Chemistry of Natural Compounds and Bioorganic Chemistry

Transformations of sclareol oxide by bromination. Synthesis of driman-8α,11-diol from sclareol oxide

*A. N. Aricu, I. Yu. Andreeva, and P. F. Vlad**

Institute of Chemistry, Academy of Sciences of Republic of Moldova, MD 2028, Kishinev, 3 ul. Academiei, Republic of Moldova. Fax: (373 2)73 9954

Depending on reaction conditions, the reaction of sclareol oxide with *N*-bromosuccinimide affords either 12-bromo- or 12,16-dibromosclareol oxide, whereas the reaction of sclareol oxide with bromine in methanol gives 12-monobromide or (13*S*)-11,12-dibromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabdane. Dehydrobromination of the latter with potassium hydroxide in toluene in the presence of polyethylene glycol gives (13*S*)-12-bromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabd-11-ene, ozonolysis of which followed by reduction of the ozonide with $LiAlH_4$ affords drimane-8α,11-diol.

Key words: sclareol oxide, bromination; drimane-8α,11-diol; *N*-bromosuccinimide; bromine; dehydrobromination; ozonolysis.

The bisnorlabdane derivative, sclareol oxide (**1**), is formed by the oxidation of sclareol (**2**)[1–3] and by the degradation of manoyl oxide (**3**).[4,5] The accessibility of oxide **1** makes it attractive as a synthon for the synthesis of higher as well as lower drimane sesquiterpenoids. However, chemists have not yet directed their attention to the transformation of oxide **1** into homodrimane compound ambrox (**4**), which is especially valuable for perfumery.[2,3,6]

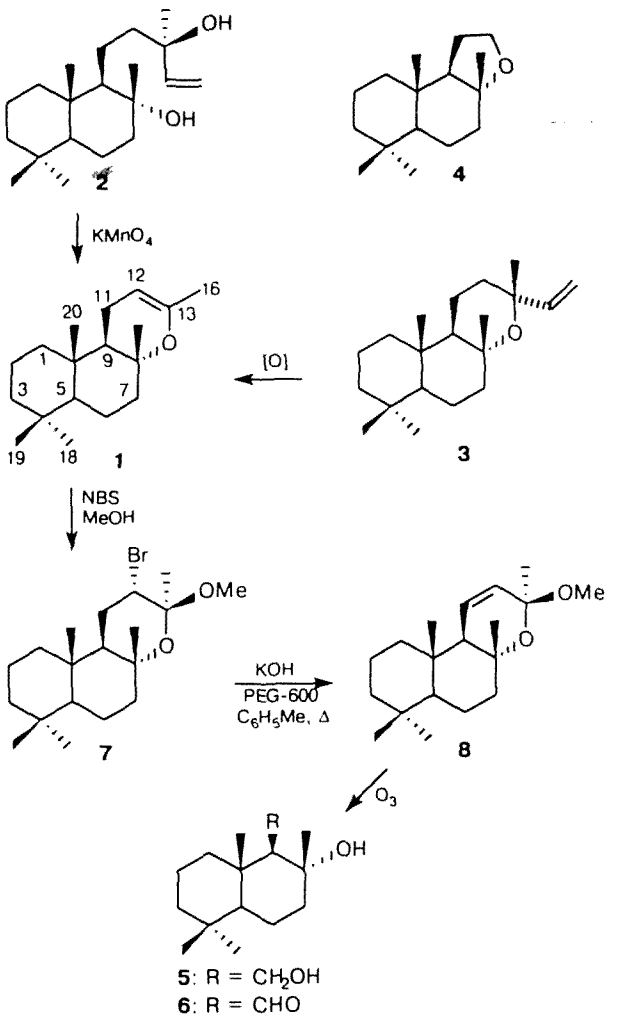
Recently, a synthesis of drimane-8α,11-diol (**5**) and 8α-hydroxydrimane-9-carbaldehyde (**6**) from oxide **1** has been described; the key steps of the synthesis are bromination of oxide **1** with *N*-bromosuccinimide (NBS) in methanol to afford bromomethoxylation product **7**, and dehydrobromination of the latter into (13*S*)-8α,13-epoxy-13-methoxy-14,15-bisnorlabd-11-ene (**8**) with powdered KOH in refluxing toluene in the presence of polyethylene glycol PEG-600 as a phase-transfer catalyst (Scheme 1).[7]

In order to solve some research problems, we needed drimanediol **5**, which was thought to be obtainable using the above method[7] from sclareol oxide **1**. However, all the attempts to reproduce this synthesis failed. It was found that bromoketal **7** (revealed by TLC) obtained from oxide **1** is extremely unstable and decomposes even as the reaction mixture is being treated to form the vinylic bromide, 12-bromosclareol oxide (**9**). The structure of the latter was established by the data of elemental analysis, its IR and ^1H NMR spectra, and ozonolysis. According to the IR spectroscopy data, its molecule contains a tetrahydropyran ring (THP ring), a double bond and a bromine atom. In the ^1H NMR spectrum,

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 11, pp. 2785—2789, November, 1996.

1066-5285/96/4511-2644 $15.00

Scheme 1

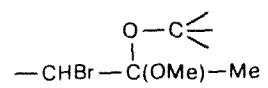


signals of five methyl groups were observed, among them methyl groups at a carbon atom bonded to an oxygen atom and a methyl group at a double bond. The ^{1}H NMR data also indicate that the double bond is substituted completely, *i.e.*, the bromine atom is vinylic. The structure of compound **9** was determined unambiguously when its ozonolysis followed by reduction of ozonide with $LiAlH_4$ yielded sclarediol (**10**).

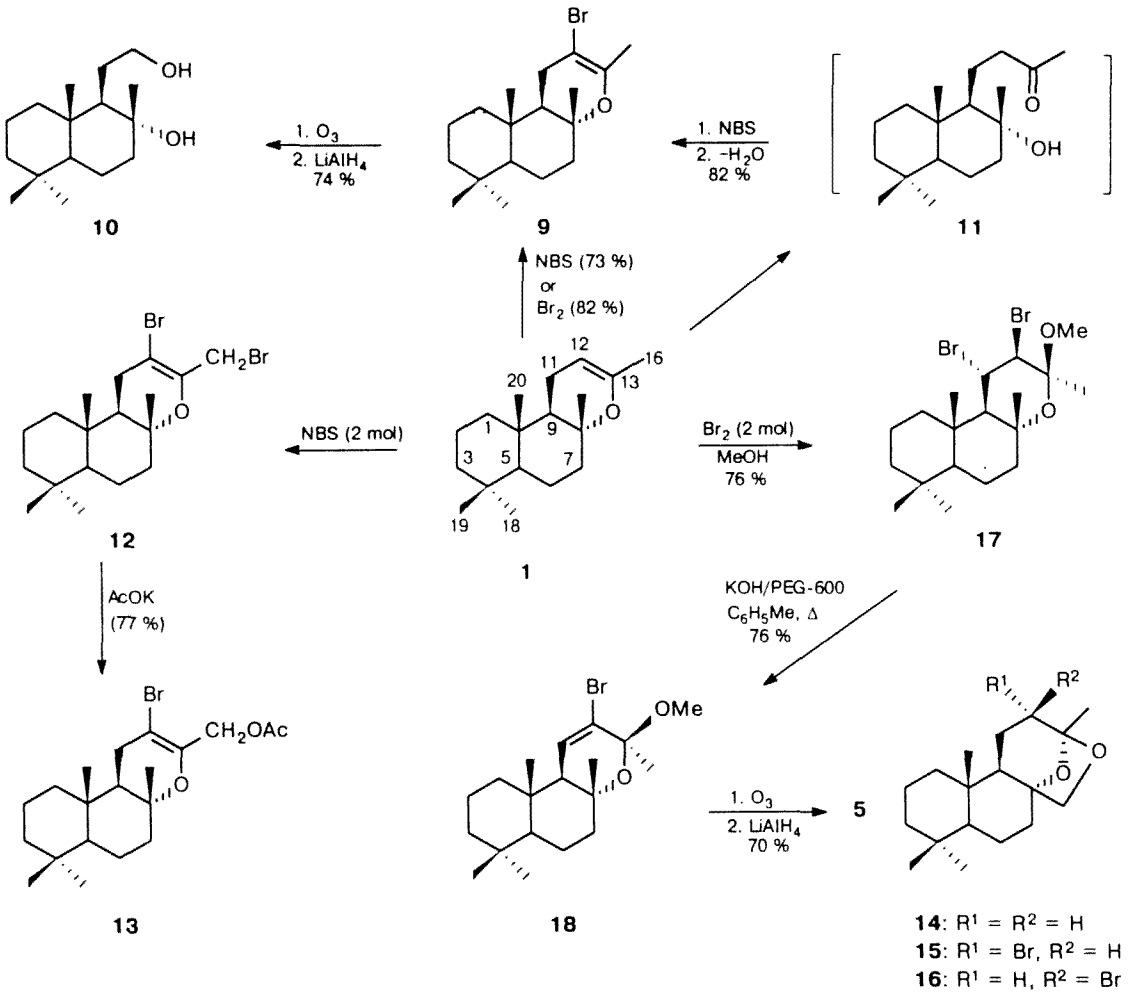
Vinylic bromide **9** was also prepared in high yield (82 %) by bromination of sclareol oxide **1** with a stoichiometric amount of NBS in CCl_4. Apparently, in this case hydroxyketone **11** is involved in the reaction; sclareol oxide **1** is in equilibrium with **11**, thus there is a small amount of the latter in sclareol oxide (Scheme 2). Finally, vinylic bromide **9** is formed in the same yield in the reaction of oxide **1** with an equimolar amount of bromine in methanol. Methoxybromide **7** is an intermediate in the reaction.

Bromination of sclareol oxide **1** with two molar equivalents of NBS gives 12,16-dibromosclareol oxide **12**. Its structure was established on the basis of spectral data and elemental analysis. In the IR spectrum of **12**, absorption bands characteristic of C—Br bonds, a double bond, and a THP ring are present, and in the ^{1}H NMR spectrum, the signals of four methyl groups, one of them attached to a carbon atom bonded with an oxygen atom, and the AB spin system of the $>C-CH_2Br$ group were observed. The absence of low-field signals in the ^{1}H NMR spectrum shows that the double bond in the compound studied is substituted completely, and, hence, one of the bromine atoms is vinylic. The latter assumption is also confirmed by the fact that only one bromine atom undergoes nucleophilic substitution in the reaction with potassium acetate, thus giving 16-acetoxy-12-bromosclareol oxide (**13**), whose structure was confirmed by spectral data and elemental analysis (see Experimental). Dibromide **12** is formed by the reaction of monobromide **9** with NBS, which was confirmed in a separate experiment.

The nature of the reaction product also changes in the bromination of sclareol oxide **1** in methanol with 2 eq. of Br_2. According to the elemental analysis, the reaction product (yield 76 %) contains two bromine atoms and a methoxy group; the spectral data are in agreement with this conslusion. In the IR spectrum of the compound studied, absorption bands characteristic of a $>C-Br$ bond, a methoxy group, and a THP ring are present, but the absorption bands of a double bond are absent. In the ^{1}H NMR spectrum, singlets of five methyl groups are observed, including signals of one methyl group at a carbon atom bonded with one oxygen atom and one methyl group at a carbon atom connected with two oxygen-containing functional groups. The latter signal is located in rather low field at 1.66 ppm, which is close to the position of the signal of the corresponding methyl group in the ^{1}H NMR spectrum of bridged ketal **14** (1.42 ppm) and, in particular, to its position in the ^{1}H NMR spectra of 12α- and 12β-bromoketals **15** and **16** (1.57 ppm).[8] The above facts show that the structural fragment is present in the molecule of the compound studied. The ^{1}H NMR data also indicate that the two bromine atoms are vicinal, not geminal. In the ^{1}H NMR spectrum, there are three one-proton doublets of doublets: at 2.08 ppm the doublet of doublets of H—C(9), at 2.44 ppm the doublet of doublets of H—C(12), and at 2.75 ppm the doublet of doublets of H—C(11), which is coupled with the protons at C(9) and C(12) (see the J value). As can be seen from the value of J (12—14 Hz), all of these three protons are axial. The axial configuration of H—C(12) is also indicated by its through field interaction with the axial proton at C(9) (J = 2 Hz), hence the signals of these protons are doublets of doublets. This coupling can take place only if the protons are in the *cis*-1,3-diaxial position. Therefore, both bromine atoms are equatorial. The methoxy group at the



Scheme 2



C(13) atom has an axial configuration, because it deshields the methyl group at the C(8) atom by 0.17 ppm and, hence, is *cis*-arranged in relation to the methyl group.

Thus, considering the above data, one can conclude that compound **17** is the product of bromination of sclareol oxide **1** by two moles of bromine in methanol. The formation of this dibromide evidently proceeds *via* compounds **7** and **8** as intermediates, while *trans*-diaxial addition of bromine at the double bond of compound **8** should occur for the twisted conformation of the dihydropyran ring. Only in this case, the conversion of the THP ring of the adduct of bromine to olefin **8** affords methoxydibromide **17** with an equatorial bromine atoms and an axial methoxy group. It is interesting that in the bromination of sclareol oxide **1** with excess bromine, methoxybromide **7** eliminates hydrogen bromide, not methanol.

Debromination of compound **17** would afford unsaturated methoxyoxide **8**. However, attempts to eliminate bromine from dibromide **17** by heating it in DMF,[9] by treating it with sodium thiosulfate in DMSO[10] or with $LiAlH_4$ in THF,[11] or by treating it with Zn dust in acetic acid failed.

When heated with solid KOH in toluene in the presence of PEG-600,[13] dibromide **17** eliminates one molecule of hydrogen bromide and transforms into (13*S*)-12-bromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabd-11-ene (**18**), whose structure was established by spectral methods. Its IR spectrum possesses bands of a $\geq$C—Br bond, a methoxy group, a THP ring, and a double bond. The ^{1}H NMR spectrum contains signals of five methyl groups (one of them located at a carbon atom bonded to two oxygen-containing functional groups), a methoxy group, and the doublets of H—C(9) and H—C(11). Its structure was ultimately determined by ozonolysis followed by reduction of the ozonide with $LiAlH_4$: drimane-8α,11-diol (**5**) was obtained in a yield of 70 %. Thus, the sequence of transformations **1**→**17**→**18**→**5** can serve as a route for the preparation of drimanediol **5** from available sclareol oxide **1** in an overall yield of 40 %.

Experimental

Melting points were determined on a Boetius heating stage. The IR spectra were recorded with a Specord 71 instrument in CCl_4. The ^1H NMR spectra were recorded with a Bruker AC-80 spectrometer (80 MHz) in $CDCl_3$; tetramethylsilane was used as the internal standard. Silica gel L (40/100 and 100/160 μ) was used for column chromatography, and silica gel LS (5/40 μ) containing 13 % of gypsum was used for TLC. GLC analysis was carried out with a Chrom-5 chromatograph (FID, a 3.5 m x 3 mm glass column containing 5 % XE-60 on Chromaton N-AW-HMDS (0.16—0.2 mm)). Solutions of compounds in organic solvents were dried over anhydrous sodium sulfate.

Bromination of sclareol oxide 1 with *N*-bromosuccinimide. a. NBS (0.81 g, 4.6 mmol) and $CaCO_3$ (1 g, 10 mmol) were added to a solution of sclareol oxide **1** (1.2 g, 4.6 mmol) in MeOH (20 mL) at 20—22 °C The reaction mixture was stirred for 20 min, water (20 mL) was added, and the resulting solution was extracted with ether (3×20 mL). The ethereal extract was washed with water (2×20 mL), dried, and filtered, and the solvent was removed *in vacuo*. The reaction product (1.38 g) was chromatographed on a column with SiO_2 (30 g). 12-Bromosclareol oxide **9** (1.14 g, 73 %) was eluted with light petroleum ether, m.p. 97—98 °C (from light petroleum ether). Found (%): C, 63.40; H, 8.65; Br, 23.58. $C_{18}H_{29}BrO$. Calculated (%): C, 63.34; H, 8.56; Br, 23.41. IR, ν/cm^{-1}: 605, 725 (C—Br); 1367, 1375 (CMe_2); 1657 (>C=C<); 1115 (THP ring). ^1H NMR, δ: 0.85 (s, 6 H, C(4) and C(10)—CH_3); 0.91 (s, 3 H, C(4)—CH_3); 1.20 (s, 3 H, C(8)—CH_3); 1.91 (t, 3 H, C(13)—CH_3, J = 3 Hz). According to the TLC data, bromide **9** is formed from the primary, most polar product of the bromination of sclareol oxide **1** during the workup of the reaction mixture.

b. Sclareol oxide **1** (1.2 g, 4.6 mmol) in CCl_4 (20 mL) was brominated with NBS (0.81 g, 4.6 mmol) in the presence of $CaCO_3$ (1 g, 10 mmol) with stirring at *ca.* 20 °C for 40 min and treated as described above. After chromatography of the reaction product (1.4 g) on a column with SiO_2 (30 g), bromide **9** (1.28 g, 82 %) was obtained (m.p. 97—98 °C, identical to the product prepared according to procedure **a**).

c. Calcium carbonate (1 g, 10 mmol) and NBS (1.62 g, 9.2 mmol) were added to a solution of sclareol oxide **1** (1.2 g, 4.6 mmol) in CCl_4 (20 mL). The mixture was stirred for 40 min and treated as described above. The reaction product (1.8 g) was chromatographed on a column with SiO_2 (30 g). 12,16-Dibromosclareol oxide **12** (1.68 g, yield 88 %) was eluted with light petroleum ether, m.p. 96—97 °C (from light petroleum ether). Found (%): C, 51.31; H, 6.59; Br, 38.02. $C_{18}H_{28}Br_2O$. Calculated (%): C, 51.44; H, 6.70; Br, 38.05. IR, ν/cm^{-1}: 515, 613, 670 (C—Br); 1089, 1117 (THP ring); 1375, 1385 (CMe_2); 1650 (>C=C<). ^1H NMR, δ: 0.85 (s, 6 H, C(4)—CH_3 and C(10)—CH_3); 0.92 (s, 3 H, C(4)—CH_3); 1.22 (s, 3 H, C(8)—CH_3); 3.90 and 4.26 (both d, AB spin system, 2 H, C(16)—CH_2, J = 10.5 Hz).

Ozonolysis of 12-bromosclareol oxide (9). An ozone-oxygen mixture was passed through a solution of bromide **9** (100 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) at −65 to −70 °C until the reaction was completed (TLC monitoring). Ozone was removed from the reaction mixture by bubbling nitrogen (5 min), and the reaction mixture was allowed to warm to *ca.* 20 °C. The solvent was removed *in vacuo* at *ca.* 20 °C. The residue was dissolved in anhydrous ether (5 mL), $LiAlH_4$ (45 mg) was added, and the mixture was refluxed for 2 h. The excess hydride was decomposed with ethyl acetate, 10 % H_2SO_4 (5 mL) was added, and the resulting solution was extracted with ether (3×20 mL). The ethereal extract was washed with water (2×20 mL), dried, filtered, and the solvent was removed *in vacuo*. The reaction product (65 mg) was chromatographed on a column with SiO_2 (3 g). 11-Homodrimane-8α,12-diol (**10**) (52 mg, yield 74 %) was eluted with a 4:1 (v/v) light petroleum ether—Et_2O mixture, m.p. 130—131 °C (from light petroleum ether). According to the spectral and chromatographic data, the product is identical to the authentic sample of diol **10**.

Reaction of 12,16-dibromosclareol oxide 12 with potassium acetate. Dibromide **12** (1.6 g, 3.8 mmol) in DMF (10 mL) was added to a solution of freshly fused CH_3COOK (0.74 g, 7.6 mmol) in DMF (20 mL) at *ca.* 20 °C. The mixture was stirred at *ca.* 20 °C for 30 min and at 65—70 °C for 5 h; water (20 mL) was added, and the resulting solution was extracted with ether (3×20 mL). The ethereal extract was washed with water (2×20 mL), 10 % H_2SO_4 (20 mL), and water (3×20 mL), dried, and filtered, and the solvent was removed *in vacuo*. The reaction product (1.44 g) was chromatographed on a column with SiO_2 (30 g). Extremely unstable, liquid 16-acetoxy-12-bromosclareol oxide **13** (1.17 g, yield 77 %) was eluted with a 9:1 light petroleum ether—Et_2O mixture. Found (%): C, 60.24; H, 7.81; Br, 20.07. $C_{20}H_{31}BrO_3$. Calculated (%): C, 60.15; H, 7.77; Br, 20.05. IR, ν/cm^{-1}: 598, 630 (C—Br); 1017, 1075, 1115 (THP ring); 1225, 1733 (OAc); 1660 (>C=C<). ^1H NMR, δ: 0.85 (s, 6 H, C(4)—CH_3 and C(10)—CH_3); 0.91 (s, 3 H, C(4)—CH_3); 1.21 (s, 3 H, C(8)—CH_3); 2.11 (s, 3 H, OAc); 4.72 (d, 2 H, C(16)—CH_2, J = 2.4 Hz).

Bromination of sclareol oxide 1 with bromine. a. Bromine (0.73 mg, 0.23 mL, 4.6 mmol) was added dropwise to a stirred mixture of $CaCO_3$ (1 g) and a solution of sclareol oxide **1** (1.2 g, 4.6 mmol) in CH_3OH (10 mL). The mixture was stirred at *ca.* 20 °C for 30 min, water (20 mL) was added, and the resulting solution was extracted with ether (3×20 mL). The ethereal extract was washed with water (2×20 mL), dried, and filtered, and the solvent was removed *in vacuo*. The reaction product (1.44 g) was chromatographed on a column with SiO_2 (30 g). Bromide **9** (1.29 g, 82 %) was eluted with light petroleum ether, m.p. 97—98 °C (from light petroleum ether), the product was identical to that prepared by the reaction of sclareol oxide **1** with a stoichiometric amount of NBS (see above).

b. Bromine (1.46 mg, 0.46 mL, 9.2 mmol) was added dropwise to a stirred mixture of $CaCO_3$ (1 g) and a solution of sclareol oxide **1** (1.2 g, 4.6 mmol) in CH_3OH. The mixture was stirred at *ca.* 20 °C for 20 min and treated as for the synthesis of **9** (**a**). The reaction product (2.15 g) was chromatographed on a column with SiO_2 (60 g). Crystalline (13*S*)-11,12-dibromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabdane (**17**) (1.57 g, yield 76 %) was eluted with light petroleum ether, m.p. 107—109 °C (from light petroleum ether), $[\alpha]_D^{20}$ + 75.5° (*c* 2.4, $CHCl_3$). Found (%): C, 50.46; H, 7.10; Br, 35.73. $C_{19}H_{32}Br_2O_2$. Calculated (%): C, 50.46; H, 7.08; Br, 35.40. IR, ν/cm^{-1}: 626, 667 (C—Br); 1047 (OCH_3); 1045, 1100 (THP ring). ^1H NMR (Varian 200), δ: 0.79 (s, 3 H, C(10)—CH_3); 0.82 (s, 3 H) and 0.87 (s, 3 H, C(4)—$(CH_3)_2$); 1.39 (s, 3H, C(8)—CH_3); 1.66 (s, 3 H, C(13)—CH_3); 2.08 (dd, 1 H, C(9)—H, J_1 = 12 Hz; J_2 = 2 Hz); 2.44 (dd, 1 H, C(12)—H, J_1 = 14 Hz; J_2 = 2 Hz); 2.75 (dd, 1 H, C(11)—H, J_1 = 14 Hz, J_2 = 12 Hz); 3.31 (s, 3 H, OCH_3).

Dehydrobromination of (13*S*)-11,12-dibromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabdane (17). A solution of (13*S*)-11,12-dibromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabdane (**17**) (400 mg, 0.88 mmol) in toluene (5 mL) was

added to a refluxing solution of PEG-600 (72 mg) in a fine suspension of KOH (90 mg, 1.6 mmol) in toluene (20 mL). The reaction mixture was heated at 100 °C for 4 h and cooled, water (20 mL) was added, and the resulting solution was acidified with 10 % H_2SO_4 and extracted with ether (3×20 mL). The ethereal extract was dried and filtered, and the solvent was removed *in vacuo*. The residue (327 mg) was chromatographed on a column with SiO_2 (10 g). Crystalline (13*S*)-12-bromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabd-11-ene (**18**) (250 mg, 76 %) was eluted with light petroleum ether, m.p. 77—79 °C (from light petroleum ether). The product is unstable and decomposes on storage. Found (%): C, 61.38; H, 8.47; Br, 21.64. $C_{19}H_{31}BrO_2$. Calculated (%): C, 61.45; H, 8.41; Br, 21.52. IR, ν/cm^{-1}: 585, 610 (C—Br); 940 (OCH_3); 1040, 1112 (THP ring); 1630 (>C=C<). ^{1}H NMR, δ: 0.80 (s, 6 H, C(4)—CH_3 and C(10)—CH_3); 0.87 (s, 3 H, C(4)—CH_3); 1.29 (s, 3 H, C(8)—CH_3); 1.43 (s, 3 H, C(13)—CH_3); 2.08 (d, 1 H, C(9)—H, *J* = 1.5 Hz); 3.30 (s, 3 H, OCH_3); 6.17 (d, 1 H, C(11)—H, *J* = 1.5 Hz).

Ozonolysis of (13*S*)-12-bromo-8α,13-epoxy-13-methoxy-14,15-bisnorlabd-11-ene (18). An ozone-oxygen mixture was passed through a solution of compound **18** (200 mg, 0.54 mmol) in CH_2Cl_2 (5 mL) at −65 to −70 °C until the reaction was completed (5 min, TLC control). Ozone was removed from the solution with nitrogen. The mixture was allowed to warm to *ca.* 20 °C, and the solvent was removed *in vacuo* at *ca.* 20 °C. The residue was dissolved in anhydrous ether (10 mL), $LiAlH_4$ (95 mg, 25 mmol) was added, and the mixture was refluxed for 2 h. After the usual workup (see above), the reaction product prepared (102 mg) was chromatographed on a column with SiO_2 (10 g). Drimane-8α,11-diol **5** (94 mg, yield 70 %) was eluted with a 4:1 light petroleum ether—Et_2O mixture, m.p. 121—122 °C (from light petroleum ether ether). According to the spectral (^{1}H NMR, IR) and chromatographic data, the product is identical to the authentic sample.

References

1. L. Ruzicka, C. F. Seidel, and L. L. Engel, *Helv. Chim. Acta*, 1942, **25**, 621.
2. I. C. Coste-Manier, J. P. Zahra, and B. Waegell, *Tetrahedron Lett.*, 1988, **29**,1017.
3. A. F. Barrero, E. J. Alvarez-Manzaneda, J. Altarejos, S. Salido, and J. M. Ramos, *Tetrahedron*, 1993, **45**, 10405.
4. R. C. Cambie, K. N. Joblin, and A. F. Preaston, *Aust. J. Chem.*, 1971, **24**, 583.
5. R. C. Cambie, S. C. Moratti, P. S. Rutledge, R. J. Weston, and P. D. Woodgate, *Austr. J. Chem.*, 1990, **43**, 1151.
6. P. F. Vlad and M. N. Koltsa, *Sintez i primenenie dushistykh soedinenii iz labdanovykh diterpenoidov* [*Synthesis and Use of Fragrant Compounds from Labdane Diterpenoids*], Shtiintsa, Kishinev, 1988, 182 p. (in Russian).
7. J. Kangasmetsa and H. Bivehed, *Abstracts of VIII International Conference on Organic Synthesis, (IUPAC)*, Helsinki, 23—27 July, 1990, 52.
8. P. K. Grant, H. T. L. Liau, and M. J. Nicolls, *Austr. J. Chem.*, 1973, **26**, 1815.
9. R. Caputo, P. Monaco, G. Palumbo, L. Previtera, and L. Mangoni, *R. Ac. Sci. fis. e mat. Soc. naz. sci. Napoli*, 1983, **50**, 299, *Ref. Zhurn. Khim.*, 1984, 21E 81.
10. K. M. Ibne-Rasa, R. Tahir, and A. Rahman, *Chem. Ind.*, 1973, 232.
11. J. F. King and R. G. Pews, *Canad. J. Chem.*, 1964, **42**, 1294.
12. R. H. Schlessinger and R. X. Nugent, *J. Am. Chem. Soc.*, 1962, **104**, 1116.
13. E. V. Dehmlow and M. Lissel, *Tetrahedron*, 1981, **37**, 1653.

Received July 9, 1996