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Enantioselective Syntheses of 10-Oxo-11(*E*)-octadecen-13-olide and Related Fatty Acid

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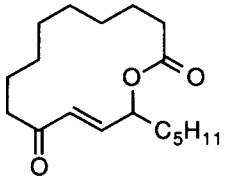
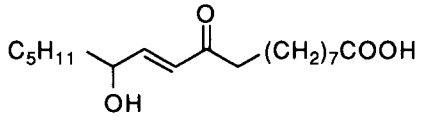
Abstract: The first, and short-step, syntheses of *S* and *R* enantiomers of 10-oxo-11(*E*)-octadecen-13-olide (**1**) and its seco-acid **2**, cytotoxic fatty acid derivatives from corn, were achieved from linoleic acid (**3**) by the combined use of lipoxygenase-catalyzed asymmetric oxygenation and cobalt porphyrin-catalyzed reduction-oxygenation as key-step reactions. © 1997 Elsevier Science Ltd.

10-Oxo-11(*E*)-octadecen-13-olide (**1**) and its seco-acid **2**, recently isolated from corn, have been reported to have cytotoxic activity against various tumor cells.[1, 2] Since their absolute configuration has not been determined, we attempted to synthesize both enantiomers of **1** and **2** for the purpose of elucidation of their structure-activity relationship. We report in this paper the first, and short-step, syntheses of *S* and *R* enantiomers of **1** and **2** from linoleic acid (**3**) by the combined use of lipoxygenase-catalyzed oxygenation and cobalt porphyrin-catalyzed reduction-oxygenation as the key-step reactions.

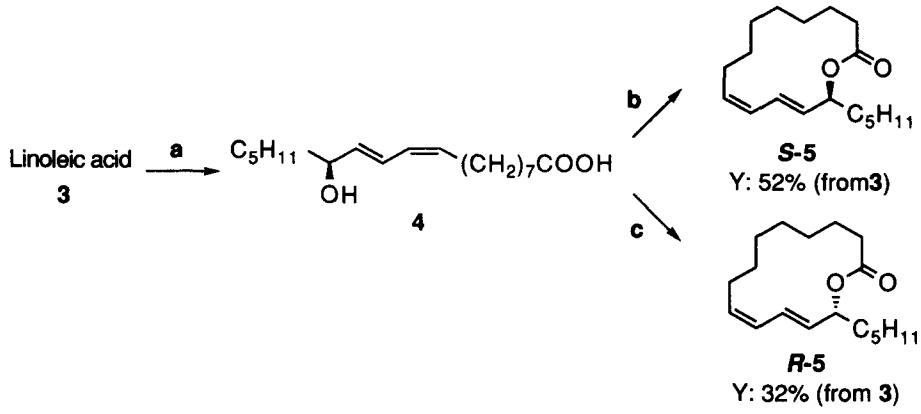


1



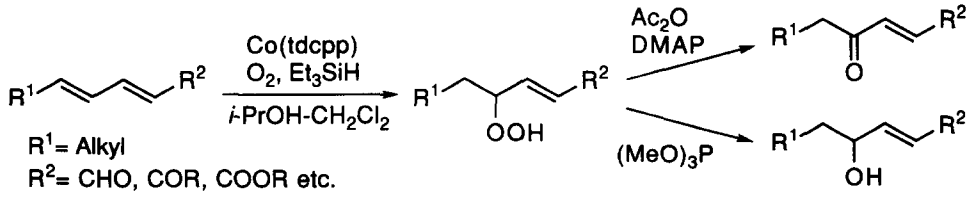
2

The synthesis of enantiomers of coriolide **5**, important intermediates of chiral **1**, is depicted in Scheme 1. We chose **3** as the starting material, because the natural **1** and **2** were probably biosynthesized *via* a lipid peroxidation pathway of the unsaturated fatty acid.[3] Peroxygenation of **3** (4.0 mmol) in the presence of 80 mg of soybean lipoxygenase (type I-B, 1.1×10^5 units/mg, Sigma) was carried out under 1 atm of oxygen in 0.1 M/ pH 9.0 sodium borate buffer (40 ml) followed by reduction with $NaBH_4$[4] to provide 13*S*-hydroxy acid **4**, which was cyclized by the Yamaguchi method[5] to afford (*S*)-coriolide (***S*-5**)[6] in 52% yield from **3**; $[\alpha]^{25}_D$ +33.0 (c 2.82, hexane), lit.; $[\alpha]^{24}_D$ +32 (c 2.56, hexane).[7] On the other hand, inversion-cyclization of **4** by the Mitsunobu method[8] afforded (*R*)-coriolide (***R*-5**) in 32% yield from **3**; $[\alpha]^{25}_D$ -31.9 (c 1.73, hexane).[9]

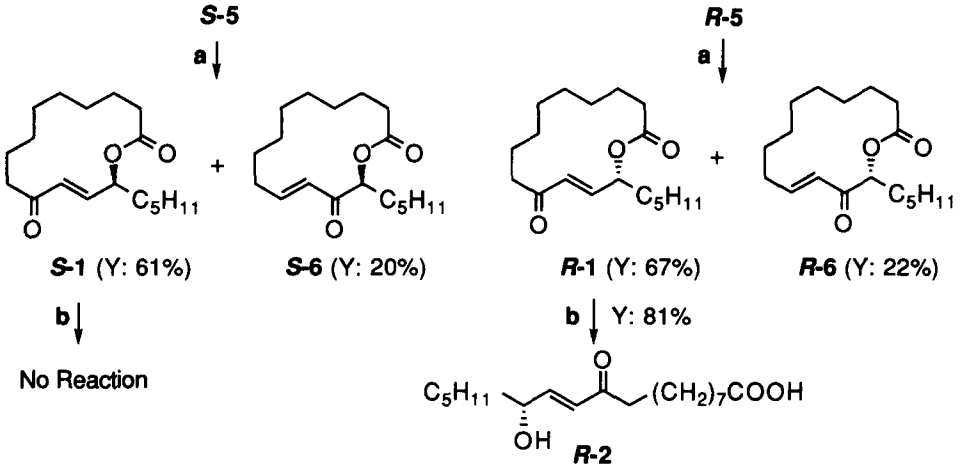


Scheme 1. Reagents: **a**, **3** (4.0 mmol), lipoxygenase (80 mg), O_2 (1 atm), 0.1 M/ pH 9.0 sodium borate buffer (40 ml), 0 °C, 1 h, then $NaBH_4$ (2.64 mmol); **b**, **4** (crude, from 4.0 mmol of **3**), 2,4,6-*tri*-Cl-PhCOCl (4.4 mmol), Et_3N (4.8 mmol), THF (10 ml), rt, 2 h, then DMAP (24 mmol), benzene (300 ml), reflux, 8 h; **c**, **4** (crude, from 3.25 mmol of **3**), EtO_2C-N=N-CO_2Et (6.5 mmol), Ph_3P (6.5 mmol), THF (300 ml), -15 °C, 2 h, then rt, 12 h.

We have already reported that dienes having electron-withdrawing group(s) were regioselectively converted into the corresponding hydroperoxy, oxo and hydroxy compounds *via* cobalt porphyrin-catalyzed reduction-oxygenation followed by appropriate post-treatment in one pot (Scheme 2).[10] This method was applied to construction of the enone moiety in **1** and **2** (Scheme 3). The macrolides ***S*-5** and ***R*-5** were allowed to react with oxygen (1 atm) and triethylsilane (1.2 equiv.) in the presence of 0.001 equiv. of [5,10,15,20-(2,6-dichlorophenyl)porphinato]cobalt (II) (abbreviated to Co(tdcpp)) at room temperature followed by the treatment of the intermediary hydroperoxides with acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP), to afford ***S*-1** and ***R*-1** in 61% and 67% yields, respectively, along with ***S*-6** and ***R*-6** as a by-product: ***S*-1**; $[\alpha]^{25}_D$ -49.0 (c 0.378, $CHCl_3$) and ***R*-1**; $[\alpha]^{25}_D$ +48.8 (c 1.06, $CHCl_3$). Thus, **3** was converted into ***S*-1** and ***R*-1** in 4 steps in 32% and 21% overall yields. Since attempts for the basic or aciditic hydrolysis of ***S*-1** and ***R*-1** resulted in a complicated mixture, enzymatic hyrolysis was tried. Lipase PS-catalyzed hydrolysis of ***R*-1** in tetrahydrofuran (THF)-0.1 M/pH 7.0 buffer (1:7) gave ***R*-2** in 81% yield; $[\alpha]^{25}_D$ -14.6 (c 0.80, MeOH). On the other hand, ***S*-1** was not hydrolyzed under the same conditions.

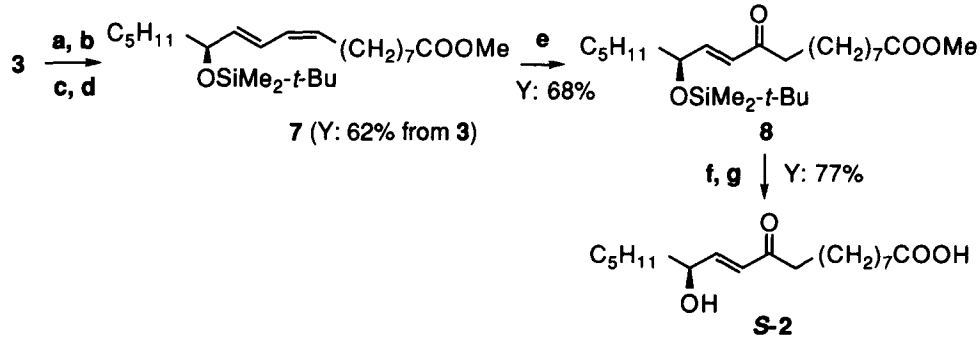


Scheme 2.



Scheme 3. Reagents: **a**, **5** (1.0 mmol), Co(tdcpp) (0.001 mmol), O_2 (1 atm), Et_3SiH (1.2 mmol), *i*-PrOH-CH_2Cl_2 (1:1, 5 ml), rt, 2 h, then Ac_2O (1.5 mmol), DMAP (0.1 mmol), CH_2Cl_2 (7 ml), rt, 5 h; **b**, **1** (0.26 mmol), lipase PS (150 mg, 2 wt eq.), THF- 0.1 M/ pH 7.0 phosphate buffer (1:7, 8 ml), rt, 48 h.

Synthesis of *S*-**2** was accomplished by another synthetic pathway (Scheme 4). Lipoxygenase-catalyzed oxygenation of **3** followed by esterification with CH_2N_2, reduction with $NaBH_4$, and protection with *t*-$BuMe_2SiCl$ gave dienoic ester **7** in 62% yield from **3**. The Co(tdcpp)-catalyzed reduction-oxygenation of **7** in the same manner as described above predominantly produced the desired **8** in 68% yield; $[\alpha]^{25}_D$ -3.08 (c 2.76, $CHCl_3$). It is probable that **7** was selectively oxygenated at the 10-position on account of the bulky *t*-butyldimethylsilyloxy group at the 13-position. Deprotection of **8** by lipase PS-catalyzed hydrolysis and then *n*-$Bu_4N^+F^-$ afforded *S*-**2** in 77% yield; $[\alpha]^{25}_D$ +15.8 (c 2.11, MeOH).



Scheme 4. Reagents: **a**, **3** (4.0 mmol), lipoxygenase (80 mg), O_2 (1 atm), 0.1 M/ pH 9.0 sodium borate buffer (40 ml), 0 °C, 1 h; **b**, CH_2N_2 (excess), Et_2O (30 ml), rt; **c**, $NaBH_4$ (2.0 mmol), MeOH (10 ml), 0 °C→rt, 1 h; **d**, *t*-$BuMe_2SiCl$ (8.0 mmol), imidazole (16 mmol), THF (15 ml), rt, 60 h; **e**, **7** (0.68 mmol), Co(tdcpp) (0.00068 mmol), O_2 (1 atm), Et_3SiH (0.82 mmol), *i*-PrOH-CH_2Cl_2 (1:1, 3.4 ml), rt, 2 h, then Ac_2O (1.05 mmol), Et_3N (1.05 mmol), DMAP (0.07 mmol), CH_2Cl_2 (7 ml), rt, 5 h; **f**, **8** (1.08 mmol), lipase PS (1.0 g, 2.0 wt eq.), 0.1 M/pH 7.0 phosphate buffer (10 ml), rt, 24 h; **g**, *n*-$Bu_4N^+F^-$ (2.16 mmol), THF, rt, 24 h.

EI-MS, IR, ^{1}H- and ^{13}C-NMR spectra of the synthetic enantiomers of **1** and **2** were coincident with those of natural products from corn.[1,2] It was found that the natural **1** and **2** were racemates by comparing optical rotations of the natural products[1,2] with those of the synthetic products. The *in vitro* cytotoxic activity of both the natural and synthetic products was preliminarily evaluated against tumorial cell P388: IC_{50} (μg/ml) natural **1**, 0.61; ***S*-1**, 0.48; ***R*-1**, 0.69; natural **2**, 5.7; ***S*-2**, 7.9; ***R*-2**, 5.7.[11] The result shows that the IC_{50} values of **1** and **2** are scarcely affected by their stereochemistry. Further evaluation of the cytotoxic activity of chiral **1** and **2** and their derivatives against various tumorial cell lines is now in progress.

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11. The cytotoxic activity was assayed by the same method as described in ref. 1.

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