the ketone **32** (42 mg, 0.125 mmol) in THF (2.0 ml) was added and the resulting solution was stirred for 30 min at 0 °C. MeI (23 µl, 0.374 mmol) was added and stirring was continued for 35 min. The reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification of the residue on short silica gel column and MPLC (eluent ethyl acetate–*n*-hexane = 1 : 10) provided inseparable mixture of TBDMS ether **33** (36 mg, 83%) as a colorless oil which had δ_H (200 MHz) 0.05 (s, 6H), 0.90 (s, 9H), 0.98 (s, 1H), 1.18 (s, 0.3H), 1.22 (s, 0.7H), 1.34 (s, 0.3H), 1.38 (s, 0.7H), 1.00–1.95 (m, 12.3H), 2.55 (m, 0.7H), 3.91 (m, 0.3H) and 4.18 (dd, *J* 7.3, 3.0, 0.7H).

(1*R*,6*R*,7*S*,8*RS*,11*R*)-11-Hydroxy-2,2,6,8-tetramethyltricyclo-[5.2.2.0^{1,6}]undecan-9-one 34

To a solution of the TBDMS ether **33** (36 mg, 0.104 mmol) in THF (2 ml) was added TBAF (520 µl, 0.520 mmol, 1.0 M solution in THF) at room temperature under a nitrogen atmosphere. After being stirred for 3 h, the reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification of the residue on a short silica gel column and MPLC (eluent ethyl acetate–*n*-hexane = 1 : 1) provided alcohol **33** (22 mg, 90%, **34a**–**34b** = 1 : 2.3) as white crystals.

The *exo*-methyl alcohol **34** had mp 142–143 °C; $[\alpha]_D^{20}$ −37.2 (*c* 0.344); ν_{max}/cm^{-1} 3640, 2930, 2872, 1732, 1453 and 1016; δ_H (200 MHz) 0.98 (s, 3H), 1.05–2.10 (m, 11H), 1.18 (3H, s), 1.25 (d, 3H, *J* 7.1), 1.35 (s, 3H) and 4.30 (dd, *J* 6.2, 4.3, 1H); δ_C (50 MHz) 17.3, 18.8, 21.8, 24.9, 26.2, 32.2, 32.6, 33.1, 35.4, 45.3, 48.1, 56.3, 63.7, 77.1 and 221.3; *m*/*z* 236 (M$^+$, 22%), 163 (74), 123 (100), 95 (38), 69 (30) and 41 (51) (Found: M$^+$, 236.1705. Calc. For $C_{15}H_{24}O_2$: *M*$^+$, 236.1776).

The *endo*-methyl alcohol **34b** had mp 110–112 °C; $[\alpha]_D^{20}$ −3.4 (*c* 0.409); ν_{max}/cm^{-1} 3635, 2951, 2872, 1731, 1468, 1452 and 1006; δ_H (200 MHz) 0.97 (s, 3H), 1.01 (d, *J* 7.2, 3H), 1.05–2.05 (m, 10H), 1.22 (s, 3H), 1.40 (s, 3H), 2.59 (qd, *J* 7.2, 4.9, 1H) and 4.30 (dd, *J* 7.7, 3.4, 1H); δ_C (50 MHz) 11.4, 18.5, 22.3, 24.7, 26.5, 30.3, 33.5, 33.9, 36.3, 41.9, 47.6, 54.5, 64.8, 69.3 and 221.9; *m*/*z* 236 (M$^+$, 23%), 193 (6), 163 (77), 123 (100), 95 (38) and 41 (51) (Found: M$^+$, 236.1744. Calc. For $C_{15}H_{24}O_2$: *M*$^+$, 236.1776).

(1*R*,6*R*,7*S*,8*S*,11*R*)-2,2,6,11-Tetramethyl-10-oxotricyclo-[5.2.2.0^{1,6}]-8-undecyl methane sulfonate 35

To a solution of the alcohol **34** (9 mg, 0.038 mol) in DCM (1 ml) was added DMAP (0.5 mg, 0.004 mol), triethylamine (13 µl, 0.094 mol) and methanesulfonyl chloride (6 µl, 0.075 mol) at 0 °C under a nitrogen atmosphere. After being stirred at room temperature overnight, the reaction mixture was directly chromatographed on a short silica gel column. After evaporation of solvent, purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 1) provided mesylate **35** (9 mg, 76%) as a colourless oil which had δ_H (200 MHz) 0.99 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.30 (d, *J* 7.2, 3H), 1.05–1,85 (m, 7H), 2.05–2.20 (m, 2H), 2.29 (s, 1H), 3.05 (s, 3H) and 4.78 (dd, *J* 7.1, 3.3, 1H); δ_C (50 MHz) 11.3 (q), 18.3 (t), 21.9 (q), 24.6 (q), 26.4 (q), 29.8 (t), 31.9 (t), 33.5 (s), 36.0 (t), 38.5 (q), 41.7 (d), 47.7 (s), 53.0 (d), 60.3 (s) 78.5 (d) and 219.5 (s).

(1*R*,6*R*,7*S*,8*R*,11*R*)-2,2,6,11-Tetramethyl-10-oxotricyclo-[5.2.2.0^{1,6}]-8-undecyl methanesulfonate 35b

To a solution of the alcohol **34b** (23 mg, 0.098 mmol) in DCM (1 ml) was added DMAP (1.2 mg, 0.010 mol), triethylamine (34 µl, 0.244 mol) and methanesulfonyl chloride (15 µl, 0.195 mol) at 0 °C under nitrogen atmosphere. After being stirred at room temperature overnight, the reaction mixture was directly chromatographed on a short silica gel column. After evaporation of solvent, purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 1) provided mesylate **35** (29 mg, 94%) as a colorless oil which had δ_H (200 MHz) 0.98 (s, 3H), 1.10 (d, *J* 7.24, 3H), 1.23 (s, 3H), 1.15–1.80 (m, 6H), 1.92 (dd, *J* 14.9, 8.0, 1H), 2.21 (ddd, *J* 14.8, 3.2, 1.3, 1H), 2.38 (d, *J* 5.1, 1H), 2.78 (qd, *J* 7.3, 5.1, 1H), 3.03 (s, 3H) and 5.13 (dd, *J* 8.0, 3.2, 1H); δ_C (50 MHz) 17.1 (q), 18.7 (t), 21.6 (q), 24.8 (q), 26.0 (q), 30.6 (q), 32.0 (q), 33.0 (s), 35.1 (t), 38.5 (q), 44.6 (d), 48.2 (s), 54.3 (d), 63.1 (s), 83.4 (d) and 218.8 (s).

(1*R*,6*R*,7*S*,8*R*,11*S*)-2,2,6,9-Tetramethyltetracyclo-[6.2.1.0^{1,6}.0$_{7,9}$]undecan-10-one = (cyclomyltaylan-5-one 36

From the mesylate 35. To a stirred solution of sodium methoxide prepared from NaH (4 mg, 0.086 mol, 60% in mineral oil) in anhydrous ethanol (0.3 ml) was added a solution of the mesylate **35** (9 mg, 0.029 mol) in ethanol (1 ml) at room temperature under a nitrogen atmosphere. After being stirred for 2 h, the reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was washed with water and

brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuum* followed by purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 30) provided ketone **36** (5 mg, 77%) as a colorless oil which had $[\alpha]_D^{20}$ +22.5 (*c* 0.730); ν_{max}/cm^{-1} 2944, 2894, 1734, 1458, 1377, 1225, 968 and 885; δ_H (200 MHz) 0.83 (s, 3H), 1.07 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.10–1.20 (m, 2H), 1.40–1.65 (m, 4H) and 1.70–1.95 (m, 4H); δ_C (125 MHz) 8.85, 18.78, 21.43, 25.31, 25.47, 26.78, 27.05, 28.44, 31.30, 33,43, 35.31, 39.17, 44.45, 55.75 and 215.98.

From the mesylate 35. To a stirred solution of sodium ethoxide prepared from NaH (11 mg, 0.276 mol, 60% in mineral oil) in anhydrous ethanol (0.5 ml) was added a solution of the mesylate **35** (29 mg, 0.092 mol) in ethanol (1.5 ml) at room temperature under a nitrogen atmosphere. After being stirred for 2.5 h, the reaction was quenched by addition of aq. ammonium chloride and the aqueous layer was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification of the residue by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 10) provided ketone **36** (19 mg, 93%) as a colorless oil.

(1*R*,6*R*,7*S*,8*R*,11*S*)-2,2,6,9-Tetramethyltetracyclo-[6.2.1.$0^{1,6}$.$0^{7,9}$]undecan-10-ol = (+)-cyclomyltaylan-5α-ol 1

To a solution of the ketone **36** (12 mg, 0.056 mol) in ether (1 ml) was added LAH (3 mg, 0.084 mol) at 0 °C under a nitrogen atmosphere. After being stirred for 30 min, the reaction was quenched by addition of aq. ammonium chloride and the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuum gave the residue which was purified by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 5) to afford (+)-cyclomyltaylan-5α-ol **1** (10 mg, 81%) which had $[\alpha]_D^{20}$ +32.9 (*c* 0.307); δ_H (500 MHz) 0.89 (s, 3H), 0.89–0.90 (m, 1H), 0.93 (d, 5.5), 0.98 (s, 3H), 1.01 (s, 3H), 1.13 (s, 3H), 1.13–1.18 (m, 1H), 1.22 (dd, *J* 10.8, 1.0, 1H), 1.32–1.36 (m, 1H), 1.36 (dd, *J* 10.8, 1.0, 1H), 1.47 (m, 1H), 1.60 (ddddd, *J* 13.6, 13.6, 13,6, 4.2, 4.2, 1H), 1.88 (ddd, *J* 13.6, 13.6, 4.8, 1H), 1.99 (ddd, *J* 13.6, 13.6, 4.3, 1H) and 3.64 (br d, *J* 4.5, 1H); δ_C (125 MHz) 12.74 (q), 17.79 (d), 19.18 (t), 23.16 (q), 23.27 (s), 25.75 (q), 28.00 (t), 29.33 (q), 32.09 (s), 32.57 (t), 34.41 (d), 37.26 (t), 45.30 (s), 51.95 (s) and 86.02 (d).

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