A Facile Method for the Reductive Deoxygenation of Aliphatic Oxygen-Functionalized Compounds

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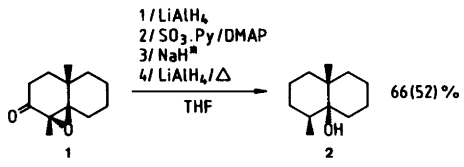
A one-pot three-step sequence for the reductive removal of oxygen from aliphatic carboxylic acids, ketones, aldehydes and alcohols to yield alkanes or alkyl groups has been developed. This was achieved by reducing the substrates to the alcohol level with lithium aluminium hydride followed by *in situ* preparation of the corresponding alkyl sulfate which is finally treated with a second portion of lithium aluminium hydride. Yields as determined by gas liquid chromatography were in the range 89–99 %. Preparative experiments with 1-decanol and decanoic acid afforded 92 and 81 % yield, respectively, of distilled decane. The effect of various additives on the yield of the reaction is reported. Improvement of a recently reported method for the conversion of 1,4a-dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one into *r*-1,*t*-4a-dimethylperhydronaphthalen-*c*-8a-ol [(±)-geosmin] and some observations concerning the reduction of cholesterol are also discussed.

In a recent paper[1] we reported how the reductive removal of the oxo moeity of 1,4a-dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one (**1**) can be performed. This method, which utilizes lithium aluminium hydride (LAH) in tetrahydrofuran (THF) to reduce the ketone to the corresponding alkoxide (no hydrolysis step), then makes use of sulfur trioxide–pyridine complex[2] (SO–Py) to form the monoalkyl sulfate *in situ*, from the alkoxide. Treatment of the alkyl sulfate solution with LAH at reflux temperature yielded the desired deoxygenated proct. In this case, the epoxy moiety of **1** was also reduced to yield the racemic form of geosmin[3] (**2**) (Scheme 1).

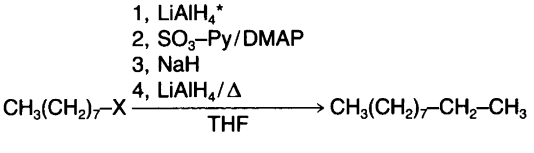


Scheme 1. * Introduced in this work. The yield within parentheses refers to an earlier study (Ref. 1).

This one-pot reaction sequence proceeded in 52 % isolated yield from the epoxy ketone **1** to the saturated tertiary alcohol **2**. Considering the rather hindered position of the sulfate group (secondary, β-carbon branched and 90 % equatorial isomer) and the fact that four different processes are carried out, this result should be regarded as quite satisfactory. It was therefore rather natural to assume that substrates with other reducible oxygen functionalities, i.e. carboxylic acids, aldehydes and the corresponding alcohols, could be reduced to alkanes or alkyl groups by this method. Unfortunately, the method was found not to be useful with substrates containing aromatic nuclei; the SO_3–Py complex sulfonates the aromatic rings much faster than it forms alkyl sulfates from metal alkoxides. Initial experiments with decanal were carried out under conditions similar to Ref. 1, except for the LAH which was used as a solid in this work and the use of 20 mol % of 4-*N*,*N*-dimethylaminopyridine (DMAP) as a sulfonation catalyst (see the Experimental section).

The yields of decane obtained in these initial experiments were only moderate [66–69 % as determined by gas liquid chromatography (GLC)], despite the much less hindered structure of decyl sulfate compared with the epoxy sulfate described above. This result was not improved by the use of filtered solutions of LAH. In an attempt to improve the yield of the reaction, various modifications of the reaction conditions were made; these are reported below.

Methods. The reduction–sulfonation proceeded almost to completion (≥ 95 %) with decanal, and the objective was



(X = $-CH_2CH_2OH$, $-CH_2CHO$, $-COCH_3$, $-CH_2COOH$)

Scheme 2. * LAH is omitted when X = CH_2CH_2OH.

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therefore to explore the conditions of the final step. For this, decyl alcohol was used as the test substrate. The following variations were tested.

(1) The use of dimethoxyethane (DME) to obtain a higher reaction temperature.
(2) The addition of tetramethylethylenediamine (2 equivs.) to alter the extent of cation aggregation in solution.
(3) The addition of dry cobalt chloride (20 mol %) to obtain 'CoH_x', which has been reported to improve the LAH reduction of alkyl tosylates.[4]
(4) The addition of sodium hydride to the sulfate solution to introduce sodium ions without introducing any competing anions. The latter is only possible with alcohols as substrates, where the deprotonation of the pyridinium monoalkylsulfate results in the removal of the anion by hydrogen evolution. This was attempted because the reduction of dry sodium dodecyl sulfate with LAH has been reported to give a quantitative yield of dodecane.[5]
(5) The replacement of SO_3–Py by sulfur trioxide–trimethylamine complex (SO_3–TMA)[6] in order to perform the reaction in absence of the reducible pyridine. Both 1,2- and 1,4-dihydropyridines are reducing agents which may also influence the outcome of the reaction.

The findings of this study were then applied to the reduction of decanoic acid, 2-decanone, decanal and 1-decanol to optimize the experimental conditions. Experiments with compound **1** and with cholesterol were also carried out. All experiments above were monitored with GLC using dodecane or hexadecane as an internal standard. To examine the preparative capability of the method, preparative runs (20 mmol) were made with 1-decanol and decanoic acid. In these experiments the products were purified by distillation. The reduction of **1** was also performed with lithium triethyl borohydride (Super Hydride), as an alternative to LAH, and in a preparative run.

Table 1. Yield of decane when decyl sulfate prepared from 1-decanol *in situ* is reduced with LAH under various conditions.

Entry	Conditions[a]	Yield (%)[b]
1	THF/−/3 LAH solid	71
2	THF/−/5 LAH solid	70
3	THF/−/3 LAH solution	68
4	DME/−/3 LAH solid	61
5	THF/2 TMEDA/3 LAH solid	62
6	THF/0.2 $CoCl_2$/3 LAH solid	48
7	THF/1 NaH/3 LAH solid	97
8	THF/1.5 NaH/3 LAH solid	98–99

[a]Refers to solvent/additive/amount of LAH. In all cases the decyl sulfate was prepared by treatment of 5 mmol of 1-decanol in 25 ml of dry solvent with 7.5 mmol of SO_3–Py and 1 mmol of DMAP with stirring for 3 h at ambient temperature. The additive (mol equivs. as stated: was then added and the stirring was continued at ambient temperature for 1 h. Then 15 or 25 mmol of LAH was added and the reaction mixture was heated at reflux temperature for 10 h. In all reactions any increase in yield was insignificant after 8 h. [b]The yields quoted refer to GLC determinations, using dodecane or hexadecane as an internal standard. The range in entry 8 is based on four experiments.

Results

The SO_3–TMA complex was found to be totally unreactive towards alcohols or alkoxides under the conditions used. In Table 1 the reaction conditions for the reported experiments are given as footnotes in the table.

The results in Table 1 clearly show that the presence of sodium ions is crucial for this reaction. The effect is even more pronounced in the reduction of 2-decanone, as is evident when the yields of the experiments with 2-decanone in Table 2 are compared. The optimum stoichiometries of reagents and reaction times used with different types of functionality are summarized in Table 3.

Preparative experiments with 1-decanol and decanoic acid. In the preparative runs 20 mmol of the substrates in 100 ml of THF were treated under the conditions given in Table 3 for the functionality in question. The yields after isolation by acidic work-up and distillation were 92 % for the alcohol and 81 % for the acid. The purity of the decane thus obtained was, in both cases, > 99 % by GLC analysis.

Table 2. Reduction–sulfonation–reduction of decanal, 2-decanone and decanoic acid with LAH/NaH in the final reduction step.

Substrate	Conditions[a]	Reaction time/H[b]	Yield (%)[c]
Decanal	0.3 LAH/−/3 LAH	10	66–69
Decanal	0.3 LAH/1 NaH/3 LAH	10	86–87
Decanal	0.3 LAH/1.5 NaH/3 LAH	10	91–93
2-Decanone	0.3 LAH/−/3 LAH	10 (120)	7 (9)
2-Decanone	0.3 LAH/1 NaH/3 LAH	96	68
2-Decanone	0.3 LAH/2 NaH/3 LAH	96	94
2-Decanone	0.3 LAH/2 NaH/5 LAH	52	94–95[d]
Decanoic acid	1.1 LAH/1.5 NaH/3 LAH	10	71
Decanoic acid	1.1 LAH/2.5 LAH/4 LAH	10	88–89

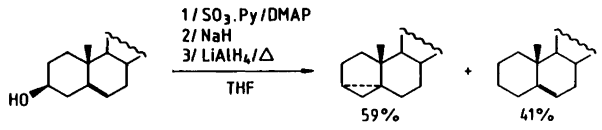
[a]The first figure indicates the number of equivalents of LAH used to reduce the substrates to the corresponding alkoxides. With decanal and 2-decanone this was done by addition of the LAH at ambient temperature and stirring for 30 in. Decanoic acid was treated under reflux for 30 min. The *in situ* transformation of the alkoxide to the alkyl sulfate were performed as described above, except for the decanoic acid where 2 equivs. of SO_3–Py was used. All reactions were performed on the same scale and in the same way as those in Table 1. [b]The reaction times refer to the time of the final reduction step. [c]Where a range is quoted, three or more experiments were performed. [d]In the high yield reactions with 2-decanone the formation of 1-decene, (*E*)-2-decene and (*Z*)-2-decene was observed (in less than 1 % yield of each isomer).

Table 3. Summary of optimum conditions and yields for the reduction of different oxygen functionalities.

Substrate	Reaction steps and conditions[a]			
	Reduction 1	Sulfonation	Reduction 2	Overall yield (%)
1-Decanol	–/–/–	1.5/1.5	3/10	98–99
Decanal	0.3/30/25	1.5/1.5	3/10	91–93
2-Decanone	0.3/30/25	1.5/2.0	5/52	94–95
Decanoic acid	1.1/30/65	2.0/2.5	4/10	88–89

[a]The figures in the table are interpreted as follows: Reduction 1: *xx/yy/zz* = equiv. LAH/time (min.)/temp (°C), Sulfonation: *xx/yy* = equiv. SO_3–Py/equiv. NaH. All sulfonations were performed at room temperature in the presence of 0.2 equivs. of DMAP. A total reaction time of 4 h were applied in all cases. The addition of NaH was done after 3 h. Reduction 2: *xx/yy* = equiv. LAH/time (h.) at reflux temperature.

Reduction of cholesterol. When cholesterol (5 mmol) was treated under conditions as given in Table 3 for the sulfonation of 1-decanol and final reduction of 2-decyl sulfate (2-decanone entry), the reaction gave rise to two products in a ratio 59:41. The minor product was shown to be the expected cholest-5-ene by spectral and chromatographic comparison with authentic material (GLC, TLC, MS), while the major product was shown to be 3α,5-cyclo-5α-cholestane.[7] The evidence for this was: (a) the presence of a high-field multiplet (0.3–0.5 ppm, cyclopropyl) in the ^1H NMR spectrum of the product mixture and (b) the mass spectrum which exhibited the required molecular ion (*m/z* = 370). Furthermore, the reduction of 3β-tosyloxycholest-3-ene (cholesteryl tosylate) with LAH is reported[7] to yield a similar mixture of products. An explanation for this behavior is also given in Ref. 7 (Scheme 3).



Scheme 3. Deoxygenation of cholesterol.

Conversion of 1,4a-dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one into r-*1*,t-*4a-dimethylperhydronapthalen*-c-*8a-ol, [(±)-geosmin].* Reduction of **1** was performed in accordance with Ref. 1 using filtered LAH or Super Hydride solutions (0.27 and 1.05 mol equivs., respectively) for the initial reduction of the keto moiety (with hydride solutions it was easier to control the exact amount of hydride added). The epoxy alkoxides obtained were then treated as described in the entry for 2-decanone in Table 3 using solid LAH or Super Hydride solutions for the final reduction step. In these reactions no increase in yield could be observed after 10 h at reflux temperature in THF. Noted that this is a much shorter time than for the less hindered 2-decyl sulfate (see Tables 2 and 3). The yield of **2** as determined by GLC was 72 % when LAH was used and 55 % with Super Hydride. In the latter case **2** was accompanied by 18 % of 1,4a-dimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydronapthalen-8a-ol[1] (Fig. 1). The identification of this compound was made by comparison with authentic material (GLC, TLC, MS).

In a preparative experiment using LAH, **2** was obtained in 66 % yield after isolation by chromatography and distillation. The purify of the product was > 98 % by GLC.

Fig. 1. 1,4a-Dimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydronaphthalen-8a-ol.

Discussion

Various transition metal ions, i.e. copper(I)[8] and cobalt (II)[4] have been reported to enhance the yield of S_N2 substitutions of alkyl sulfonates in reactions with LAH and similar reagents. These observations have been rationalized by the ability of transition metals to form hydrides of the type 'MH_x' (sometimes with alkyl ligands) in reactions with LAH, which in turn might be more reactive toward sulfonates than LAH itself. Our observation, that a similar enhancement is observed when sodium ions are added to reactions where monoalkyl sulfates are reduced by LAH, requires other explanations. This is because sodium hydride is a very poor reducing agent (NaH alone caused no reduction of the alkyl sulfates). We believe that this effect is due to an alteration in the electrophilic catalysis by the sodium cation compared with the lithium cation, i.e. that the sodium ion improves the leaving-group-ability of the sulfate group more than the lithium ion. Another explanation is that a suppression of the reduction of the oxygen–sulfur double bond is obtained by the presence of sodium ions – such reduction would probably render the sulfur functionality useless as a leaving group. It is thus possible that sodium aluminium hydride would be equally efficient, but this has not yet been investigated. The more rapid reduction of **1** compared with 2-decanone, despite the much more hindered structure of the former, can be explained in terms of the possible intramolecular reduction of **1** (Fig. 2).

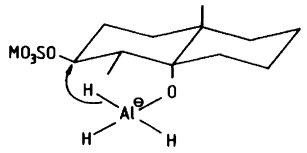


Fig. 2. Intramolecular substitution.

Conclusions

We have found that the above-described deoxygenation scheme performed as a one-pot reaction is a much more effective means for this task than the commonly employed procedure via sulfonates in three discrete steps. The discovery of the promoting effect of sodium ions on the yield of the sulfate reduction has broadened the scope of this reaction (an earlier[2] study concerning a one-pot sulfonation–LAH reduction reported only the deoxygenation of allylic alcohols). The high yields combined with suppression of elimination, even with secondary hindered substates, make this process very competetive. Replacement of LAH with the deuteriated or tritiated analogues, would also furnish a convienient entry to isotopically labelled substances. We also managed to raise the overall yield of our recently reported[1,9] total synthesis of (±)-geosmin (**2**) from 35 % to 45 %, based on ethyl vinyl ketone.

Experimental

General techniques. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AC80 or a AC250 instrument, using deuteriochloroform as the solvent with Me_4Si as an internal reference. Mass spectra were obtained using an HP GS/MSD 5830/5970 system at 70 eV, and are reported as *m/z* (% relative intensity)[assignment]. IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GLC analyses were carried out on capillary columns coated with DB-5 (J&W 15 m), Supelcowax (Supelco 15 m) or SPB-20 (Supelco 30 m) all with 0.53 mm i.d. using an FID. Peak areas were measured with a Spectra Physics integrator. Preparative experiments were carried out under a protective atmosphere of dry nitrogen except during the additions of reagents.

Chemicals. Tetrahydrofuran p.a. (Merck) and dimethoxyethane p.a. (Merck) were distilled directly into the reaction flasks under an atmosphere of dry nitrogen. Tetramethylethylenediamine (Merck) was distilled from calcium hydride. Cobalt chloride p.a. (Fluka) was dried under vacuum (0.05 mmHg at 75 °C) for 12 h. 1-Decanol (Merck), decanal (Merck), 2-decanone (Janssen) and decanoic acid (Merck) were distilled prior to use. Sulfur trioxide–pyridine complex (Merck), sulfur trioxide–trimethylamine complex (Aldrich), lithium aluminium hydride (Merck), lithium triethylborohydride 1.0 M solution in THF (Aldrich) and sodium hydride 60 % in mineral oil (Janssen) were used as received. Filtered solutions of LAH were prepared and standardized according to the method of Brown.[10]

Comments to experiments given in Table 1 and 2. Experimental conditions for all experiments are given in the table footnotes. The procedure is similar for all experiments in the tables and the reduction of 2-decanone to decane is given here as a representative example.

Analytical synthesis of decane from 2-decanone. In a two-necked 100 ml Erlenmeyer flask containing a magnetic stirring bar were placed 5 mmol of 2-decanone (0.78 g) and a carefully weighed amount (0.55–0.65 g) of dodecane (internal standard. THF (25 ml) was then distilled directly into the flask. The flask was removed from the solvent still and equipped with a reflux condenser and the system was placed under a positive pressure of dry nitrogen. This was followed by the careful addition of 1.5 mmol of solid $LiAlH_4$ (0.12 g) to the stirred solution. After 30 min, 7.5 mmol of SO_3–pyridine complex (1.20 g) and 1 mmol of DMAP (0.12 g) were added and the stirring continued for 3 h. After this time 10 mmol of NaH (0.40 g 60 % suspension in oil) were added and the mixture was stirred for a further 1 h after which 25 mmol of solid $LiAlH_4$ (0.95 g) were cautiously added. The mixture was than heated at reflux and samples were withdrawn at regular intervals for determination of the yield by GLC analysis. This reaction was found to be complete within 52 h. Decane was obtained in 95 % yield, and was accompanied by small amounts (< 2 %) of isomeric decenes.

Preparative-scale procedures

Synthesis of decane from 1-decanol. In a 250 ml Erlenmeyer flask containing a magnetic stirring bar were dissolved 20 mmol of 1-decanol (3.16 g) in dry THF (80 ml). To this solution were added 30 mmol of SO_3–pyridine complex (4.80 g) and 4 mmol DMAP (0.49 g) and the reaction was stirred for 3 h when 30 mmol NaH (1.20 g 60 %) were carefully added. After an additional hour of stirring, 60 mmol of solid $LiAlH_4$ (2.28 g) were added in portions to the mixture as rapidly as possible, but with control of the foaming (which suddenly ceased when a part of the hydride had been added). The flask was then equipped with a condenser and heating at reflux temperature for 10 h completed the reaction. The mixture was cooled and cautiously poured into ice-cooled 4 M hydrochloric acid. When all of the solids had dissolved the mixture was extracted with pentane (4×50 ml). The combined pentane extracts were washed with 2 M sodium hydroxide solution (3×50 ml) and water (2×50 ml) and then dried ($MgSO_4$). After filtration, the solvent was removed by careful evaporation and the residue was distilled in a Kugelrohr apparatus to yield 2.61 g (92 %) of pure decane, b.p. 60 °C (oven temp)/10 mmHg. The purity was > 99 % (GLC).

Synthesis of decane from decanoic acid. In a 250 ml Erlenmeyer flask equipped with a reflux condenser and a magnetic stirring bar, were dissolved 20 mmol decanoic acid (3.44 g) in dry THF (80 ml). This was treated with 28 mmol solid $LiAlH_4$ (1.06 g) at reflux temperature for 30 min. After the reaction had been cooled to room temperature, 40 mmol of SO_3–pyridine complex (6.36 g) and 4 mmol DMAP (0.49 g) were added to the flask. The reaction was stirred for 3 h when 50 mmol of NaH (2.00 g 60 % suspension) were added, and stirring was continued for a further hour. 80 mmol of solid $LiAlH_4$ (3.04 g) were then cautiously added and the reaction mixture was heated at reflux temperature for 10 h. Work-up as described above yielded 2.31 g (81 %) of pure decane.

r-*1*,t-*4a-Dimethylperhydronaphthalen*-c-*8a-ol.* (**2**) This compound was prepared from 2.30 mmol* **1** (0.507 g, 88 % in **1**)[9] according to the method given in Ref. 1, with the following modifications. The amount of solvent used was 10 ml (THF) and the LAH solution used in the reduction of the keto moiety was 0.50 M in $LiAlH_4$ (1.40 ml). The amounts of SO_3–pyridine complex, DMAP and NaH were in accordance with the above example with 2-decanone (3.92 mmol 0.620 g, 0.53 mmol 0.065 g and 5.22 mmol 0.209 g 60 % in oil respectively). Reaction times for these steps were 3 and 1 h, respectively. For the final treatment of the mixture, solid LAH was used (13.0 mmol 0.500 g) and the reaction time was 10 h. The isolated yield was 0.271 g (66 %). The purity was > 98 % (GLC).

* The amounts of reagents used (2.61 mmol) were calculated based on all of the hydride-consuming equivalents in the starting material.

Physical properties of compounds. The decane prepared by above methods exhibited IR, MS, ^1H NMR and ^{13}C NMR spectra identical with an authentical sample as well as identical retention times on several capillary GC columns. The spectral and chromatographic behavior of **2** prepared as described above was identical with an authentical sample and is reported in full detail in Ref. 1.

3α,5-Cyclo-5α-cholestane. MS: 370(87)[M^+], 355 (56), 257 (38), 215 (74), 95 (71), 43 (100).

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