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Efficient synthesis of onoceranediol from 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane

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An efficient one-step synthesis of the diacetate of the tetracyclic triterpenoid onoceranediol (**4**) by radical cleavage of the readily available 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane is described. Drim-9(11)-en-8α-yl acetate (**7**) is formed in this reaction as a by-product. Onoceranediol diacetate **4** is converted into onoceranediol on treatment with $LiAlH_4$, and acetate **7** is transformed into drim-9(11)-en-8α-ol on saponification.

Key words: onoceranediol, drim-9(11)-en-8α-ol, 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane, hydroperoxides, radical cleavage, terpenoids.

Previously,[1] in a study of the oxidation of 11-bishomodriman-8α-ol-12-one (**1**) with trifluoroperoxyacetic acid, we found that, depending on the conditions, the reaction yields either drimane-8α,11-diol 11-monoacetate (**2**) (yield ~100%) or 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane (**3**) as a mixture of epimers at C(12) (yield 75%) together with compound **2**.

This communication describes an improved, more facile and efficient method for the transformation of hydroxyketone **1**, obtained from commercial norambreinolide in 65% yield,[1] into hydroperoxide **3** (Scheme 1). Treatment of a solution of **1** in an ethanol— acetic acid mixture with 30% hydrogen peroxide gives hydroperoxide **3** in an almost quantitative yield. Unlike many other compounds of this class, this hydroperoxide is stable on long-term storage in a refrigerator or even at room temperature. Due to stability combined with ready availability and structural peculiarity, bishomodrimanic hydroperoxide **3** is an appropriate starting compound for the synthesis of a number of terpenoids.

While performing research along this line, we synthesized the diacetate of the tetracyclic triterpenoid onoceranediol **4** (see Ref. 2) from hydroperoxide **3**.

Tertiary alkoxy radicals are known to undergo β-cleavage of C—C bonds to give carbon radicals and carbonyl compounds.[3,4] The carbon radicals, in turn, are stabilized either through dimerization or by transformation into olefins with proton abstraction. Hence, the alkoxy radical **5**, formed from hydroperoxide **3**, can be converted into onoceranediol diacetate **4** (see Ref. 2) and/or drim-9(11)-en-8α-ol acetate (**7**) (see Refs 5, 6) *via* the intermediate acetoxy-substituted radical **6**.

In order to carry out the reductive cleavage of hydroperoxide **3**, we studied its reaction with $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2 \cdot H_2O$ under various conditions. We found that in a $AcOH—H_2O$ mixture (9 : 1), compound **3** is converted almost completely into its precursor, namely, hydroxyketone **1**. When methanol is used as the solvent, onoceranediol diacetate **4** is the major product (yield 68%), formed together with unstable drim-9(11)-en-8α-ol acetate (**7**) (the yield of the crude product is 28%). Attempts to increase the yield of compound **7** by varying the reaction time and/or temperature and the reactant ratio, including the use of a stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$, have been unsuccessful.

The reaction of hydroperoxide **3** in MeOH with $FeSO_4 \cdot 7H_2O$ without $Cu(OAc)_2 \cdot H_2O$ under the same experimental conditions gave the same products **4** and **7** but in lower yields (59% and 25%, respectively).

The structure of diacetate **4** was established on the basis of elemental analysis, IR, ^1H and ^{13}C NMR, and mass spectra,* and by reduction with $LiAlH_4$ to give to known onoceranediol **8** (see Ref. 2). Acetate **7** was treated, without purification, with an ethanol solution of KOH to give alcohol **9**, which was identified by chromatography and by spectroscopic comparison with an authentic sample.[7]

As was to be expected in view of the instability of tertiary acetoxy groups, the mass spectrum of diacetate **4** exhibits no molecular ion peak, but contains a medium-intensity peak with m/z 410, corresponding to fragment

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* The ^1H and ^{13}C NMR spectral patterns of diacetate **4** and, first of all, the number of characteristic singlets are consistent with the C_2-symmetry of the molecule.

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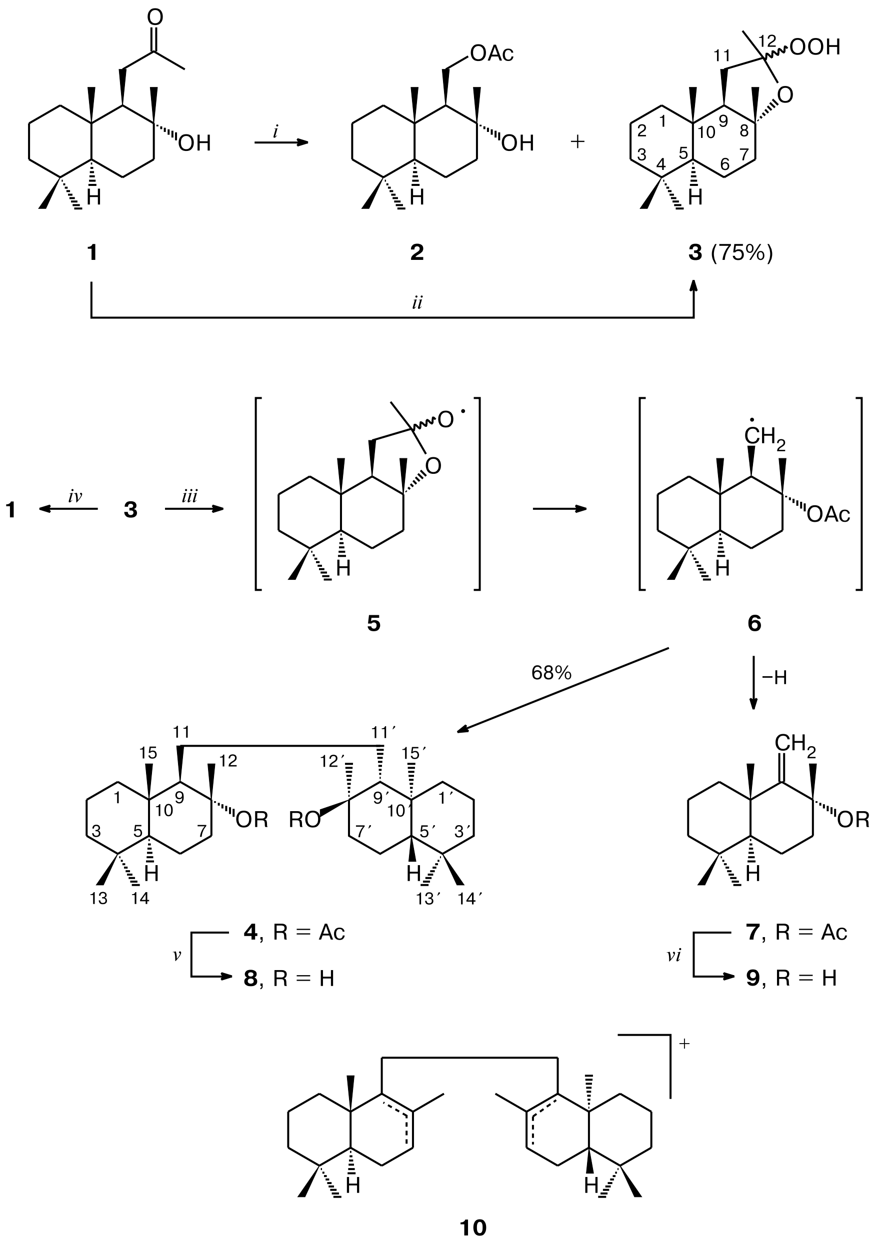
Scheme 1



Reagents, conditions, and product yields: *i.* CF_3CO_3H; *ii.* 30% H_2O_2, EtOH—AcOH, 30 min, –20 °C, yield 99%; *iii.* $FeSO_4 \cdot 7H_2O$—$Cu(OAc)_2 \cdot H_2O$, MeOH, 0 °C, 30 min; *iv.* $FeSO_4 \cdot 7H_2O$, $Cu(OAc)_2 \cdot H_2O$, AcOH : H_2O (9 : 1), yield 85%; *v.* $LiAlH_4$, Et_2O, 2 h, 15 °C, yield 88%; *vi.* KOH, EtOH, 20 h, 20 °C, yield 5.8%.

10 resulting from abstraction of two acetic acid molecules from compound **4**. Further fragmentation of the radical ion with m/z 410 involves cleavage of the C(11)—C(11′) bond giving rise to the bicyclic radical ion $C_{15}H_{26}$ (m/z 206), which then decomposes to give a set of ions typical of the mass spectra of bicyclic drimanic sesquiterpenoids and labdane diterpenoids.[8]

In conclusion, we demonstrated that the stable, readily available 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane (**3**) is a suitable starting compound for the efficient preparation of tetracyclic triterpenoid onocerane derivatives.

Experimental

Melting points were determined on a Boetius hot stage. IR spectra were recorded on a Specord 75 spectrophotometer, while ^1H and ^{13}C NMR, on a Bruker AM-400 spectrometer

(400.13 and 100.62 MHz) in $CDCl_3$ using Me_4Si as the internal standard. The ^{13}C NMR signals were assigned using the DEPT technique and by comparison with the spectra of known related compounds.[9,10] Mass spectra (EI, 70 eV) were recorded on a GC/MS Agilent 6890/5973 instrument. The reactions were monitored by TLC on Silufol plates, which were visualized by I_2 vapor. Solutions of compounds in organic solvents were dried with anhydrous $MgSO_4$.

Preparation of 12-hydroperoxy-8α,12-epoxy-11-bishomodrimane (3) from bishomodriman-8α-ol-12-one (1). A 30% aqueous solution of H_2O_2 and glacial AcOH (7 mL, 7.34 g, 122.28 mmol) were added to a solution of hydroxy ketone **1** (1.0 g, 3.75 mmol) (see Ref. 1) in EtOH (20 mL), and the mixture was stirred for 30 min at room temperature. Then the reaction was diluted with water (200 mL) and allowed to stand for 2 h at the same temperature. The precipitated white solid was filtered off, washed with water (3×10 mL), and dried in air to give compound **3** as a crystalline solid, yield 1.05 g (99%), m.p. 139—143 °C. According to ^1H NMR data, the hydroperoxide **3** formed was a mixture (1 : 1) of α- and β-epimers at C(12) (intensity ratio of the $C(13)H_3$ singlets at 1.48 and 1.52 ppm). The product was identical to the compound we obtained previously.[1]

Reaction of hydroperoxide 3 with $FeSO_4 \cdot 7H_2O$ and $Cu(OAc)_2 \cdot H_2O$. Methanol (15 mL) and hydroperoxide **3** (300 mg, 1.06 mmol) were added to 7.5 mL of a saturated solution of $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) in MeOH and the mixture was stirred for 10 min. To the resulting solution placed in an ice bath, $FeSO_4 \cdot 7H_2O$ (300 mg, 1.08 mmol) was added, and stirring was continued for additional 30 min. Then the reaction mixture was diluted with water (30 mL) and extracted with ether (3×30 mL). The extract was washed with water (2×10 mL) and dried. Evaporation of ether gave a crystalline residue (280 mg), which was treated with MeOH. A greater part of the crystals did not dissolve; these were filtered and washed with MeOH to give 190 mg (68%) of a pure crystalline product, which was identified as compound **4**, m.p. 189—190 °C (*cf.* Ref. 2: m.p. 189—191 °C). IR (mineral oil), ν/cm^{-1}: 1700, 1230 (OAc). ^1H NMR, δ: 0.78 (s, 6 H, C(10)Me and C(10´)Me); 0.79, 0.86 (both s, 6 H each, $C(4)Me_2$ and $C(4´)Me_2$); 1.47 (s, 6 H, C(8)Me and C(8´)Me); 1.94 (s, 6 H, 2OAc). ^{13}C NMR, δ: 15.67 (C(15) and C(15´)); 18.45 (C(2) and C(2´)); 20.02 (C(6) and C(6´)); 20.87 (2 $\underline{C}H_3COO$); 21.43 (C(13) and C(13´)); 23.09 (C(12) and C(12´)); 28.89 (C(11) and C(11´)); 33.17 (C(4) and C(4´)); 33.35 (C(14) and C(14´)); 38.63 (C(7) and C(7´)); 39.13 (C(10) and C(10´)); 39.40 (C(1) and C(1´)); 41.93 (C(3) and (C(3´)); 55.61 (C(5) and (C(5´)); 59.00 (C(9) and C(9´)); 88.40 (C(8) and C(8´)); 170.15 (2 $CH_3\underline{C}OO$). MS, m/z (I_{rel} (%)): 410 $[M - 2AcOH]^+$ (32), 395 $[410 - Me]^+$ (88), 206 (38), 191 (85), 177 (32), 163 (26), 149 (38), 137 (100), 109 (50), 123 (50), 95 (80), 81 (80), 69 (73). Found (%): C, 76.89; H, 11.14. $C_{34}H_{58}O_4$. Calculated (%): C, 76.93; H, 11.01.

After separation of 190 mg of onoceranediol diacetate (**4**), the filtrate was concentrated to give 80 mg of an oily product, which was hydrolyzed without purification due to instability. The residue (80 mg) was treated with a 10% solution of KOH in EtOH (1.6 mL, 178 mg, 3.17 mmol). The reaction mixture was kept at room temperature for 20 h. After addition of water (8 mL), the solution was extracted with ether (3×10 mL). The extract was washed with water (3×2 mL), dried, and concentrated to give 60 mg of a product, which was chromatographed on a column with 1.8 g of Al_2O_3 (neutral, activity 3.5). Elution with hexane gave 14 mg of a colorless oily product, which crystallized on storage in a refrigerator, m.p. 49—50 °C (from hexane) and was identified as drim-9(11)-en-8α-ol (**9**) (*cf.* Ref. 7: m.p. 50—51 °C). Yield 5.8% based on hydroperoxide **3**. IR (thin layer), ν/cm^{-1}: 3400, 3105, 1633, 1075, 907. ^1H NMR, δ: 0.77 (s, 3 H, C(10)Me); 0.80 and 1.02 (both s, 3 H each, $C(4) Me_2$); 1.34 (s, 3 H, C(8)Me); 4.77 and 5.15 (both br.s, 1 H each, $C(11)H_2$). ^{13}C NMR, δ: 19.06 (C(2)); 20.20 (C(15)); 21.63 (C(13)); 22.40 (C(12)); 30.52 (C(6)); 33.26 (C(14)); 33.80 (C(4)); 39.01 (C(1)); 40.03 (C(10)); 41.77 (C(3)); 44.20 (C(5)); 53.48 (C(11)); 73.38 (C(7)); 103.66 (C(9)); 166.64 (C(8)).

Deacetylation of onoceranediol diacetate (4) with $LiAlH_4$. Diacetate **4** (50 mg, 0.094 mmol) was added to a suspension of $LiAlH_4$ (66 mg, 1.74 mmol) in anhydrous Et_2O (25 mL), and the mixture was stirred for 2 h at 15 °C. Water (5 mL) and 5% HCl (2 mL) were added dropwise with ice cooling. The aqueous layer was separated and extracted with ether (3×5 mL). The organic layer was combined with the ether extract, washed with saturated brine (3×2 mL), dried, and concentrated. The crystalline residue (42 mg) was recrystallized from MeOH to give 37 mg (88%) of a product identical to onoceranediol **8** (see Ref. 2), m.p. 261—262 °C (see Ref. 2: m.p. 267—269 °C). IR (mineral oil), ν/cm^{-1}: 3354 (OH). ^1H NMR, δ: 0.74 (s, 6 H, C(10) Me and C(10´) Me); 0.78, 0.86 (both s, 6 H each, $C(4)Me_2$ and $C(4´)Me_2$); 1.13 (s, 6 H, C(8)Me and C(8´)Me). ^{13}C NMR, δ: 15.70 (C(15) and C(15´)); 18.55 (C(2) and C(2´)); 20.46 (C(6) and C(6´)); 21.42 (C(13) and C(13´)); 24.41 (C(12) and C(12´)); 29.39 (C(11) and C(11´)); 33.25 (C(4) and C(4´)); 33.40 (C(14) and C(14´)); 38.42 (C(10) and C(10´)); 39.50 (C(1) and C(1´)); 42.12 (C(3) and C(3´)); 43.59 (C(7) and C(7´)); 56.17 (C(5) and C(5´)); 63.16 (C(9) and C(9´)); 74.62 (C(8) and C(8´)).

References

1. K. I. Kuchkova, Y. M. Chumakov, Y. A. Simonov, G. Bocelli, A. A. Panasenco, and P. F. Vlad, *Synthesis*, 1997, 1045.
2. E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 1959, **81**, 1738.
3. R. Decorzant, C. Vial, F. Naf, and G. M. Whitesides, *Tetrahedron*, 1987, **43**, 1871.
4. Ph. A. Christensen, *Tetrahedron*, 1988, **44**, 1925.
5. K. Wada, S. Tanaka, and S. Marubo, *Agric. Biol. Chem.*, 1983, **47**, 1075.
6. M. A. F. Leite, M. H. Sarragiotto, P. M. Imamura, and A. J. Marsaioli, *J. Org. Chem.*, 1986, **51**, 5409.
7. P. F. Vlad, A. N. Aryku, A. G. Chokyrlan, *Izv. Akad. Nauk. Ser. Khim.*, 2004, 423 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 443].
8. S. O. Almqvist, C. R. Enzell, and F. W. Wehrli, *Acta. Chem. Scand.*, 1975, **B29**, 695.
9. B. L. Buckwalter, I. R. Burfitt, A. A. Nagel, E. Wenkert, and F. Naf, *Helv. Chim. Acta*, 1975, **58**, 1657.
10. A. F. Barrero and J. Altarejos, *Magn. Res. Chem.*, 1993, **31**, 299.

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