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Note

Asymmetric organocatalysis with glycosyl-β-amino acids: direct asymmetric aldol reaction of acetone with aldehydes

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Abstract—Direct asymmetric aldol reaction of acetone with aromatic aldehydes was achieved in good yields and high enantioselectivity using 5-amino-5-deoxy-β-L-*ido*-(α-D-*gluco*)-heptofuranuronic acids as a new class of organocatalysts.

Keywords: Asymmetric catalysis; Aldol reactions; Glycosylamino acids; 5-Amino-5-deoxy-heptofuranuronic acids

Access to enantiomerically pure compounds in the fields of pharmaceuticals, agrochemicals and fragrances using asymmetric catalysis is a great challenge for chemists. The asymmetric aldol reaction has extensively been used[1] for the C–C bond stereoselective synthesis of β-hydroxycarbonyl compounds by Evans,[2] Heathcock,[3] Masamune,[4] Mukaiyama,[5] Barbas and Cordova[6,7] and Hayashi[8] groups. Asymmetric aldol reactions can be classified into the following five types: (i) chiral auxiliary assisted aldol reactions based on the use of stoichiometric amounts of the chiral appendages; (ii) chiral Lewis acid and Lewis base catalysed reactions; (iii) heterobimetallic bifunctional Lewis acid/Bronsted base catalysed reactions; (iv) antibody or enzyme catalysed reactions and; (v) organocatalysis[9] with L-proline[10] or its structural analogs. Undoubtedly, organometallic catalysis, despite some limitations, is reasonably well developed, but there are many problems with organometallic catalysts in terms of production process in the chemical and pharmaceutical industry and metal toxicity for chemotherapeutic agents.[11] Among the small organic molecules as organocatalysts, L-proline and its derivatives,[12] dipeptides, amino alcohols and acyclic amino acids were used successfully in terms of stereoselection and yields for direct aldol reactions with different substrates.

Carbohydrates have long been used in asymmetric catalysis as chiral ligand in search for high catalytic activities and enantioselectivities in several reactions *via* suitable ligand tuning.[13,14] There are many advantages associated with them as they are readily available, highly functionalised, and have several stereogenic centres. Here, we report the use of 5-amino-5-deoxy-β-L-*ido*-(α-D-*gluco*)-heptofuranuronic acids,[15,16] recently synthesised by us as new antituberculous agents, in direct asymmetric aldol reactions of different aromatic aldehydes and acetone with increased enantioselectivity and good yields. To the best of our knowledge, this is a first report where a glycosyl-β-amino acid of this type has been used as an organocatalyst in direct asymmetric aldol reactions.

The 5-amino-5-deoxy uronic acids have been synthesised by 1,4-conjugate addition of ammonia to the uronates followed by hydrolysis of the esters into acids as reported earlier in our group.[15,16] In earlier studies, these were obtained as diastereoisomeric mixtures and the individual isomers were not isolated in pure forms. In the present study, however, the individual pure diastereomers were separated by column chromatography and characterised for their use as organocatalyst.

First, we carried out the reaction of 3-nitrobenzaldehyde with acetone in the presence of 20 mol % of

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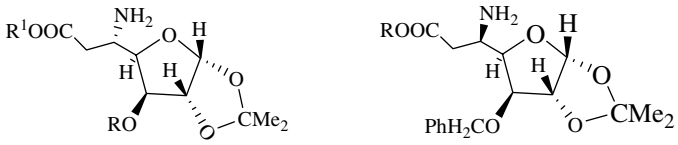
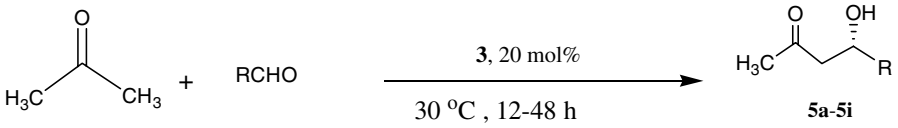


1, R=CH_2Ph, R^1=C_2H_5
2, R=CH_3, R^1=H
3, R=CH_2Ph, R^1=H

4a, R=C_2H_5
4, R=H

Chart 1. Glycosylamino acid derivatives used as catalyst.



Scheme 1. Aldol reaction of different aldehydes with acetone in the presence of catalyst **3**.

glycosylamino acids and either ester derivatives **1**–**4** (Chart 1) as organocatalysts under different experimental conditions. Among all the above amino acid derivatives, glycosylamino acid **3** (***C*-5** *S*-configurated) proved to be of high catalytic efficiency as the yield was 65% with 90% ee (Scheme 1). The reaction of 3-nitrobenzaldehyde with acetone in the presence of organocatalyst **4** with the *R* configuration at C-5 was sluggish as compared to that of the β-amino acid **3** at ambient temperature and the enantioselectivity was 68% only, as evidenced from HPLC of the product isolated by column chromatography. However, the reaction of 3-nitrobenzaldehyde with acetone using compound **1**, a glycosyl-β-aminoester as organocatalyst, did not proceed at all under the above reaction condition. The glycosylamino acid **2** having a 3-*O*-methyl substituent in the furanose ring, when used as an organocatalyst in the above reaction, resulted in 55% yield with only 18% enantioselectivity. The results are summarised in Table 1.

The above reaction of 3-nitrobenzaldehyde with acetone in the presence of glycosylamino acid **3** was carried out under different experimental conditions such as solvent, temperature and the amount of catalyst. In DMF, MeCN, THF and water, the above reaction did not proceed at ambient temperature even after 9 h and we did not pursue it further. However, in Me_2SO the formation of the aldol product could be detected only after 9 h and the reaction was complete after 30 h, but the isolation of the aldol product was difficult in this case as compared to neat acetone. The above reaction was also carried out under the influence of 10 and 50 mol % of organocatalyst **3**. While the former led to low yield of the product, the latter did not lead to any improvement in the yield of the desired product. The above reaction did not proceed at 0 °C even after several hours.

To see the generality of the above glycosylamino acid **3** as an organocatalyst in direct asymmetric aldol reaction, a variety of aromatic aldehydes were reacted with acetone under the above mentioned optimal reaction conditions. The results are depicted in Table 2. All the reactions were catalysed by 20 mol % of the glycosyl-

Table 1. Reaction of 3-nitrobenzaldehyde with acetone under catalysis of different glycosyl-β-amino acids leading to the formation of aldol product **5a**

Entry	Catalyst	Temperature (°C)	% ee	Yield (%) (mol % of the catalyst **1**–**4**)
1	**1**	0–60	—	No reaction (20)
2	**2**	30	18	59 (20)
3	**3**	30	—	10 (10)
		30	90	65 (20)
		30	90	60 (50)
4	**4**	30	—	No reaction
		60	68	55 (20)

Table 2. Aldol products of different aldehydes with acetone in the presence of 20 mol % of catalyst **3**

Compounds	R	Reaction time (h)	Yield[a] (%)	% ee[b,c]
5a	3-Nitrophenyl	12	65	90[c] 83[b]
5b	2-Nitrophenyl	18	67	99[c]
5c	4-Nitrophenyl	15	60	86[c]
5d	4-Florophenyl	24	57	76[c]
5e	4-Bromophenyl	48	52	3.0[c]
5f	3-Chlorophenyl	30	59	34[c]
5g	3,4,5-Trimethoxyphenyl	24	35	50[c]
5h	4-Pyridyl	18	60	36[c]
5i	4-Chlorophenyl	32	45	77[c]

[a] Yield represents the combined yield of enantiomers.
[b] ee (reaction in Me_2SO) determined by HPLC conducted at 23 °C.
[c] ee (reaction in neat acetone) determined by HPLC conducted at 23 °C.

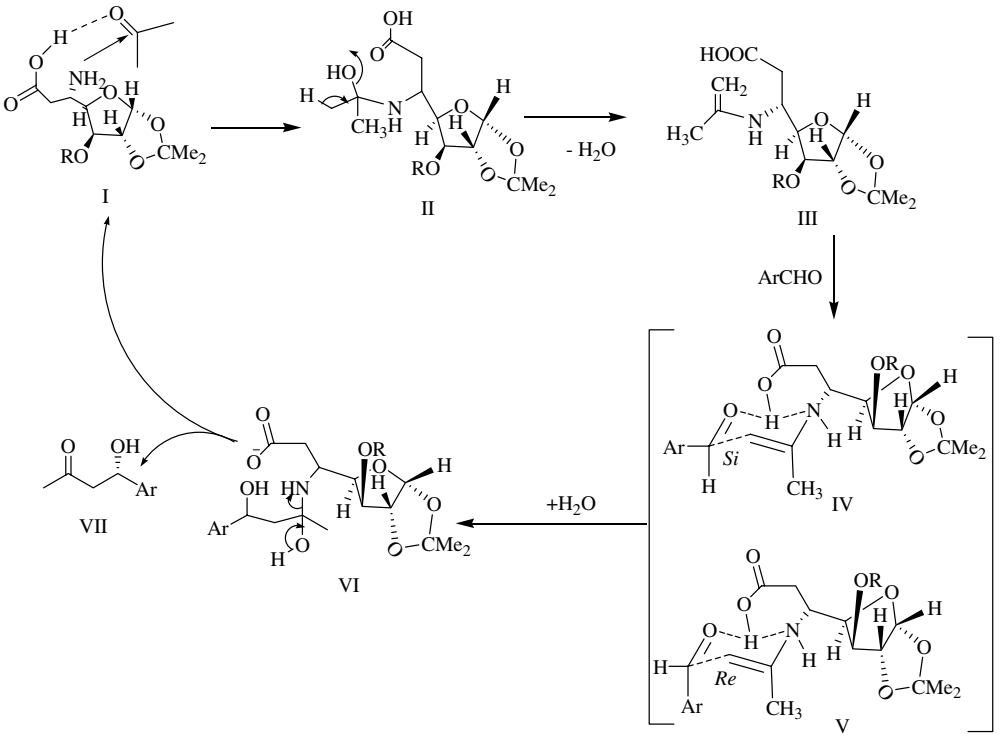


Chart 2. Proposed mechanism for the aldol reaction catalysed by glycosyl-β-amino acids.

amino acid at ambient temperature. Both the highest yield (67%) and maximum enantioselectivity (99%) were observed with 2-nitrobenzaldehyde.

In several instances, dehydrated products were also obtained along with the aldol products. The ratio of dehydrated products increased with increase in temperature and the enantioselectivities in the aldol products were also diminished.

Reaction mechanism: The mechanism proposed here resembles the direct aldol reactions catalysed by L-proline and its analogues (see Chart 2).[6–8] It is presumed that the reaction proceeds *via* the formation of an enamine **III**, through the carbinolamine intermediate **II** resulting from the reaction between the glycosylamino acid **I** and acetone. The formed enamine then attacks the carbonyl carbon atom of the aldehyde group to form a C–C bond resulting in an amine–aldol intermediate **VI** with high enantiofacial selectivity. The glycosylamino acid acts as an acid/base co-catalyst and facilitates each step of the reaction comprising the nucleophilic attack of the amine to the carbonyl group of acetone, dehydration of the carbinolamine intermediate, C–C bond formation and hydrolysis of the amine–aldol to give the aldol product and regenerate the catalyst. The hydrogen bonding involving the glycosylamino acid group and the aldehyde substrate is considered to be important to the high enantioselectivity. The enantioselection in this reaction may be explained in terms of highly organised bicyclic hydrogen bonded transition states **IV** and **V**, resembling the metal free Zimmerman–Traxler type transition states.[17] The enantioselection in the reaction is due to selective *Si* facial attack of the β-carbon of the enamine. As it is clear that in transition state **V**, a 1,3-synaxial interaction between phenyl and methyl groups would disfavour the *Re* face attack, the major product would be formed *via* transition state **IV** by *Si* face attack only.

Application as organocatalyst of these β-glycosylamino acids for other addition reactions is further under study.

1. Experimental

1.1. General methods

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light and/or spraying a 20% $KMnO_4$ aq soln. Column chromatography was performed on silica gel (230–400 mesh, E. Merck). IR spectra were recorded as thin films or in chloroform soln with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-300 in $CDCl_3$. Chemical shift values are reported in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); *J* in hertz. FAB mass spectra were performed using a mass Spectrometer Jeol SX-102 and

ESI mass spectra with Quattro II (Micromass). Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer. Optical rotations were measured in a 1.0 dm tube with a Rudolf Autopol III polarimeter in $CHCl_3$. Acetone was dried and stored over anhyd K_2CO_3. Glycosylamino acid derivatives **1**–**4** were prepared by our earlier reported protocol,[15,16] however, in the present study pure diastereoisomers were isolated by column chromatography and characterised individually.

1.2. General procedure for the preparation of 5-amino-3-*O*-benzyl (methyl)-β-L-*ido*-(α-D-*gluco*)-heptofuranuronic acid derivatives (1–4)

A mixture of ethyl 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranosyl-5-enuronate (5.0 g, 14.36 mmol) and ethanolic ammonia (25 mL) was magnetically stirred in a closed vessel for 24 h. The solvent and excess of ammonia were evaporated under diminished pressure. The crude product (5.24 g), thus obtained, was chromatographed over SiO_2 column (60–120) using 6:3 hexane–EtOAc→49:1 $CHCl_3$–MeOH to give the minor isomer, ethyl 5-amino-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuro- (**4a**), 0.942 g (20%), followed by a mixture of minor and major isomers, 0.47 g (10%), and finally the major isomer (**1**), 3.29 g (70%).

1.2.1. Ethyl 5-amino-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate (1). Colourless oil; R_f 0.19 (5:2 hexane–EtOAc); $[\alpha]_D$ −59.43 (*c* 0.17, MeOH); IR (KBr): ν_{max} cm^{-1} 3390.6 (OH), 2983.7, 2831.6 (CH_3 and CH_2 str.), 1732 (COOH); ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (m, 5H, Ar*H*), 5.95 (d, 1H, *J* 3.8 Hz, H-1), 4.74, 4.42 (d, 2H, *J* 11.8 Hz, OCH_2Ph), 4.66 (d, 1H, *J* 3.8 Hz, H-2), 4.12 (q, 2H, *J* 7.12 Hz, OCH_2Me), 3.97 (dd, 1H, *J* 3.3 Hz, 7.9 Hz, H-4), 3.87 (d, 1H, *J* 3.2 Hz, H-3), 3.62 (m, 1H, H-5), 2.25 (m, 2H, H-6), 2.21 (br s, 2H, NH_2), 1.48, 1.32 (s, 6H, CMe_2), 1.25 (t, 3H, *J* 7.8 Hz, –OCH_2*Me*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.12 (C=O), 137.37, 129.09, 128.94 and 128.32 (Ar*C*), 112.09 (*C*Me_2), 105.47 (C-1), 83.77 (C-2), 82.58 (C-4), 81.96 (C-3), 72.03 (–O*C*H_2Ph), 60.82 (O*C*H_2Me), 47.82 (C-5), 38.65 (C-6), 27.14, 26.69 (CMe_2), 14.59 (–OCH_2*Me*). HRMS: Calcd for $C_{19}H_{27}O_6N$ $[M+H]^+$: 366.19166; found: *m*/*z* 366.19126.

1.2.2. 5-Amino-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-β-L-*ido*-heptofuranuronic acid (2). A mixture of ethyl 3-*O*-methyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranosyl-5-enoate (5.0 g, 18.45 mmol) and ethanolic ammonia (25 mL) was magnetically stirred in a closed vessel for 24 h. The solvent and excess of ammonia were evaporated under diminished pressure. The crude product (5.31 g), thus obtained, was chromatographed over SiO_2 column (60–120) using 1:1 hexane–EtOAc→97:3 $CHCl_3$–MeOH to give the minor isomer, ethyl 5-amino-3-*O*-methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranuronate, 0.19 g (25%), followed by a mixture of minor and major isomers, 0.954 g (20%), and finally the major isomer ethyl 5-amino-3-*O*-methyl-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranuronate 2.62 g (55%).

The above major isomer (2.62 g, 9.09 mmol), aq EtOH (50%, 30 mL) and Et_3N (25 mL) were stirred for 50 h at ambient temperature. The solvent was evaporated under diminished pressure to give a residual mass, which was subjected to column chromatography over an SiO_2 (1:9, $CHCl_3$–MeOH) to give the desired compound **2** as a colourless powder; 2.37 g, (99%); mp 200 °C; R_f 0.5 (97:3 $CHCl_3$–MeOH); $[\alpha]_D$ −48.5 (*c*, 0.175, CH_3OH); IR (KBr): ν_{max} cm^{-1} 3348.6 (OH), 2900, 2800 (CH_3 and CH_2 str.),1728 (COOH); ^1H NMR (200 MHz, $CDCl_3$): δ 5.99 (s, 1H, H-1), 4.33 (d, 1H, *J* 3.4 Hz, H-2),4.33 (d, 1H, *J* 6.5 Hz, H-4), 4.07 (d, 1H, *J* 4.9 H-3), 3.79 (m, 1H, H-5), 3.44 (s, 3H, OMe), 2.27 (m, 2H, H-6), 1.43, 1.25 (s, 6H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.50 (C=O), 111.5 (*C*Me_2), 105.19, (C-1), 83.77 (C-2), 82.57 (C-4), 81.93 (C-3), 47.81 (C-5), 38.62 (C-6), 27.13, 26.69 (CMe_2). HRMS: Calcd for $C_{17}H_{23}NO_6$ $[M+H]^+$: 262.1291; found: *m*/*z* 262.1281.

1.2.3. 5-Amino-3-*O*-benzyl-5-deoxy-β-L-*ido*-heptofuranuronic acid (3). It was obtained by hydrolysing the above compound **1** (3.29 g, 9.01 mmol) with aqueous EtOH (50%, 50 mL) and Et_3N (30 mL) for 50 h. The compound was purified by column (SiO_2, 60–120) chromatography using 1:9 $CHCl_3$–MeOH and obtained as a colourless powder; 3.04 g (99%); mp 164 °C; R_f 0.3 (49:1 $CHCl_3$–MeOH); $[\alpha]_D$ −62.5 (*c* 0.175, MeOH); IR (KBr): ν_{max} cm^{-1} 3398 (OH), 2993, 2933(CH_3 and CH_2 str.), 1620 (COOH); ^1H NMR (200 MHz, $CDCl_3$): δ 7.28–7.26 (m, 5H, ArH), 5.85 (s, 1H, H-1), 5.04 (br s, 1H, OH), 4.75–4.62 (m, 3H, H-2 and CH_2 Ph), 4.34 (s, 1H, H-4), 4.00 (s, 1H, H-3), 3.81 (s, 1H, H-5), 2.57 (m, 2H, H-6), 1.49, 1.25 (CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.36 (C=O), 135.84, 126.73, 126.20 (ArC), 109.58 (*C*Me_2), 102.86, (C-1), 79.51 (C-2), 78.55 (C-4), 77.60 (C-3), 69.24 (O*C*H_2Ph), 60.82 (O*C*H_2Me), 46.98 (C-5), 34.68 (C-6), 26.91, 26.47 (CMe_2). HRMS: Calcd for $C_{17}H_{23}NO_6$ $[M+H]^+$: 338.16036; found: *m*/*z* 338.16054.

1.2.4. 5-Amino-3-*O*-benzyl-1,2-*O*-isopropylidene-5-deoxy-α-D-*gluco*-heptofuranuronic acid (4). It was obtained by hydrolysing the above compound **4a** (0.942 g, 2.58 mmol) with aq EtOH (50%, 20 mL) and Et_3N (10 mL) for 50 h and purified by column chromatography (SiO_2, 60–120) using 1:9 $CHCl_3$–MeOH. Colourless powder 0.872 g (99%); mp 184 °C; R_f 0.3 (49:1 $CHCl_3$–MeOH); $[\alpha]_D$ +58.53 (*c*, 0.175, CH_3OH); IR (KBr): ν_{max}

cm^{-1} 3397 (OH), 2999, 2936 (CH_3 and CH_2 str.), 1629 (COOH); ^1H NMR (200 MHz, $CDCl_3$): 7.78–7.32 (m, 5H, Ar*H*), 5.91 (s, 1H, H-1), 4.77 (d, 1H, *J* 12.3 Hz, OCH_APh), 4.69 (d, 1H, *J* 12.7 Hz, OCH_BPh), 4.53 (s, 1H, H-2), 4.37 (s, 1H, H-4), 4.23 (s, 1H, H-3), 3.84 (m, 1H, H-5), 3.48 (br s, 1H, OH), 2.65 (m, 2H, H-6), 1.44, 1.25 (s, 6H, CMe_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.36 (C=O), 136.84, 126.73, 126.20, 125.7, (Ar*C*), 108.98 (*C*Me_2), 101.86 (C-1), 79.21 (C-2), 78.15 (C-4), 77.20 (C-3), 68.94 (–O*C*H_2Ph), 60.52 (O*C*H_2Me), 46.28 (C-5), 33.68 (C-6), 26.11, 25.57 (CMe_2). HRMS: Calcd for $C_{17}H_{23}NO_6$ $[M+H]^+$: 338.1604; found: *m*/*z* 338.1610.

1.3. Typical procedure for the aldol reaction

To a stirred soln in anhyd acetone (3 mL) of the required aldehyde (1 mmol), the glycosylamino acid (20 mol %) was added. The reaction mixture was stirred at ambient temperature for 12–48 h. The solvent evaporated and the residue was purified through flash column chromatography on silica gel (1:3 hexane–EtOAc) to give the pure adducts.

1.3.1. 4-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (5a). From 3-nitrobenzaldehyde (1.0 g); light yellow oil, 0.897 g (65%), R_f 0.5 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +22 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3423.2 (OH stretching) cm^{-1}; FABMS: *m*/*z* 210 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 8.24 (s, 1H, Ar*H*), 8.14 (d, 1H, *J* 8.1 Hz, Ar*H*), 7.71 (d, 1H, *J* 7.7 Hz, Ar*H*), 7.53 (t, 1H, *J* 9.2 Hz) 5.26 (m, 1H, C*H*OH), 3.60 (d, *J* 3.1 Hz, exchangeable 1H), 2.88 (m, 2H CH_2), 2.23 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.9 (C=O), 148.7, 145.5 (ArC), 132.2, 129.8, 125.2, 122.8 (Ar*C*H), 69.1 (*C*HOH), 51.9 (*C*H_2), 31.0 (*C*H_3). Enantiomeric excess 90%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), minor; t_R 3.31 and major; t_R 3.63. Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.66; H, 5.54; N, 6.59.

1.3.2. 4-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (5b). From 2-nitrobenzaldehyde (1.0 g); light yellow oil; 0.93 g (67%); R_f 0.6 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ −36 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3441.6 (OH stretching) cm^{-1}; FABMS: *m*/*z* 210 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (m, 2H, Ar*H*), 7.62, 7.39 (dd, *J* 6.5 and 0.9 Hz, 2H, Ar*H*), 5.68 (d, 1H, *J* 9.2 Hz, C*H*OH), 3.76 (br s, exchangeable 1H, –OH), 3.13 (dd, 1H, *J* 17.8 and 1.8 Hz, CH_A), 2.68 (dd, 1H, *J* 17.9, 9.8 Hz CH_B), 2.24 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.0, (C=O); 147.5, 138.9 (ArC), 134.2, 128.6, 128.5, 124.8 (Ar*C*H), 65.9 (*C*HOH), 51.5 (*C*H_2), 30.8 (*C*H_3). Enantiomeric excess 99.9%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), major; t_R 3.63. Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.56; H, 5.44; N, 6.89.

1.3.3. 4-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (5c). From 4-nitrobenzaldehyde (10 g); light yellow oil; 0.82 (60%), R_f 0.4 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +23 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3428.4 (OH stretching) cm^{-1}; FABMS: *m*/*z* 210 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 8.20 (d, 1H, *J* 8.6 Hz, Ar*H*), 7.53 (d, 1H, *J* 8.6 Hz, Ar*H*), 5.27 (m, 1H, C*H*OH), 3.69 (br s, exchangeable 1H, –O*H*), 2.83 (m, 2H, CH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.8 (C=O); 150.9, 147.5 (ArC), 126.0, 124.0 (Ar*C*H), 69.2 (*C*HOH), 51.9 (*C*H_2), 31.0 (*C*H_3). Enantiomeric excess 86%, determined by HPLC (9:1 Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), minor t_R 3.28 and major; t_R 3.71. Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.36; H, 5.14; N, 6.49.

1.3.4. 4-Hydroxy-4-(4′-fluorophenyl)-butan-2-one (5d). From 4-fluorobenzaldehyde (1.0 g); light yellow oil; 0.836 g (57%); R_f 0.5 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +19 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3443.4 (OH stretching); ESIMS: *m*/*z* 205 $[M+Na]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (m, 2H, Ar*H*), 7.01 (t, 2H, Ar*H*), 5.10 (m, 1H C*H*OH), 3.3 (br s, exchangeable 1H, –O*H*), 2.82 (m, 2H, CH_2), 2.13 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.78, (C=O), 160.0, 139.2 (ArC), 128.2, 127.7, 116.2, 115.8 (Ar*C*H), 69.4 (*C*HOH), 52.4 (*C*H_2), 31.0 (*C*H_3). Enantiomeric excess 76%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), minor; t_R 3.39 and major isomer; t_R 3.55. Anal. Calcd for $C_{10}H_{11}O_2F$: C, 65.92; H, 6.09. Found: C, 65.78; H, 6.14.

1.3.5. 4-Hydroxy-4-(4′-bromophenyl)-butan-2-one (5e). From 4-bromobenzaldehyde (1.0 g); light yellow oil 0.680 g (52%); R_f 0.6 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +15 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3431.5 (OH stretching); FABMS: *m*/*z* 241 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (dd, *J* 8.4 and 1.8 Hz, 2H, Ar*H*), 7.25 (dd, *J* 8.34 and 1.8 Hz, 2H, Ar*H*), 5.11 (m, 1H, C*H*OH), 3.42 (d, 1H, *J* 2.8 Hz, CHO*H*), 2.82 (m, 2H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.1 (C=O), 142.5 (ArC), 131.9, 127.8 (Ar*C*H), 109.9 (ArC), 69.5 (*C*HOH), 52.2 (*C*H_2), 31.1 (*C*H_3). Enantiomeric excess 3%, determined by HPLC (Chiradex column, 4:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), major; t_R 3.31 and minor; t_R 3.47. Anal. Calcd for $C_{10}H_{11}O_2Br$: C, 49.41; H, 4.56. Found: C, 49.61; H, 4.44.

1.3.6. 4-Hydroxy-4-(3′-chlorophenyl)-butan-2-one (5f). From 3-chlorobenzaldehyde (1.0 g); light yellow oil

0.833 g (59%), R_f 0.4 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +12 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3433.2 (OH stretching), ESIMS *m/z* 221 $[M+Na]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37 (s, 1H, Ar*H*), 7.29 (m, 3H, Ar*H*), 5.13 (t, 1H, *J* 9.2 Hz, C*H*OH), 3.42 (d, 1H, *J* 2.8 Hz, CHO*H*), 2.84 (m, 2H, CH_2), 2.18 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.2 (C=O), 145.2, 134.8 (ArC), 130.2, 128.1, 126.2, 124.1 (Ar*C*H), 69.5 (*C*HOH), 52.1 (CH_2), 31.1 (CH_3). Enantiomeric excess 34%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), major; t_R 3.55 and minor; t_R 3.76. Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 63.35; H, 6.50. Found: C, 63.41; H, 6.44.

1.3.7. 4-Hydroxy-4-(3′,4′,5′-trimethoxyphenyl)-butan-2-one (5g). From 3′,4′,5′-trimethoxybenzaldehyde (1.0 g); light yellow oil, 0.453 g (35%), R_f 0.4 (7:3 hexane–EtOAc) $[\alpha]_D^{27}$ +20 (*c* 0.5, $CHCl_3$); R_f 0.6 (7:3 hexane–EtOAc); IR (Neat): ν_{max} cm^{-1} 3421.9 (OH stretching), ESIMS: $m/z = 277$ $[M+Na]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 6.59 (s, 1H, Ar*H*), 5.10 (m, 1H, C*H*OH), 3.85 (s, 9H, $3\times OCH_3$), 3.3 (br s, exchangeable 1H, CHO*H*), 2.84 (m, 2H, CH_2), 2.21 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.9 (C=O), 153.7, 138.9 (ArC), 102.9 (Ar*C*H), 70.4 (*C*HOH), 61.2, 56.2 ($3\times OCH_3$) 52.5 (CH_2), 31.1 (CH_3). Enantiomeric excess 50%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), minor; t_R 3.41 and major; t_R 3.7. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.61; H, 7.44.

1.3.8. 4-Hydroxy-4-(4′-pyridyl)-butan-2-one (5h). From 4′-pyridylcarboxaldehyde (1.0 g); light brown oil 0.925 g (60%), R_f 0.2 (3:2 hexane–EtOAc); $[\alpha]_D^{27}$+15 (*c* 0.75, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3429.1 (OH stretching); ESIMS: *m/z* 166 $[M+H]^+$; ^1H NMR (200 MHz, $CDCl_3$): δ 8.51 (m, 2H, Py*H*), 7.28 (m, 2H, Py*H*), 5.16 (t, 1H, C*H*OH), 3.9 (br s, exchangeable 1H, CHO*H*), 2.82 (m, 2H, CH_2), 2.16 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.9, (C=O), 153.2 (PyC), 150.7, 149.8, 122.4, 121.1 (Py*C*H), 68.5 (*C*HOH), 52.0 (CH_2), 31.1 (CH_3) Enantiomeric excess 36%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 0.7 mL/min), minor; t_R 4.72 and major; t_R 5.07. Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.61; H, 6.44; N, 8.56.

1.3.9. 4-Hydroxy-4-(4′-chlorophenyl)-butan-2-one (5i). From 4-chlorobenzaldehyde (1.0 g); colourless oil; 0.635 g (45%); R_f 0.4 (7:3 hexane–EtOAc); $[\alpha]_D^{27}$ +15 (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} cm^{-1} 3433.2 (OH stretching); ESIMS: *m/z* 221 $[M+Na]^+$; ^{1}HNMR (200 MHz, $CDCl_3$): δ 7.30–7.26 (s, 4H, Ar*H*), 5.11 (t, 1H, *J* 8.08 Hz C*H*OH), 3.85 (br s, exchangeable 1H, CHO*H*), 2.80 (m, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.2 (C=O), 141.7, 133.7 (ArC), 129.0, 127.4 (ArCH), 69.5 (*C*HOH), 52.2 (CH_2), 31.1 (CH_3). Enantiomeric excess 77%, determined by HPLC (Chiradex column, 9:1 MeCN–water, UV 254 nm, flow rate 1.0 mL/min), minor isomer; t_R 2.40 and major isomers; t_R 2.56. Anal. Calcd for $C_{10}H_{11}O_2Cl$: C, 63.35; H, 6.50. Found: C, 63.54; H, 6.68.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.08.007.

References

1. Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601.
2. (a) Evans, D. A.; Nelson, J. V.. In *Topics in Stereochemistry*; John Wiley and Sons: New York, 1982; Vol. 13, p 1; (b) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123; (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111; (d) Evans, D. A.; Batroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
3. (a) Heathcock, C. H.. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, p 111; (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247–248; (c) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076–7077; (d) Danda, H.; Hanesan, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173–181.
4. (a) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2 (Heathcock, C. H., Ed.), Chapter 1.7, pp 239–275; (b) Masamune, S.; Ali, S.; Snitman, D.; Garvey, D. S. *Angew. Chem.* **1980**, *92*, 573–575; (c) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568; (d) Masamune, S.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281.
5. (a) Mukaiyama, T.. In *The Directed Aldol Reaction in Organic Synthesis*; John Wiley and Sons: New York, 1982; Vol. 28, p 203; (b) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, *9*, 1011–1013; (c) Mukaiyama, T.; Narasaka, K.; Banno, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509; (d) Kobayashi, S.; Uchiro, H.; Shiina, I.; Sato, T.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761–1772.
6. (a) Wagner, J.; Lerner, R. A.; Barbas, C. F., III *Sciences* **1995**, *270*, 1797–1800; (b) Bjornestedt, R.; Zhong, G.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1996**, *118*, 11720–11724; (c) Zhong, G.; Gofffman, T.; Lerner, R.

A.; Danishefsky, S.; Barbas, C. F., III *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132; (d) Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffman, T.; Gramatikova, S.; Bjornestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, I. A.; Lerner, R. A. *Science* **1997**, *278*, 2085–2092; (e) Hoffman, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779; (f) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner, R. A., ; Barbas, C. F., III *Angew. Chem., Int. Ed.* **1998**, *37*, 2481–2484; (g) Sinha, S. C.; Barbas, C. F., III; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14603–14608; (h) List, B.; Lerner, R. A.; Barbas, C. F., III *Org. Lett.* **1999**, *1*, 59–62; (i) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **1999**, *121*, 7283–7291; (j) Zhong, G.; Lerner, R. A.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **1999**, *38*, 3738–3741; (k) Tanaka, F.; Barbas, C. F., III *Chem. Commun.* **2001**, *8*, 769–770; (l) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (m) Cordova, A.; Notz, W.; Zhong, G.; Bctancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843.

7. (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Wei-Wei, L. *Chem. Commun.* **2005**, 3586–3587; (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946–4948; (c) Xu, Y.; Córdova, A. *Chem. Commun.* **2006**, 460–462; (d) Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem. Eur. J.* **2005**, *11*, 7024–7029; (e) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7028–7032; (f) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38–42.
8. Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *45*, 958–961.
9. (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96; (c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961; (d) Kumargurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (e) Bogevig, A.; Juhl, K.; Kumargurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793.
10. (a) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027–1031; (b) Limbach, M. *Tetrahedron Lett.* **2006**, *47*, 3843–3847; (c) Chandrasekhar, S.; Reddy, N. R.; Sultana, S. S.; Narsihmulu, Ch.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338–345; (d) Zheng, Y.; Avery, M. A. *Tetrahedron* **2004**, *60*, 2091; (e) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
11. Fubini, B.; Arean, L. O. *Chem. Soc. Rev.* **1999**, *28*, 373–382.
12. Tang, Z.; Jiang, F.; Yang, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.
13. (a) Dieguez, M.; Pamies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189–3215; (b) Aghmiz, M.; Aghmiz, A.; Diaz, T.; Masedeu, B. A.; Claver, C.; Castillon, S. *J. Org. Chem.* **2004**, *69*, 7502–7510; (c) Dieguez, M.; Pamies, O.; Diaz, Y.; Ruiz, A.; Claver, C.; Castillon, S. *Coord. Chem. Rev.* **2004**, *248*, 2165–2192; (d) Guiu, E.; Munoz, B.; Castillon, S.; Claver, C. *Adv. Synth. Catal.* **2003**, *345*, 169–171.
14. (a) Castillon, S.; Claver, C.; Diaz, Y. *Chem. Soc. Rev.* **2005**, *34*, 702–713; (b) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem. Eur. J.* **2001**, *7*, 3086–3094; (c) Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C. *Chem. Comm.* **2000**, 1607–1608.
15. Tripathi, R. P.; Tripathi, R.; Tiwari, V. K.; Bala, L.; Sinha, S.; Srivastva, A. K.; Srivastava, R.; Srivastava, B. S. *Eur. J. Med. Chem.* **2002**, *37*, 773–779.
16. Tripathi, R. P.; Tiwari, V. K.; Mishra, R. C.; Reddy, V. J. M.; Saxena, J. K. *J. Carbohydr. Chem.* **2002**, *21*, 591–604.
17. Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, Benjamin *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479.