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TETRAHEDRON: *ASYMMETRY*

# A new and short enantioselective synthesis of (*R*)-pantolactone

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**Abstract**

Dihydro-4,4-dimethyl-2(3*H*)-furanone **6**, the key intermediate to (*R*)-pantolactone **2**, has been synthesized in two steps via the radical cyclization of bromoether **5**. Silyl enol ether **7**, prepared from **6**, on Sharpless asymmetric dihydroxylation gave (*R*)-pantolactone **2** in moderate yield and excellent enantioselectivity. 

## 1. Introduction

Calcium pantothenate **1a** is a member of the vitamin B complex and exhibits its biological activity as a component of coenzyme A.[1] Pantothenic acid occupies a central position in intermediary metabolism and is indeed involved in numerous biochemical reactions and enzymatic processes. (*R*)-Pantolactone **2** is an important starting material for the large-scale production of calcium pantothenate (**1a**, vitamin B group),[1] (*R*)-panthenol (**1b**, bactericide),[2] (*R*)-pantetheine (**1c**, growth factor)[3] and (*R*)-pantoyl taurine (**1d**, bacterial growth inhibitor).[4] It has also been widely used as a chiral auxiliary or a chiral building block for the synthesis of natural products.[5] Several processes have been developed for the preparation of the key intermediate, (*R*)-pantolactone **2** such as: (i) resolution of racemates with recycling;[6] (ii) asymmetric hydrogenation with optically active Rh complexes;[7] and (iii) microbiological synthesis[8] and others.[9] However, these methods to obtain **2** involve many steps, affording intermediates often in low yields. We wish to report here that a short and efficient synthesis of (*R*)-pantolactone **2** can be achieved in four steps starting from methallyl alcohol by employing two key reactions, viz. radical cyclization and Sharpless asymmetric dihydroxylation.

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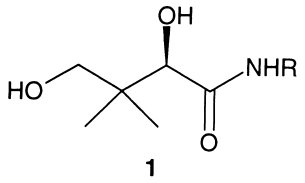


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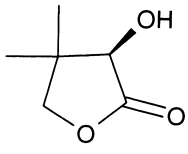


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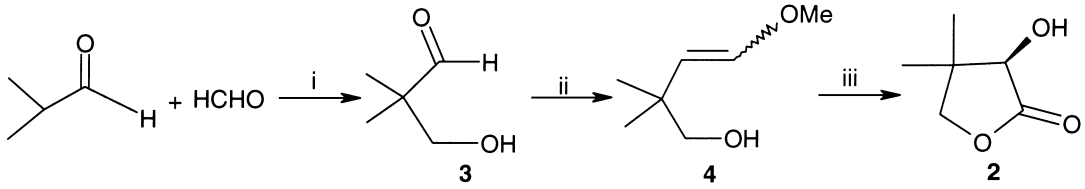
R = a = -$(CH_2)CO_2]_2Ca$ c = -$(CH_2)_2CONH(CH_2)_2SH$
b = -$(CH_2)_2OH$ d = -$(CH_2)_2SO_3H$

Sharpless asymmetric dihydroxylation (AD) of olefins using catalytic amounts of $OsO_4$ in the presence of cinchona alkaloid derivatives, leading to a wide variety of enantiomerically pure vicinal diols, has become one of the most useful and reliable organic reactions.[10] Moreover, it has been well-established that poor *E/Z* ratios in the preparation of enol ethers is not necessarily damning with regard to the enantioselectivity realized upon AD of the *E/Z* mixture.[11] Accordingly, we synthesized hydroxy enol ether **4** [*E/Z*=2:3 as determined from $^1$H NMR (200 MHz)] in 80% yield by the Wittig olefination of the hydroxy aldehyde, **3**,[12] with $CH_3OCH_2PPh_3Cl$ using $^t$BuOK as base. The *E/Z* mixture of enol ether **4** was subjected to Sharpless AD using hydroquinidine 1,4-phthalazinediyl diether {$(DHQD)_2PHAL$} as chiral ligand, followed by the acidic work-up, furnishing the required (*R*)-pantolactone **2** in <10% yield (45% ee) {$[\alpha]_D^{25}$−22.8 (c, 2 in $H_2O$); lit.[6] $[\alpha]_D^{25}$ −50.7 (c, 2.05 in $H_2O$)} (Scheme 1).

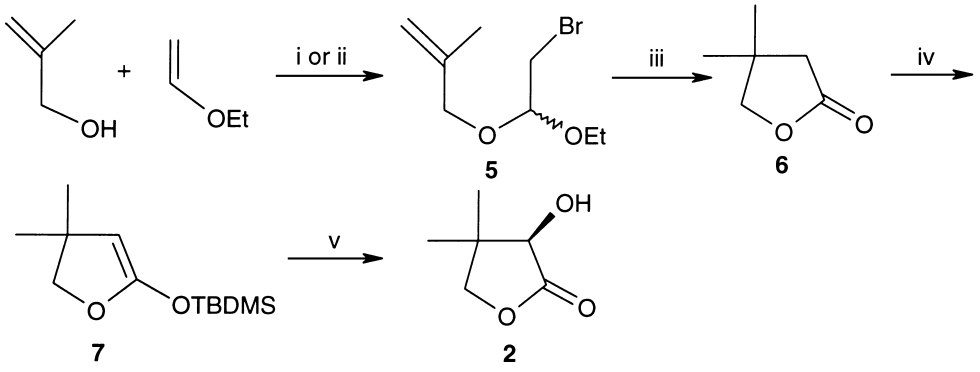



3 4 2

Scheme 1. (i) $K_2CO_3$, 0°C; (ii) KO$^t$Bu, $CH_3OCH_2PPh_3Cl$, ether, 10 h; (iii) $OsO_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, 25°C followed by acidic work-up

Hence, we began to look for a more efficient synthetic route (Scheme 2) in which the key intermediate **6** was obtained via the radical cyclization. Radical cyclization has been recognized as an attractive method for construction of organic molecules, and the characteristic advantages such as high extent of reactivity, regioselectivity and stereoselectivity would be promising for natural product synthesis.[13] Accordingly, the bromoacetal **5**, the key radical precursor, was obtained by two routes: (i) addition of ethyl vinyl ether to a cold solution (−48°C) of methallyl alcohol and *N*-bromosuccinimide (NBS) in $CH_2Cl_2$ afforded **5** in 85% yield;[14] and (ii) the bromination of ethyl vinyl ether using $Br_2$ at −78°C in $Et_2O$ followed by in situ treatment of the dibromo product at −5°C with methallyl alcohol and $PhNMe_2$ as base also furnished **5** in 82% yield.[15] The bromo ether **5** was then subjected to radical cyclization ($^n$$Bu_3SnCl/NaCNBH_3$/AIBN) and it is to be noted that the cyclized product was difficult to isolate due to its volatility. Hence, addition of Jones' reagent directly to the reaction mixture after radical cyclization was done to afford β,β-dimethyl-γ-butyrolactone **6** in 78% yield. The isolation of silyl enol ether **7**, from the lactone **6** using various bases such as $^n$BuLi, LDA in THF, $^t$BuOK, LiHMDS, HMDS and imidazole and $Et_3N/ZnCl_2$ at various temperatures (−78°C to reflux) was not successful,[16] possibly due to the steric hindrance offered by the presence of *gem*-dimethyl groups. However, enolization of lactone **6** has been achieved[17] using LDA as base at −78°C in THF and HMPA followed by quenching the enolate with *tert*-butyldimethylsilyl chloride (TBDMSCl) to produce enol ether **7**, which again decomposed when we attempted to purify it either by distillation or by column chromatography. Hence, the crude silyl enol ether **7** was subjected to Sharpless AD at 0°C using $(DHQD)_2PHAL$ as ligand to produce the required (*R*)-pantolactone **2** in 60%

yield and 92% ee {$[\alpha]_D^{25}$ −46.7 (c, 2 in $H_2O$)}. The low yield of (*R*)-pantolactone **2** in this step could be attributed to its high solubility in water during work-up.




Scheme 2. (i) NBS, $CH_2Cl_2$, −48°C, 3 h, 85%; (ii) $Br_2$, $Et_2O$, −78°C to −5°C, $PhNMe_2$, 12 h, 82%; (iii) $^nBu_3SnCl$, $NaCNBH_3$, AIBN, $^t$BuOH, 90°C, 6 h, followed by Jones' oxidation, 78%; (iv) LDA, HMPA, THF, TBDMSCl, −78°C to 25°C; (v) $OsO_4$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $^t$BuOH:$H_2O$ (1:1), 0°C, 18 h, 60%

In conclusion, we have achieved a short and efficient synthesis of (*R*)-pantolactone **2**, using Sharpless asymmetric dihydroxylation as the key step for introducing chirality. Only four steps including a high yielding radical cyclization are effectively needed for the synthesis of **2** by this route.

## 2. Experimental

All solvents were distilled and dried before use. Chromatography was performed over silica gel (60–120 mesh). IR spectra were recorded on a Perkin–Elmer 137 E spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker 200 MHz instruments using TMS as an internal standard. The mass spectra (MS) were recorded on an automated Finnigan MAT 1020C mass spectrometer using ionization energy of 70 eV. The optical rotations were carried out on a Jasco 181 digital polarimeter at 25°C using sodium D light.

### *2.1. Preparation of α,α-dimethyl-β-hydroxy propionaldehyde **3***

To a stirred mixture of isobutyraldehyde (1 g, 0.014 mol) and 40% formalin (1.13 g, 0.015 mol) in an ice-bath, solid $K_2CO_3$ (1.9 g, 0.014 mol) was added in small portions at such a rate that the temperature of the reaction mixture did not exceed 20°C. After all the $K_2CO_3$ had been added, the stirring was continued for 1.5 h and then the mixture brought to room temperature. The viscous liquid was extracted with ether (3×20 ml), dried over anhyd. $Na_2SO_4$ and concentrated to give impure **3** as a solid, which was further purified by distillation (63°C/10 mmHg) and the distillate immediately crystallized to give **3**. Yield: 0.99 g (70%); $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.1 (s, 6H), 3.4 (s, 2H), 9.8 (s, 1H).

### *2.2. Preparation of hydroxy enol ether **4***

Chloromethyl methyl ether (MOM chloride) (5 g, 0.062 mol) was added in one portion to a solution of $Ph_3P$ (15.43 g, 0.059 mol) in 35 ml of dry $CH_2Cl_2$ under nitrogen. The reaction mixture was allowed to reflux for 12 h, cooled to room temperature and diluted with 25 ml of benzene. All the $CH_2Cl_2$ and unreacted MOM chloride was distilled off at atmospheric pressure and the remaining residue was

repeatedly slurried in fresh benzene, which was then filtered off. This process was repeated two more times and after the last solvent removal the flask containing the white solid was attached to vacuum line and dried for 10 h to give methoxymethylenetriphenyl phosphonium chloride. Yield: 18 g (90%); $^1$H NMR (200 MHz, $CDCl_3$): δ 3.7 (s, 3H), 5.9 (d, *J*=4 Hz, 2H), 7.75–7.9 (m, 15H).

Potassium *tert*-butoxide (1.23 g, 0.011 mol) was added in three portions to vigorously stirred slurry of methoxymethylenetriphenylphosphonium chloride (3.76 g, 0.011 mol) in 25 ml diethyl ether. Within 5 min a red solution resulted and this was allowed to stir for another 1.5 h. Hydroxy aldehyde **3** (1 g, 0.0098 mol) was diluted to 5 ml with dry diethyl ether and this solution was added over 10 min to the reaction mixture. The reaction was then allowed to stir at room temperature for 10 h, at which time 10 ml of water was added followed by 10 ml of pet. ether. The aqueous layer was separated and the organic layer was washed with water and brine, dried over $Na_2SO_4$ and concentrated to give impure olefin, which, on column chromatography purification (10% ethyl acetate in pet. ether), gave 2:3 (*E*) and (*Z*) isomers [determined by $^1$H NMR (200 MHz)] of hydroxy enol ether **4**. Yield: 1.02 g (80%); IR (neat, $cm^{-1}$): 3400–3300, 1610, 1100; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.1 (s, 6H), 3.5 (s, 2H), 3.6 (s, 3H), 4.15 (d, *J*=6.5 Hz, 1H), 5.8 (d, *J*=6.5 Hz, 1H), 4.7 (d, *J*=13 Hz, 1H), 6.35 (d, *J*=13 Hz, 1H) {mixture of *cis* and *trans* isomers}.

### 2.3. Preparation of (R)-pantolactone *2*

To a well-stirred mixture of $(DHQD)_2PHAL$ (0.018 g, 0.023 mmol), $K_3FeCN_6$ (2.27 g, 6.9 mmol), $K_2CO_3$ (0.94 g, 6.9 mmol), $OsO_4$ (0.0012 g, 0.0046 mmol) and methane sulfonamide (0.22 g, 2.3 mmol) in *tert*-butanol–water (5 ml each) at 0°C, the hydoxy enol ether **4** (0.3 g; 2.3 mmol) was added. The reaction mixture was stirred for 16 h at 0°C. Solid sodium sulphite (1 g) was added and the reaction mixture was stirred for an additional hour. $CH_2Cl_2$ (20 ml) was added to the reaction mixture and, after the separation of the layers, the aqueous phase was continuously extracted with $CH_2Cl_2$. The combined organic extracts were dried over $Na_2SO_4$ and concentrated to give impure **2**, which was further purified by column chromatography (20% ethyl acetate in pet. ether) to give **2** as solid (for characterization of **2** vide infra under experimental). Yield: 0.024 g (8%); mp 88°C; $[\alpha]_D^{25}$ −22.8 (c, 2 in $H_2O$); lit. $[\alpha]_D^{25}$ −50.7 (c, 2.05 in $H_2O$).

### 2.4. Preparation of bromo ether *5* using NBS

Ethyl vinyl ether (2 g, 0.0278 mol) has been added dropwise over a 15 min period to a mixture of methallyl alcohol (4 g, 0.0556 mol) and *N*-bromosuccinimide (4.95 g, 0.0278 mol) in 20 ml $CH_2Cl_2$ at −48°C. The reaction mixture was stirred for 3 h at −48°C, then brought to room temperature and extracted with $CH_2Cl_2$ (2×25 ml). The organic layer was separated and washed with NaOH (10%), $H_2O$ and brine, dried over $Na_2SO_4$ and concentrated to give crude **5** which, after column chromatography purification (5% ethyl acetate in pet. ether), gave pure **5**. Yield: 5.24 g (85%); IR (neat, $cm^{-1}$): 1655, 1446, 1120, 1061, 901, 619; $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, *J*=5.5 Hz, 3H), 1.8 (s, 3H), 3.35 (d, *J*=5 Hz, 2H), 3.7 (q, *J*=4 Hz, 2H), 4.0 (d, *J*=7 Hz, 2H), 4.7 (t, *J*=5 Hz, 1H), 4.95 (d, *J*=18 Hz, 2H); $^{13}$C NMR (50.3 MHz, $CDCl_3$): δ 15.41, 19.73, 31.93, 62.70, 70.84, 101.40, 112.76, 141.90; MS *m/z* (% rel. intensity): 222.5 ($M^+$, 1), 179 (2), 154 (28), 153 (23), 151 (28), 150 (30), 129 (63), 126 (40), 125 (60), 123 (100), 100 (35), 99 (27), 85 (20), 72 (23), 71 (21), 55 (25), 54 (22); elemental analysis: $C_8H_{15}O_2Br$ requires C, 43.24; H, 6.76; Br, 36.03%. Found C, 43.25; H, 6.80; Br, 36%.

### 2.5. Preparation of bromo ether **5** using $Br_2$

Bromine (1.4 ml, 0.0278 mol) was added dropwise to a solution of ethyl vinyl ether (2 g, 0.0278 mol) in 20 ml ether at −78°C. The reaction mixture was stirred for 5 min and the dibromo product formed was in situ treated with methallyl alcohol (2 g, 0.0278 mol) and *N*,*N*-dimethylaniline (3.4 g, 0.0278 mol) at −5°C. The reaction mixture was then brought to room temperature and stirred overnight. White precipitate formed and was dissolved by the addition of 15 ml of water. It was then extracted with ether (2×50 ml), washed with 50% HCl (to remove the *N*,*N*-dimethylaniline), water, $NaHCO_3$, and brine, dried over $Na_2SO_4$ and concentrated to give pure bromo ether **5** (for characterization of **5** vide supra under experimental). Yield: 5.1 g (82%).

### 2.6. Preparation of dihydro-4,4-dimethyl-2(3H)-furanone **6**

To a magnetically stirred solution of bromo ether **5** (1 g, 0.0045 mol) in 30 ml *tert*-butanol were added tributyltin chloride (0.3 g, 0.0009 mol), sodium cyanoborohydride (0.42 g, 0.0068 mol) and a catalytic amount of AIBN. The reaction mixture was refluxed for 6 h under nitrogen and then cooled to room temperature. The cyclized product was in situ subjected to Jones' oxidation by diluting the reaction mixture with 20 ml acetone and treating with Jones' reagent till the yellow color persisted. After the reaction was complete (4 h), the supernatant solution was decanted from the green gum. The insoluble residue was then washed with ether (5×25 ml). The combined organic extracts were then washed with water, $NaHCO_3$ and brine, dried over $Na_2SO_4$ and concentrated to give crude lactone **6**, which was further purified by column chromatography (15% ethyl acetate in pet. ether) to give pure **6**. Yield: 0.4 g (78%); bp 98°C/12 mm; IR (neat, $cm^{-1}$): 1790, 1490, 1420, 1380, 1285, 1170, 1030; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.2 (s, 6H), 2.3 (s, 2H), 3.95 (s, 2H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): δ 25.3, 36.3, 42.6, 79.3, 177.2; MS *m/z* (% rel. intensity): 115 (M+1, 20), 114 ($M^+$, 30), 112 (13), 86 (5), 70 (73), 69 (65), 68 (30), 56 (100), 54 (25); elemental analysis $C_6H_{10}O_2$ requires: C, 63.16; H, 8.77%. Found: C, 63.15; H, 8.8%.

### 2.7. Preparation of (R)-pantolactone **2**

To a well-stirred solution of diisopropylamine (0.36 g, 3.6 mmol) in 10 ml of THF at 0°C, a 2.5 M solution of *n*-BuLi (0.23 g, 3.6 mmol) in hexane was added. After 30 min the solution was cooled to −78°C and lactone **6** (0.39 g, 3.4 mmol) was added over 10 min. After 3 h a solution of *tert*-butyldimethylsilyl chloride (0.77 g, 5 mmol) in HMPA (1 ml) was added over 1 min. The reaction mixture was then stirred at room temperature for 1 h, diluted with 15 ml ice-cold pet. ether and washed quickly with ice-cold water and brine, dried over $Na_2SO_4$ and concentrated to give crude enol ether **7**.

To a well-stirred mixture of $(DHQD)_2PHAL$ (0.028 g, 0.035 mmol), $K_3FeCN_6$ (3.45 g, 10.5 mmol), $K_2CO_3$ (1.42 g, 10.5 mmol), $OsO_4$ (0.0018 g, 0.007 mmol) and methanesulfonamide (0.33 g, 3.5 mmol) in *tert*-butanol–water (5 ml each) at 0°C, the crude enol ether of **7** (0.8 g; 3.5 mmol) was added. The reaction mixture was stirred for 16 h at 0°C. Solid sodium sulphite (1 g) was added and the reaction mixture was stirred for an additional hour. $CH_2Cl_2$ (20 ml) was added to the reaction mixture and, after separation of the layers, the aqueous phase was continuously extracted with $CH_2Cl_2$. The combined organic extracts were dried over $Na_2SO_4$ and concentrated to give **2** as a thick liquid, which was further purified by column chromatography (20% ethyl acetate in pet. ether) to give pure **2** as a solid. Yield: 0.27 g (60**%**); mp 90°C; IR (neat, $cm^{-1}$): 3400–3300, 1785, 1480, 1410, 1390, 1300, 1180, 100, 900; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.1 (s, 3H), 1.2 (s, 3H), 3.95 (q, *J*=8 Hz, 2H), 4.15 (s, 1H); $^{13}C$ NMR (50.3

MHz, $CDCl_3$): δ 18.8, 22.8, 40.8, 75.5, 76.5, 178.0; $[\alpha]_D^{25}$ −46.7 (c, 2 in $H_2O$); lit.[6] $[\alpha]_D^{25}$ −50.7 (c, 2.05 in $H_2O$).

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