Formal Synthesis of (+)-Altholactone by Stereoselective Epoxidation Using Magnesium Monoperoxyphthalate (MMPP)†

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Synthesis of (+)-altholactone has been achieved starting from *L*-tartaric acid using (2*S*,3*R*,4*R*,5*R*)-2-hydroxymethyl-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran as key intermediate. The key epoxy ring was introduced by monoperoxyphthalate (MMPP) in high stereoselectivity (8.4:1).

Keywords magnesium monoperoxyphthalate, stereoselective epoxidation, (+)-altholactone

(+)-Altholactone, a member of new type of cytotoxic natural styryl lactone, has been known to possess antitumor activity against murine P338 leukemia and show lethality to brine shrimp.[1] Recently, a report on its structure-activity relationship[2] and papers on the application of new synthetic methodology in its total synthesis[3] have been published. Several groups have reported the total synthesis of (+)-altholactone, in which (2*S*,3*R*,4*R*,5*R*)-2-hydroxymethyl-3,4-bis (methoxymethoxy)-5-phenyltetrahydrofuran (**12**) is the key intermediate.[4,5,7,8] Due to unique structure and cytotoxic activity of (+)-altholactone, a shorter and more efficient enantiocomplementary synthesis of this tetrahydrofuran skeleton **12** is still significant.

We started the synthesis from (+)-2, 3-*O*-isopropylidene-*L*-threitol (**2**), which is available readily from *L*-tartaric acid by known procedure (Scheme 1).[9] The two chiral centers in compound **2** could be transferred to C-2 and C-3 in (2*S*,3*R*,4*R*,5*R*)-2-hydroxymethyl-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran (**12**). Monoprotection of diol **2** with TBDPSCl or TBDMSCl in THF gave **3a** or **3b** in 83% or 87% yield, respectively. The aldehyde **4a** was obtained in 97% yield by Swern oxidation. Wittig olefination of the aldehyde **4a** with benzylidenetriphenylphosphorane gave a 1:3 (*Z*/*E*) mixture of **5a** in a combined yield of 86%, which was difficult to be separated and was transferred to pure *E* isomer **6a** in 91% yield by treatment with thiophenol in refluxing benzene in the presence of 2,2′-azobisisobutyronitrile. Deprotection of ketal **6a** in hot aqueous acetic acid (AcOH: H_2O = 4:1) provided the *trans*-allylic diol **7a** in 87% yield. **7b** was prepared in a similar way.

In order to secure the required stereochemistry at C-4 and C-5 position in **12**, it is necessary to epoxidize stereoselectively from the desired β-face of **7** (**a** or **b**). Table 1 shows the results on the epoxidation of allylic alcohols **7a** and **7b** with *m*-CPBA, Sharpless's reagents (*i.e.*, Ti(OPr-*i*)$_4$, *t*-BuOOH plus *L*-(+)-DIPT or *D*-(−)-DIPT) and magnesium monoperoxyphthalate (MMPP), respectively. *m*-CPBA gave poor selectivity either in the case of **7a** (1:1.2) or **7b** (1:1.5) in favor of the undesired diastereoisomer **9a** or **9b**. That means that coexistence of the chiral allylic and chiral homoallylic hydroxy group counteracts their effect on the direction of peroxyacid attack to double bond. Sharpless epoxidation using ligand *L*-(+)-DIPT gave only undesired **9a** or **9b** exclusively, while *D*-(−)-DIPT resulted in no reaction at all. That is consistent with the enantioselection rule in kinetic resolution of secondary allylic alcohols using Sharpless's epoxidation reagent.[6] Only MMPP gave the desired epoxide **10a** with high stereoselectivity (**10a**:**9a** = 8.4:1). It is interesting to find that if the deprotected

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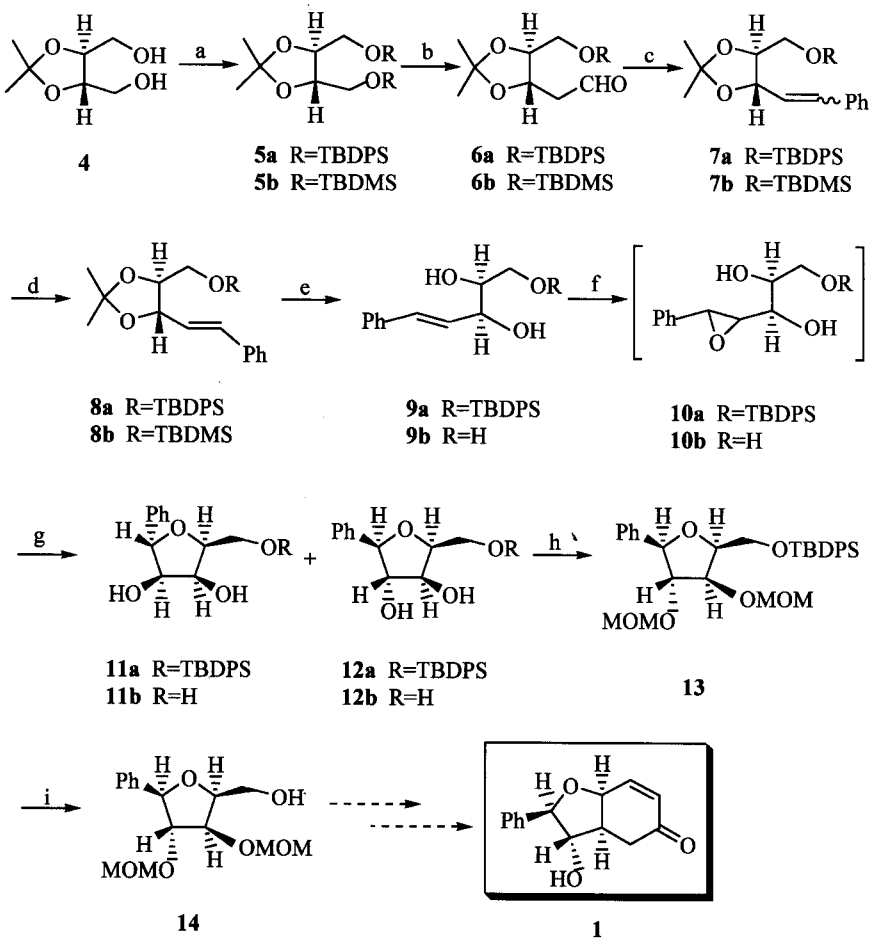
Scheme 1



Reagents and conditions: (a) NaH-TBDPSCl/THF. (b) $(COCl)_2$-DMSO/Et_3N/CH_2Cl_2, −78 ℃. (c) $(Ph_3P^+CH_2Ph)Br^-$-*n*-BuLi/THF, −40 ℃. (d) PhSH-AIBN/benzene, reflux. (e) AcOEt/H_2O, 60 ℃. (f) MMPP/acetone, r.t.. (g) SiO_2/CH_2Cl_2, r.t.. (h) CH_3OCH_2Cl-Et_3N/THF, reflux. (i) TBAF/THF, r.t..

Scheme 2

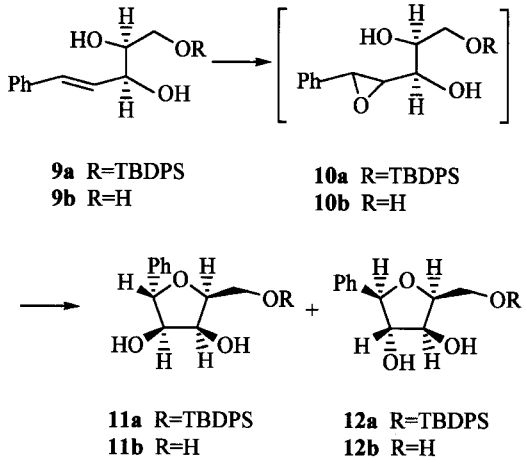


Table 1 Epoxidation of **7a**, **7b** under different conditions

Epoxidation reagent	**7a** **10a/9a** (yield)	**7b** **10b/9b** (yield)
m-CPBA	1:1.2 (64%)	1:1.5 (79%)
MMPP	8.4:1 (78%)	1.4:1 (74%)
L-(+)-DIPT	**9a** (87%)	**9b** (87%)
D-(−)-DIPT	no reaction	

7b was epoxidized by MMPP the stereoselectivity became much worse (**10b**:**9b** = 1.4:1). Since the separation of a pair of diastereoisomeric epoxidation products through column chromatography was unsuccessful, their configurations were assigned based on the specific optical rotations of successive cyclization products **9** and **10** in comparison with the published data.[7,8] The assignment is also in consistence with the fact that compound **9** could form ace-

tonide with dimethoxypropane, but the desired compound **10** could not. The *anti* diols **10** were then protected as methoxymethyl (MOM) ether to provide **11** in 79% yield. The silyl ether in **11** was removed by tetrabutylammonium fluoride to give **12** in 94% yield. The remaining elaboration towards (+)-altholactone could be achieved by the known procedures.[4,5,7,8] Since the diastereoisomer of **12**, (2*R*,3*S*,4*R*,5*R*)-2-hydroxymethyl-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran, could be prepared through **9a** or **9b** and *D*-tartaric acid could replace *L*-tartaric acid as starting material, two pairs of enantioisomers of 2-hydroxymethyl-3,4-bis(methoxymethoxy)-5-phenyltetrahydrofuran: (2*S*,3*R*,4*R*,5*R*), (2*R*,3*S*,4*R*,5*R*), (2*R*,3*S*,4*S*,5*S*), (2*S*,3*R*,4*S*,5*S*), could be efficiently prepared by this route, which will lead to two pairs of enantioisomers of altholactone.

Recently using MMPP[10-12] as an oxidation reagent has attracted much attention due to its cheapness and high stability at ambient temperature. As we know, there are a few reports on the stereoselectivity in the epoxidation of alkenes with MMPP. The successful stereoselective epoxidation using MMPP in our formal synthesis of (+)-altholactone shows that it is possible to use MMPP in certain cases as a stereoselective epoxidation reagent that could be complementary to the Sharpless reagent, *m*-CPBA and so on. Further investigation on the mechanism causing the high stereoselective epoxidation of double bonds in this case is under way in this laboratory.

Experimental

Infrared spectra were recorded on a Shimadzu-IR 440 spectrometer with liquid films. Proton NMR spectra were recorded on a Varian XL-200 (200 MHz) or a Bruker AMX-300 (300 MHz) spectrometer using TMS as the internal standard in $CDCl_3$. Mass spectra were obtained with a Finnigan MAT MS-4021 spectrometer. Elemental analyses were performed on a Carlo Erba 1106. Dichloromethane was dried over CaH_2 and then distilled. Tetrahydrofuran was distilled over Na/benzophenone.

Preparations of **3a** and **3b**

To a solution of **2** (3.24 g, 20 mmol) in dried THF (50 mL) was added sodium hydride (0.66 g, 22 mmol), followed by *tert*-butyldiphenylsilyl chloride (TBDPSCl) (6.05 g, 22 mmol) in dried THF (20 mL). After being stirred at room temperature for 2 h, the mixture was poured into water (100 mL), extracted with ether (3 × 100 mL), washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (petroleum ether (60—90 ℃) : ethyl acetate = 10 : 1) to give 6.62 g (83 %) of **3a** as colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.04 (s, 9H, 3 × CH_3), 1.40 (s, 6H, 2 × CH_3), 2.56 (br, 1H, OH), 3.64—4.24 (m, 6H, 2 × CH_2O, 2 × CHO), 7.25—7.80 (m, 10H, 2 × Ph); IR (film) ν: 3450 (br, OH), 1420, 1110, 820, 700, 610 cm^{-1}; MS (70 eV) *m/z* (%): 344 ($M^+ - C_4H_8$, 2.0), 323 ($M^+ - C_6H_5$, 0.21), 199 (100). Anal. calcd for $C_{23}H_{32}O_4Si$: C 69.00, H 8.00; found C 69.32, H 7.96.

3b was prepared in 87% yield as colorless oil in a similar way except that *tert*-butyldiphenylsilyl chloride (TBDPSCl) was replaced by *tert*-butyldimethylsilyl chloride (TBDMSCl). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.08 (s, 6H, 2 × CH_3), 0.92 (s, 9H, 3 × CH_3), 1.42 (s, 6H, 2 × CH_3), 2.17 (br, 1H, OH), 3.60—4.04 (m, 6H, 2 × CH_2O, 2 × CHO); IR (film) ν: 3500 (br., OH), 1250, 1080 cm^{-1}; MS *m/z* (%): 276 (M^+, 12.8), 275 ($M^+ - 1$, 33.8), 261 ($M^+ - OH$, 16.8), 219 (100).

Preparations of **4a** and **4b**

To a cooled (−78 ℃) solution of $(COCl)_2$ (1.43 g, 11.2 mmol) in CH_2Cl_2 (25 mL) was added DMSO (1.66 g) in CH_2Cl_2 (6 mL). After being stirred for 5 min, a solution of **3a** (4 g, 10 mmol) in CH_2Cl_2 (16 mL) was added. After stirring for 2 h at −78 ℃, triethylamine (5 g) in CH_2Cl_2 (20 mL) was added and the temperature was gradually raised to 0 ℃ within 1 h. The mixture was poured into a cold phosphate buffer (pH = 7, 250 mL) and the products were extracted with ether (3 × 100 mL), the organic layer was washed with water and concentrated. The residue was diluted with ether (200 mL), washed with water, and dried over Na_2SO_4. After removal of solvent *in vacuo* 3.7 g (97%) of crude **4a** was obtained, which was submitted for further use without purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.05 (s, 9H, 3 × CH_3), 1.42 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.83 (d, 2H, J = 4.4 Hz, CH_2O), 4.12—4.30 (m, 1H, CHO), 4.45 (dd, 1H, J = 1.4, 4.5 Hz, CHO), 7.28—7.80 (m, 10H, 2 × Ph), 9.84 (d, 1H, J = 1.35 Hz, CH = O); IR (film) ν: 1725 (s,

CHO), 1420, 1110, 820, 700 cm^{-1}; MS *m/z* (%): 341 ($M^+ - C_4H_9$, 1.9), 241 (100), 199 (57.3).

4b was obtained from **3b** in 87% yield in the same way. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.08 (s, 6H, 2 × CH_3), 0.9 (s, 9H, 3 × CH_3), 1.47 (s, 3H, CH_3), 3.80 (d, 2H, J = 4.4 Hz, CH_2O), 4.08—4.16 (m, 1H, CHO), 4.30—4.39 (m, 1H, CHO), 9.77 (d, 1H, J = 1.54 Hz, CH = O); IR (film) ν: 1725 (s, CHO), 1250, 1080 cm^{-1}; MS *m/z* (%): 274 (M^+, 0.05), 131 (43.4), 59 (100).

Preparations of **6a** *and* **6b**

n-BuLi (2.5 mol/L in hexane, 8.8 mL) was injected to a suspenson of benzyl triphenylphosphonium bromide (9.52 g, 22 mmol) in dried THF (50 mL) at −40 ℃. After stiring for 1 h under N_2 a solution of **4a** (7.96 g, 20 mmol) in dried THF (20 mL) was added. After stirring for another 1 h, 10 % aqueous NH_4Cl (100 mL) solution was added. The mixture was extracted with ethyl acetate (3 × 100 mL). The organic phases were combined, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography the residue gave 8.12 g (86 %) of *E* and *Z* mixture, which could not be separated. The mixture was dissolved in a solution of thiophenol (0.4 mL), AIBN (200 mg) and benzene (100 mL) and refluxed for 0.5 h. It was then concentrated *in vacuo* and chromatographed on silica gel column (petroleum ether (60—90 ℃): ethyl acetate = 30 :1) to give 7.4 g (91 %) of **6a** as colorless oil. $[\alpha]_D^{25}$ −9.8 (*c* 2.11, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.05 (s, 9H, 3 × CH_3), 1.48 (s, 6H, 2 × CH_3), 3.70—3.95 (m, 3H, CH_2O, CHO), 4.62 (t, 1H, J = 7.3 Hz, CHO), 6.16 (dd, 1H, J = 7.3, 15.8 Hz, CH =), 6.63 (d, 1H, J = 15.8 Hz, PhCH =), 7.26—7.78 (m, 15H, 3 × Ph); IR (film) ν: 1420, 1110, 740, 700 cm^{-1}; MS *m/z* (%): 471 ($M^+ - 1$, 2.3), 357 (75.1), 117 (100). Anal. calcd for $C_{30}H_{36}O_3Si$: C 76.27, H 7.63; found C 76.54, H 7.47.

6b was obtained in 74.8 % yield in the same way. $[\alpha]_D^{25}$ −21.6 (*c* 1.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.08 (s, 6H, 2 × CH_3), 0.84 (s, 9H, 3 × CH_3), 1.39 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.71—3.85 (m, 3H, CH_2O, CHO), 4.45 (t, 1H, J = 7.8 Hz, CHO), 6.12 (dd, 1H, J = 7.23, 15.7 Hz, CH =), 6.63 (d, 1H, J = 15.7 Hz, PhCH =), 7.05—7.40 (m, 5H, Ph); IR (film) ν: 1280, 1270, 1250, 840, 700 cm^{-1}; MS *m/z* (%): 348 (M^+, 1.9), 291 (9.3), 117 (100). Anal. calcd for $C_{20}H_{32}O_3Si$: C 68.97, H 9.20; found C 68.69, H 9.21.

Preparations of **7a** *and* **7b**

To a solution of acetic acid (12 mL) in water (6 mL) was added **6a** (3 g, 6.4 mmol). After being stirred for 2 h at 60 ℃, the mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Column chromatography (petroleum ether (60—90 ℃): ethyl acetate = 6:1) gave 2.4 g (87 %) of **7a**. $[\alpha]_D^{25}$ −4.4 (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.08 (s, 9H, 3 × CH_3), 2.75 (br, 2H, 2 × OH), 3.60—3.90 (m, 2H, CH_2O), 4.12 (dd, 1H, J = 7.12, 14.29 Hz, CHO), 4.32—4.55 (m, 1H, CHO), 6.18 (dd, 1H, J = 6.59, 16.07 Hz, CH =), 6.65 (d, 1H, J = 16.1 Hz, PhCH =), 7.25—7.74 (m, 15H, 3 × Ph); IR (film) ν: 3350 (br, OH), 1420, 1110, 730, 700 cm^{-1}; MS *m/z* (%): 415 (M^+ − OH, 0.53), 355 (M^+ − Ph, 0.29), 117 (100). Anal. calcd for $C_{27}H_{32}O_3Si$: C 75.00, H 7.41; found C 74.79, H 7.51.

7b was prepared in 90% yield as above. $[\alpha]_D^{25}$ −23.3 (*c* 1.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 2.14—2.98 (br, 3H, 3 × OH), 3.70—3.90 (m, 1H, CHO), 3.95—4.42 (m, 3H, CH_2O, CHO), 6.26 (dd, 1H, J = 8.9, 15.9 Hz, CH = C), 6.72 (d, 1H, J = 7.5 Hz, PhCH =), 7.28—7.43 (m, 5H, Ph); IR (film) ν: 3405 (br, OH), 1380, 740, 690 cm^{-1}; MS *m/z* (%): 194 (M^+, 0.17), 177 (M^+ − OH, 2.92), 159 (100). Anal. calcd for $C_{11}H_{14}O_3$: C 68.04, H 7.22; found C 68.27, H 7.32.

Preparations of **9a** *and* **10a**

A. *Epoxidation with* MMPP *and successive cyclization*

To a solution of **7a** (1.12 g, 2.6 mmol) in acetone was added 1.35 g (3.5 mmol) of magnesium monoperoxyphthalate (MMPP). After being stirred overnight the mixture was diluted with ether (20 mL), filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), to which silica gel (5 g, 100—200 mesh) was added at room temperature. After being stirred overnight the reactant was filtered, washed with CH_2Cl_2

and concentrated. Column chromatography (petroleum ether (60—90 ℃) : ethyl acetate = 3 : 1) of the residue gave 97 mg (8%) of **9a** and 818 mg (70%) of **10a**.

9a Colorless oil. $[\alpha]_D^{25}$ − 31.4 (*c* 0.15, $CHCl_3$) [lit.[7b] − 31.5 (*c* 1.56, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.09 (s, 9H, 3 × CH_3), 3.57 (d, 1H, J = 10.3 Hz, CHO), 3.82 (dd, 1H, J = 5.8, 11 Hz, CHO), 3.97—4.13 (m, 1H, CHO), 4.31—4.35 (m, 1H, CHO), 4.45 (dd, 1H, J = 5.5, 10.7 Hz, CHO), 4.90 (d, 1H, J = 5.8 Hz, CHO), 7.25—7.55 (m, 10H, 2 × Ph), 7.75—7.82 (m, 5H, Ph); IR (film) ν: 3405 (br, OH), 1430, 1110, 700 cm^{-1}; MS *m/z* (%): 373 (M^+ − H_2O − C_4H_9, 0.98), 313 (4.61), 193 (M^+ − $OSiPh_2Bu^t$, 100). Anal. calcd for $C_{27}H_{32}O_4Si$: C 72.32, H, 7.14; found C 72.54, H 7.12.

10a Colorless syrup. $[\alpha]_D^{25}$ − 42 (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.09 (s, 9H, 3 × CH_3), 4.05—4.08 (m, 1H, CHO), 4.14—4.17 (m, 2H, CH_2O), 4.19—4.20 (m, 1H, CHO), 4.39 (dd, 1H, J = 3.6, 5.7 Hz, CHO), 4.66 (d, 1H, J = 5.7 Hz, CHO), 7.30—7.51 (m, 10H, 2 × Ph), 7.70—7.79 (m, 5H, Ph); IR (film) ν: 3405 (br, OH), 1430, 1110, 700 cm^{-1}; MS *m/z* (%): 430 (M^+ − H_2O, 1.19), 390 (M^+ − 1 − C_4H_9, 1.03), 373 (M^+ − H_2O − C_4H_9, 1.67), 193 (M^+ − $OSiPh_2Bu^t$, 100); HRMS calcd for $C_{27}H_{32}O_4Si$ + Na 471.1968, found 471.1973.

B. *Epoxidation with m-CPBA and successive cyclization*

To a solution of **7a** (690 mg, 1.6 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (346 mg, 2 mmol) at room temperature. After stirring for 2 h at room temperature ether was added. The mixture was washed with 20% $Na_2S_2O_3$ solution and saturated NaCl solution, dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), to which camphylsulfonic acid (20 mg) was added at room temperature. After being stirred overnight the reaction mixture was concentrated, flash column chromatography (petroleum ether (60—90 ℃) : ethyl acetate = 3 : 1) of the residue gave 259 mg (35%) of **9a** and 208 mg (29 %) of **10a**.

C. *Sharpless asymmetric epoxidation and successive cyclization*

Under nitrogen atmosphere 4Å molecular sieve (1 g), $Ti(OPr\text{-}i)_4$ (0.75 mL, 2.5 mmol) and *L*-(+)-diisopropyl tartrate (DIPT) (675 mg, 2.88 mmol) were added to CH_2Cl_2 (20 mL) at 20 ℃. After stirring for 0.5 h **7a** (1.04 g, 2.4 mmol) and BuOOH (TBHP) (1.5 mL, 2.64 mmol) were added and then stirred for three days. Water (5 mL) and acetone (25 mL) were added and the precipitate was filtered through kieselguhr and washed with CH_2Cl_2. Concentration of the filtrate *in vacuo* gave crude epoxidation product, which was treated with camphylsulfonic acid (20 mg) in CH_2Cl_2 (100 mL). After stirring overnight at room temperature work-up as usual gave 895 mg of **9a** (87%).

Preparations of **9b** *and* **10b**

A. *Epoxidation with* MMPP *and successive cyclization*

7b (388 mg, 2 mmol) was reacted with MMPP (1.2 g, 3 mmol) in acetone (10 mL) as **7a**. 123 mg (32%) of **9b** and 176 mg (42%) of **10b** were obtained.

9b $[\alpha]_D^{25}$ − 40.7 (*c* 0.21, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.82—3.00 (br, 3H, 3 × OH), 4.08—4.52 (m, 4H, CH_2O, 2 × CHO), 4.58—4.66 (dd, 1H, J = 4.9, 11.2 Hz, CHO), 4.82 (d, 1H, J = 7.2 Hz, CHO), 7.36—7.55 (m, 5H, Ph); IR (film) ν: 3450 (br, OH), 1480, 1110 cm^{-1}, MS *m/z* (%): 210 (M^+, 0.35), 192 (M^+ − H_2O, 35.82), 107 (100). Anal. calcd for $C_{11}H_{14}O_4$: C 62.86, H 6.67; found C 62.71, H 6.67.

10b $[\alpha]_D^{25}$ − 23.7 (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.82—2.82 (br, 3H, 3 × OH), 4.05—4.45 (m, 3H, CH_2O, CHO), 4.58—4.75 (m, 2H, 2 × CHO), 4.82 (d, 1H, J = 7.7 Hz, CHO), 7.45—7.65 (m, 5H, Ph); IR (film) ν: 3450 (br, OH), 1450, 1110 cm^{-1}; MS *m/z* (%): 211 (M^+ + 1, 2.09), 209 (M^+ − 1, 2.98), 193 (M^+ − OH, 55.57), 192 (M^+ − H_2O, 22.11), 175 (M^+ + 1 − $2H_2O$, 55.57), 174 (M^+ − $2H_2O$, 41.17), 43 (100). Anal. calcd for $C_{11}H_{14}O_4$: C 62.86, H 6.67; found C 62.99, H 6.64.

B. *Epoxidation with m-CPBA and successive cyclization*

7b (388 mg, 2 mmol) in CH_2Cl_2 (20 mL) was treated with *m*-CPBA (525 mg, 3 mmol) as **9a**. 134 mg (32 %) of **10b** and 197 mg (47 %) of **9b** were obtained.

C. *Sharpless asymmetric epoxidation and successive cyclization*

7b (485 mg, 2.5 mmol) reacted with Sharpless reagent as **9a** and 416 mg (87 %) of **9b** was obtained.

Preparation of **11**

To a solution of **10a** (986 mg, 2.2 mmol) in dried THF (20 mL) was added methoxymethyl chloride (1.2 mL) and Et_3N (3 mL). After being refluxed for 2 h the mixture was diluted with ether (100 mL), washed with water, dried over Na_2SO_4 and concentrated. Column chromatography (petroleum ether (60—90 ℃) : ethyl acetate = 8 : 1) of the residue gave 932 mg (97%) of **11**. $[\alpha]_D^{25}$ -25.5 (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.07 (s, 9H, 3 × CH_3), 3.16 (s, 3H, CH_3O), 3.35 (s, 3H, CH_3O), 3.95—4.32 (m, 5H, CH_2O, 3 × CHO), 4.61—4.85 (m, 5H, CHO, 2 × OCH_2O), 7.25—7.50 (m, 10H, 2 × Ph), 7.65—7.80 (m, 5H, Ph); IR (film) ν: 1430, 1160, 1110, 700 cm^{-1}; MS *m/z* (%): 279 (M^+ - OTBDPS, 0.14), 91 (47.73), 45 (100). Anal. calcd for $C_{31}H_{40}O_6Si$: C 69.40, H 7.46; found C 69.04, H 7.44.

Preparation of **12**

To a solution of **11** (804 mg, 1.5 mmol) in dried THF (50 mL) tetrabutylammonium fluoride (1 N solution in THF, 1.7 mL) was added. After stirring for 8 h at room temperature the solvent was removed *in vacuo*. Column chromatography (petroleum ether (60—90 ℃) : ethyl acetate = 5 : 1) of the residue gave 420 mg (94%) of **12**. Colorless oil, $[\alpha]_D^{25}$ 65.9 (*c* 0.207, $CHCl_3$) [lit.[7b] $[\alpha]_D^{27}$ 66.3 (*c* 1.13, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.70—2.10 (br 1H, OH), 3.32 (s, 3H, CH_3O), 3.33 (s, 3H, CH_3O), 3.95—4.35 (m, 5H, CH_2O, 3 × CHO), 4.61—4.73 (m, 4H, 2 × OCH_2O), 4.78 (d, 1H, J = 4.4 Hz, CHO), 7.25—7.50 (m, 5H, Ph); IR (film) ν: 3450 (br, OH), 1450, 1140, 700 cm^{-1}; MS *m/z* (%): 297 (M^+ - 1, 0.52), 281 (M^+ - OH, 0.03), 161 (35.88), 46 (100). Anal. calcd. for $C_{15}H_{22}O_6$: C 60.40, H 7.38; found C 60.24, H 7.55.

References

1 (a) Loder, J. W.; Neam, R. H. *Heterocycles* **1977**, *7*, 113.
(b) Atef Ebrahin El-Zayat, A.; Ferrigni, N. R.; McCloud, T. G.; Mckenzie, A. T.; Byrn, S. R.; Cassady, J. M.; Chang, Ching-Jer; Mclaughlin, J. L. *Tetrahedron Lett.* **1985**, *26*, Z955.

2 Bermejo, A.; Leonce, S.; Cabedo, N.; Andreu, I.; Caignard, D. H.; Atassi, G.; Cortes, D. *J. Nat. Prod.* **1999**, *62*, 1106.

3 Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161 and references cited therein.

4 (a) Gesson, J. D.; Jacocesy, J. C.; Mondan, M. *Tetrahedron Lett.* **1987**, *28*, 3949.
(b) Gesson, J. D.; Jacocesy, J. C.; Mondan, M. *Tetrahedron* **1989**, *45*, 2627.

5 Giunouley, J. G.; Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 976.

6 Katsuki, T; Martin, V. S. *Org. React.* **1996**, *48*, 32 and references cited therein.

7 (a) Tadano, K.; Ueno, Y.; Ogawa, S. *Chem. Lett.* **1988**, 111.
(b) Tadano, K.; Ueno, Y.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2328.

8 Sung, H. K.; Wan, J. K. *Tetrahedron Lett.* **1989**, *30*, 5915.

9 Hungerbuhler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.

10 Brougham, P; Cooper, M. S.; Commeson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.

11 Marshall, J. A.; Crute III, T. D.; His, J. D. *J. Org. Chem.* **1992**, *57*, 115.

12 Ye, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1997**, *62*, 3748.

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