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Synthesis of 8-methyl-*trans,trans*-cyclodeca-3,7-dien-1β-ol and biotransformation into 4aβ-methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1,7β-diol by *Cichorium intybus*.

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Abstract: The biotransformation of 8-methyl-*trans,trans*-cyclodeca-3,7-dien-1β-ol (**6**) into *trans*-decaline **7** by a suspension of fresh chicory root (*Cichorium intybus*) was investigated. In this paper, the synthesis of **6** as well as its enzymatic transfomation into **7**, is presented. A transannular cyclization mechanism of the enzymatically acquired products is proposed.

Introduction

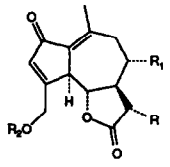
Lactucin and lactucopicrin have long been known to occur in the roots of chicory (*Cichorium intybus*) and to be partly responsible for its bitterness [1]. These, and other sesquiterpene lactones possessing a guaiane, eudesmane or germacrane structure, have been isolated from fresh chicory roots [2-4] and are presented in figure 1. At present the roots are a waste product, produced at the harvest of the edible chicory sprouts. They can be used as a cheap starting material for the elucidation of the biosynthesis of sesquiterpenes in *C. intybus* and other members of the Compositae family.

Germacrane type sesquiterpenes are considered to be important intermediates in the biosynthesis of guaiane, eudesmane, elemane and other types of of sesquiterpenes [5-7]. The biotransformation of the germacrane cichorioside C into the guaiane dihydrolactucine in chicory roots, reported by Leclercq [8], revealed the synthetic capability of these species and induced us to investigate this cyclization reaction more closely.

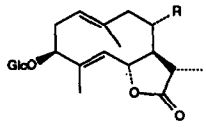
Since dihydrolactucine is isolated from chicory roots as a single enantiomer, an enzyme catalyzed cyclization reaction is likely to be involved. To obtain more insight in this reaction, chicory roots were incubated with a germacrane-like compound to serve as a model system.

Results and discussion.

Despite the fact that a large number of germacranes have been identified, the synthesis of these compounds is not well developed due to the lack of suitable methods for the construction of 10-membered rings

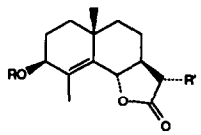


name	R	R_1	R_2
lactucine	CH_2	OH	H
8-deoxylactucine	CH_2	H	H
lactucopicrine	CH_2	*p*-$HOC_6H_4CH_2COO$	H
dihydrolactucine	CH_3	OH	H
dihydro-8-deoxylactucine	CH_3	H	H
dihydrolactucopicrine	CH_3	*p*-$HOC_6H_4CH_2COO$	H
crepidiaside B	CH_3	H	Glc
cichorioside B	CH_3	OH	Glc



sonchuside A R = H

cichorioside C R = OH



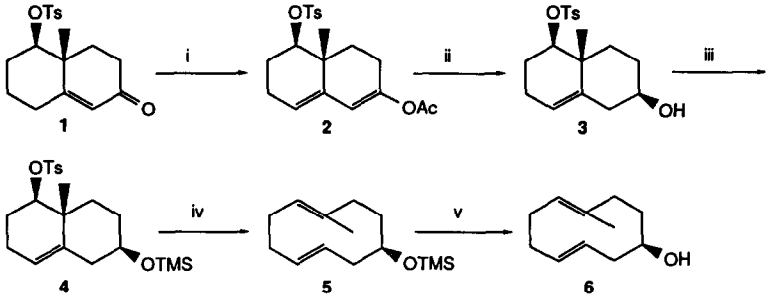
sonchuside C R = Glc R' = CH_3

cichoriolide A R = H R' = CH_2

Figure 1: Sesquiterpene lactones isolated from *C. intybus*

with appropriate functional groups [9-11]. For the synthesis of a less functionalized model compound we opted for the fragmentation of an appropriately functionalized hydronaphthalene using Marshall's method [12]. Thus 8-methyl-*trans,trans*-cyclodeca-3,7-dien-1β-ol (**6**) was synthesised in nine steps in an *overall* yield of 50% as described in scheme 1.

Tosylate **1** was prepared from the readily available Wieland-Miescher ketone [13-16]. Isomerization of the double bond was achieved by converting tosylate **1** into the dienol acetate **2** and selective reduction to the alcohol **3** using $NaBH_4$. Protection of the alcohol function of **3** as its TMS-ether and hydroboration of the double bond followed by base treatment yielded the protected 10-membered ring **5** in 65% yield. Deprotection of **5** with TBAF in THF gave the desired alcohol **6** in 99% yield.



Scheme 1

i: NaI, Ac_2O, $(CH_3)_3SiCl$; ii: $NaBH_4$; iii: HMDS, $(CH_3)_3SiCl$, pyridine; iv: 1) $BH_3.S(CH_3)_2$, THF, 2) NaOH; v: TBAF.

The alcohol was administered to a suspension of crushed chicory root and incubated for 7 days to give the two epimeric alcohols **7** in a 1:2 ratio. Analytical GC experiments using a chiral column revealed the racemic nature of both epimers **7a** and **7b**. The products could be isolated after silylation and flash chromatography over deactivated Al_2O_3 as their di-TMS derivates **8**. Separation of the isomers **8a** and **8b** was performed by preparative capillary GC. Incubation of **6** with a boiled chicory root suspension showed no reaction.

After completion of the incubation, the isolated alcohols **7** showed no absorbance at 200 nm, indicating a totally saturated structure. Mass spectroscopy (GC-MS) of **7** revealed a mass increase of 18 units in comparison with **6**, indicating the incorporation of a water molecule during the reaction. After silylation, flash chromatography and separation of the isomers, ^{13}C NMR spectra revealed that the methyl group of the isomers resonates at 15.91 and 16.70 ppm respectively. These findings exclude a guaiane-like structure because the methyl group of guaianes resonates around 30 ppm in ^{13}C NMR [17]. A carotane-like structure was also rejected because the bridgehead methyl group of carotanes resonates between 20-30 ppm [18]. So, an eudesmane structure for both isomers was most likely.

A clear distinction between *cis*- and *trans*-eudesmanes can be made by means of ^{13}C NMR. The bridgehead methyl group of *trans*-eudesmanes resonates around 18 ppm, whereas for *cis*-eudesmanes this signal is located around 30 ppm [19]. Further proof was obtained when an authentic sample of 4aβ-methyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-1α,7β-diol (**7'**) was compared with the crude alcohol **7** [20]. Both retention time and the fragmentation spectrum of **7'** were identical on GC-MS to that of the product most abundantly formed. The ^{13}C NMR of **7'** appeared to be almost identical to that of the purified di-TMS-ether **8b**. The ^1H NMR also showed only minor differences, due to the presence of the bulky TMS group. The small quintet of H-1 in the ^1H NMR of the minor product indicates that a large axial-axial coupling is missing, thus revealing the axial position of the hydroxyl group at C-7 (**8a**).

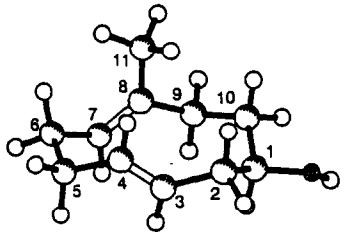
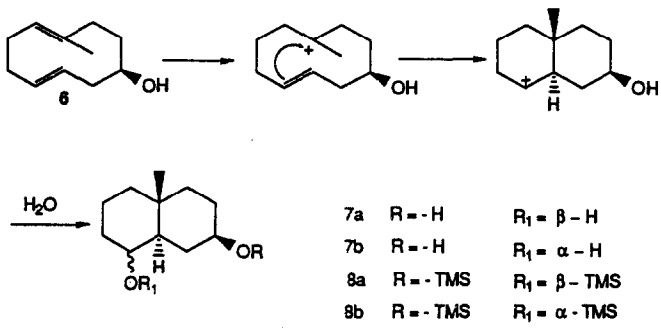


Figure 2: MM2 energy optimized calculation of compound **6**.

These findings are in agreement with MM2 calculations performed on compound **6**. The energy optimized structure of **6** shows a conformation in which the methyl group and H-3 are *trans*-orientated, as depicted in figure 2. If we assume that this conformation does not change dramatically upon reaction, a *trans*-eudesmane, *cis*-guaiane or *cis*-carotane-like structure can be expected upon cyclisation.

Thus we can conclude that a chicory root suspension is able to convert the 10-membered ring **6** into the *trans*-decaline compound **7**.



Scheme 2: Proposed biotransformation of **6** into **7** by *C. intybus*.

Protonation of the upper double bond, stabilisation of the tertiairy cation, transannular cyclisation and subsequent incorporation of a water molecule from the surrounding medium probably accounts for the formation of the products (scheme 2). The fact that both **7a** and **7b** are enantiomers, formed in a 1 : 1 ratio, implicates that enzymes in *C. intybus* are not stereoselective towards compound **6**.

Experimental

The ^{1}H NMR spectra were recorded at 90, 200 and 500 MHz; the ^{13}C NMR were recorded at 50 MHz. Chemical shifts are reported in δ units from the internal standard tetramethylsilane in chloroform-*d* as the solvent, unless otherwise noted. Analytical HPLC was performed on a Varian 5000 HPLC equipped with a C-18 reversed-phase column (250 x 4.6 mm) using MeOH-H_2O (1:1; flow 1 ml/min) as the solvent system and a Spectroflow 773 absorbance detector set at 200 nm. Reactions were monitored by TLC on Merck silicagel 60 F_{254} (layer thickness 0.2 mm) and petroleum ether (40-60)-EtOAc as the solvent system. The compounds were detected with UV (254 nm) and iodine vapour. Mass spectral data were obtained with a Hewlett Packard 5890 GC-MS (30 m x 0.25 mm) equipped with a Hewlett Packard 5970 series mass selective detector using a capillary DB-17 column and helium as the carrier gas. Accurate mass measurements were obtained with a MS 902 equipped with a VG-ZAB console. IR spectra were recorded on a Jasco A-100 infrared spectrophotometer. Preparative GC was performed with a Gerstel preparative DCS system using a Hewlett Packard methyl silicone pre-column (5 m x 0.53 cm; d_f = 2.65 μm) and a Quadrex methyl silicone main column (25 m x 0.53 cm; d_f = 5.0 μm) in two separate Hewlett Packard 5890 II gas chromatographs using hydrogen as the carrier gas. Melting points are uncorrected. All solvents were distilled before use. Compound **6** was emulsified in water using a Vibra Cell© sonificator with a micro tip at 20% pulse for a 10 minute time period.

2-Acetoxy-4aβ-methyl-5β-p-toluenesulfonyl-3,4,4a,5α,6,7-hexahydronaphthalene (2).

To a stirred mixture of 16.80 g of **1** (50.3 mmol) and 27.84 g of NaI in 200 ml of acetic anhydride, cooled to 0°C, was added dropwise 16.50 ml of $(CH_3)_3SiCl$. The reaction mixture was stirred at 0°C for 2h, after which the solvents were evaporated *in vacuo*. The residue was taken up in 150 ml of CH_2Cl_2 and washed with sat.

$NaHCO_3$ (2 x 100 ml) and 2 M $Na_2S_2O_3$ (2 x 100 ml). The aqueous layers were extracted with 2 x 150 ml of CH_2Cl_2. The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and evaporated *in vacuo* yielding 16.70 g of **2** (44.4 mmol, 88%) as a solid. An analytical sample was recrystallized from EtOH. ^1H NMR (200 MHz): δ 7.78 (dd, 2H, J = 6.8 Hz, J = 1.6 Hz); δ 7.29 (d, 2H, J = 8.2 Hz); δ 5.76 (d, 1H, H-1, J = 2.1 Hz); δ 5.30 (t, 1H, H-8, J = 3.6 Hz); δ 4.42 (dd, 1H, H-5α, J = 11.3 Hz, J = 4.7 Hz); δ 2.42 (s, 3H, Tos-CH_3); δ 2,40-2.15 (m, 3H); δ 2.25-1.85 (m, 3H); δ 2.09 (s, 3H, $OOCCH_3$); δ 1.71 (ddd, 1H, J = 12.5 Hz, J = 5.6 Hz, J = 1.4 Hz); δ 1.18 (dt, 1H, J = 12.5 Hz, J = 6.1 Hz); δ 1.04 (s, 3H, 4aβ-CH_3); ^{13}C NMR: CH_3: δ 21.40, 20.78, 17.39; CH_2: δ 32.02, 24.49, 24.05, 24.05; CH: δ 129.50, 127.50, 122.71, 115.60, 86.90; C: δ 168.90, 148.11, 144.30, 136.56, 134.13, 36.43; Mass spectrum: Calc. for (M^+): 376.1352; Found: 376.1343: IR: ν^{KBr}: 1760, 1365, 1210, 1190, 1175, 1120, 940 cm^{-1}; Mp: 109-110.5 °C.

4a,β-Methyl-5β-p-toluenesulfonyl-1,2α,3,4,4a,5α,6,7-octahydronaphth-2β-ol (3)

To a stirred suspension of 15.35 g of **2** (40.8 mmol) in 300 ml of abs. EtOH, cooled to 0°C, $NaBH_4$ (14 g, 370 mmol) was added and the reaction was stirred for 16h at room temperature. After adding carefully 10 ml of acetic acid, the reaction mixture was evaporated to dryness. The residue was taken up in 150 ml of CH_2Cl_2 and washed with 100 ml of sat. $NaHCO_3$. The aqueous layer was extracted with 2 x 100 ml of CH_2Cl_2. The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and evaporated *in vacuo* yielding 13.44 g of **3** (40.0 mmol, 98%) as a light-yellow oil. An analytical sample was crystallized from petroleum ether (40-60)-EtOAc 1 : 1.

^1H NMR (200 MHz): δ 7.71 (dd, 2H, J = 8.4 Hz, J = 1.9 Hz); δ 7.26 (d, 2H, J = 8.1 Hz); δ 5.19 (broad s, 1H, H-8); δ 4.32 (dd, 1H, H-5α, J = 11.2 Hz, J = 4.6 Hz); δ 3.37 (m, 1H, H-2α); δ 2.51 (broad s, 1H, -OH); δ 2.36 (s, 3H, Tos-CH_3); δ 2.24 (ddd, 1H, J = 13.7 Hz, J =4.8 Hz, J = 1.8 Hz); δ 2.20-1.90 (m, 3H); δ 1.80-1.65 (m, 5H); δ 1.36 (ddt, 1H, J = 12.6 Hz, J = 12.0 Hz, J = 3.9 Hz); δ 1.00 (s, 3H, 4aβ-CH_3); ^{13}C NMR: CH_3: δ 21.36 17.73; CH_2: δ 40.76, 35.41, 30.53, 24.43, 24.15; CH: δ 129.49, 127.36, 120.71, 89.01, 70.59; C: δ 144.30, 138.61, 134.19, 38.26; Mass spectrum: Calc. for (M^+ - *p*-TsOH): 164.1201; Found: 164.1201: IR: ν^{KBr}: 3600-3400 (broad -OH), 1605,1360,1215, 1185, 935 cm^{-1}; Mp: 117-119 °C (dec.).

4a,β-Methyl-2β-trimethylsilyloxy-5β-p-toluenesulfonyl-1,2α,3,4,4a,5α,6,7-octahydronaphthalene (4)

To a stirred solution of 13.00 g of **3** (38.7 mmol) and 8.2 ml of hexamethyldisilazane (HMDS) in 50 ml of dry pyridine was added dropwise 4.9 ml of $(CH_3)_3SiCl$. The reaction mixture was stirred for 45 minutes after which time 3 ml of water was added. The solution was taken up in 75 ml of $CHCl_3$ and washed with 100 ml of 5% HCl and 100 ml of sat. $NaHCO_3$. The aqueous layers were extracted with 2 x 75 ml of $CHCl_3$. The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and evaporated *in vacuo* to yield 15.43 g of **4** (37.6 mmol, 97%) as a light-brown oil. An analytical sample was crystallized from petroleum ether (40-60)-EtOAc 1 : 1.

^1H NMR (200 MHz): δ 7.77 (d, 2H, J = 8.4 Hz); δ 7.31 (d, 2H, J = 8.2 Hz); δ 5.23 (broad s, 1H, H-8); δ 4.40 (dd, 1H, H-5α, J = 11.2 Hz, J = 4,5 Hz); δ 3.40 (m, 1H, H-2α); δ 2.42 (s, 3H, Tos-CH_3); δ 2.16 (d, 2H, H-1, J = 7.3 Hz); δ 2.01 (m, 2H); δ 1.85-1.30 (m, 5H); δ 1.05 (s, 3H, 4aβ-CH_3); δ 1.10-0.90 (m, 1H) δ 0.10 (m, 9H, -OTMS); ^{13}C NMR: CH_3: δ 21.41, 17.76, 1.60; CH_2: δ 40.84, 35.41, 30.67, 24.47, 24.20; CH: δ 129.48, 127.42, 120.89, 88.94, 70.82; C: δ 144.25, 138.51, 134.45, 38.29; Mass spectrum (m/e): 73

(53), 91 (43), 108 (34), 129 (100), 146 (69), 229 (34), 236 (23), 253 (18), 393 (4), 408 (0.5); Calc. for (M^+): 408.1790; Found: 408.1789;IR: ν^{KBr}: 1600, 1250, 1190, 1090, 860 cm^{-1}; Mp: 82-84.5 °C.

8-Methyl-1β-trimethylsilyloxy-trans,trans-cyclodeca-3,7-diene (5)

To a stirred solution of 14.30 g of **4** (35.0 mmol) in 100 ml of dry THF, cooled to 0°C, under a nitrogen atmosphere was added dropwise 45 ml of 2M $BH_3.S(CH_3)_2$ complex. The reaction mixture was stirred for 1h at 0°C and was allowed to warm slowly to room temperature. After 2.5 days, 3 ml of water was added followed by 30 ml of 2 M NaOH. The mixture was stirred for 3h and extracted with ether. The organic layer was washed with brine (2 x 75 ml), the combined aqueous layers were extracted with 2 x 75 ml of ether. The combined organic layers were washed with brine (75 ml), dried over $MgSO_4$ and evaporated *in vacuo* to yield a yellow oil. Purification over deactivated Al_2O_3 with CH_2Cl_2 yielded, after evaporation of the solvent, 5.40 g of **5** (22.7 mmol, 65%) as a light-yellow oil.

^1H NMR (200 MHz): δ 5.25-4.65 (m, 3H, H-3,4,7); δ 3.52 (m, 1H, H-1α); δ 2.46 (broad d, 1H, H-2, J = 14.1 Hz); δ 2.40-0.70 (m, 9H); δ 1.30 (s, 3H, $-CH_3$); δ 0.12-0.07 (m, 9H); ^{13}C NMR: CH_3: δ 16.58, -0.18; CH_2: δ 43.24, 38.22, 37.23, 32.69, 26.89; CH: δ 132.39, 125.16, 124.72, 75.75; C: 137.40; Mass spectrum (m/e): 41 (60), 67 (100), 82 (80), 91 (22), 109 (16), 111 (10), 133 (15), 151 (3), 166 (1).; IR: ν^{CDCl_3}: 1600, 1365, 1210 cm^{-1}.

8-Methyl-trans,trans-cyclodeca-3,7-dien-1β-ol (6)

To a stirred solution of **5** (5.40 g, 22.7 mmol) in 60 ml of THF 1M TBAF in THF (11 ml) was added dropwise. After 3h, the reaction mixture was washed with 3 x 50 ml of water. The combined aqueous layers were extracted with 3 x 50 ml of ether. The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$ and evaporated *in vacuo* to yield a yellow oil. Purification over deactivated Al_2O_3 yielded 3.74 g of **6** (22.5 mmol, 99%) as a light-yellow oil which solidified upon freezing.

^1H NMR (500 MHz): δ 5.04 (dddd, 1H, H-4, J = 15.4 Hz, J = 10.6 Hz, J = 4.8 Hz, J = 2.4 Hz); δ 4.81 (ddd, 1H, H-3, J = 15.2 Hz, J = 11.5 Hz, J = 3.2 Hz); δ 4.77 (dd, 1H, H-7, J = 11.1 Hz, J = 5.6 Hz); δ 3.62 (dt, 1H, H-1α, J = 9.9 Hz, J = 3.5 Hz); δ 2.56 (dd, 1H, H-2β, J = 13.4 Hz, J = 2.1 Hz); δ 2.37 (dd, 1H, J = 12.9 Hz, J = 6.5 Hz); δ 2.13 (dt, 1H, J = 12.7 Hz, J = 2.2 Hz); δ 2.05-1.95 (m, 4H); δ 1.90-1.75 (m, 3H); δ 1.33 (s, 3H, $-CH_3$); ^{13}C NMR: CH_3: δ 16.57; CH_2: δ 42.72, 38.10, 36.79, 32.63, 26.86; CH: δ 131.96, 125.37, 124.96, 75.21; C: δ 136.97; Mass spectrum (m/e): 39 (48), 41 (65), 55 (45), 67 (100), 68 (52), 79 (58), 82 (80), 91 (23), 109 (16), 133 (13), 166 (0.3); Calc. for (M^+): 166.1357; Found: 166.1357; IR: ν^{KBr}: 3600-3100 (broad -OH), 1675, 1455, 1055, 985 cm^{-1}; Mp: 24.5-28 °C.

Plant material:

A suspension of fresh chicory root (30% w/v) was produced by mortaring the peeled root in a solution of 0.25 M sucrose, 3 mM tris(hydroxymethyl)aminomethane HCl (Tris) and 0.1% (w/v) Bovine Serum Albumin (BSA). The pH of this sucrose/Tris/BSA-solution (STB) was set at 7.0 using 2-morpholino-ethanesulfonic acid (MES).

Small-scale incubations:

It was possible to obtain a 1.9 mM emulsion of **6** in water by sonification. This solution was used for small-scale experiments to determine possible enzyme activity. The suspensions shown in table 1 were

incubated for 5 days after which complete conversion of **6** by the chicory root suspension was shown. A boiled sample (10 minutes) of chicory root suspension was used as an enzyme blank. Both enzyme- and substrate blank showed no reaction.

Table 1

chicory-susp.	enzyme blank	substrate blank
200 µl chicory suspn.	200 µl boiled chicory suspn.	250 µl substrate soln.
250 µl substrate soln.	250 µl substrate soln.	750 µl STB-soln.
550 µl STB-soln.	550 µl STB-soln.	

Bulk-incubation:

57 mg **6** was dissolved in EtOH/water (1 : 24) and poured into a stirred suspension of 22 g mortared chicory root in 155 ml STB-solution under a stream of nitrogen. This suspension was incubated for 7 days at room temperature in a 3-necked round bottom flask which was covered with aluminum foil to exclude light.

Isolation and purification of the products:

The plant material was removed by filtration and the medium was extracted with 3 x 100 ml of 5% isopropanol in EtOAc. The combined organic layers were washed with 100 ml brine, dried over $MgSO_4$ and evaporated *in vacuo* to yield 127 mg of a dark-yellow oil. The extract was silylated as described in the synthesis of **4** and purified on deactivated Al_2O_3 yielding 67 mg of **8**.

Spectral data:

7 (minor): ^{1}H NMR (200 MHz) [21]: δ 4.08 (broad t); δ 0.83 (s, -CH_3); ^{13}C NMR [22]: CH_3: δ 15.90; CH: δ 70.72, 66.66, 44.08; Mass spectrum (m/e): 41 (100), 43 (63), 55 (86), 67 (88), 79 (67), 81 (63), 95 (61), 107 (45), 109 (63), 133 (57), 148 (37), 151 (20), 166 (20), 184 (22).

7 (major) : ^{1}H NMR (200 MHz) δ 3.55 (m); δ 3.38 (m); δ 0.87 (s, -CH_3); ^{13}C NMR: CH_3:δ 16.71; CH: δ 71.98, 70.45, 49.73; Mass spectrum (m/e): 41 (100), 43 (66), 55 (85), 57 (63), 67 (94), 79 (63), 81 (74), 95 (73), 96 (64), 107 (45), 109 (66), 122 (26), 123 (35), 133 (34), 135 (17), 137 (24), 141 (18), 148 (21), 166 (36), 184 (15).

7':^{1}H NMR (200 MHz): δ 3.58 (quintet, 1H, J = 5.1 Hz); δ 3.39 (dt, 1H, J = 10.3 Hz, J = 4.4 Hz); δ 2.16 (m, 1H, J = 9.4 Hz, J = 4.5 Hz, J = 2.4 Hz); δ 2.00 (m, 1H, J = 12.4 Hz, J = 3.2 Hz); δ 1.78 (m, 1H); δ 1.56 (m, 4H); δ 1.39 (m, 4H); δ 1.09 (m, 4H); δ 0.89 (s, 3H); ^{13}C NMR; CH_3: δ 16.71; CH_2: δ 40.00, 36.99, 36.10, 32.15, 30.70, 20.08; CH: δ 71.28, 69.71, 49.84; C: δ 34.60; Mass spectrum (m/e): 41 (100), 43 (61), 55 (86), 57 (46), 67 (82), 79 (55), 81 (60), 95 (70), 96 (51), 107 (36), 109 (64), 122 (21), 123 (32), 133 (32), 137 (19), 141 (15), 148 (18), 151 (20), 166 (30), 184 (17); IR: ν^{KBr}: 3600-3100 (broad -OH), 2930, 2850, 1460, 1145, 1055 cm^{-1}; Mp: 122.5-124 ^{0}C.

8a: ^{1}H NMR (500 MHz): δ 4.03 (quintet, 1H, J = 2.8 Hz); δ 3.31 (dt, 1H, J = 10.6 Hz, J = 4.5 Hz); δ 1.85 (m, 1H); δ 1.81 (ddd, 1H, J = 13.6 Hz, J = 5.7 Hz, J = 2.9 Hz); δ 1.57 (m, 5H); δ 1.45 (dt, 1H, J = 12.6 Hz, J = 2.7 Hz); δ 1.29 (m, 2H); δ 1.12 (m, 3H); δ 0.78 (s, 3H); δ 0.06 (s, 18 H); ^{13}C NMR: CH_3: δ 16,12, 0.37, 0.18; CH_2: δ 40.64, 36.90, 35.67, 31.10, 29.33, 20.48; CH: δ 70.94, 66.89, 44.23; C: δ 34.64; Mass spectrum (m/e): 73 (100), 75 (78), 149 (75), 183 (21), 195 (20), 238 (21), 285 (4), 328 (11).

8b: ^{1}H NMR (500 MHz); δ 3.52 (heptet, 1H, J = 5.2 Hz); δ 3.34 (dt, 1H, J = 10.2 Hz, J = 4.5 Hz); δ 2.01 (m, 1H); δ 1.86 (m, 1H, J = 12.5 Hz, J = 3.4 Hz); δ 1.63 (m, 1H): δ 1.53 (m, 3H); δ 1.35 (dt, 1H, J = 13,5 Hz, J = 3.5 Hz); δ 1.32 (m, 1H); δ 1.22 (m, 1H); δ 1.11 (dt, 1H, J = 14.1 Hz, J = 5.0 Hz); δ 0.99 (m, 3H); δ 0.82 (s, 3H); δ 0.10 (s, 9H); δ 0.08 (s, 9H); ^{13}C NMR: CH_3; δ 16.92, 0.27*; CH_2: δ 40.31*, 36.63, 33.08, 31.52, 20.42; CH: δ 72.20, 70.67, 49.94; C: δ 33.08; Mass spectrum (m/e): 73 (100), 75 (98), 149 (56), 191 (17), 195 (17), 204 (16), 285 (5), 299 (6), 328 (14).

* Two overlapping peaks

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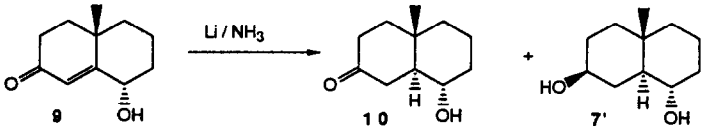
Notes and references

1. Schenck G., Graf H., *Arch. Pharm.*, 277, 257-261 (1939).
2. van Beek T.A., Maas P., King B.M., Leclercq E., Voragen A.G.J. and de Groot Ae., *J. Agric. Food Chem.*, **38**, 1035-1038 (1990).
3. Seto M., Miyase T., Umehara K., Ueno A., Hirano Y. and Otani N., *Chem. Pharm. Bull.*, **36** , 2423-2429 (1988).
4. Pyrek J.S., *Phytochemistry*, **24**, 186-188 (1985).
5. Sakui N., Kuroganagi M., Ishitobi, Y., Sato M. and Ueno A., *Phytochemistry*, **31**, 143-147 (1992).
6. Sutherland J.K., *Tetrahedron*, **30**, 1651-1660 (1974).
7. Parker W., Roberts J.S.and Ramage R., *Quart. Rev.*, **21**, 331-363 (1967).
8. Leclercq E., *Sesquiterpene Lactones and Inulin from Chicory Roots: Extraction, Identification, Enzymatic Release and Sensory Analysis*, PhD.-thesis, Wageningen Agricultural University 1992.
9. Takahashi T., Kitamura K., Nemo H. and Tsuji J., *Tetrahedron Lett.*, **24**, 3489-3492 (1983)
10. Takahashi T., Nemo H. and Tsuji J., *Tetrahedron Lett.*, **24**, 2005-2008 (1983).
11. Takahashi T., Nemo H. and Tsuji J., *Tetrahedron Lett.*, **24**, 3485-3488 (1983).
12. Marshall J.A. and Bundy G.L., *Chem. Commun.*, 854 (1967).
13. Buchsacher P. and Furst A., *Org. Synth.*, **63**, 37, (1985).
14. Marshall J.A., Seitz D.E., Snyder W.R. and Goldberg B., *Synthetic Comm.*, **79**, 4 (1974).
15. Sondheimer F. and Elad D., *J. Am. Chem. Soc.*, **80**, 1967-1971 (1958).
16. Heathcock C.H., Badger R.A. and Patterson Jr., J.W., *J. Am. Chem. Soc.*, **89**, 4133-4145 (1967).
17. Atta-ur-Rahman and Ahmad V.U., *^{13}C NMR of Natural Products*, Volume 1, 331-431 (1992).
18. Atta-ur-Rahman and Ahmad V.U., *^{13}C NMR of Natural Products*, Volume 1, 480-494 (1992).
19. Kesselmans R.P.W., Wijnberg J.B.P.A., de Groot Ae. and van Beek T.A., *J. Essent. Oil Res.*, **4**, 201-217 (1992).
20. Compound **7'** was obtained as a byproduct in the reduction of **9**, *unpublished results*.



21. The presence of numerous endogenous compounds from *C. intybus* led to such a complex spectrum of the crude reaction mixture that further assignments could not be made.
22. Due to the complexity of the DEPT-^{13}C NMR, it was only possible to assign CH and CH_3 signals.

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