Stereoselective synthesis of α-alkyl-α-hydroxylphenylacetic acid Part (I):asymmetric alkylation of (*S*)-mandelic acid

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An effective asymmetric synthesis of α-alkyl-α-hydroxyl phenyl acetic acid using benzaldehyde as steric hindrance agent has been accomplished by utilising the readily available and inexpensive chiral starting material, (S)-mandelic acid. The *ee* was determined by ^{1}H NMR with Eu(hfc)$_3$ as shift reagent.

Keywords: asymmetric synthesis, alkylation, tertiary hydroxyl acid

Tertiary hydroxy acids are highly important intermediates in the asymmetric synthesis of a variety of medicinal agents.[1] A number of useful synthetic methods for the preparation of enantiomerically pure α-branched α-hydroxy acids have been developed. Generally, optically active α-hydroxy acids are obtained through microbial methods,[2] enzymatic syntheses[3] and enantioselective syntheses using chiral auxiliaries.[4] However, when using microbial methods, it is difficult to isolate the product from the fermentation broth and the purification for the product can be complex and expensive. Enzymatic syntheses may need a stoichiometric amount of expensive cofactors whilst purified enzymes are expensive. Usually, the chiral auxiliary is very expensive and is not available for large-scale production. Furthermore, the recovery of chiral auxiliary can be difficult. Hence a practical, stereoselective and cost-effective process for synthesising tertiary α-hydroxyl acid is required.

In 1999, Mitsuya reported a diastereoselective synthetic route in which the (*R*)-α-cyclohexyl-α-hydroxyphenyl acetic acid with only 86%*ee* was obtained.[5] Recently, a new enantioselective synthesis of α-cyclohexyl-α-hydroxyphenyl acetic acid employing the Sharpless asymmetric dihydroxylation of α-cyclohexylstyrene as the key step was reported.[6] However, only 92% *ee* of the *tert*-α-hydroxy acid was obtained. Therefore, there remains some room for the development of more efficient methods to produce optically active tertiary hydroxy acids.

Herein we present our diastereoselective synthesis of acid **1** by using benzaldehyde and S-mandelic acid as starting materials. The acids **1** were prepared in 61–80% yields from **2**.

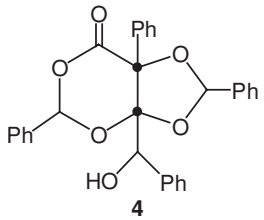
Results and discussion

Our synthetic strategy for the synthesis of acid **1** was envisioned according to Scheme 1 in which (*S*)-(+)-mandelic acid benzaldehyde derivative **2** was used as a chiral controller for the diastereoselective C–C bond forming process at the C–5 carbon of dioxolone lactone **2** with RX, to provide enantiopure strategic lactone **3**. The lactone **3** is then hydrolysed to (*S*)-acid **1** by simple methodology.

The *ee* of the compounds were obtained by determining the $\delta_{\text{-OCH3}}$ of their methyl esters of **1a–1d** with Eu(hfc)$_3$ as shift reagent.

Reagents and conditions: (a) benzylaldehyde, cat. TsOH, H_2SO_4 anhydrous pentane, crystallisation with diethyl ether/*n*-pentane, 60%; (b) LDA, THF, -78°C, 30min then RX, 80%; crystallisation in heptane, >90%; (c) KOH, MeOH, then 1N HCl, quant;

It was reported that the enol ions could react with acetal **2** to produce self-addition product **4** showed below.[7] However, in our experiment we found that a somewhat lower concentration of the enol ions and slow addition of the acetal-**2** to the reaction system could avoid this competing reaction.



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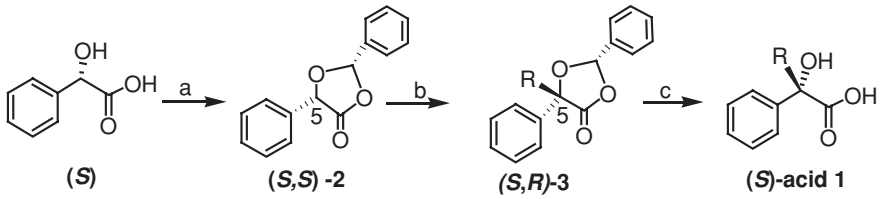
In the *cis*-aldolate **2**, the benzyl group attached to 2-C and 5-C position has the *cis*-configuration. The alkylation could be proceed through a six-membered cyclic transition state (Scheme 2) which resulted in the attack of the electrophilic reagents with high stereoselectivity. When deprotonation occurred, the benzyl group is attached to the 3-C still adopted its original orientation, which significantly affected the attacking orientation of the RX. The electrophilic groups would attack 5-C position from the opposite face of benzyl group that attached to 3-C position in order to avoid steric hindrance. This stereoselective attacking of the RX would result in the *trans*-addition products in which the benzyl group of 5-C position still adopted *cis*-configuration with that of 2-C.



(*S*) **(*S,S*) -2** ***(S,R)*-3** **(*S*)-acid 1**

(1a) R=CH_3; (1b) R=$(CH_3)_2CH$

(1c) R=$(CH_2)_5$; (1d) R=$(CH_2)_6$

Scheme 1

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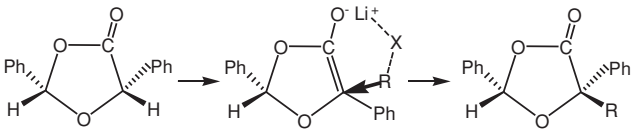
Table 1 Asymmetric synthesis of (*S*)-α-alkyl-α-hydroxyl-phenylacetic acid

	RX	Yield (%) [a]	$[\alpha]_D^{25}$	%*ee*[b]	configuration
1a	CH_3I	80	+34.3°	91	*S*
1b	$(CH_3)_2CHI$	77	+30.6°	94	*S*
1c	$(CH_2)_5Br$	62	+1.8°	90	*S*
1d	$(CH_2)_6Br$	61	+21.8°	89	*S*

[a]Overall yields of the last three steps from **2**. [b]Determined by ^{1}H NMR of the $\delta_{\text{-OCH3}}$ with Eu(hfc)$_3$ as shift reagent.



Scheme 2

The results of alkylation of (*S*)-mandelic acid were summarised in Table 1. From the results we can see that the steric hindrance by the benzene ring at 3-C was very strong in this method.

In summary, a cost-effective asymmetric synthesis of α-alkyl-α-hydroxyphenyl acetic acid using benzaldehyde as steric hindrance reagent has been accomplished by utilising the readily available and inexpensive starting material, (*S*)-mandelic acid. The synthetic strategy can be further extended to the asymmetric synthesis of (*S*)- or (*R*)-*tert*-α-hydroxy acid related derivatives.

Experimental

The solvents, *n*-pentane, tetrahydrofuran were dried and purified according to standard procedures. LDA was purchased from Aldrich Chemical Company. ^{1}H NMR and ^{13}C NMR were recorded at JNM-ECA-400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as the internal standard. Mass spectra were recorded by FAB methods on a MAT-711 mass spectrometer. Elemental analysis was performed on a Perkin-Elmer 240C analyzer. Optical rotations were measured with Jasco DIP-370 polarimeter. Melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected. All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Thin-layer chromatography (TLC) was performed on a silica gel HS GF_{254}.

*cis-(2S,5S)-2,5-Diphenyl-1,3-dioxolan-4-one ((S,S)-***2***)*: To a suspension of (*S*)-mandelic acid (50.0 g, 328 mmol) in pentane (500 ml) was added benzaldehyde (139.1 g, 1.31mol), followed by addition of *p*-TsOH (1.64 g) and 0.1 g sulfuric acid at nitrogen atmosphere at 22 °C. A Dean-Stark trap was added to the reaction flask. The mixture was warmed to 36 °C and allowed to reflux for 24h. The reaction mixture was cooled to room temperature and, 10 wt % aqueous $NaHCO_3$ was added. The organic layer was separated and the aqueous layer was extracted with ether (100 ml × 3). The combined organic layer was washed with water and brine, dried with Na_2SO_4, filtered and concentrated in vacuum. The crude product was crystallised twice with diethyl ether-pentane to give pure (*S, S*)-**2** (60% yield). m.p. 83–84 °C, = + 66.6°. ^{1}H NMR ($CDCl_3$) δ 5.41 (s, 1H), 6.55 (d, *J* = 1Hz, 1H), 7.30-7.65 (m, 10H). Mass spectrum (*m*/*e*) 240 (M^+). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.95; H, 4.99.

*cis-(2S,5R)-2,5-Diphenyl-5-methyl-1,3-dioxolan-4-one ((S,R)-***3***).* To a –78 °C solution of Lithium diisopropylamide (120 g, 110mmol, 10 % in hexane solution) in Et_2O (100 ml) was added *cis*-(2*S*,5*S*)-2,5-diphenyl-1,3-dioxolan-4-one (24.0 g, 100 mmol, dissolved in 100 ml of Et_2O). The reaction mixture was stirred for 30 min at –78 °C, followed by the addition of neat iodomethane (31.0 g, 200 mmol). After stirring for 2 h at –78 °C, saturated NaH_2PO_4 solution (100 ml) was added. The reaction mixture was poured into a separatory funnel containing saturated NH_4Cl solution (200 ml). The aqueous layer was separated and extracted with Et_2O (200 ml × 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 24.0 g of crude aldol product **3** which was used in the next step without purification.

To a solution of 24.0 g crude *cis*-(2*S*,5*R*)-2,5-diphenyl-5-methyl-1,3-dioxolan-4-one **3** in MeOH (50 ml) and water (100 ml) was added solid KOH (50.0 g). The reaction was allowed to reflux for 3 h. After cooling to room temperature, the reaction mixture was poured into 100 ml water and extracted with Et_2O (100 ml × 3) and discarded. The aqueous layer was acidified to pH 1with 2 N HCl, and the resulting mixtures were extracted with ethyl acetate (3 × 200 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide 15 g colorless needle crystal m.p. $[\alpha]_D$ + 34.3° of *(S)-α-methyl-α-hydroxyphenyl acetic* and **(1a)** (80%): ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H), 7.30–7.65 (m, 5H, Ar–H). ^{13}C NMR δ 26.0, 75.5, 76.6, 125.1, 128.2, 141.7, 180.4. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.89; H, 6.15%.

(S)-α-isopropyl-α-hydroxyl phenyl acetic and **(1b)**: Needle crystal of compound **1b** was prepared from (*S, S*)-**2** and iodo*iso*propane (77%). m.p. 116–117 °C. = + 30.6°(c=2.2, ethanol). ^{1}H NMR ($CDCl_3$) δ *0.70* (d, *J* = 7.8 Hz, 3H), 1.05 (d, *J* = 7.8 Hz, 3H), 2.63 (m, 1H), 7.65–7.20 (m, 5H). ^{13}C NMR δ 15.7, 17.2, 35.0, 76.7, 80.9, 125.0, 127.0, 128.2, 140.1, 180.2. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.95; H, 7.35%.

(S)-α-cyclopentyl-α-hydroxyl phenyl acetic and **(1c)**: Needle crystal of compound **1c** was prepared from (*S, S*)-**2** and bromo cyclopentane (62%). m.p. 123–124 °C. = + 31.8°(c = 4.0, ethanol). ^{1}H NMR ($CDCl_3$) δ 1.33–1.80 (m, 8H), 2.88 (m, 1H), 7.24 (td, *J* = 1.2, 6.6 Hz,1H), 7.34 (td, *J* = 1.2, 6.6 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR δ 25.60, 25.90, 26.06, 26.72, 46.83, 78.54, 125.77, 126.84, 127.72, 143.19, 176.08. Mass spectrum (*m*/*e*) 220 (M^+). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.35%.

(S)-α-cyclohexyl-α-hydroxyl phenyl acetic and **(1d)**: Colourless needle crystal of compound **1d** was prepared from (*S, S*)-2 and bromocyclohexane (61%). m.p. 139–141 °C. = + 21.8°(c = 2.0, ethanol). ^{1}H NMR (DMSO-D_6) δ 1.01–1.76 (m, 10H), 2.17 (m, 1H), 5.20 (bs, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR δ 25.57, 26.27, 26.42, 27.52, 81.15, 126.10, 127.85, 128.24, 140.03, 180.97. Mass spectrum (*m*/*e*) 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.53; H, 7.81%.

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References

1 (a) C. Bugno, S.M. Colombani, P. Dapporto, G. Garelli, P. Giorgi, A. Subissi and L. Turbanti, *Chirality* 1997, 721. (b) E.R. Atkinson, D.D. McRitchi, L. F. Schoer, *J. Med. Chem.*1997, **20**, 1612.
2 T. Yamagami, E. Takazu, T. Koji, **U.S.** 5,326,702.
3 H.-P. Schaer, G. Oreste, G. Daniel, L. Rente, S. Elke, S. Gottfried, **U.S.** 5,098,841.
4 A. G. Myers, **U.S.** 5,488,131.
5 M. Mitsuya, K. Kawakami, Y. Ogino, et al. *Bioorg. Med. Chem. Lett.* 1999, **9**, 2037.
6 P. Gupta, R. A. Fernandes and P. Kumar, *Tetrahedron Lett.* 2003, **44**, 4231-4232.
7 D. Seebach, R. Naef and G. Calderarj, *Tetrahedron* 1984, **40**, 1313.