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Synthesis of Sterically Hindered Long-Chain Alkenols via Organolithium Compounds

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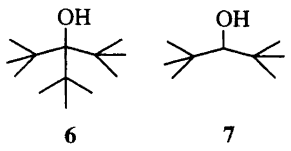
The synthesis of sterically hindered primary, secondary and tertiary alcohols is reported. An unusual monoalkylation/reduction occurs on treatment of a fully α-substituted methyl carboxylate with *t*-BuLi. A mechanism not involving a ketone intermediate but a β-H abstraction from *t*-BuLi prior to or after alkylation is proposed.

We are currently studying the synthesis of some long-chain alkenols in which the carbon α or β to the oxygen atom bears alkyl groups of different size. Since a hindered ketone and a Grignard reagent with β-hydrogens are prone to side reactions[1–3] such as enolization and reduction at the expense of the normal 1,2-addition, a synthetic route employing an α-disubstituted ester **1a** as the starting material was developed (Scheme 1). An organolithium reagent was chosen instead of a Grignard reagent since higher addition to reduction ratios are generally encountered by the use of the former.[1,4,5]

The ester **1a** was allowed to react with *t*-BuLi at −70 or 0 °C. The di-*tert*-butyl derivative **2** was not formed even in trace amounts at either reaction temperature according to the NMR spectra measured from the crude product mixtures. The *sec* mono-*tert*-butyl alkenol **3** was isolated as the sole product in both cases instead. However, the related tri-*tert*-butyl carbinol **6** (Scheme 2) has been obtained from hexamethylacetone and *t*-BuLi at −70 °C.[6] The authors say that the ketone reduction product **7** appears as a by-product only at temperatures higher than −40 °C.[6,7]

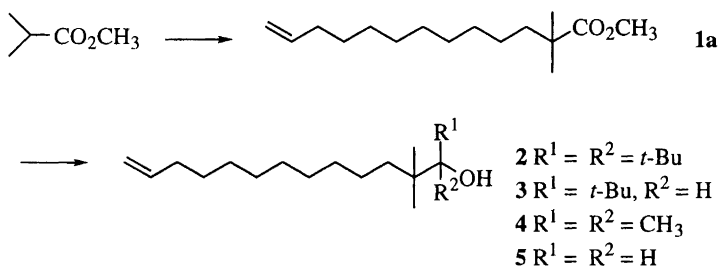
We found that tri-*tert*-butyl carbinol **6** is formed along with the di-*tert*-butyl carbinol derivative **7** in the ratio 2:3 at 0 °C. At −70 °C **6** and **7** were formed in the ratio 3:1. Furthermore, the *tert*-alkenol **8** was produced along with the ketone **9** (Scheme 3) as a 1:1 mixture from the ester **1b** and *t*-BuLi at −70 °C or 0 °C with no traces of the corresponding *sec* mono-*tert*-butyl alkenol.

These findings clearly indicate that the long hydrocarbon chain together with the steric hindrance caused by the alkyl groups around the oxygen moiety in the ester **1a** prevent the normal 1,2-addition. Obviously both these factors are required for monoalkylation–reduction to occur since aliphatic cage derivatives of **6** with adamantyl, bicyclo[2.2.2]octyl and norbornyl substituents



6 **7**

Scheme 2.



Scheme 1.

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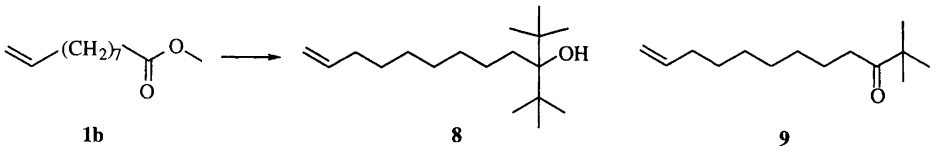


Scheme 3.

have been synthesized from a ketone and an organolithium reagent.[8–11]

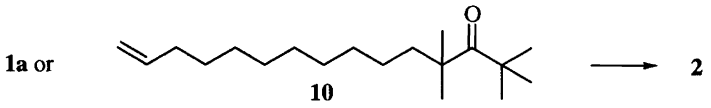
According to the literature, organolithium or Grignard reagents react with carbonyl compounds to afford addition products in high yields in the presence of anhydrous cerium(III) chloride.[12–14] Thus, an attempt was made to synthesize **2** via a cerium chloride promoted nucleophilic addition[14] of *t*-BuLi at −70 °C to the ester **1a** or to the ketone **10** (Scheme 4), prepared from **1a** and *t*-BuLi at −70 °C. In both cases only the starting material **1a** or **10** was recovered.

Almost complete suppression of reduction and enolization is observed, in the absence of $CeCl_3$ or other additives, if a ketone is added to a solution of *t*-BuLi in THF at −78 °C, but not *vice versa*.[15] In an attempt to react the ketone **10** with *t*-BuLi accordingly,[15] mainly unchanged starting material remains even after 7 h, along with a very small amount (< 5%) of the mono-*tert*-butyl derivative **3**, according to the ^1H and ^{13}C NMR spectra measured from the crude product mixture. Thus it appears that in the alkylation–reduction of the ester **1a** to the alcohol **3**, the ketone **10** is not an intermediate.

An analogous alkylation–reduction of methyl pivalate to hexamethylacetone and the *sec*-alcohol **7** using *tert*-butyl chloride and sodium has been previously mentioned with little detail and no mechanistic discussion.[16] Other ester-into-*sec*-alcohol conversions have been performed with RMgX in the presence of $LiBH_4$,[17] Cp_2TiCl_2[18] or DIBAL.[19] A mechanism involving a ketone intermediate was suggested for the first mentioned reaction.[17] Replacing RMgX by RLi produced *tert* alcohols.[17]

For the reaction of the aliphatic ester **1a** and *t*-BuLi we suggest the following mechanism [Fig. 1(a,b)] which takes into account the fact that the ketone **10** is not reduced under our conditions. Compound **3** is formed when a β-hydrogen atom is abstracted from *t*-BuLi with simultaneous formation of lithium methoxide and isobutene, or alternatively, the β-hydrogen atom abstraction could occur prior to alkylation involving a reduction to an aldehyde in the first step. The normal 1,2-addition pathway is prevented by the long hydrocarbon chain. We realize that alternative single-electron processes may also be depicted for the **1a** → **3** reaction.

The other long-chain alkenols **4** and **5** in Scheme 1 were obtained by treating the ester **1a** with CH_3Li at 0 °C or with $LiAlH_4$ in refluxing THF, respectively.



Scheme 4.

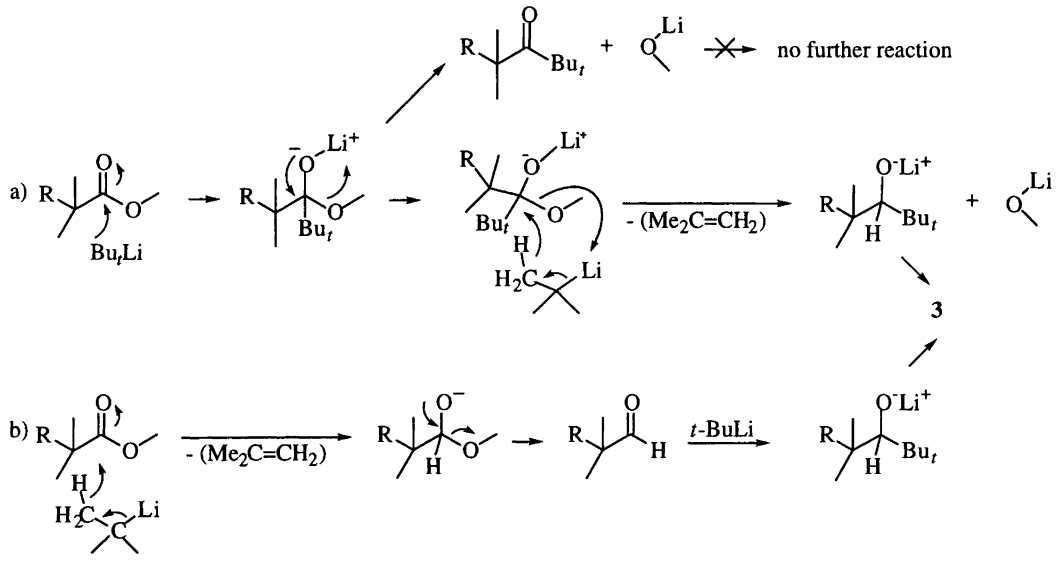


Fig. 1. (a), (b) Proposed mechanisms for the reduction of the ester **1a** by *t*-BuLi.

Experimental

^1H, ^{13}C and 2 D NMR spectra (HSQC and HMBC) were recorded on a Varian Unity 500 MHz, Varian Inova 300 MHz or Varian Gemini 200 MHz spectrometer using $CDCl_3$ as the solvent unless otherwise stated. Infrared spectra were obtained on a Bio-Rad SPC 3200 spectrometer. Mass spectra and high-resolution mass spectra were recorded on a JEOL JMS-SX102 with an EI potential of 70 eV. Flash chromatography was carried out with Merck Silica gel 60 (0.063–0.200 mm). Preparative layer chromatography was performed on aluminium oxide 60 F 254 PLC plates (Merck). All reactions were performed under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone. 11-Bromoundecene (from Lancaster), methyl isobutyrate (from Aldrich) and anhydrous $CeCl_3$ (from Fluka) were used as received. Methyl 9-decenoate (**1b**), synthesized by Neste, was distilled before use.

Ester **1a**. LDA was prepared from BuLi (1 equiv.) and diisopropylamine (1 equiv.) at −40 °C and then kept at 0 °C for 15 min.[20] Methyl isobutyrate (1 equiv.) was added at −70 °C and the mixture was stirred at that temperature for 90 min. 11-Bromoundecene (1.5 equiv.) was added to the mixture at −70 °C and the reaction mixture was allowed to warm to 0 °C over 1 h. It was then stirred overnight at room temperature. The reaction was quenched with 10% NH_4Cl (aq.) at 0 °C. The crude product was purified by flash chromatography on silica gel with gradient elution using hexane and dichloromethane as solvents. The yield of the pure ester was 4.0 g (80%).

Compound **3**. The ester **1a** was treated with *t*-BuLi (3.5 equiv.) in THF at 0 °C for 4 h, then left at room temperature overnight or at −70 °C for 5 h and then quenched as stated above. The crude product (yield 0.95 g, 80%) was purified by preparative Al_2O_3 (neutral) layer chromatography using a hexane–dichloromethane (7:3) eluent system. The yield of the pure **3** was 0.24 g (25%), its structure being assigned by 2 D NMR techniques at different temperatures. The characteristic feature in these spectra is the CHOH proton resonance. When the ^1H NMR spectrum was measured at 27 °C in CD_2Cl_2, the methine proton showed an unresolved doublet signal at δ 3.05 ppm. The OH proton resonance was a singlet of chemical shift 1.50 ppm. The coupling constant of 5.5 Hz for the CH and OH protons was determined from the ^1H NMR spectrum measured at −40 °C. At that temperature the CH and OH resonances are each divided into a doublet, the former having a chemical shift of 3.05 ppm and the latter 1.62 ppm. By lowering the measurement temperature to −70 or −90 °C, the OH proton resonance was observed to shift to δ 1.75 or 1.95 ppm in the ^1H NMR spectra. IR (KBr): ν_{max} 3519, 2922, 1639, 1473, 995, 914 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2): δ 5.80 (m, 1 H, C=CH), 4.90 (m, 2 H, CH_2=C), 3.05 (unresolved d, 1 H, C*H*OH), 2.00 (m, 2 H, C=C–CH_2), 1.50 (s, OH), 1.46 (m, 2 H), 1.36 (m, 2 H), 1.20–1.30 (br, 6 CH_2), 1.00 (s, 9 H, *t*-Bu), 0.80 (s, 3 H, CH_3), 0.70 (s, 3 H, CH_3). ^{13}C NMR (500 MHz, CD_2Cl_2): δ 139.5, 114.1, 84.0, 42.3, 40.0, 37.5, 34.0, 31.0, 29.94, 29.87, 29.7, 29.4, 29.2, 29.0, 25.9, 25.5, 24.3. HRMS: calc. for $C_{19}H_{38}O$ 282.2923, found 282.2909.

Compound **4**. The ester **1a** was treated with CH_3Li (3.5 equiv.) at 0 °C for 2 h 30 min, and then stirred at room temperature overnight. The crude product (122 mg) was purified as described above for compound **3** using dichloromethane as the eluent. The yield of **4** was 50 mg (41%). IR (KBr): ν_{max} 3443, 2932, 1642, 1470, 1378, 1115, 908 cm^{-1}. ^1H NMR (500 MHz): δ 5.80 (m, 1 H, C=CH), 4.90 (m, 2 H, CH_2=C), 2.00 (m, 2 H, C=C–CH_2), 1.40 (s, OH), 1.38 (m, 2 H), 1.34–1.22 (br, 7 CH_2), 1.20 (s, 6 H), 0.90 (s, 6 H). ^{13}C NMR (500 MHz): δ 139.9, 114.8, 76.4, 40.5, 37.6, 34.5, 31.6, 30.4, 30.3, 30.2, 29.8, 29.7, 26.0, 25.4, 22.1. HRMS: calc. for $C_{17}H_{34}O$ 254.2609, found 254.2599.

Compound **5**. The ester **1a** was reduced with $LiAlH_4$ (1.5 equiv.) by refluxing the mixture in THF. The yield of the compound **5** after purification by flash chromatography on silica gel (CH_2Cl_2 eluent) was 0.50 g (55%). IR (KBr): ν_{max} 3352, 2916, 1643, 1410, 1041, 908 cm^{-1}. ^1H NMR (200 MHz): δ 5.80 (m, 1 H, C=CH), 5.00 (m, 2 H, CH_2=C), 3.30 (s, 2 H, CH_2OH), 2.00 (m, 2 H C=C–CH_2), 1.50 (s, OH), 1.20–1.40 (br, 8 CH_2), 0.90 (s, 6 H, CH_3). ^{13}C NMR (200 MHz): δ 139.3, 114.1, 72.1, 38.7, 35.0, 33.8, 30.6, 29.7, 29.6, 29.5, 29.2, 29.0, 23.9. HRMS: calc. for $C_{15}H_{30}O$ 226.2297, found 226.2299.

Compound **8**. Methyl 9-decenoate was treated with *t*-BuLi (3.5 equiv.) in THF at 0 or −70 °C as described for compound **3**. The raw product (0.58 g) was a 1:1 mixture of the *tert*-alkenol **8** and ketone **9**. Compound **8** was purified by flash chromatography on neutral Al_2O_3 using a gradient elution [petroleum ether (b.p. 30–65 °C)–diethyl ether mixtures]. The yield of pure **8** was 119 mg (21%). IR (KBr): ν_{max} 3550, 2940, 1640, 1470, 1365, 1000, 920 cm^{-1}. ^1H NMR (300 MHz): δ 5.80 (m, 1 H, C=CH), 5.00 (m, 2 H, CH_2=C), 2.00 (m, 2 H, C=C–CH_2), 1.58 (t, 2 H), 1.54 (s, OH), 1.20–1.40 (br, 5 CH_2), 1.00 (s, 18 H, 2 *t*-Bu). ^{13}C NMR (300 MHz): δ 139.2, 114.4, 79.8, 42.6, 34.2, 33.7, 30.9, 30.1, 29.7, 29.4, 28.8, 27.0. EI-MS (*m/z*) 250 ($M-H_2O$), 211 ($M-t$-Bu).

Compound **10**. The ester **1a** was treated with *t*-BuLi (1 equiv.) at −70 °C for 30 min. The crude product (119 mg) was isolated as above and purified by preparative Al_2O_3 (neutral) layer chromatography using a toluene–pentane (1:9) eluent system. The yield of **10** was 38 mg (32%). IR (KBr): ν_{max} 2931, 1682, 1482, 1047, 982, 912 cm^{-1}. ^1H NMR (300 MHz): δ 5.80 (m, 1 H, C=CH), 5.00 (m, 2 H, CH_2=C), 2.05 (m, 2 H,

C=C–CH_2), 1.56 (m, 2 H), 1.36 (m, 2 H), 1.32–1.20 (br, 5 CH_2 and 5 CH_3), 1.12 (m, 2 H). ^{13}C NMR (300 MHz): δ 219.1, 139.5, 114.4, 49.8, 46.0, 41.9, 34.1, 30.6, 29.9, 29.8, 29.7, 29.4, 29.2, 28.8, 26.8, 25.6. HRMS: calc. for $C_{19}H_{36}O$ 280.2766, found 280.2779.

Attempted synthesis of compound **2**. A suspension of anhydrous $CeCl_3$ (3.5 or 1.5 equiv.) and dry THF was stirred overnight at room temperature. *t*-BuLi (3.5 or 1.5 equiv.) was added at −70 °C and mixed for 1.5 h at −70 °C followed by addition of the ester **1a** (1 equiv.) or ketone **10** (1 equiv.). Stirring was continued for 7 h at −70 °C. Quenching and isolation of the product was performed as described earlier. In each case only the starting material was recovered.

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