Synthesis of (±)-Geosmin. Part 2.[§] A One-Pot Four-Step Conversion of 1,4a-Dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one into (±)-Geosmin

Lars Hansson and Rolf Carlson*

Dept of Organic Chemistry, University of Umeå, S-901 87 Umeå, Sweden

Hansson, L. and Carlson, R., 1990. Synthesis of (±)-Geosmin. Part 2. A One-Pot Four-Step Conversion of 1,4a-Dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one into (±)-Geosmin. – Acta Chem. Scand. 44: 1042–1045.

A one-pot four-step procedure for the conversion of 1,4a-dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one into (±)-geosmin is presented. The synthesis was achieved by a reduction–derivatization–double reduction sequence, which afforded the title compound in 35 % overall yield from ethyl vinyl ketone. Some other possible routes to (±)-geosmin have been investigated. A high yield synthesis of the C-1 epimer of (±)-geosmin using the same epoxide as the starting material is also described. Comparison with other previously reported total syntheses of the title compound is presented.

For use as a reference material in a GC–MS study of volatile mold metabolites, we needed to prepare (±)-geosmin, the racemic counterpart of naturally occurring (−)-geosmin. The chemical structure of this compound was deduced by Gerber,[1a] in cooperation with Marshall and Hochstetler[1b] in 1968, to be r-1,t-4a-dimethylperhydronapthalen-c-8a-ol (1). It has a characteristic smell of soil which is detected at very low concentration levels. The total synthesis of (±)-geosmin and also the enantioselective synthesis of both enantiomers have previously been reported by several authors.[1b,2–5] Refs. 3 and 4 were published during the course of this work and the results are similar to those reported here. Here we report that it is possible to transform 1,4a-dimethyl-1α,8aα-epoxyperhydronaphthalen-2-one (2) into 1 using fewer operations than in the methods previously reported. Three potential routes were considered as one-pot reactions.

(a) The treatment of 2 with hydrazine hydrate in ethanol to obtain 1,4a-dimethyl-trans-3,4,4a,5,6,7,8,8a-octohydronaphthalen-8a-ol[6] (3), via the Wharton reaction,[7] followed by reduction of the unsaturation by the in situ generation of diimide[8,9] to yield 1. Diimide could be generated by the addition of hydrogen peroxide to the reaction mixture or by addition of copper(II) sulfate and bubbling of oxygen through the solution.

(b) The reduction of the epoxy moiety of 2 with a sodium borohydride/diphenyl diselenide reagent[10] in ethanol to yield c-8a-hydroxy-r-1,t-4a-dimethylperhydronaphthalen-2-one[2] (4) followed by a direct dithioketalization–desulfurization sequence. This could be achieved by treatment of the reaction mixture with 1,2-ethanedithiol and an acidic catalyst followed by Raney nickel.

(c) Selective reduction of the keto moiety of 1 with lithium aluminium hydride in THF followed by tosylation of the alkoxide in situ, and then further treatment of the epoxy tosylate with lithium aluminium hydride.[3,4]

Here we report that the use of a sequence similar to (c) affords purified 1 in 52 % yield, using a one-pot procedure. When the epoxide precursor, 1,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (5), was prepared according to a procedure recently reported[11] by us, the overall yield of 1 was 35 % based on ethyl vinyl ketone in only three discrete operations (Scheme 1).

Methods

The reactions in the schemes were carried out in accordance with Refs. 7–10 and 12 or as given in the Experimental. The substrate 2 used in all experiments was prepared according to the method in Ref. 11. Material so produced contained 88 % of the desired α-epoxide and the
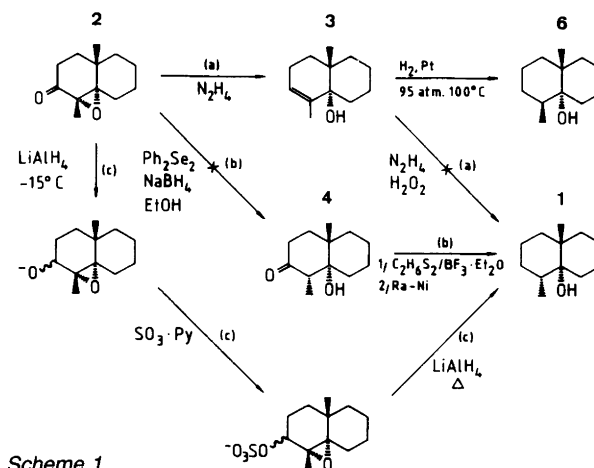
Scheme 1.

* To whom correspondence should be addressed.

yields reported are based on the actual content of this compound. Results obtained in the hydrogenation step in (a) led us to run some hydrogenation experiments on isolated **3**. If successful, this would still constitute a shorter route than any previously described. Screening of reagents for the derivatization of the hydroxy group in the epoxy alkoxide in (c) was carried out. The results are given below. In this study, yields were determined by GLC, as is the case with the screening experiments to determine significant experimental variables (not reported). Other yields reported refer to isolated purified products.

Results

(a) The formation of **3** proceeded smoothly when **2** was treated with hydrazine hydrate (10 equiv.) in ethanol. When the mixture was treated with hydrogen peroxide (5 equiv.) at room temperature no reduction of the substrate was observed. Increase of the excess of the reducing agent and higher reaction temperature was equally unsuccessful in obtaining the desired olefin reduction. The unchanged substrate was completely recovered. The use of copper(II) sulfate and oxygen was also unsuccessful. Reduction of less hindered unsaturated olefinic bonds in similar structures, such as the 2,3-double bond of the diene obtained by treating **5** with phenylhydrazine and butyl lithium,[13] occurred readily with copper(II) sulfate and oxygen over 24 h at room temperature. Isolated samples of **3** were subjected to low-pressure hydrogenation (4 atm) in a Parr apparatus under several different conditions: 10 % Pd on carbon in methanol, methanol/acetic acid and methanol/acetic acid/ small amounts of sulfuric acid at room and elevated temperature (50–60 °C). Adam's catalyst in ethanol or ethanol/ acetic acid in the same temperature range, was also employed. Reduction of the substrate was observed only when the reaction was conducted in the presence of a small amount of sulfuric acid. In this experiment an isomeric mixture of saturated 1,4a-dimethylperhydronaphthalenes (GC–MS M⁺ m/z 166) was obtained. This was not an unexpected result, since **3** easily eliminates water under acidic conditions. However, high-pressure hydrogenation using Adam's catalyst in ethanol at 95 atm and 100 °C for 36 h cleanly reduced **3** to a saturated 1,4a-dimethylperhydronaphthalen-8a-ol in high yield. To our disappointment this compound was found to be r-1,c-4a-dimethylperhydronaphthalen-t-8a-ol[6] (**6**), the C-1 epimer of **1** (NMR, GC–MS, TLC). It is interesting to note that the reaction did not suffer from hydrogenolysis of the hydroxy group, despite the allylic position and the harsh reaction conditions employed. The presence of **1** in the crude material was <1 % (not detected). The overall yield of **6**, based on ethyl vinyl ketone was 46 %, in a four-step sequence. The ¹H NMR characterization of **3** showed that earlier assignments[6] of the vinylic signals in mixtures of **3** and the corresponding cis isomer are incorrect.

(b) The reduction of **2** with the sodium borohydride/ diphenyl diselenide failed to produce the expected **4** both at room temperature as described in Ref. 10 and at reflux temperature in ethanol (both 95 % rectified spirit and absolute ethanol were tried). The addition of acetic acid to the reaction mixture had no effect. Unconverted **2** was recovered in all attempts. When a sample of **4**, prepared according to the method of Ayer et al.,[2] was added to an ethanol solution containing the above reagent, followed by the addition of 1,2-ethanedithiol and boron trifluoride–diethyl ether, **1** was formed after final treatment with Raney nickel at reflux temperature. The yield was, however, not determined.

(c) When **2** was treated with lithium aluminium hydride (0.25 equiv.) added dropwise as a clear solution in THF at −15 °C, the conversion of the substrate was complete within 1 h. TLC and GC–MS analysis showed two epimeric epoxy alcohols (equatorial:axial 90:10) as the main products. To such a mixture was added p-toluenesulfonyl chloride (1.5 equiv.) and 4-(N,N-dimethylamino)pyridine (DMAP 0.05 equiv.) to obtain the tosylates of the lithium and aluminium epoxy alkoxides. This reaction was allowed to proceed for 24 h. TLC analysis showed that two new products had been formed but that the conversion of the epoxy alkoxides was not complete, so the reaction was allowed to proceed for another 24 h after which lithium aluminium hydride (3 equiv.) was added as a solution in THF. This mixture was then heated at reflux for 3 h. Samples from this reaction showed on GC–MS analysis that **1** had actually been formed in low yield, the main product being the diols[3] formed in the reduction of underivatized epoxy alcohols. To improve the derivatization step an investigation of some alternative methods and derivatives were investigated, see Table 1.

The results given in Table 1 show that the use of pyridine/ sulfur trioxide complex[12,14] is superior with respect to both yield and rate of the reaction. If diols were produced by the use of an excess of hydride under reflux conditions prior to the derivatization step, the final yield is lowered (entry 5). Only in the cases where chlorosulfonic acid or pyridine/ sulfur trioxide complex were used, did complete derivatization of the epoxy alkoxides occur. The formation of epoxy alkoxides and the reduction of the derivatives were performed in the same way in all entries, except entry 5

Table 1. Yields of **1** in the reduction–derivatization–double reduction sequence when different derivatives are used.

Entry	Reagent	Time/h[a]	Conv. (%)[b]	Yield (%)
1	TsCl, DMAP	170	80–90	14
2	MsCl, DMAP	72	90–95	23
3	ClSO₃H	1	100	40
4	SO₃–Py	2	100	55
5	SO₃–Py	2	100	33

[a]This refers to the time in the derivatization step. [b]This refers to the conversion of the epoxy alkoxides and was estimated by observing the residual epoxy alcohols in GLC after aqueous work-up of samples from the reaction mixture.

(see the Experimental). The experimental conditions for the pyridine/sulfur trioxide reagent were established using a statistical screening experiment.[15]

Discussion

The possibility of conducting several discrete reaction steps as an efficient one-pot procedure is largely dependent on solvent compatibility with the reagents involved. This indicates that there is a need for comprehensive studies of the scope of new reactions with regard to solvent variation. If such information were commonly available, the successful adaptation of one-pot procedures for multistep reactions would be facilitated. Unfortunately, this is not common practice today. The isolated yield (52 %) of 1 in the method reported here is higher than the overall yield (46 %) of the three discrete steps reported in Ref. 3. The use of alkyl sulfate derivatives as a means of substituting hydroxy groups for hydrogen has been described with allylic[12] and primary[14] alcohols as substrates. This work shows that this methodology can be extended to relatively hindered secondary substrates. A comparison with previously reported total syntheses of 1 is given in Table 2. The yields given are based on the commercially available starting material needed in each case.

Conclusions

The synthesis of 1 described in this paper is more efficient than methods previously described. High-pressure hydrogenation of 3, affords a complementary route, leading to the other of the two 1,4a-dimethyl-*trans*-perhydronaphthalen-8a-ols in good yield.

Experimental

General techniques. See part 1.

Table 2. Comparison of the overall yield and number of steps in previously reported total syntheses of geosmin and the result reported in this work.

Entry	References	No. of steps	Yield (%)[a]	Based on[b]
1	1, 16	12	10	A
2	2, 17	5	10	B
3	3, 17	5	16	B
4[c]	4	6	27	C, D[d]
5	11, this work	3	35	D

[a]Calculation of yields was based on B and D in entries 2–5 rather than 2-methylcyclohexanone because they are about 20 times more expensive than the latter. [b]A is 2,6-dimethylcyclohexanone, B is 1-chloro-3-pentanone, C is the imine derived from 2-methylcyclohexanone and α-methylbenzylamine and D is ethyl vinyl ketone. [c]This refers to an enantioselective synthesis of (−)-geosmin. [d]Because stoichiometric amounts of C and D were used calculation of the yield may be based on either material.

Chemicals. All solvents were of AR grade (Merck or Labscan) and were used without further treatment with exception of tetrahydrofuran, which was distilled from sodium–benzophenone under an argon atmosphere. Clear solutions of lithium aluminium hydride in THF were prepared according to the method described by Brown.[18] The hydride concentration of such solutions was determined by gas volumetry. Methanesulfonyl chloride, *p*-toluenesulfonyl chloride, pyridine/sulfur trioxide complex, chlorosulfonic acid (Merck) and diphenyl diselenide (Janssen) were used as received.

Condition used in the derivatization step reaction (c) (Table 1). All reactions were run with 5 mmol of 2 and with hexadecane as an internal standard for GLC analyses. After complete reduction of the keto moiety as indicated by TLC, the following procedures were used. Entry 1, 1.5 equiv. of methanesulfonyl chloride and 0.1 equiv. of DMAP were added at room temperature and stirring was continued for the time specified. Entry 2, as above but with *p*-toluenesulfonyl chloride. Control experiments of entry 1 and 2 were also run in the presence of 1.5 equiv. of pyridine, but this did not effect the rate or the conversion. Entry 3, 1.05 equiv. of chlorosulfonic acid were added carefully at −15 °C, and the mixture was then allowed to reach to room temperature in 1 h. Entry 4, as entry 3, but using pyridine/sulfur trioxide as the reagent, and 1 h of additional stirring at room temperature. Entry 5, in this case the use of an excess of lithium aluminium hydride (1.5 equiv.) and reflux temperature was employed in the initial reduction step to form a mixture of dialkoxides instead of epoxy alkoxides. The derivatization was performed as in entry 4.

r-1,t-4a-Dimethylperhydronaphthalen-c-8a-ol (1). To a stirred mixture of 2 (20 mmol, 3.88 g) or (4.41 g, 88 % in 2) in dry THF (30 ml) at −15 °C under an argon atmosphere was added a solution of LiAlH$_4$ in THF (4.0 ml, 1.45 M). The mixture was allowed to reach room temperature over 1 h and was then stirred for another 1 h. To this solution of epoxy alkoxides was added solid pyridine/SO$_3$ complex (23 mmol, 3.70 g) and the stirring was continued for 2 h. The resulting alkyl sulfates were then treated with LiAlH$_4$ in THF (50 ml, 1.45 M) and the reaction was run to completion by heating at reflux for 5 h. After cooling, a solution of triethanolamine in THF (19.5 ml, 4 M) was cautiously added, followed by the addition of water (1.4 ml). To the resulting suspension was added 100 ml of diethyl ether and stirring was continued for 5 h. The salts were filtered off and thoroughly extracted with diethyl ether. The combined extracts were washed successively with 10 % acetic acid, 2 M NaOH and water, and then dried (MgSO$_4$). After removal of the solvent, the residual oil was chromatographed (Silica 60 Merck 9385, hexane/ethyl acetate). Distillation of the combined geosmin fractions using a Kugelrohr apparatus yielded 1 (1.89 g, 52 %) b.p. 110–112 °C/8 mmHg as a colorless oil. The purity as determined by GLC was > 98 %.

1,4a-Dimethyl-trans-*3,4,4a,5,6,7,8,8a-octahydronaphthalen-8a-ol* (**3**). To a stirred solution of hydrazine hydrate (375 mmol, 18.2 ml) in absolute ethanol (40 ml) was added dropwise a solution of **2** (33 mmol, 6.40 g) or (7.30 g 88% in **2**) in absolute ethanol (20 ml) over 2 h. The mixture was heated at reflux temperature for 3 h. The solvent was removed and the residue was dissolved in hexane. The hexane solution was washed with water and dried (MgSO$_4$). After removal of the solvent the residue was chromatographed as above to yield 5.50 g of **3** (86%). The purity of the product was > 98% by GLC analysis.

r-1,c-4a-Dimethylperhydronaphthalen-t-8a-ol (**6**). A solution of **3**, 20 mmol (3.60 g) and Adam's catalyst, 200 mg, in ethanol was pressurized in a hydrogenation bomb at 95 atm and 100 °C for 36 h. When the reduction was complete, the catalyst was filtered off, and the solvent removed from the filtrate by evaporation. The crude product was chromatographed as above. The yield of **6** after distillation of the concentrated fractions from the chromatographic purification as above was 2.93 g (81%) b.p. 110–112 °C/8 mmHg. The product solidified in the cooled receiver, m.p. 24 °C. The purity was > 98% as determined by GLC.

Physical properties of compounds. Mass spectra were taken at 70 eV and are reported as *m/z* (% relative intensity) [assignment]. IR spectra are reported in cm^{-1} (intensity s,m,w).

r-1,t-4a-Dimethylperhydronaphthalen-c-8a-ol (**1**). B.p. 110–112 °C/8 mmHg. ^{1}H NMR: δ 1.24 (s, 1 H), 1.03 (s, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR: δ 74.4, 37.2, 35.6, 35.0, 34.2, 30.4, 29.8, 21.3, 20.7, 20.6, 20.2, 14.8. MS: 182 (4) [M^+], 125 (13), 112 (100), 111 (24), 97 (16), 55 (35), 43 (41), 41 (44). IR (neat): 3630 (w), 3520 (wb), 2940 (s), 2865 (s), 1465 (m), 1445 (m), 1380 (m), 945 (m).

r-1,c-4a-Dimethylperhydronaphthalen-t-8a-ol (**6**). M.p. 24–25 °C b.p. 110–112 °C/8 mmHg ^{1}H NMR: δ 1.38 (s, 1 H), 1.10 (s, 3 H) 1.02 (d, *J* = 7.9 Hz, 3 H). ^{13}C NMR: δ 75.3, 40.8, 38.0, 36.9, 35.2, 32.2, 28.1, 21.5, 21.3, 20.7, 16.9, 16.6. MS: 182 (3) [M^+], 125 (16), 112 (100), 111 (24), 97 (15), 55 (31), 43 (37), 41 (35). IR (neat): 3620 (w), 3490 (mb), 2930 (s), 2855 (s), 1460 (m), 1445 (m), 1385 (m), 950 (m).

1,4a-Dimethyl-trans-*3,4,4a,5,6,7,8,8a-octahydronaphthalen-8a-ol* (**3**). ^{1}H NMR: δ 5.29 (br s, 1 H), 1.67 (d, *J* = 1.6 Hz, 3 H), 0.94 (s, 3 H). MS: 180 (13) [M^+], 162 (82), 147 (66), 123 (100), 82 (81), 55 (87), 43 (79), 41 (83). IR: 3640 (w), 3525 (m), 2950 (s), 1460 (m), 1440 (m), 1385 (m).

References

1. (a) Gerber, N. N. *Tetrahedron Lett.* (1968) 2971; (b) Marshall, J. A. and Hochstetler, A. R. *J. Org. Chem. 33* (1968) 2593.
2. Ayer, W. A., Browne, M. L. and Fung, S. *Can. J. Chem. 54* (1976) 3276.
3. Gosselin, P., Joulain, D., Laurin, P. and Rouessac, F. *Tetrahedron Lett.* (1989) 1775.
4. Revial, G. *Tetrahedron Lett.* (1989) 4121.
5. *Poster abstract PC-146*, ESOC IV, Aix-en-Provence, France 1985.
6. Marshall, J. A. and Hochstetler, A. R. *J. Org. Chem. 31* (1966) 1020.
7. Wharton, P. S. and Bohlen, D. H. *J. Org. Chem. 26* (1961) 3615.
8. Ohno, M. and Okamoto, M. *Org. Synth. 49* (1969) 30.
9. van Tamelen, E. E., Dewey, R. S. and Timmons, R. J. *J. Am. Chem. Soc. 83* (1961) 22957.
10. Miyashita, M., Suzuki, T. and Yoshikoshi, A. *Tetrahedron Lett. 28* (1987) 4293.
11. Hansson, L., Carlson, R. and Sjöberg, A.-L. *Acta Chem. Scand. 44* (1990) 1036.
12. Corey, E. J. and Achiwa, K. *J. Org. Chem. 34* (1969) 3667.
13. Grieco, P. A., Oguri, T., Wang, C.-L. J. and Williams, E. *J. Org. Chem. 42* (1977) 4113.
14. Haines, T. H. *Lipids 5* (1970) 149.
15. Box, G. P. E., Hunter, W. G. and Hunter, J. S. *Statistics for Experimenters*, Wiley, New York 1978.
16. Marshall, J. A. and Schaeffer, D. J. *J. Org. Chem. 30* (1965) 3642.
17. Zoretic, P. A., Branchaud, B. and Mastreone, T. *Tetrahedron Lett.* (1975) 527.
18. Brown, H. C. *Organic Synthesis via Boranes*, Wiley New York, Chichester, Brisbane, Toronto 1975.