Catalytic Epoxypolyene Cyclization via Radicals: A Simple Total Synthesis of Sclareol Oxide and its 8-Epimer

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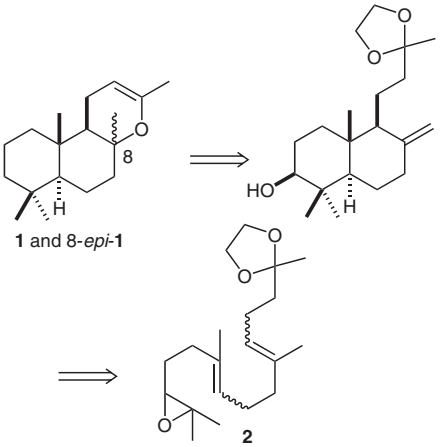
Abstract: A short synthesis of sclareol oxide from epoxyfarnesyl acetone in six steps is described. The strategy features a titanocene-catalyzed epoxypolyene cyclization for the construction of the carbocyclic core structure. The *exo* olefin formed during the termination of the cyclization is essential for the ensuing functional group modification that results in the preparation of the dihydropyran.

Key words: catalysis, epoxypolyene cyclization, natural products, radicals, titanocene

Sclareol oxide (**1**) is a constituent of the essential oils of *Salvia sclarea*, a plant found in the Mediterranean region.[1] It constitutes an important starting material for the semi-synthesis of a number of important compounds, such as ambrox®[2] and *ent*-thallusin.[3] The latter case reveals one of the disadvantages of employing natural products as starting materials, they are usually only available as one enantiomer. To increase the undisputed usefulness of sclareol oxide, we present here a total synthesis of **1**[4] that allows its preparation racemically or as either enantiomer from epoxyfarnesyl acetone acetal (**2**) that can be readily synthesized from farnesyl acetone (**3**) in enantiomerically pure form via dihydroxylation.[5]

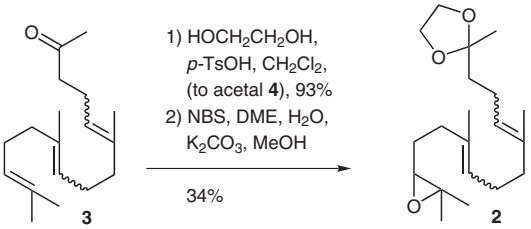
During the last years the radical chemistry originating from titanocene-catalyzed epoxide opening has attracted a great deal of attention.[6] Within this context the first examples of radical epoxypolyene cyclizations have recently been reported by the group of Cuerva and Oltra.[7] Their radical tandem sequence is advantageous compared to the classical cationic polycyclizations[8] because radical generation proceeds under much milder conditions than cation generation and the tandem cyclization can be terminated by a β-hydride elimination. We have reported a short synthesis of building blocks for the preparation of puupehedione.[9] These examples highlight the mildness and functional group tolerance of the radical reactions.

Our synthetic analysis of **1** from **2** is depicted in Scheme 1. Epoxyfarnesyl acetone acetal (**2**) was prepared by a slight modification of the original procedure.[10] It turned out that farnesyl acetone acetal (**4**, intermediate in Scheme 2) can be obtained from farnesyl acetone **3** in much higher yield if dichloromethane is employed in the acetalization step than the commonly used solvents benzene or toluene. Epoxidation of **4** to yield **2** was achieved by the classical van Tamelen procedure using NBS in H_2O–DME[11] as shown in Scheme 2.



Scheme 1 Strategy for the synthesis of **1** from **2**

The pivotal titanocene-catalyzed epoxypolyene cyclization of **2** proceeded smoothly to yield the bicyclic alcohol **5** in 40% yield. Deoxygenation of **5** was carried out by a Barton–McCombie reaction[12] via xanthate **6**. It should be noted that the stereocenter of the epoxide controls the formation of all other stereocenters in **5** and therefore in **7**. Thus, the use of enantiomerically pure **2** in either form will lead to a synthesis of both enantiomers of **5** and therefore **1**. This is also of some relevance for the synthesis of other natural products, e.g. thallusin.[3] From **6**, the synthesis of **1** and its 8-epimer were completed in just two steps by epoxidation with MCPBA to yield **8**, epoxide opening with $LiAlH_4$ and dihydropyran formation during acidic work-up. Sclareol oxide (**1**) could be readily separated from 8-*epi*-**1** by column chromatography. These results are summarized in Scheme 3.



Scheme 2 Improved synthesis of **2**

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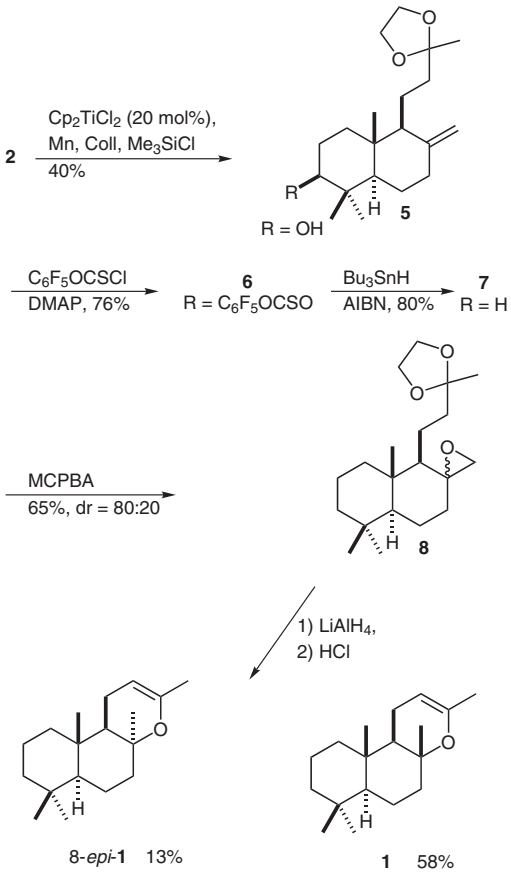

Scheme 3 Synthesis of **1** and 8-*epi*-**1** from **2**

We did not attempt to optimize the diastereoselectivity of the epoxidation as 8-*epi*-**1** constitutes an interesting starting material for the synthesis of compounds that are interesting for olfactory studies, such as isoambrox®, that has moreover been synthesized and characterized for the first time.

In summary, we have devised a synthetic route to **1** and 8-*epi*-**1** in only six steps from commercial farnesyl acetone. The epoxypolyene cyclization proceeded highly stereoselectively, and our approach can also be used for the synthesis of the enantiomerically pure compounds.

All reactions were performed in oven-dried (100 °C) glassware under argon. THF was freshly distilled from K. Et_2O was freshly distilled from Na/K. CH_2Cl_2, MeOH and benzene were freshly distilled from CaH_2. Products were purified by flash chromatography on Merck silica gel 50. Yields refer to analytically pure samples. Isomer ratios were determined by suitable ^1H NMR integrals of cleanly separated signals. NMR: Bruker AMX 300, AM 400; ^1H NMR, $CHCl_3$ (7.26 ppm) in the indicated solvent as internal standard in the same solvent; ^{13}C NMR, $CDCl_3$ (77.16 ppm) as internal standard in the same solvent; integrals in accord with assignments, coupling constants are measured in Hz and always constitute $J_{H,H}$ coupling constants. IR spectra: Perkin-Elmer 1600 series FT-IR as neat films on KBr plates. Flash chromatography was carried out according to the procedure of Still.[13]

Farnesyl acetone was purchased from Fluka in the form of a mixture of four stereoisomers containing 31% of the all-*trans* isomer (GC-MS analysis with an authentic sample as standard). This mixture was used as received because it is easier to isolate **5** than to separate stereoisomers of the starting material. As it is known that *cis* isomers do not undergo cyclization under our experimental conditions,[14] the yields are based on the all-*trans* isomer contents of the starting mixture. Compound **2** was prepared according to known procedure.[10]

Farnesyl Acetone Acetal (4)

To a solution of commercial farnesyl acetone (**3**; 10.0 g, 38.1 mmol) in CH_2Cl_2 (250 mL), were added ethylene glycol (7.10 g, 114.3 mmol) and *p*-TsOH (728 mg, 3.81 mmol). The mixture was refluxed for 24 h using a Dean–Stark apparatus. Then, the mixture was washed with H_2O and sat. aq $NaHCO_3$, the organic layer was separated and dried ($MgSO_4$). The solvent was removed and the residue was purified by flash chromatography (cyclohexane–EtOAc, 95:5) to give a colorless oil; yield: 10.84 g (93%).

The ^1H NMR and ^{13}C NMR spectra are in full agreement with previously reported data.[10]

Bicyclic Alcohol 5

THF (15 mL) was added to a mixture of Cp_2TiCl_2 (159 mg, 0.64 mmol) and Mn dust (1.36 g, 24.8 mmol) under argon and the suspension was stirred at r.t. until it turned green (about 15 min). Then, a solution of 2,4,6-collidine (3.01 g, 24.8 mmol), and Me_3SiCl (1.35 g, 12.4 mmol) in THF (5 mL) was added and the mixture was stirred for 5 min. After the addition of a solution of **2** (1.00 g, 3.11 mmol) in THF (5 mL), the mixture was stirred at r.t. overnight. Aq 2 N HCl was added, and the mixture was extracted with *t*-BuOMe. The combined organic layers were dried ($MgSO_4$) and the solvent was removed. The residue was dissolved in THF and 1 M solution of Bu_4NF in THF (3.24 g, 12.4 mmol) was added and stirring continued for 30 min. After dilution with *t*-BuOMe, and washing the solution with brine, the organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was purified by flash chromatography (cyclohexane–EtOAc, 9:1) to afford **5** as a colorless oil;[7a] yield: 123 mg (40%); R_f = 0.13 (cyclohexane–EtOAc, 80:20).

IR (neat): 3450, 2940, 1715, 1645, 1450, 1375, 1221, 1130, 1060, 1040, 945, 890, 865, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (dd, *J* = 2.4, 1.0 Hz, 1 H), 4.56 (dd, *J* = 2.4 Hz, 1.4 Hz, 1 H), 3.89–3.97 (m, 4 H), 3.24 (dd, *J* = 11.4, 3.6 Hz, 1 H), 2.38 (ddd, *J* = 12.8, 4.2, 2.5 Hz, 1 H), 0.81–2.01 (m, 13 H), 1.30 (s, 3 H), 0.98 (s, 3 H), 0.76 (s, 3 H), 0.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.05, 110.48, 107.04, 78.98, 64.75, 64.73, 56.74, 54.75, 39.54, 39.25, 38.27, 38.02, 37.22, 28.43, 28.06, 24.10, 23.93, 18.13, 15.53, 14.51.

HRMS-EI: *m*/*z* calcd for $C_{20}H_{34}O_3$: 322.2508; found: 322.2514.

Xanthate 6

To a stirred solution of **5** (274 mg, 0.85 mmol) and DMAP (313 mg, 2.56 mmol) in CH_2Cl_2 (6 mL), was added $C_6F_5O(CS)Cl$ (446 mg, 1.70 mmol) at 0 °C, and the solution was stirred for 4 h at r.t. Then, EtOAc was added and the mixture was washed with H_2O, the organic layer was separated and dried ($MgSO_4$) and the solvent was removed. The residue was purified by flash chromatography (cyclohexane–EtOAc, 98:2) to yield **6** (356 mg, 76%) as a colorless oil that slowly decomposed on silica gel; R_f = 0.63 (cyclohexane–EtOAc, 75:25).

IR (neat): 755, 970, 1055, 1135, 1235, 1375, 1455, 1525, 1645, 1715, 2970 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.98 (dd, *J* = 12.0 Hz, 1 H), 4.87 (s, 1 H), 4.61 (s, 1 H), 3.98–3.87 (m, 4 H), 2.43 (ddd, *J* = 12.8, 4.0, 2.4 Hz, 1 H), 2.14–1.35 (m, 13 H), 1.31 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.76 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.85, 147.41, 110.41, 107.61, 95.24, 64.78, 64.74, 56.53, 54.82, 39.40, 38.98, 38.02, 37.97, 36.75, 28.13, 23.90, 23.75, 22.97, 18.25, 16.93, 14.60 (some signals were not observed due to C–F coupling).

HRMS-EI: *m/z* calcd for $C_{27}H_{33}F_5O_4S$: 548.2012; found: 584.2020.

Reduction of Xanthate 6 to Compound 7

Xanthate **6** (473 mg, 0.86 mmol) was dissolved in benzene (80 mL). AIBN (28 mg, 0.17 mmol) and Bu_3SnH (754 mg, 2.59 mmol) were added, and the mixture was stirred at reflux for 4 h. Then, the solvent was removed. The residue was purified by flash chromatography (cyclohexane–EtOAc, 98:2) to yield **7** (211 mg, 80%) as a colorless oil;[15] R_f = 0.63 (cyclohexane–EtOAc, 75:25).

IR (neat): 2935, 1720, 1645, 1460, 1375, 1205, 1065, 890 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (d, *J* = 1.4 Hz, 1 H), 4.55 (d, *J* = 1.3 Hz, 1 H), 3.88–3.97 (m, 4 H), 2.37 (ddd, *J* = 12.7, 4.2, 2.4 Hz, 1 H), 0.97–2.11 (m, 15 H), 1.31 (s, 3 H), 0.86 (s, 3 H), 0.80 (s, 3 H), 0.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.75, 110.59, 106.61, 64.76, 64.74, 57.08, 55.69, 42.35, 39.87, 39.25, 38.48, 38.10, 33.78, 33.72, 24.59, 23.94, 21.88, 19.54, 18.05, 14.52.

HRMS-EI: *m/z* calcd for $C_{20}H_{34}O_2$: 306.2559; found: 306.2554.

Epoxide 8

To a solution of **7** (206 mg, 0.68 mmol) in CH_2Cl_2 (12 mL), was added MCPBA 70% (333 mg, 1.35 mmol) and the mixture was stirred at 0 °C for 6 h. Then, CH_2Cl_2 was added and the solution was washed with aq 2 N NaOH, dried ($MgSO_4$) and the solvent was removed. The residue was purified by flash chromatography (cyclohexane–EtOAc, 85:15) to afford **8** as an 80:20 mixture of diastereomers; colorless oil; yield: 139 mg (65%); R_f = 0.45 (cyclohexane–EtOAc, 75:25).

IR (neat): 810, 855, 1065, 1140, 1205, 1375, 1460, 1720, 2945 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (br s, 4 H), 2.75 (dd, *J* = 4.3, 1.7 Hz, 1 H), 2.67 (d, *J* = 4.3 Hz, 1 H)*, 2.47 (d, *J* = 4.3 Hz, 1 H), 2.27 (d, *J* = 4.3 Hz, 1 H)*, 1.93–0.95 (m, 16 H), 1.27 (s, 3 H), 0.88 (s, 3 H), 0.82 (s, 3 H), 0.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.22, 110.04*, 64.80*, 64.76*, 64.59, 64.58, 59.16, 57.52*, 55.35*, 55.20, 54.09, 52.68*, 50.90, 48.90*, 42.25*, 42.15, 41.42*, 40.57, 40.52, 40.09*, 39.18, 38.82*, 36.71, 36.18*, 33.65, 33.65*, 33.60*, 33.55, 24.01*, 23.60, 22.01, 21.80, 20.29*, 18.84, 18.67*, 16.49, 16.16*, 15.44*, 14.68, 14.53*.

The NMR assignments marked with asterisks belong to the diastereomer present in smaller amount.

HRMS-EI: *m/z* calcd for $C_{20}H_{34}O_3$: 322.2508; found: 322.2513.

Sclareol Oxide (1) and *epi*-Sclareol Oxide (8-*epi*-1)

To a suspension of $LiAlH_4$ (521 mg, 13.7 mmol) in Et_2O (30 mL), was added compound **8** (138 mg, 0.428 mmol) and the mixture was stirred at r.t. for 2 h. Then, H_2O and aq 36% HCl were added, and the mixture was extracted with *t*-BuOMe, the organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was purified by flash chromatography (cyclohexane–EtOAc, 75:25) to yield sclareol oxide (**1**) (65 mg, 58%) and *epi*-sclareol oxide (8-*epi*-**1**) (15 mg, 13%) as colorless oils.

1[1,2,4]

R_f = 0.31 (cyclohexane–EtOAc, 98:2).

^{1}H NMR (400 MHz, C_6D_6): δ = 4.47–4.51 (m, 1 H), 2.09 (dt, *J* = 12.5, 3.2 Hz, 1 H), 1.74–1.86 (m, 2 H), 1.79 (d, *J* = 1.6 Hz, 3 H), 1.68 (*pseudo* td, *J* = 13.1, 3.9 Hz, 1 H) 1.26–1.56 (m, 6 H), 1.20 (br s, 3 H), 1.13 (ddd, *J* = 13.8, 12.3, 3.4 Hz, 1 H), 1.03 (*pseudo* td, *J* = 13.5, 3.7Hz, 1 H), 0.81 (dd, *J* = 12.5, 2.3 Hz, 1 H), 0.80 (s, 3 H), 0.75 (s, 3 H), 0.72 (dm, *J* = 3.8 Hz, 1 H), 0.69 (s, 3 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 148.56, 94.42, 76.16, 56.28, 52.75, 42.16, 41.65, 39.48, 36.84, 33.55, 33.24, 21.75, 20.75, 20.47, 20.01, 18.95, 18.73, 15.21.

8-*epi*-1

R_f = 0.19 (cyclohexane).

IR (neat): 910, 960, 1075, 1120, 1160, 1385, 1460, 1710, 2935, 3445 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 4.41 (ddq, *J* = 6.1, 2.2, 1.1 Hz, 1 H), 2.09 (dt, *J* = 13.8, 2.3 Hz, 1 H), 2.04 (dt, *J* = 8.2, 2.3 Hz, 1 H), 1.72 (s, 3 H), 1.75–1.63 (m, 2 H), 1.59 (*pseudo* qt, *J* = 13.6, 3.4 Hz, 1 H), 1.44–1.35 (m, 4 H), 1.30 (td, *J* = 13.5, 4.7 Hz, 1 H), 1.18 (s, 3 H), 1.16–1.11 (m, 1 H), 1.09 (s, 3 H), 0.88 (s, 6 H), 0.71 (dd, *J* = 12.2, 2.0 Hz, 1 H), 0.69 (dd, *J* = 13.2, 3.2 Hz, 1 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 149.83, 95.44, 74.94, 55.57, 49.52, 42.36, 41.04, 40.54, 38.49, 33.93, 33.40, 27.05, 22.24, 20.80, 19.34, 19.04, 18.67, 13.96.

HRMS-EI: *m/z* calcd for $C_{18}H_{30}O$: 262.2297; found: 262.2302.

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