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Synthesis of (+)-Methyl (R,E)-6-Benzyloxy-4-hydroxy-2-hexenoate and Its Mesylate Derivative

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SYNTHESIS OF (+)-METHYL (*R,E*)-6-BENZYLOXY-4-HYDROXY-2-HEXENOATE AND ITS MESYLATE DERIVATIVE

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Abstract: Methyl (*E*)-6-benzyloxy-4-hydroxy-2-hexenoate is prepared in both racemic and enantiopure form through reaction between (2-benzyloxy)ethyloxirane and the dianion of phenylselenoacetic acid followed by esterification with diazomethane, oxidation to the selenoxide and subsequent pyrolysis in 72% overall yield.

Recently we have undertaken a systematic study on the stereochemical course of the 1,3-dipolar cycloaddition reaction of cyclic nitrones to α,β-unsaturated lactones of different ring sizes.[1] One of the five membered lactones that we have prepared and used as dipolarophile in these cycloadditions is 5-(2-benzyloxy)-ethyl-2(5*H*)-furanone, **1**,[1a] a polyfunctionalized C_6-synthon which has a synthetic value

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related to an undergoing programme in the field of alkaloid synthesis. We needed also a C_6-synthon equivalent to **1** with the primary alcohol protected and presenting the *E* configuration of the double bond. Actually our target molecules were methyl (*E*)-6-benzyloxy-4-hydroxy-2-hexenoate, **2**, and methyl (*E*)-6-benzyloxy-4-mesyloxy-2-hexenoate, **3** (Figure 1). Neither of these products had been previously described; the first synthesis of an equivalent synthon to **2** and **3**, namely ethyl (*S,E*)-4,6-dihydroxy-2-hexenoate, **4**, was reported by Labelle *et al.*[2]

γ-Hydroxy-α,β-unsaturated esters are useful structural units, already employed in the synthesis of alkaloids,[3] functionalized amino acids,[4] amino sugars,[5] and β-lactams.[6] In addition, several natural products contain this moiety.[7] Two general entries to these multifunctionalized compounds are known: i) Burgess *et al.*[8] have described the preparation of homochiral γ-hydroxy-α,β-unsaturated esters through the reaction of aldehydes with sulphinyl acetates in the presence of piperidine, the SPAC reaction, followed by a biocatalytic resolution. These authors reported among others the synthesis of methyl (*R,E*)-6-(dimethylthexylsilyloxy)-4-hydroxy-2-hexenoate, **5**; ii) Zwanenburg *et al.*[9] published in 1990 a stereospecific synthesis of this type of esters in a six step sequence with low overall yields (≈20%).

Our first purpose was to prepare **2** by selective benzylation of diol **4**. Using the modification of Herradon,[10] alcohol **6** was synthetized from (*S*)-malic acid in the expected yield, according to the literature precedents.[2] Swern oxidation of **6** followed by a Wittig condensation gave, in our hands, a 1:1 mixture of (*E*)- and (*Z*)-**7** in a 62% yield (Figure 2). This result differs from that described by Labelle: 60% yield of (*E*)-olefin. When we tried to transform alcohol (*S*)-**4** into its benzylate derivative **2**, all our attempts including the use of *N*-benzyltrifluoroacetamide[11] failed.

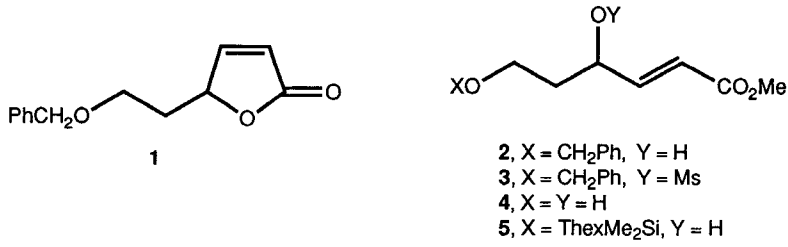


FIG. 1

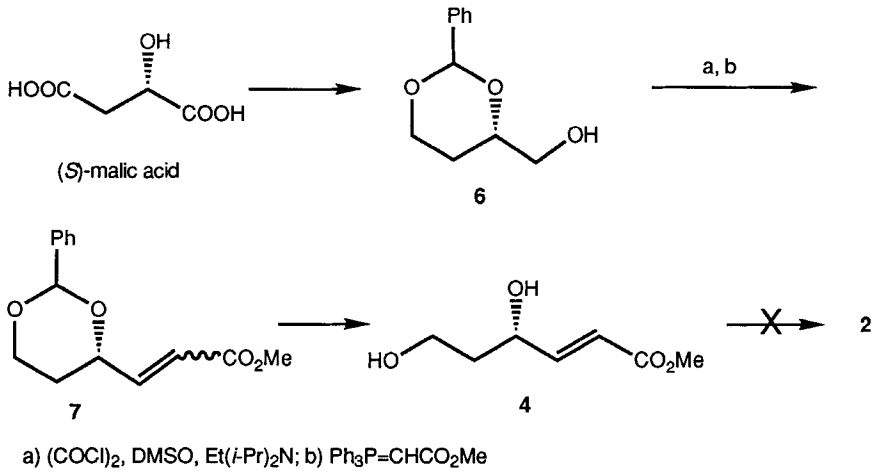
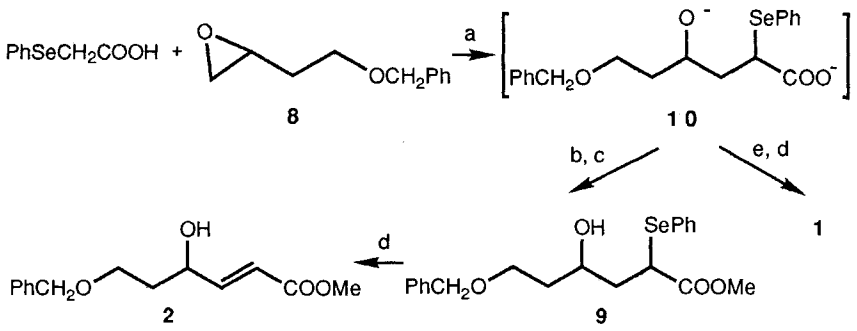


FIG. 2

This result forced us to search for a new access to **2** and **3**. As mentioned above we had previously prepared lactone **1** (Figure 3). This was effected starting with an easy condensation reaction between the dianion of phenylselenoacetic acid and (2-benzyloxy)ethyloxirane, **8**.[1a] We visualized that a slight modification of the process could yield the (*E*)-unsaturated ester. To avoid lactonization of the intermediate α-phenylseleno-γ-hydroxy acid, this was rapidly converted into the ester **9**. The best results were obtained when the solution of the dianion **10** was



a) 2 eq. LDA; b) maleic acid/-15 °C; c) CH_2N_2; d) H_2O_2, THF, 0 °C; e) AcOH reflux

FIG. 3

acidified to pH=3 with an aqueous solution of maleic acid at -15 °C. Vigorous stirring, careful control of the temperature, and selection of the acidifying agent showed to be crucial during the acidification step. Maleic acid (pK_a=1.83[12]) allows diprotonation of the dianion **10** (phenylselenoacetic acid has pK_a=3.75[13]), avoiding too acidic conditions which tend to favour lactonization. Then an ether extracted solution of the hydroxy acid was treated immediately with diazomethane at low temperature. The subsequent oxidation of the ester **9** using hydrogen peroxide occured with simultaneous elimination of phenylseleninic acid affording ester **2** in a 72% overall yield. Product **2** was characterized by its spectroscopic data and correct elemental analysis. The assignment of the double bond configuration was based on the value of 15.6 Hz for the coupling constant $J_{2,3}$.

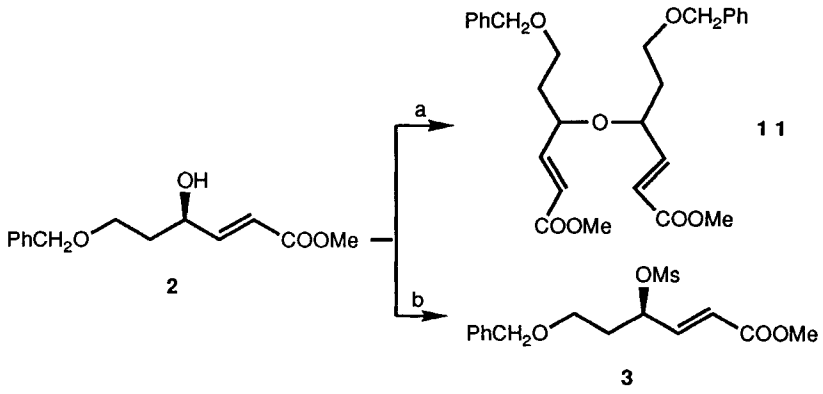
Oxirane **8** was prepared in its racemic form in a 72% overall yield by conventional methods starting from 3-buten-1-ol.[14] In addition, we also synthetized (*R*)-(+)-**8** in a 67% overall yield using a very recently published synthesis in which (*S*)-aspartic acid is the starting material.[15]

From (*R*)-(+)-**8** the unsaturated ester (*R*)-(+)-**2** was synthesized as described above.

The addition of mesyl chloride to a pyridine solution of alcohol **2** allowed only the isolation of the ether **11** in 87% yield (Figure 4). On the contrary, the slow addition of a methylene chloride diluted solution of **2** to a pyridine solution of mesyl chloride afforded the desired ester **3** in 74% yield, that was completely characterized by its spectroscopic data and correct elemental analysis. The ir spectrum shows no absorption in the region 3600-3050 cm^{-1} and the pmr spectrum indicates the *E* configuration of the double bond ($J_{2,3}$=15.7 Hz) and the presence of the mesyl group (singlet at δ 3.00). Product (*R*)-**3** has $[\alpha]_D$=37.2 ° (c=0.5 in $CHCl_3$).

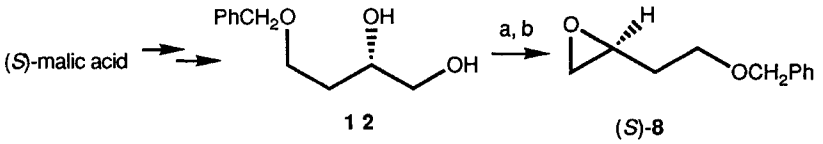
The synthesis of the pure isomer (*S*)-**8** had been already described in the literature from the diol **12** (Figure 5).[16] We prepared (*S*)-(-)-**8** by treatment of the corresponding mesylate derivative (instead of the tosylate as described) with DBU. Therefore, access to the ester (*S*)-(-)-**2** is also possible.

The method described herein represents a new general way to prepare (*E*)-γ-hydroxy-α,β-unsaturated esters, since the reaction conditions should be compatible with other functionalized oxiranes, and it competes advantageously with those previously described in several aspects: i) the monosubstituted oxiranes used as starting material are easily accessible by a variety of approaches, for instance, Haase *et al.*[17] have recently described the synthesis of monosubstituted (non-functionalized) oxiranes in both enantiomeric forms using alkenes as starting materials; ii) the synthesis is run in a simple two-step process, preparation of the saturated α-seleno ester and oxidation-elimination; and iii) (*E*)-γ-hydroxy-α,β-unsaturated esters can be prepared in their homochiral form in a very high overall yield.



a) MsCl, pyr; b) addition of **2** to the MsCl solution

FIG. 4



a) MsCl; b) DBU

FIG. 5

Experimental Section

Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. The 400 MHz ^{1}H nmr and 100 MHz ^{13}C nmr spectra were recorded on a Bruker AM-400-WB or AC-400-NB spectrometer from deuterated chloroform solutions; chemical shifts are given in ppm relative to TMS (δ values). Mass spectra (70 eV for electron impact and ammonia as reagent gas for chemical ionization) were recorded on a Hewlett-Packard 5989 gc-ms system; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

Tetrahydrofuran (THF) was distilled from sodium-benzophenone and diisopropylamine was distilled before its use. Flash chromatographies were performed on silica gel (230-400 mesh).

Methyl (*E*)-6-benzyloxy-4-hydroxy-2-hexenoate, 2

To a THF solution (50 mL) of LDA, prepared from 3.47 mL (24.8 mmol) of diisopropylamine and 15.4 mL of 1.6 M *n*-BuLi (24.7 mmol) in hexane, at 0 °C under argon atmosphere, a solution of 2.40 g (11.2 mmol) of phenylselenoacetic acid in 10 mL of anhydrous THF was added. The mixture was stirred for 30 minutes until a white solid appeared. Then, a solution of 2.01 g (11.2 mmol) of (2-benzyloxy)ethyloxirane, **8**,[14] in 8 mL anhydrous THF was added and the reaction mixture was stirred at room temperature for 18 h. The mixture was cooled to -15 °C and it was acidified to pH ≈ 3 by addition of a solution of acid maleic (5.85 g, 50.4 mmol) in water (25 mL). The organic phase was rapidly separated and water (10 mL) and ether (10 mL) were added to the remaining interphase and aqueous layers. The resulting organic phase was separated, dried over anhydrous sodium sulphate and concentrated to 50 mL. During this process the temperature was kept at 0 °C. The solution was cooled to -78 °C and treated with diazomethane (22.5 mmol) prepared in four batches. The mixture was stirred at 0 °C until no more diazomethane was present.

The solvent was removed and THF (50 mL) and 30% hydrogen peroxide (7.65 mL, 67.5 mmol) were added at 0 °C. The mixture was stirred 30 min at this temperature and another 30 min at room temperature. The THF was removed, CH_2Cl_2 (50 mL) was added and the solution was washed with saturated $NaHCO_3$ solution. Purification of the residue (2.8 g) by flash chromatography using hexane-ethyl acetate (3:2) as eluent gave 2.03 g (8.1 mmol, 72% yield) of a colorless oil,

identified as **2**: ir (film) 3431 (br), 2950, 2923, 2864, 1722, 1659, 1437, 1273, 1170, 1100, 742, 699 cm^{-1}; ^1H nmr 7.38-7.27 (m, 5H, Ph), 6.93 (dd, $J_{3,2}$=15.6 Hz, $J_{3,4}$=4.2 Hz, 1H, H_3), 6.12 (dd, $J_{2,3}$=15.6 Hz, $J_{2,4}$=1.9 Hz, 1H, H_2), 4.55 (m, 1H, H_4), 4.52 (s, 2H, CH_2Ph), 3.74 (s, 3H, OMe), 3.78-3.68 (m, 2H, H_6), 3.21 (br s, 1H, OH), 1.97 (m, 1H, H_5), 1.82 (m, 1H, H_5); ^{13}C nmr 166.8 (CO), 149.9 (C_3), 137.6/128.3/127.6/127.5 (Ph), 119.7 (C_2), 73.2 (CH_2Ph), 69.7 (C_4), 67.7 (C_6), 51.3 (OMe), 35.6 (C_5); MS (CI/NH_3) *m/z* 268 (M^++18). Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.08; H, 7.18.

Enantiomer (*R*)-**2**: $[\alpha]_D$=6 °, c=2.0 in chloroform.

Methyl (*E*)-6-benzyloxy-4-mesyloxy-2-hexenoate, 3

Mesyl chloride (0.67 mL, 8.5 mmol) was dissolved in pyridine (4 mL) at 0 °C and under argon atmosphere. A solution of **2** (0.428 g, 1.7 mmol) in amylene stabilised methylene chloride (40 mL) was slowly (90 min) added at room temperature. The mixture was stirred for 16 h. The reaction mixture was washed several times with 10% HCl until the aqueous solution was acid. The organic phase was washed with brine, dried over anhydrous sodium sulphate, and the solvent was removed. Purification of the product (0.516 g) by flash chromatography using hexane-ethyl acetate (4:1) as eluent afforded a colorless oil (0.414 g, 74% yield) identified as **3**: ir (film) 3030, 2953, 2936, 2868, 1725, 1666, 1454, 1437, 1360, 1316, 1278, 1175, 1089, 923 cm^{-1}; ^1H nmr 7.30 (m, 5H, Ph), 6.90 (dd, $J_{3,2}$=15.7 Hz, $J_{3,4}$=6.1 Hz, 1H, H_3), 6.12 (d, $J_{2,3}$=15.7 Hz, 1H, H_2) 5.42 (q, $J_{4,3}$=$J_{4,5}$=$J_{4,5'}$=6.4 Hz, 1H, H_4), 4.51 (d, J=11.7 Hz, 1H, CH_2Ph), 4.48 (d, J=11.7 Hz, 1H, CH_2Ph), 3.76 (s, 3H, OMe), 3.58 (m, 2H, H_6), 3.00 (s, 3H, Ms), 2.03 (m, 2H, H_5); ^{13}C nmr 165.8 (CO), 143.4 (C_3), 137.9/128.4/127.8 (Ph), 123.1 (C_2), 77.6 (C_4), 73.2 (CH_2Ph), 65.0 (C_6), 51.7 (OMe), 38.7 (Ms), 35.1 (C_5); MS *m/z* 327 (M^+-1, 0.1), 232 (3), 200 (2), 126 (24), 98 (42), 97 (30), 91

(100), 90 (35). Anal. Calcd. for $C_{15}H_{20}O_6S$: C, 54.86; H, 6.12; S, 9.76. Found: C, 55.34; H, 6.05; S, 9.27.

Enantiomer (*R*)-**3**: $[\alpha]_D$=37.2 °, c=0.5 in chloroform.

(*S*)-(2-Benzyloxy)ethyloxirane, (*S*)-8

A) Mesyl chloride (2.1 mL, 26 mmol) was added to a stirred solution of (*S*)-4-benzyloxy-1,2-butanediol, **12**,[16] (4.62 g, 23.5 mmol) in anhydrous pyridine (45 mL) at 0 °C under argon atmosphere. The mixture was left to react at room temperature until no more **12** was present (20 h, tlc analysis using hexane-ethyl acetate 1:1). Chloroform was added (70 mL) and the organic phase was washed with 1 M sulphuric acid until the aqueous layer was acid. The organic phase was washed with brine, dried over anhydrous sodium sulphate, and the solvent was removed. Purification of the product (7.02 g) by flash chromatography using hexane-ethyl acetate (3:2) as eluent afforded the following fractions: (*S*)-4-benzyloxy-1,2-dimesyloxybutane (0.611 g, 1.73 mmol, 7.3% yield) and (*S*)-4-benzyloxy-1-mesyloxy-2-butanol (5.02 g, 18.3 mmol, 78% yield) as a colorless oil. (*S*)-4-Benzyloxy-1,2-dimesyloxybutane: ^{1}H nmr 7.30 (s, 5H, Ph), 5.3-4.9 (m, 1H, H_2), 4.5 (s, 2H, CH_2Ph), 4.5 (dd, $J_{1,1}$=11.2 Hz, $J_{1,2}$=3.4 Hz, 1H, H_1), 4.3 (dd, $J_{1,1}$=11.2 Hz, $J_{1,2}$=6.9 Hz, 1H, H_1), 3.75 (t, J=5.6 Hz, 2H, H_4), 3.10 (s, 6H, Ms), 2.10-1.95 (br q, J≈5.7 Hz, 2H, H_3). (*S*)-4-Benzyloxy-1-mesyloxy-2-butanol: ^{1}H nmr 7.30 (s, 5H, Ph), 4.60 (s, 2H, CH_2Ph), 4.50-4.00 (m, 3H, 2xH_1 and H_2), 3.70 (t, J=6.1 Hz, 2H, H_4), 3.10 (s, 3H, Ms), 2.10-1.80 (m, 2H, H_3).

B) With the help of a syringe, DBU (5.17 mL, 34.7 mmol) was added to a stirred solution of (*S*)-4-benzyloxy-1-mesyloxy-2-butanol (5.5 g, 20.0 mmol) in anhydrous THF (12 mL) under argon atmosphere. After 20 h of reaction, ether (100 mL) was added and the mixture was washed with water (2 x 45 mL). The organic phase was dried over anhydrous magnesium sulphate and the solvent was removed.

Flash chromatography of the crude product (3.18 g) using hexane-ethyl acetate (3:2) as eluent yielded oxirane (*S*)-**8** (2.26 g, 12.7 mmol, 63% yield): $[\alpha]_D$=-15.1 °, c=2.0 in chloroform. Lit.[16] $[\alpha]_D$=-14.5 °, c=2.51 in chloroform.

4,4'-Bisoxi[methyl (*E*)-6-benzyloxy-2-hexenoate], 11

Mesyl chloride (46 mg, 0.40 mmol) was added to a solution of ester **2** (57 mg, 0.23 mmol) in anhydrous pyridine (3 mL) at -15 °C. The mixture was kept 3 h at this temperature and another 2 h at 25 °C. Methylene chloride (3 mL) was added and the solution was washed with 10% HCl until the aqueous phase was acid. The organic layer was washed with brine, dried over anhydrous sodium sulphate, and the solvent was removed. The obtained residue was filtered through silica gel to afford a colorless oil (49 mg, 87% yield) identified as ether **11**: ^{1}H nmr 7.40-7.20 (m, 10H, Ph), 6.84 (dd, $J_{3,2}$=15.4 Hz, $J_{3,4}$=7.7 Hz, 2H, H_3), 5.96 (dd, $J_{2,3}$=15.4 Hz, $J_{2,4}$=1.1 Hz, 2H, H_2), 4.64 (m, 2H, H_4), 4.49 (d, J=11.0 Hz, 2H, CH_2Ph), 4.47 (d, J=11.0 Hz, 2H, CH_2Ph), 3.75 (s, 6H, OMe), 3.65 (ddd, J=11.6 Hz, J=7.7 Hz, J=4.7 Hz, 2H, H_6), 3.56 (dt, J=11.6 Hz, J≈J≈5.4 Hz, 2H, H_6), 2.10-1.90 (m, 4H, H_5); ^{13}C nmr 166.2 (CO), 146.1 (C_3), 138.0/128.4/127.7/127.6 (Ph), 122.1 (C_2), 73.2 (CH_2Ph), 66.1 (C_6), 56.7 (C_4), 51.7 (OMe), 37.8 (C_5).

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