Chemistry of Natural Compounds, Vol. 36, No. 2, 2000

SYNTHESIS OF DRIMAN-8α,11-DIOL FROM SCLAREOL THROUGH 8α,12-EPOXY-14,15-BISNORLABDAN-13-ONE

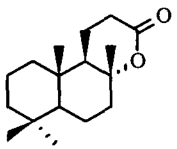
A. N. Aryku and P. F. Vlad

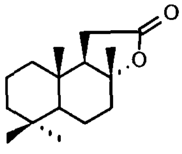
UDC 547.546/599

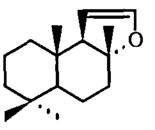
A four-step synthesis of driman-8α,11-diol from sclareol in 44% total yield is described that includes the intermediates (12R)-8α,12-epoxy-14,15-bisnorlabdan-13-one, (12S)-8α,12-epoxy-12-acetoxy-13,14,15,16-tetranorlabdane and 8α,12-epoxy-13,14,15,16-tetranorlabd-11-ene.

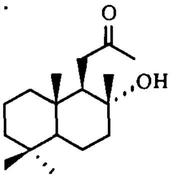
Key words: (+)-Driman-8α,11-diol, sclareol, (12R)-8α,12-epoxy-14,15-bisnorlabdan-13-one, (12S)-8α,12-epoxy-12-acetoxy-13,14,15,16-tetranorlabdane, 8α,12-epoxy-13,14,15,16-tetranorlabd-11-ene, synthesis.

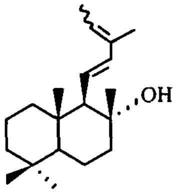
(+)-Driman-8α,11-diol (**1**) is a valuable intermediate in the synthesis of natural biologically active drimane sesquiterpenes [1-3]. Diol **1** was first prepared in low yield from ambreinolide (**2**) [2], the cleavage product of several labdane diterpenes [4]. Later Ohloff and Giersch [5] synthesized **1** from norambreinolide (**3**), another cleavage product of many labdanes [4], through the key intermediate **4**. The effectiveness of this method is difficult to estimate because the experimental details are not reported [5]. An alternative approach to the conversion of **3** to **1** in total yield of 62% in which the key compound is 14,15,16-trinorlabdan-8α-ol-12-one (**5**) has been described [6]. Diol **1** is conveniently and simply prepared by ionization of a mixture of isomeric neoabienols (**6**) (yield 74%) [7].

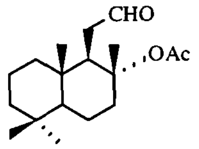

2

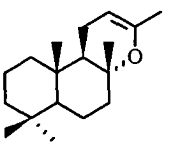

3

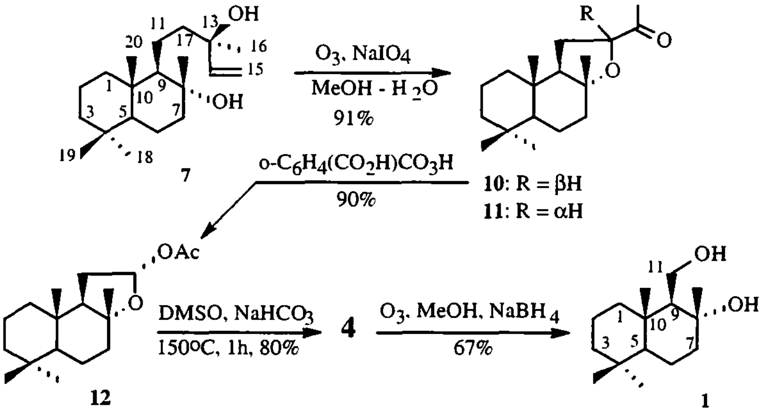

4


5


6


8


9



Although **3** can be prepared from several labdanes, sclareol (**7**) remains the principal starting material for its production, including on an industrial scale. It was the starting material for synthesizing **1**, for which key compounds were its well known cleavage products acetoxyaldehyde **8** (total yield 69%) [3] and sclareoloxide (**9**) (total yield 38%) [8]. However, costly and/or toxic reagents were used in these syntheses.

Institute of Chemistry, Academy of Sciences of the Republic of Moldova, Kishinev, fax (3732) 73 97 75, e-mail: presidiu@academy.as.md. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 124-125, March-April, 2000. Original article submitted May 8, 2000.

0009-3130/00/3602-0156$25.00

We considered another readily obtained cleavage product of sclareol (**7**), namely a C-12 epimeric mixture of 8α,12-epoxy-14,15-bisnorlabdan-13-ones (**10** and **11**), which is promising for synthesizing **1**. Ozonolysis conveniently produces a mixture of ketones **10** and **11** (yield 80-83%, **10**:**11** ratio = 9:1) from **7** according to a recent report of Barton et al. [9]. Oxidation of **10** by *m*-chloroperbenzoic acid produces epoxyacetate **12** in 89% yield [10]. The conversion of **12** that was obtained by a different method into **1** has been described [5]. However, as already noted, no experimental data were reported. Therefore, we now present our results for the synthesis of **1** from **10**.

Compound **10** was prepared by ozonolysis of **7** in the presence of sodium periodate in aqueous methanol according to the literature method [9] and chromatography of the reaction product on a silica gel column [10]. Instead of *m*-chloroperbenzoic acid to oxidize **10** by a Baeyer—Villiger reaction, we used the cheap and safe monoperphthalic acid, which is easily prepared according to the literature method [11]. The yield of **12** (90%) is the same as that for oxidation of **10** by *m*-chloroperbenzoic acid [10]. The spectral properties of **10** and **12**, which were not reported before [9, 10], confirm their structures.

Acetic acid was eliminated from **12** by heating it in DMSO in the presence of $NaHCO_3$ under Ar at 150°C. The structure of the unstable dihydrofuran **4**, which was isolated by chromatography in 80% yield, was confirmed by spectral and elemental analysis in addition to its further transformation. It is noteworthy that according to IR spectra the pyrolysis product contains a small impurity of carbonyl compounds. Ozonolysis of **4** in methanol with subsequent reduction of the products by $NaBH_4$ produces **1** in 67% yield. The total yield based on sclareol **7** (four steps) was 44%. It is noteworthy that this method of synthesizing **1** from **7** through **10** is relatively simple and the reagents used are available and safe.

EXPERIMENTAL

Melting points were measured on a Boetius apparatus. IR spectra were recorded on a Specord 74 IR spectrometer in CCl_4; ^1H NMR spectra, on a Bruker AC-80 (80 MHz) instrument in $CDCl_3$ with TMS internal standard (signals are given on the δ scale). Silica gel (grade L 40/100 and 100/160 nm) was used for column chromatography; silica gel (grade L 5/10 nm containing 18% gypsum), for TLC. Solutions of compounds in organic solvents were dried over anhydrous $NaSO_4$.

(12R)-8α,12-Epoxy-14,15-bisnorlabdan-13-one (10). Sclareol (**7**, 1 g, 3.2 mmole) was ozonolyzed in aqueous methanol containing $NaIO_4$ by the literature method [9]. The reaction product (953 mg) was chromatographed on a column packed with silica gel (30 g) with elution by a mixture of petroleum and diethyl ethers (9:1) to give 821 mg (91% yield) of **10** as a white crystalline material with mp 71-73°C. IR spectrum (cm^{-1}): 989, 1035, 1112 (oxidized ring), 1714 ($-COCH_3$). ^1H NMR spectrum (ppm): 0.83 (s, 6H, C-4– and C-10–CH_3 groups), 0.87 (s, 3H, C-4–CH_3), 1.16 (s, 3H, C-8–CH_3), 2.20 (s, 3H, $COCH_3$), 4.39 (dd, 1H, J = 3.8 and 9 Hz, C-12–H). According to the literature [10], mp 71-73°C.

Oxidation of 10 with Monoperphthalic Acid. A solution of the epoxyketone (1 g, 3.6 mmole) in absolute diethylether (20 ml) was treated with $NaHCO_3$ (1.3 g, 15.5 mmole), cooled to 0°C, and treated with an ether solution (5 ml) of monoperphthalic acid (1.39 g, 7.7 mmole). The reaction mixture was held for 24 h at 0°C, washed with saturated $NaHCO_3$ solution (30 ml) and water (2×20 ml), dried, filtered, and evaporated under vacuum. The solid (996 mg) was chromatographed on a silica-gel (30 g) column with elution by a mixture of petroleum and diethyl ethers (8:2) to give 950 mg (90% yield) of **12** as a white crystalline material with mp 90-93°C (hexane). IR spectrum (cm^{-1}): 976, 1005 (oxygen ring), 1225, 1725 (OAc). ^1H NMR spectrum (ppm): 0.86 (s, 3H) and 0.91 (s, 3H) [C-4–$(CH_3)_2$], 1.17 (s, 3H, C-10–CH_3), 1.28 (s, 3H, C-8–CH_3), 2.09 (s, 3H, OAc), 6.27 (m, 1H, J = 4 Hz, C-12–H).

Elimination of Acetic Acid from 12. A solution of **12** (200 mg, 0.85 mmole) in DMSO (6 ml) was treated with $NaHCO_3$ (71 mg, 0.85 mmole). The mixture was heated at 150°C under Ar until the reaction finished (1 h, TLC monitoring). The reaction mixture was diluted with water (10 ml) and extracted with ether (2×10 ml). The ether extract was washed with H_2SO_4 (10%, 10 ml) and water (2×10 ml), dried, filtered, and evaporated under vacuum. The solid (156 mg) was chromatographed on a silica-gel (10 g) column with elution by petroleum ether to give 128 mg (80%) of liquid **4**. IR spectrum: =C–OC (1064, 1215), *cis*-C=C (657, 712, 1570, 1780), –CHO (1700, 1720). ^1H NMR spectrum (ppm): 0.83 (s, 3H) and 0.89 (s, 3H) [C-4–$(CH_3)_2$], 1.17 (s, 3H, C-10–CH_3), 1.27 (s, 3H, C-8–CH_3), 5.63 (t, 1H, J = 7 Hz, C-11–H), 6.26 (m, 1H, C-12–H).

Found (%): C 81.74, H 11.68. $C_{16}H_{28}O$. Calc. (%): C 81.35, H 11.36.

Ozonolysis of 4. An ozone—oxygen mixture was passed through a solution of **4** (128 mg, 0.54 mmole) in methanol (10 ml) at -70°C until the reaction finished (TLC monitoring). The ozone was removed from the solution by nitrogen. The mixture was allowed to warm to room temperature (20°C), treated with $NaBH_4$ (100 mg, 26 mmole), stirred at 20°C for 4 h, diluted with HCl (5%, 10 ml), and extracted with ether (2×20 ml). The extract was dried and filtered. The solvent was removed under vacuum. The solid (110 mg) was chromatographed on a silica-gel (10 g) column with elution by a mixture of petroleum and diethyl ethers (4:1) to give 87 mg (67%) of **1** with mp 121-122°C (petroleum ether), which was identical to an authentic sample.

REFERENCES

1. P. F. Vlad, M. N. Koltsa, and G. N. Mironov, *Izv. Ross. Akad. Nauk, Ser. Khim.*, No. 5, 896 (1997).
2. S. W. Pellettier, S. Lajsic, Y. Ohtsuka, and Z. Djarmati, *J. Org. Chem.*, **40**, 1607 (1975).
3. A. F. Barrero, E. A. Manzaneda, J. Altarejos, S. Salido, J. M. Ramos, J. S. J. Simmonds, and W. M. Blaney, *Tetrahedron*, **51**, 7435 (1995).
4. P. F. Vlad and M. N. Koltsa, *Synthesis and Application of Fragrances from Labdane Diterpenoids* [in Russian], Shtiintsa, Kishinev (1988).
5. G. Ohloff and W. Giersch, *Croat. Chem. Acta*, **58**, 491 (1985).
6. K. I. Kuchkova, Yu. M. Chumakov, Yu. A. Simonov, G. Bocelli, A. A. Panasenko, and P. F. Vlad, *Synthesis*, No. 9, 1045 (1997).
7. M. N. Koltsa, G. N. Mironov, A. N. Aryku, and P. F. Vlad, *Khim. Prir. Soedin.*, 43 (1991).
8. A. N. Aryku, I. Yu. Andreeva, and P. F. Vlad, *Izv. Akad. Nauk, Ser. Khim.*, No. 11, 2785 (1996).
9. D. H. R. Barton, D. K. Taylor, and C. Tse, *Tetrahedron Lett.*, **51**, 9505 (1994).
10. D. H. R. Barton, S. I. Parekh, D. K. Taylor, and C. Tse, *Tetrahedron Lett.*, **51**, 5801 (1994).
11. M. I. Goryaev, G. A. Tolstikov, and L. A. Emchibanova, *Zh. Prikl. Khim.*, **34**, 946 (1961).