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Note

A new route for the synthesis of (*R*)-glyceraldehyde acetonide: A key chiral building block

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A new route for the synthesis of (*R*)-glyceraldehyde acetonide *via* asymmetric dihydroxylation of allyl 4-methoxybenzoate using the $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$ catalyst system is described. This route involves the asymmetric dihydroxylation of allyl 4-methoxybenzoate, acetonide protection of vicinyl dihydroxyl groups followed by cleavage of *p*-methoxybenzoate ester and subsequent oxidation to give the (*R*)-glyceraldehyde acetonide.

Keywords: (*R*)-Glyceraldehyde acetonide, asymmetric dihydroxylation, allyl 4-methoxybenzoate, chiral building block, Swern oxidation

(*R*)-Glyceraldehyde acetonide (**Figure 1)** is a valuable chiral substrate susceptible to various transformations which is useful for stereocontrolled synthesis. Optically pure *(R)*-glyceraldehyde actonide is widely used as a key chiral building block in enantioselective syntheses of a variety of natural products[1]. Synthesis of bengamide E (Ref. 2), (*R*)-(+)-tanikolide[3], (*R*)- and (*S*)-4-[(methoxycarbonyl)-methyl]-2-azetidinones[4], (*R*)-(+)-hexanolide[5], (*S*)-(+)-2-methyl-4-octanol[6] and (+)-5-*epi*-cytoxazone[7] were performed utilizing **1** as a chiral substrate. D-Pentitols, 2-deoxy-D-pentitols and 2-amino-2-deoxy-D-pentitols[8], substituted β-lactams[9], D-erythrose and D-threose derivatives[10] were prepared by using **1** as a key chiral building block. It is also useful for the preparation of α-hydroxy and α,β-dihydroxy aldehydes[11] which are useful intermediates for the synthesis of arachidonic acid metabolites. The use of (*R*)-glyceraldehyde acetonide in sugar synthesis is widespread and has been fairly reviewed recently[12].

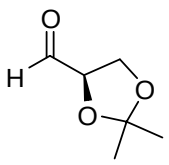
The first preparation of (*R*)-glyceraldehyde actonide was reported by Baer and Fischer in 1939 (Ref. 13). (*R*)-Glyceraldehyde actonide has been obtained from D-mannitol by a bis-ketalization/glycol cleavage sequence using a number of ketalizing reagents[13,14], and either lead tetraacetate[13,15] or lead periodate[16] to effect glycol cleavage.

Results and Discussion

Herein is reported a new synthesis of *(R)*-glyceraldehyde acetonide *via* asymmetric dihydroxylation of allyl 4-methoxybenzoate (**Scheme I**). Allyl ester, **4** is prepared from the reaction of *p*-methoxybenzoyl chloride, **2** with allyl alcohol, **3** in the presence of triethylamine. The stereochemistry is established by carrying out the asymmetric dihydroxylation of the *p*-methoxybenzoate of allyl alcohol **4** using the $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$ catalyst system to afford (*R*)-2,3-dihydroxypropyl 4-methoxybenzoate, **5** with 89% yield and 98% *ee*.

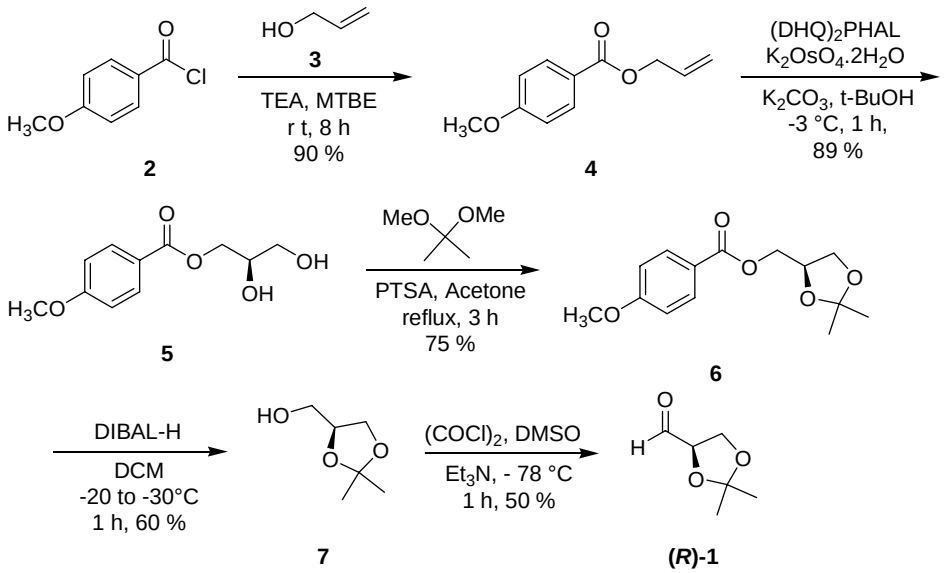
Initial studies on asymmetric dihydroxylation of allyl 4-methoxybenzoate at 0°C gave only 96.0% *ee*. This is not sufficient for kilo-lab scale preparation of compound **5** (4.0 kg scale). For this asymmetric dihydroxylation, it has been observed that temperature plays a key role in establishing enantioselectivity. Therefore, the enrichment of enantioselectivity was studied with respect to the temperature (**Table I**). The enrichment of enantioselectivity was observed as the temperature decreased. Unfortunately, the reaction mass was frozen at -5°C and below. Under these conditions, to achieve 98.0% *ee*, the optimum temperature for asymmetric dihydroxylation of allyl 4-methoxybenzoate is -3 to -4°C. This has been well proved consistently on 4.0 kg scale.

This asymmetric dihydroxylation methodology has been developed on the basis of the transition state model advanced earlier by E J Corey[17] *et al*. for the bis-cinchona alkaloid catalyzed asymmetric dihydroxylation reaction. The 4-methoxybenzoyl group functions not only to selectively protect one of



(*R*)-1

Figure 1



Scheme I

Table I — *ee* (%) with respect to temperature

Entry No.	Temperature (°C)	*ee* (%)
1	25-30°C	80.0
2	2-3°C	91.0
3	0-2°C	96.0
4	-3 to -4°C	98.0
5	-5°C and below	solidified

the hydroxy groups of the product triol for subsequent synthetic manipulation but also to provide an extended binding group that participates in hydrophobic and aryl-aryl interactions with the U-shaped binding pocket of the $(DHQ)_2PHAL$, $K_2OsO_4.2H_2O$, thereby enhancing enantioselectivity.

The diol **5**, on reaction with 2,2-dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid, gave the corresponding acetonide protected derivative **6** in 75% isolated yield. Cleavage of *p*-methoxy-benzoate ester was attempted in different alkali bases like Cs_2CO_3, LiOH, NaOH and KOH. Most of the attempts to get the required (*S*)-glycerol acetonide, **7** were unsuccessful probably because of the deacti-vation of the ester by the electron-donating *p*-methoxy substituent. To overcome this hurdle a strong reducing agent, DIBAL-H, was used successfully.

Oxidation of (*S*)-glycerol acetonide, **7** to (*R*)-**1**, has been reported[18]. However, the attempts to obtain pure aldehyde in good yield by PCC, PDC, Dess-Martin periodinane, Ley perruthenate, or TEMPO oxidation methods were unsuccessful. Finally, a practical route to **1** was found by Swern oxidation of (*S*)-glycerol acetonide, **7**.

In conclusion, a new route for the synthesis of (*R*)-glyceraldehyde acetonide *via* asymmetric dihydroxylation of allyl 4-methoxybenzoate using the $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$ catalyst system is described.

Experimental Section

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^1H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over anhydrous sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC's were run on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out over silica gel (230-400 mesh) unless otherwise stated.

Preparation of allyl 4-methoxybenzoate, 4. Allyl alcohol (180 g, 3.1 mole) and triethylamine (445.0 g,

4.4 mole) were dissolved in methyl *t*-butyl ether (2250 mL), in a round bottom flask under N_2 atmosphere and cooled to 10°C. A solution of *p*-methoxybenzoyl chloride, **2** (510.0 g, 3.1 mole) in methyl *t*-butyl ether (500 mL) was added to the reaction mass over 50 min at 10°C. The reaction mass temperature was allowed to rise to RT. The reaction- mixture was then stirred for 8 hr at RT. After completion of the reaction, the reaction-mixture was cooled to 10°C. Reaction mass was diluted with a solution of ammonium chloride (350 g) and water (1000 mL) and stirred for 15 min. Both the layers were separated and the aqueous layer was extracted with methyl *t*-butyl ether (3 × 5000 mL). The combined organic layers were washed with water followed by brine, dried over anhydrous Na_2SO_4 and filtered. Solvent was removed from the organic layer under reduced pressure to give a liquid residue. The liquid residue was distilled under reduced pressure, the distillate being collected at 130-140°C/1.3 mm Hg to give pure **4** as a clear liquid (536 g); 90% yield; ^{1}H NMR (400 MHz, $CDC1_3$): δ 8.01 (m, 2H), 6.90 (m, 2H), 6.02 (ddt, *J* = 17.2, 10.5, 5.6 Hz, lH), 5.38 (dd, *J* = 17.2, 1.5 Hz, lH), 5.26 (dd, *J* = 10.5, 1.2 Hz, lH), 4.79 (dt, *J* = 5.6, 1.3 Hz, 2H), 3.83 (s, 3H); IR (film, KBr): 1716, 1607, 1511, 1460, 1361, 1317, 1257, 1169, 1102, 1030, 848 cm^{-1}; MS: *m/z* (M+1) 193.

Preparation of (*R*)-2,3-dihydroxypropyl 4-methoxybenzoate, 5. Water (6500 mL), potassium carbonate (1080 g), potassium hexacyanoferrate (2570 g) and *t*-butanol (2800 mL) were taken into a round bottom flask. Potassium osmate dihydrate (9.5 g) followed by a solution of $(DHQ)_2$ PHAL (20.2 g) in *t*-butanol (2800 mL) were charged into the reaction mass. The reaction-mixture was cooled to -3 to -4°C. A solution of allyl 4-methoxybenzoate, **4** (500 g, 2.6 mole) in *t*-butanol (250 mL) was added at -3 to -4°C over 50 min. The reaction-mixture was then stirred at -3 to -4°C. After completion of the reaction, the reaction mixture was quenched by slow addition of sodium sulfite at -3 to -4°C. The reaction-mixture was stirred for a further 20 min at -3 to -4°C. The reaction-mixture was then filtered on a celite pad and the resulting cake was washed with methyl *t*-butyl ether (5000 mL). Both the layers were separated from the filtrate and the aqueous layer was extracted with methyl *t*-butyl ether (2 × 4000 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The obtained residue was treated with *n*-hexane (8000 mL) and the reaction mass stirred at 15-20°C for 30 min. The reaction mass was then filtered and washed with *n*-hexane (2000 mL). The obtained white solid was dried under vacuum at 25°C till constant weight (523.8 g); 89% yield; 98% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (m, 2H), 7.01 (m, 2H), 4.37 (dd, *J* = 11.2, 4.5 Hz, lH), 4.28 (dd, *J* = 11.2, 6.2 Hz, lH), 4.22 (d, *J* = 5.3 Hz, lH), 3.98 (m, lH), 3.87 (s, 3H), 3.85 (m, lH), 3.66 (m, 2H); IR (film, KBr): 3407, 1710, 1606, 1512, 1319, 1277, 1258, 1170, 1104, 1028, 848 cm^{-1}; MS: *m/z* (M+1) 227.

Preparation of (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methoxybenzoate, 6. Diol, **5** (100 g, 0.44 mole) was dissolved in 5000 mL of dry acetone. *p*-Toluenesulfonic acid (10 g) and 2,2-dimethoxy propane (120 mL, 0.98 mole) were added to the reaction mass at 25°C. The reaction-mixture was refluxed for 3 hr. After completion of reaction, the reaction mass was cooled to RT. Reaction mixture was diluted with ethyl acetate and washed with 5% aqueous $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give **6** as an oily liquid (88.3 g); 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.0 Hz, 2H), 6.9 (d, *J* = 9.0 Hz, 2H), 4.37 (dd, *J* = 11.6, 5.5 Hz, 3H), 4.2 (t, *J* = 7.6 Hz, lH), 3.9 (s, 3H), 3.8 (s, 1H), 1.5 (s, 3H), 1.4 (s, 3H); IR (film, KBr): 3407, 1716, 1606, 1512, 1316, 1257, 1168, 1103, 1028, 848, 767 cm^{-1}; MS: *m/z* (M+1) 267.

Preparation of (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol, 7. A solution of (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methoxybenzoate, **6** (80 g, 0.3 mole) and dichloromethane (360 mL) was cooled to -20 to -30°C. 1.0 M DIBAL-H in *n*-hexane (788 mL, 0.788 mole) was slowly added at -20 to -30°C over 1 hr. After completion of the addition, the reaction mass temperature was allowed to rise to -10 to -15°C. Progress of the reaction was monitored by TLC. After completion of the reaction, the excess DIBAL-H was quenched using 10% methanol/dichloromethane at -10 to -15°C. *n*-Heptane (360 mL) was added to the reaction mass at -10 to -15°C. A solution of potassium sodium tartrate tetrahydrate (190 g) and water (190 mL) was added to the reaction mass at below 0°C. The reaction mass temperature was allowed to rise to 20-25°C. The reaction mass was maintained at 20-25°C for 16 hr. Both the layers were separated and the aqueous layer was extracted with *n*-heptane (320 mL). The combined organic layer was washed with water (2 ×

200 mL), followed by brine (200 mL) and the solvent was removed under reduced pressure to give **7** as an oily liquid (23.82 g); 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.28-3.57 (br, 3H), 2.6 (br, 3H), 1.45 (s, 3H), 1.39 (s, 3H); IR (film, KBr): 3435, 2988, 2937, 1458, 1381, 1372, 1257, 1214, 1157, 1118, 1074, 1053, 971, 845, 793 cm^{-1}; MS: *m/z* (M+1) 133.

Preparation of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, 1. Freshly distilled DMSO (37.5 g, 0.48 mole), diluted in 50 mL of anhydrous dichloromethane, was added dropwise to a well stirred solution of oxalyl chloride (27.9 g, 0.22 mole) in anhydrous dichloromethane (50 mL) maintained at -78°C. The mixture became yellow and (*S*)-glycerol acetonide, **7** (26.4 g, 0.20 mole) diluted with 100 mL of anhydrous dichloromethane, was introduced dropwise to the solution which was then stirred for 15 min. Triethylamine (101 g, 1.0 mole) was added dropwise and the mixture was heated to RT. Water (500 mL) and dichloromethane (500 mL) were added to the reaction mass. The organic layer was washed with water (250 mL) and the combined aqueous layer was extracted with dichloromethane (3 × 500 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give 16.0 g of crude material which was rapidly purified by fractional distillation (bath temperature 60-90°C, 3 mm Hg). Various fractions were collected at vapor temperature (30-40°C). Purity was checked for all fractions by GC. Pure fractions were mixed together to yield the aldehyde as a colourless oil (13 g); 50% yield; $[\alpha]_D$ = +53.8° (*c* = 2 in $CHCl_3$); purity (GC): 97.1%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, 1H), 4.61–3.91 (br, 3H), 1.49 (s, 3H), 1.44 (s, 3H); IR (film, KBr) 3423, 2989, 2938, 2893, 1737, 1457, 1375, 1256, 1217, 1154, 1154, 1074, 848 cm^{-1}; MS: *m/z* (M+1) 131.

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