Isopulegol as a Model Compound: Metalation and Substitution of an Allylic Position in the Presence of an Unprotected Hydroxy Function

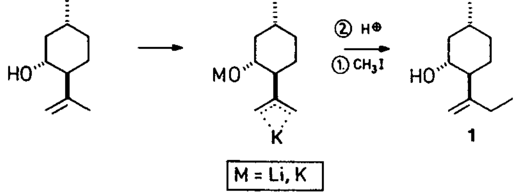
Manfred Schlosser*[a] and Martina Kotthaus[a]

Keywords: Electrophilic substitution / Metalations / Monoterpene / Protective groups / Superbase

When treated with butyllithium and potassium *tert*-butoxide for 2 h at 0 °C in hexanes, the unsaturated monoterpenic alcohol isopulegol is simultaneously deprotonated at the hydroxy function and the allylic methyl group. The metaloxy allylmetal species thus generated can be silylated, alkylated, carboxylated and oxidized to afford the expected products in good to excellent yields. Thus, a specific protection of hydroxy groups is not required, alcohols being instantaneously converted by superbases into alcoholates.

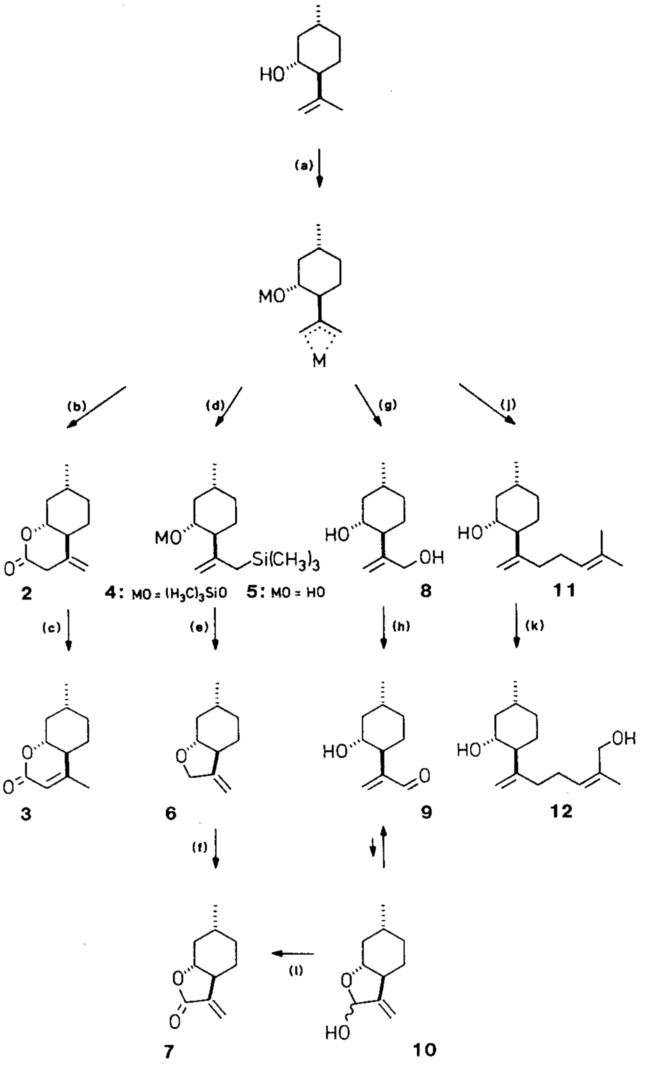
The levorotatory enantiomer of isopulegol [(1*R*,2*S*,5*R*)-2-isopropenyl-5-methylcyclohexanol] is a relatively inexpensive chiral building block. Simple and efficacious structural elaboration should be possible by proton abstraction from the allylic methyl group and subsequent reaction with an electrophile. We wanted to establish the feasibility of such a sequence in order to demonstrate the superiority of superbasic mixed-metal reagents[1−4] in the critical hydrogen/metal exchange ("metalation") step. Several examples of successful metalation of hydroxy-(or, more correctly, metaloxy-)substituted alkenes with butyllithium in the presence of potassium *tert*-butoxide have been reported.[1,4−8] In contrast, tetramethylethylenediamine-(TMEDA-)activated butyllithium, which was found suitable for the metalation of hydrocarbon-type monoterpenes,[9,10] performs poorly at best with functionalized substrates.

Smooth metalation took indeed place when isopulegol was treated with butyllithium (2.0 equiv.) and potassium *tert*-butoxide (1.0 equiv.) for 2 h in hexanes at 0°C. Subsequent addition of methyl iodide to the suspension afforded the trapping product, 5-methyl-2-(1-methylenepropyl)cyclohexanol (**1**) in 84% yield.



Scheme 1. Hydrogen/metal exchange at the allylic methyl group of lithium(potassium) isopulegolate and subsequent trapping with methyl iodide

When the slurry containing the metalated isopulegol derivative was poured on dry ice, the β,γ-unsaturated lactone **2** was obtained (43%). In basic medium it underwent isomerization to the conjugated enelactone **3** (93%). Interception with excess chlorotrimethylsilane gave the trimethyl-



Scheme 2. (a) LiC_4H_9 (2.0 equiv., 1 M in hexane) + $KOC(CH_3)_3$ (1.0 equiv.) 2 h, 0°C; (b) crushed dry-ice (excess), then pH = 3; (c) $KOC(CH_3)_3$ (catalytic amount) in tetrahydrofuran; (d) $ClSi(CH_3)_3$ (5.0 equiv.); (e) $H_5C_6{-}I{=}O$ (2 equiv.) + $BF_3 \cdot Et_2O$ (1.0 equiv.); (f) CrO_3 + pyridine; (g) $FB(OCH_3)_2$ (1.5 equiv.), then H_2O_2 + aq. NaOH; (h) MnO_2 (11 equiv.) in CH_2Cl_2; (i) Ag_2CO_3 on kieselguhr (j) $BrCH_2CH{=}C(CH_3)_2$ (1.5 equiv.); (k) $ClSi(C_2H_5)_3$ + pyridine, next LiC_4H_9 + $KOC(CH_3)_3$, then $FB(OCH_3)_2$ + H_2O_2, finally $(H_9C_4)_4N^+F^- \cdot (H_2O)_3$.

---

[a] Institut de Chimie organique de l'Université, Section de Chimie (BCh),
CH-1015 Lausanne, Switzerland

1434−193X/99/0202−0459 $ 17.50+.50/0

silyloxy-substituted silane **4** (67%), which was hydrolyzed to the hydroxylated silane **5** (66%). When either product (**4** or **5**) was allowed to react with iodosobenzene, the tetrahydrofuran **6** was formed (80%) which could be further oxidized with chromium trioxide to give the methylenelactone **7**[11] (60%). The latter compound is also accessible through the diol **8** (82%), prepared by consecutive treatment of the organometallic intermediate with fluorodimethoxyborane and hydrogen peroxide. The aldehyde **9**,[12] prepared (43%) by dehydrogenation of the diol **8** with manganese dioxide, can be converted via the lactol isomer **10** into the lactone **7** (64%) by oxidation with silver carbonate.[12,13]

Condensation of the allylpotassium species with prenyl bromide (3-methyl-2-butenyl bromide) afforded the dienol **11** (71%) which, after protection of the hydroxy by the triethylsilyloxy group, was metalated and subsequently transformed into the dienediol **12** (35% overall) by applying again the bornylation/oxidation sequence. The last two reactions may be jokingly qualified as "anticipating natural product synthesis". Although neither the alcohol **11** nor the diol **12** have been described so far, they may well be found one day as naturally occurring sesquiterpenes.

In conclusion, allylmetal species (presumably[14] containing potassium as the major, lithium as the minor π-bound[15,16] metal component) can be generated by deprotonation of olefins with superbasic reagents (such as the LIC-KOR mixture) with extreme ease, even when unprotected hydroxy groups, are present. A variety of chain-lengthened or functionalized derivatives can be prepared by simple electrophilic manipulation.

Experimental Section

General: ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded of samples dissolved in deuteriochloroform at 400, 101 and 376 MHz, respectively. Chemical shifts (δ) are given relative to the signals of tetramethylsilane, used as an internal standard. For working routine and abbreviations, see recent articles from this laboratory.[17,18] The key starting material (−)-isopulegol was purchased from Fluka. Despite a discrepancy in optical rotation numbers {$[\alpha]_D^{20} = -20.0$, $[\alpha]_{546}{}^{20} = -23.6$ (ref.[19]: $[\alpha]_{546}{}^{20} = -25.9$; all neat)}, the compound was found to be enantiomerically pure (> 98% e.e.) by ^{19}F-NMR spectroscopy of the Mosher ester and gas chromatography on a chiral capillary column (30 m, Cyclodex−B, 35→80°C applying a heating rate of 1°C/min).

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylenepropyl)cyclohexanol (**1**): (−)-Isopulegol (1.7 mL, 1.5 g, 10 mmol) and potassium *tert*-butoxide (1.1 g, 10 mmol) were added to a solution of butyllithium (20 mmol) in hexanes (20 mL). The suspension was kept at 0°C and vigorously stirred for 2 h. After methyl iodide (0.62 mL, 1.4 g, 10 mmol) had been added, stirring was continued for 1 h at 0°C. The mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried and evaporated. Upon distillation of the residue, the product (**1**) was collected as a colorless oil; b.p. 98−100°C/12 Torr; $n_D{}^{20} = 1.4236$; $[\alpha]_D^{20} = -43.5$ (C_2H_5OH, $c = 1.0$), yield 1.4 g (84%). − ^{1}H NMR: δ = 4.85 (s, 2 H), 3.47 (dt, $J = 10.4$, 4.2 Hz, 1 H), 2.0 (m, 3 H), 1.82 (ddd, $J = 12.5$, 9.6, 3.4 Hz, 1 H), 1.6 (m, 2 H), 1.45 (symm. m, 1 H), 1.23 (dq, $J = 12.4$, 3.5 Hz, 1 H), 1.03 (t, $J = 7.4$ Hz, 3 H), 0.9 (dm, $J = 6.5$ Hz, 5 H). − ^{13}C NMR: δ = 152.5, 109.1, 71.0, 53.5, 42.6, 34.4, 31.3, 30.5, 26.2, 22.1, 12.1. − MS; *m/z* (%): 168 (2) [M$^+$], 121 (46), 81 (100). − $C_{11}H_{20}O$ (168.28): calcd. C 78.51, H 11.98; found C 78.83, H 12.02. − Another reaction was performed under identical conditions, except that potassium *tert*-butoxide was replaced by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. The yield of **1** dropped to 3%.

(7*R*,9*R*,10*S*)-7-Methyl-4-methylene-3,4,4a,5,6,7,8,8a-2*H*-1-benzopyran-2-one (**2**): The isopulegol-derived organometallic reaction mixture was poured on an excess of freshly crushed dry ice. At 25°C, a 1 M solution of hydrogen chloride (20 mmol) in diethyl ether (20 mL) was added. The mixture was stirred for 15 min and filtered. When hexanes (10 mL) were added to the concentrated filtrate (5−10 mL), crystallization set in. The product (**2**) was isolated as colorless platelets; m.p. 68−69°C; $[\alpha]_D^{20} = -7.4$ (C_2H_5OH; $c = 1.0$); yield 0.78 g (43%). − IR (KBr): $\tilde{\nu}$ = 1735 (s, ν[C=O]) 1650 (m, ν[C=C]). − ^{1}H NMR: δ = 4.90 (d, $J = 16.1$, 2 H), 3.92 (dt, $J = 10.5$, 4.4 Hz, 1 H), 3.39 (d, $J = 18.8$ Hz, 1 H), 3.30 (d, $J = 18.8$ Hz, 1 H), 2.1 (m, 3 H), 1.77 (symm. m, 1 H), 1.50 (symm. m, 1 H), 1.2 (m, 2 H), 1.0 (dm, $J = 6.6$ Hz, 4 H). − ^{13}C NMR: δ = 170.3, 140.2, 109.2, 80.8, 43.0, 40.1, 38.8, 33.2, 30.6, 27.0, 21.6. − MS (CI); *m/z* (%): 198 (100) [M$^+$ + NH$_4$], 181 (91) [M$^+$ + 1], 180 (14) [M$^+$], 121 (17). − $C_{11}H_{16}O_2$ (180.25): calcd. C 73.30, H 8.95; found C 73.16, H 8.90.

(7*R*,9*R*,10*S*)-4,7-Dimethyl-4a,5,6,7,8,8a-2*H*-1-benzopyran-2-one (**3**): Lactone **2** (0.90 g, 5.0 mmol) was dissolved in tetrahydrofuran (10 mL) which contained a small amount of potassium *tert*-butoxide (approx. 0.1 g, 1 mmol). After 6 h at 25°C, a 1 M solution of hydrogen chloride (5 mmol) in diethyl ether was added. Upon distillation a colorless liquid was collected which eventually solidified; b.p. 96−98°C/5 Torr; m.p. 41−42°C; $[\alpha]_D^{20} = -88.2$ (C_2H_5OH, $c = 1.0$); yield 0.84 g (93%). − IR (KBr): $\tilde{\nu}$ = 1735 (s, γ[C=O]. − ^{1}H NMR: δ = 5.78 (symm. m, 1 H), 3.97 (dt, $J = 11.3$, 4.0 Hz, 1 H), 2.1 (m, 3 H), 1.90 (t, $J = 1.6$ Hz, 3 H), 1.78 (symm. m, 1 H), 1.54 (symm. m, 1 H), 1.29 (q, $J = 11.8$ Hz, 1 H), 1.12 (dq, $J = 12.8$, 3.3 Hz, 1 H), 1.0 (dm, $J = 6.5$ Hz, 4 H). − ^{13}C NMR: δ = 165.0, 160.9, 116.8, 80.4, 41.7, 39.4, 33.8, 30.8, 25.8, 21.6, 19.4. − MS; *m/z* (%): 181 (99) [M$^+$ + 1], 180 (46) [M$^+$], 95 (100). − $C_{11}H_{16}O_2$ (180.25): calcd. C 73.30, H 8.95; found C 73.06, H 8.78. − Lactone **3** was obtained directly (although only in 33% yield) when gaseous carbon dioxide was bubbled into the stirred reaction mixture prepared by metalation of (−)-isopulegol or when a 1 M solution of hydrogen chloride (35 mmol) in diethyl ether was added to the mixture after the latter had been poured on freshly crushed ice and the product was immediately isolated by distillation.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methylene-2-(trimethylsilyl)ethyl]-cyclohexyloxy]trimethylsilane (4): The organometallic reaction mixture, obtained as described above (see preparation of the homolog **1**), was treated with chlorotrimethylsilane (3.8 mL, 3.3 g, 30 mmol). After 1 h of vigorous stirring at 25°C, the product (**4**) was absorbed on silica gel (10 mL) and eluted with hexanes from a column filled with more silica gel (0.1 L); $n_D{}^{20} = 1.4556$, yield 2.0 g (67%). − ^{1}H NMR: δ = 4.61 (d, $J = 4.8$ Hz, 2 H), 3.46 (ddd, $J = 10.5$, 9.2, 4.5 Hz, 1 H), 1.84 (symm. m, 1 H), 1.6 (m, 5 H), 1.46 (symm. m, 1 H), 1.25 (qd, $J = 13.4$, 3.4 Hz, 1 H), 1.04 (dt, $J = 12.0$, 10.8 Hz, 1 H), 0.9 (dm, $J = 6.7$ Hz, 4 H), 0.08 (s, 9 H), 0.02 (s, 9 H). − ^{13}C NMR: δ = 151.3, 105.7, 76.5, 52.5, 45.6, 34.7, 31.7, 31.3, 29.6, 22.2, 0.4 (3 C), −1.3 (3 C). − $C_{16}H_{34}OSi_2$ (298.62): calcd. C 64.36, H 11.48; found C 64.44, H 11.13.

(1*R*,2*S*,5*R*)-5-Methyl-2-[1-methylene-2-(trimethylsilyl)ethyl]-1-cyclohexanol (5): Silane **4** (1.5 g, 5.0 mmol) was dissolved in a 1:3 (v/v) mixture (20 mL) of 2 M hydrochloric acid and tetrahydrofuran. After waiting 30 min at 25°C, the solution was absorbed on silica gel (10 mL) while being concentrated in a rotatory evaporator. Elution with a 1:1 (v/v) mixture of diethyl ether and hexanes from a column filled with more silica gel (50 mL) gave the product (**5**) as a colorless oil; $n_D^{20} = 1.3564$; $[\alpha]_D^{20} = -61.2$ (C_2H_5OH; $c = 1.0$); yield 0.75 g (66%). − ^1H NMR: $\delta = 4.77$ (d, $J = 11.8$ Hz, 2 H), 3.54 (dt, $J = 10.2$, 4.0 Hz, 1 H), 2.0 (m, 2 H), 1.7 (m, 4 H), 1.5 (m, 3 H), 1.17 (dq, $J = 12.8$, 3.1 Hz, 1 H), 0.9 (dm, $J = 6.4$ Hz, 4 H), 0.05 (s, 9 H). − ^{13}C NMR: $\delta = 149.3$, 107.7, 73.1, 55.4, 42.4, 34.6, 31.4, 30.7, 25.8, 22.2, −0.5 (3 C). − MS (CI): 227 (9) [$M^+ + 1$], 211 (12), 121 (49), 73 (100). − $C_{13}H_{26}OSi$ (226.43): calcd. C 68.96, H 11.57; found C 69.13, H 11.59.

(6*R*,8*R*,9*S*)-6-Methyl-3-methylene-2,3,3a,4,5,6,7,7a-octahydrobenzofuran (6): This product was prepared by oxidation of silane **5** (1.3 g, 4.4 mmol), dissolved in 1,4-dioxane (2.0 mL), with iodosobenzene[20] (2.0 g, 8.8 mmol) in the presence of boron trifluoride−diethyl ether (0.60 mL, 0.53 g, 4.4 mmol), as described,[21] and isolated by column chromatography on silica gel using hexanes as the eluent; $n_D^{20} = 1.3924$, yield 0.54 g (80%). − ^1H NMR: $\delta = 4.84$ (q, $J = 2.6$ Hz, 1 H), 4.80 (q, $J = 2.6$ Hz, 1 H), 4.50 (symm. m, 1 H), 4.27 (dq, $J = 13.4$, 2.4 Hz, 1 H), 3.12 (td, $J = 10.8$, 3.9 Hz, 1 H), 2.21 (ddt, $J = 11.5$, 3.8, 1.3 Hz, 1 H), 2.12 (q, $J = 12.9$, 5.1 Hz, 1 H), 1.84 (symm. m, 1 H), 1.75 (symm. m, 1 H), 1.50 (symm. m, 1 H), 1.2 (m, 2 H), 1.0 (dm, $J = 6.8$ Hz, 4 H). − $C_{10}H_{16}O$ (152.24): calcd. C 78.90, H 10.59; found C 78.93, H 10.54.

(6*R*,8*R*,9*S*)-6-Methyl-3-methylene-3a,4,5,6,7,7a-hexahydrobenzofuran-2-one (7): Benzofuran **6** (0.30 g, 2.0 mmol) was oxidized with chromium trioxide (5.5 g, 55 mmol) in the presence of pyridine (5.5 mL, 5.4 g, 68 mmol) in refluxing dichloromethane (15 mL) during 2 h, as described.[11] The product (**7**) was isolated by extraction and purified by chromatography on silica gel using a 1:2 mixture of diethyl ether and hexanes as the eluent; m.p. 35−36°C (ref.[22]: m.p. 37−39°C); $[\alpha]_D^{20} = +51.3$ ($CHCl_3$, $c = 1.78$), (ref.[22]: $[\alpha]_D^{20} = +54.4$, same conditions); yield 0.20 g (60%). − ^1H NMR: $\delta = 6.04$ (d, $J = 3.1$ Hz, 1 H), 5.36 (d, $J = 3.1$ Hz, 1 H), 3.71 (ddd, $J = 11.5$, 10.9, 3.6 Hz, 1 H), 2.34 (tq, $J = 11.5$, 3.1 Hz, 1 H), 2.24 (symm. m, 1 H), 2.07 (dq, $J = 13.0$, 3.1 Hz, 1 H), 1.80 (symm. m, 1 H), 1.2 (m, 4 H), 1.01 (d, $J = 6.6$ Hz, 3 H). − ^{13}C NMR: Ref.[12] − Analysis: Ref.[12]

2-[(1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]-2-propen-1-ol (8): The isopulegol-derived organometallic intermediate was consecutively treated with fluorodimethoxyborane−diethyl ether[23] (5.6 mL, 5.0 g, 30 mmol) and, after 15 min at −75°C, with 30% aqueous hydrogen peroxide (3.0 mL, 1.0 g, 29 mmol). After vigorous stirring at 25°C for 1 h, the reaction mixture was poured into a 3 M aqueous solution (20 mL) of sodium hydroxide and extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine (2 × 10 mL), dried and concentrated. Upon recrystallization of the residue from diethyl ether, diol **8** was obtained as colorless needles; m.p. 101−102°C (ref.[24]: m.p. 101°C); $[\alpha]_D^{20} = -40.1$ (C_2H_5OH; $c = 1.0$); yield 1.4 g (82%). − ^1H NMR: $\delta = 5.16$ (s, 1 H), 5.02 (s, 1 H), 4.08 (q, $J = 11.1$ Hz, 2 H), 3.52 (dt, $J = 10.6$, 4.2 Hz, 1 H), 2.48 (br. s, 2 H), 1.99 (symm. m, 1 H), 1.92 (ddd, $J = 13.0$, 10.4, 3.4 Hz, 1 H), 1.7 (m, 2 H), 1.50 (symm. m, 1 H), 1.3 (m, 1 H), 0.9 (dm, $J = 6.3$ Hz, 5 H). − ^{13}C NMR: Ref.[12] − Analysis: Ref.[24]

2-[(1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]-2-propenal (9): The allylic alcohol **8** (0.68 g, 4.0 mmol) and freshly precipitated manganese dioxide (3.5 g, 40 mmol) were suspended in hexane (10 mL). After 24 h of vigorous stirring at 25°C, the mixture was absorbed on silica gel (15 mL) and eluted from a column filled with more of the support (75 mL) using a 1:1 (v/v) mixture of diethyl ether and hexanes as the eluent. The aldehyde **9** was obtained as a colorless oil; $n_D^{20} = 1.439$; $[\alpha]_D^{20} = -35.3$ (acetone, $c = 1.5$) (ref.[25]: $[\alpha]_D^{20} = -37$, chloroform, $c = 4.6$); yield 0.29 g (43%). − ^1H NMR: $\delta = 9.58$ (s, 1 H), 6.36 (s, 1 H), 6,12 (s, 1 H), 3.55 (dt, $J = 10.4$, 4.3 Hz, 1 H), 2.44 (ddd, $J = 13.1$, 7.0, 3.4 Hz, 1 H), 2.04 (symm. m, 1 H), 1.7 (m, 3 H), 1.54 (symm. m, 1 H), 1.36 (dq, $J = 13.1$, 3.4 Hz, 1 H), 1.04 (symm. m, 1 H), 0.96 (dm, $J = 6.5$ Hz, 4 H). − $C_{10}H_{16}O_2$ (168.23): calcd. C 71.39, H 9.59; found C 71.08, H 9.87.

(1*R*,2*S*,5*R*)-5-Methyl-2-(5-methyl-1-methylene-4-hexenyl)cyclohexanol (11): 3-Methyl-2-butenyl bromide (prenyl bromide; 1.5 g, 10 mmol) were added to the suspension resulting from the metalation of (−)-isopulegol (10 mmol). After 15 min of stirring at 25°C, dienol **11** was isolated by distillation as a colorless oil; b.p. 137−139 g/5 Torr; $n_D^{20} = 1.3301$; $[\alpha]_D^{20} = -38.4$ (C_2H_5OH; $c = 1.0$); yield 1.6 g (71%). − ^1H NMR: $\delta = 5.11$ (symm. m, 1 H), 4.92 (s, 2 H), 3.51 (dt, $J = 10.6$, 4.2 Hz, 1 H), 2.1 (m, 2 H), 2.0 (m, 3 H), 1.91 (s, 1 H), 1.85 (ddd, $J = 13.2$, 10.0, 3.4 Hz, 1 H), 1.7 (m, 1 H), 1.68 (s, 3 H), 1.6 (m, 1 H), 1.61 (s, 3 H), 1.49 (m, 1 H), 1.27 (dq, $J = 13.2$, 3.5 Hz, 1 H), 0.95 (dm, $J = 6.6$ Hz, 6 H). − ^{13}C NMR: $\delta = 150.7$, 131.9, 123.9, 110.6, 71.1, 53.5, 42.5, 34.5, 33.6, 31.4, 30.6, 26.4, 25.6, 22.2, 17.7. − MS; m/z (%): 240 (43) [$M^+ + NH_4$], 223 (10) [$M^+ + 1$], 109 (29), 81 (100). − $C_{15}H_{26}O$ (222.37): calcd. C 81.02, H 11.78; found C 80.83, H 11.67.

(*Z*)-6-[(1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]-2-methyl-2,6-heptadien-1-ol (12): A solution of the dienol **11** (5.6 g, 25 mmol) and chlorotriethylsilane (5.0 mL, 4.5 g, 30 mmol) in pyridine (25 mL) was heated 2 h to 50°C before being concentrated to dryness. The residue was mixed with some kieselguhr and eluted with hexanes from a column filled with neutral alumina. After removal of the solvent, **(1*S*,2*R*,4*R*)-4-methyl-1-(5-methyl-1-methylene-4-hexenyl)-2-(triethylsilyloxy)cyclohexane** was collected as a colorless oil; $n_D^{20} = 1.3919$; $[\alpha]_D^{20} = -26.9$ (ethanol, $c = 1.0$); yield 8.4 g (99%) crude; 7.2 g (86%) pure. − ^1H NMR: $\delta = 5.11$ (m, symm., 1 H), 4.76 (s, 2 H), 3.48 (dt, $J = 9.9$, 4.3 Hz, 1 H), 2.1 (m, 2 H), 2.0 (m, 2 H), 1.9 (m, 1 H), 1.81 (ddd, $J = 12.8$, 9.8, 3.7 Hz, 1 H), 1.66 (s, 3 H), 1.6 (m, 2 H), 1.59 (s, 3 H), 1.42 (symm. m, 1 H), 1.25 (dq, $J = 12.6$, 3.5 Hz, 1 H), 0.90 (t, $J = 8.0$ Hz, 9 H), 0.9 (m, 2 H), 0.89 (d, $J = 6.2$ Hz, 3 H), 0.52 (q, $J = 8.4$ Hz, 6 H). − ^{13}C NMR: $\delta = 152.8$, 131.1, 124.6, 108.1, 74.8, 52.3, 45.5, 36.4, 34.6, 31.7, 26.3, 25.7, 22.3, 17.7, 7.0, 5.2. − MS (CI); m/z (%): 336 (12) [M^+], 307 (97), 204 (100), 115 (33). − $C_{21}H_{40}OSi$ (336.63): calcd. C 74.93, H 11.98; found C 75.20, H 12.32. − At −75°C, precooled tetrahydrofuran (20 mL) was added to butyllithium (10 mmol) from which the commercial solvent (hexanes) had been stripped off before. The triethyl silyl ether (3.3 g, 10 mmol) just described, *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (2.1 mL, 1.7 g, 10 mmol) and potassium *tert*-butoxide were added again at −75°C. After 6 h at −50°C, the mixture was treated with fluorodimethoxyborane−diethyl ether[23] (2.0 mL, 11 mmol), 30% aqueous hydrogen peroxide (2.0 mL) and 3 M aqueous sodium hydroxide (8.0 mL). It was vigorously stirred for 2 h at 25°C, before the yield of **(*Z*)-6-[(1*S*,2*R*,4*R*)-4-methyl-2-(triethylsilyloxy)cyclohexyl]-2-methyl-2,6-heptadien-1-ol** was determined by gas chromatography (2 m 5% SE−30, 200°C; 2 m, 8% C−20 M, 120°C [after 5 min 30°C/min]→220°C [15 min]; tetradecane as an internal standard): 48% along with 16% of starting material. The product was absorbed on silica gel (10 g) and eluted from a column filled with more silica (0.1 L) with a 1:5 (v/v) mixture of diethyl ether and hexanes; $n_D^{20} = 1.4825$; yield 1.3 g (36%). − ^1H NMR: $\delta = 5.29$ (t, $J = 6.9$ Hz, 1 H), 4.76 (d, $J = 7.4$ Hz, 2 H), 4.11 (d, $J = 2.4$ Hz, 2 H), 3.49 (dt, $J = 10.1$, 4.4 Hz, 1 H), 2.17 (sept, $J = 7.0$ Hz, 2 H), 2.1 (m, 2 H), 1.8 (m, 2 H), 1.78 (s, 3 H), 1.6 (m, 2 H), 1.41 (symm. m, 1 H), 1.24 (m, 2 H), 0.9 (m, 14 H), 0.54 (q, $J = 7.6$ Hz, 6 H). − ^{13}C NMR:

δ = 152.5, 134.3, 128.4, 108.6, 74.9, 61.7, 51.9, 45.5, 36.8, 34.5, 31.7, 25.7, 23.0, 21.2, 7.0, 5.2. − Tetrabutylammonium fluoride trihydrate (1.1 g, 4.0 mmol) was added to a solution of this product (0.71 g, 2.0 mmol) in tetrahydrofuran (4 mL). After 6 h at 25°C, the mixture was absorbed at silica gel. Elution with diethyl ether gave the diol **12** as a colorless oil; $n_D^{20} = 1.3972$; $[\alpha]_D^{20} = -24.4$ (ethanol, $c = 1.0$); yield 0.39 g (82%). − IR (film): $\tilde{\nu} = 3360$ (s, ν[O−H]) 3080 (m, ν[C−H]), 1640 (m, ν[C=C]). − ^{1}H NMR: δ = 5.20 (t, J = 6.8 Hz, 1 H), 4.71 (s, 2 H), 4.17 (d, J = 12.0 Hz, 1 H), 3.97 (d, J = 12.0 Hz, 1 H), 3.54 (dt, J = 11.8, 4.3 Hz, 1 H), 2.30 (symm. m, 1 H), 2.0 (m, 5 H), 1.83 (ddd, J = 13.4, 10.1, 3.5 Hz, 1 H), 1.77 (d, J = 0.1 Hz, 3 H), 1.73 (symm. m, 1 H), 1.65 (s, 1 H), 1.48 (symm. m, 1 H), 1.18 (symm. m, 1 H), 0.96 (q, J = 12.2 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.88 (dt, J = 13.0, 3.7 Hz, 1 H). − ^{13}C NMR: δ = 150.5, 135.5, 127.5, 110.8, 71.7, 61.5, 52.3, 42.5, 34.7, 34.6, 31.6, 31.2, 26.1, 22.3, 21.3. − MS (CI): m/z (%): 221 (1), 125 (14), 81 (100), 107 (73). − $C_{15}H_{26}O_2$ (238.37): calcd. C 75.58, H 10.99; found C 75.69, H 11.00.

Acknowledgments

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (grant 20-49′307-96), Bern, and by the Deutsche Forschungsgemeinschaft (fellowship Ko-1845/1-1), Bonn-Bad Godesberg.

---

[1] M. Schlosser, *Pure Appl. Chem.* **1988**, *60*, 1627−1634.
[2] M. Schlosser, F. Faigl, F. Franzini, H. Geneste, G. Katsoulos, G.-f. Zhong, *Pure Appl. Chem.* **1994**, *66*, 1423−1446.
[3] M. Schlosser, *Mod. Synth. Methods*, **1992**, *6*, 227−271.
[4] A. Mordini, in *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), vol. 11 (Ed.: A. Mc Killop), *Sodium and Potassium*, Pergamon, Oxford, **1995**, p. 93−128.
[5] J. Hartmann, R. Muthukrishnan, M. Schlosser, *Helv. Chim. Acta* **1974**, *57*, 2261−2275.
[6] E. Moret, M. Schlosser, *Tetrahedron Lett.* **1984**, *25*, 1449−1452.
[7] E. Moret, L. Franzini, M. Schlosser, *Chem. Ber.* **1997**, *130*, 335−339.
[8] Metalations of methyl-substituted phenols: A. S. Kende, F. H. Ebetino, T. Ohta, *Tetrahedron Lett.* **1985**, *26*, 3063−3066; R. B. Bates, T. J. Siahaan, *J. Org. Chem.* **1986**, *51*, 1432−1434; R. B. Bates, T. J. Sihaan, K. Suvannachut, S. K. Vasey, K. M. Yager, *J. Org. Chem.* **1987**, *52*, 4605−4608.
[9] R. J. Crawford, W. F. Erman, C. D. Broaddus, *J. Am. Chem. Soc.* **1972**, *94*, 4298−4306.
[10] M. Adrianome, B. Delmond, *Tetrahedron Lett.* **1985**, *26*, 6341−6342.
[11] T. J. Brocksom, R. B. dos Santos, N. A. Varanda, U. Brocksom, *Synth. Commun.* **1988**, *18*, 1403−1410.
[12] D. Friedrich, F. Bohlmann, *Tetrahedron* **1988**, *44*, 1369−1392.
[13] Alternative route consisting of the oxidation of diol **8** with silver dioxide to the corresponding α,β-unsaturated acid and subsequent cyclization with *N,N′*-dicyclohexylcarbodiimid: S. B. Balkrishna, H. W. Pinnick, *Heterocycles* **1981**, 2091−2104.
[14] M. Schlosser, J. Hartmann, *Angew. Chem.* **1973**, *85*, 544−545; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 508−509.
[15] M. Schlosser, M. Stähle, *Angew. Chem.* **1980**, *92*, 497−499; *Angew. Chem. Int. Ed. Engl.* **1989**, *19*, 487−488.
[16] M. Stähle, M. Schlosser, *J. Organomet. Chem.* **1981**, *220*, 277−283.
[17] O. Desponds, L. Franzini, M. Schlosser, *Synthesis* **1997**, 150−152.
[18] M. Schlosser, J. Porwisiak, F. Mongin, *Tetrahedron* **1998**, *54*, 895−900.
[19] R. H. Pickard, H. Hunten, W. Leweock, H. Smith de Pennington, *J. Chem. Soc.* **1920**, *117*, 1248−1263.
[20] H. Saltzman, J. G. Sharefkin, *Org. Synth., Coll. Vol.* **1973**, *5*, 658−659.
[21] M. Ochiai, E. Fujita, *Tetrahedron Lett.* **1983**, *24*, 777−780.
[22] K. Nishitani, H. Fukuda, K. Yamakawa, *Heterocycles* **1992**, *33*, 97−100.
[23] G. Rauchschwalbe, M. Schlosser, *Helv. Chim. Acta* **1975**, *58*, 1094−1099.
[24] K. H. Schulte-Elte, G. Ohloff, *Helv. Chim. Acta* **1967**, *50*, 153−165.
[25] V. R. Tadwalkar, A. S. Rao, *Indian J. Chem.* **1971**, *9*, 1416−1417.

Received August 12
[O98363]