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Non-enzymatic kinetic resolution of β-amino alcohols using C-12 higher carbon sugar as a chiral auxiliary

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Abstract—An efficient non-enzymatic kinetic resolution strategy capable of accessing optically active β-adrenergic antagonists intermediates is reported. The C-12 higher carbon sugar derived from naturally occurring sucrose was employed to probe the kinetic resolution. Excellent enantiomeric excesses (ee >99%) and high yields were obtained under very mild conditions. The chiral auxiliary could be recovered in a high reclaimed ratio (>95%) and reusable form without any decrease of the resolving ability.

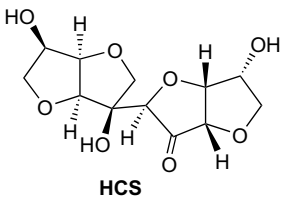
1. Introduction

Chiral β-amino alcohols are important structural elements in chiral ligands for asymmetric catalysis[1] as well as in biologically active compounds (e.g., β-adrenergic receptor blockers, which have a diverse range of clinical applications in the treatment of cardiovascular disorders such as hypertension, cardiac arrhythmia, angina pectoris, and open angle glaucoma).[2] The preparation of optically active β-amino alcohols has received considerable attention due to their different pharmacokinetic characteristics or the pharmacological activities of each enantiomer in a racemic drug[3–6] and their extensive use as chiral auxiliaries, resolving reagents, and intermediates in the synthesis of biologically important molecules.

Enantiopure β-amino alcohols can be produced by the reduction of optically active β-amino acids.[7] The kinetic resolution of β-amino alcohols through enzyme-catalyzed acylation or deacylation is also one of the most efficient methods for the synthesis of chiral β-amino alcohols.[8] Non-enzymatic kinetic resolution (NKR) is an alternative for the enzymatic process, which is considered to be a challenging issue in organic synthesis. In contrast to the large variety of enzymes and metallic catalysts reported for the kinetic resolution (KR) of racemic amino alcohols over the last decade,[9] non-enzymatic kinetic resolution methods designed for amino alcohols are rarely reported. In recent years, some effort has therefore been made to design non-enzymatic alternatives and substantial progress has been made.[10] However, most methods suffer from the multistep synthesis of chiral auxiliaries and often provide only moderate enantioselectivities.

2. Results and discussion

In our previous work, we reported a novel C-12 higher carbon sugar (denoted as HCS)[11] containing eight stereogenic centres and a two 'back to back' V-shaped molecule framework (Fig. 1). With a view to the stereochemistry of HCS, further investigations were carried out. Herein, we report the high enantioselective non-enzymatic kinetic resolution of β-amino alcohols through the formation of oxazolidine derivatives of HCS. To the best of our knowledge, no work



HCS

Figure 1. The structure of a higher carbon sugar (HCS).

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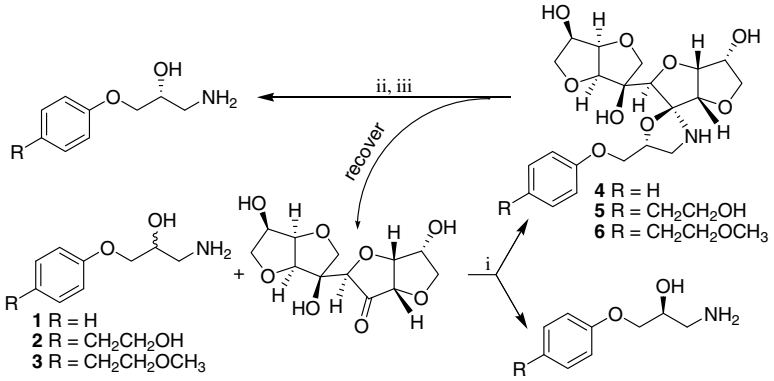


Scheme 1. Kinetic resolution of β-amino alcohols **1**, **2**, and **3**. Reagents and conditions: (i) TsOH, CH_3OH, rt; (ii) 4% hydrochloric acid, rt; (iii) 5% KOH, rt.

has been reported on the NKR of β-amino alcohols using higher carbon sugars, which were generally focused on their biological activity.[12] This procedure could be applied to the enantioselective synthesis of different intermediates of β-adrenergic receptor blockers, which are important precursors for biologically active compounds,[13] for example, betaxolol and metoprolol.

The reaction of racemic β-amino alcohols **1**, **2**, and **3** with HCS was performed in the presence of *p*-TsOH in various organic solvents such as ethanol, methanol, and isopropanol at room temperature, respectively. The carbonyl group of HCS showed an excellent reactivity and stereoselectivity toward (*R*)-isomers formed to give the corresponding oxazolidines **4**, **5**, and **6**, which were then crystallized from organic solvents. The crystallized oxazolidines **4**, **5**, and **6** obtained by filtration were then acidified to yield (*R*)-isomers. The solvent of the filtrate was evaporated under reduced pressure to afford (*S*)-isomers (Scheme 1).

The single crystals of oxazolidines **4** and **5** were obtained by recrystallization from methanol. The ORTEP drawing of **4** and **5** are shown in Figure 2. The configurations of β-carbon in **4** and **5** are (*R*) as shown in Scheme 1. The configuration of β-carbon in oxazolidine **6** was confirmed to be (*R*) by comparison with **4** and **5**. Therefore, the absolute configuration of the corresponding amino alcohols **1**, **2**, and **3** were deduced to be (*R*), while the isomers **1**, **2**, and **3** which remained in solution were accordingly deduced to be (*S*). Noticeably, for the specific rotations of **1**[14] we obtained results that were consistent with the results reported by Ulrich and Manfred,[15] but opposite to those reported by Zhang et al.[16]

To improve the yield and enantiomeric purity of the amino alcohols, we tested possible factors which could influence the process, such as molar ratios of racemic amino alcohol to HCS and temperature. It was found that the enantiomeric purity of the amino alcohols was highly dependent on the ratio of the racemic amino alcohol to HCS (Table 1). When the ratio of racemic amino alcohol to HCS was no less than 1:0.49, the corresponding oxazolidines **4**, **5**, and **6** were obtained in good yields. Anything less than this ratio led to a decrease in the enantiomeric purities of the

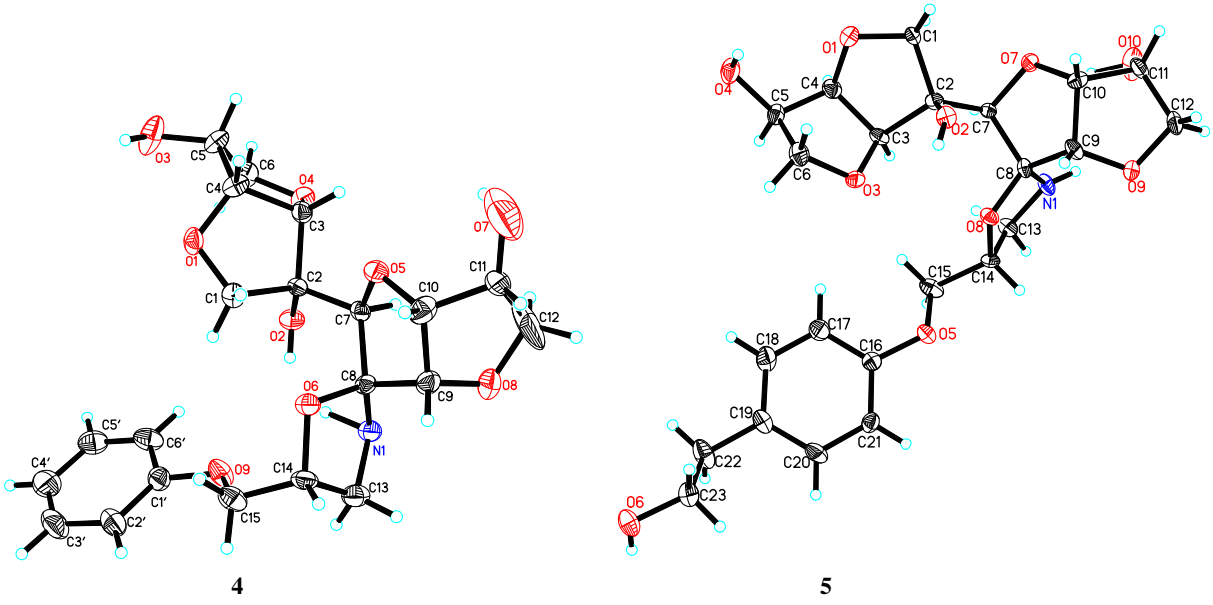
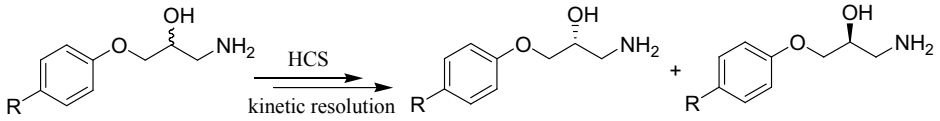


Figure 2. ORTEP diagram showing the X-ray structures of compounds **4** and **5**.

Table 1. Effect of the molar ratio of β-amino alcohols/HCS in the NKR of β-amino alcohols[a]



1 R = H, **2** R = CH_2CH_2OH, **3** R = $CH_2CH_2OCH_3$

Entry	A[b]	Mol ratio (A/HCS)	(*R*)		(*S*)	
			Yield[c] (%)	ee[d] (%)	Yield[c] (%)	ee[d] (%)
1	1	1:0.45	38.0	>99	47.0	78
2	1	1:0.49	40.5	>99	42.5	89
3	1	1:0.50	45.0	95	47.5	92
4	1	1:0.51	42.0	87	40.1	>99
5	1	1:0.55	46.5	82	37.5	>99
6	2	1:0.45	38.5	>99	46.2	75
7	2	1:0.49	39.5	>99	38.5	83
8	2	1:0.50	43.5	86	43.0	93
9	2	1:0.51	40.5	90	39.5	>99
10	2	1:0.55	45.5	80	36.6	>99
11	3	1:0.45	42.0	>99	45.0	78
12	3	1:0.49	39.0	>99	37.5	86
13	3	1:0.50	40.0	94	41.0	90
14	3	1:0.51	39.0	89	38.5	>99
15	3	1:0.55	43.4	86	40.0	>99

[a] At 25 °C.
[b] β-Aminoalcohols.
[c] Isolated yield based on the amount of racemates.
[d] Determined by HPLC using a Chiralcel OD-H columns.

(*R*)-isomers dissociated from the corresponding oxazolidines. When the ratio of racemic amino alcohol to HCS was no more than 1:0.51, the enantiomerically pure (*S*)-isomers, which were left in the solution after removing compounds **4**, **5**, and **6** were obtained. The lower enantiomeric purities were obtained when the ratio of racemic amino alcohol to HCS was above 1:0.51.

For the sake of comparison, the reaction of amino alcohols with HCS was performed in a ratio of 1:0.51 to test the effects of temperature on the resolution. As shown in Table 2, the enantiomeric excesses of amino alcohols were drastically increased when the temperature was changed from 50 °C to 25 °C. Below 25 °C, the isolated yield and enantiomeric excesses of amino alcohols were increased with a decrease of the temperature. At the same time, the reaction time was prolonged with the decrease of the temperature. At the optimized temperature (5 °C), treatment of **1**, **2**, and **3** (1 equiv) with HCS (0.51 equiv) in methanol in the presence of *p*-TsOH gave compounds **4**, **5**, and **6**, respectively, in good yields and the (*S*)-isomers of the amino alcohols with excellent enantiomeric excesses.

Table 2. Effect of on the NKR of β-amino alcohols[a]

Entry	A[b]	Temperature (°C)	Time (h)	Yields[c] (%)	ee[d] (%)	Conf.
1	1	0	40	45.5	96	(*S*)
2	1	0	20	44.1	>99	(*S*)
3	1	25	6	40.1	>99	(*S*)
4	1	50	3	38.1	55	(*S*)
5	2	0	46	44.4	96	(*S*)
6	2	5	30	45.0	>99	(*S*)
7	2	25	9	39.5	>99	(*S*)
8	2	50	5	35.1	39	(*S*)
9	3	0	48	44.2	94	(*S*)
10	3	5	35	43.6	>99	(*S*)
11	3	25	10	38.5	>99	(*S*)
12	3	50	5	37.5	43	(*S*)

[a] Molar ratio of amino alcohol/HCS = 1:0.51.
[b] β-Amino alcohols.
[c] Isolated yield based on the amount of racemates.
[d] Determined by HPLC using a Chiralcel OD-H columns.

The investigation indicated that the reactive temperature and the molar ratios of racemic amino alcohols to HCS played an important role in the KR of β-amino alcohols, especially the latter. Using the optimized reaction conditions for each particular racemic amino alcohol, β-amino alcohols **1**, **2**, and **3** were resolved with very excellent enantioselectivities. It is worth noting that the chiral auxiliary could be efficiently recovered in a reusable form by

Table 3. Resolving effect of **1** using reclaimed HCS[a]

Entry	R-T[b]	Yields[c] (%)	R-P[d] (%)	ee[e] (%)	Conf.
1	0	42.5	98.2	>99	(*R*)
2	1	41.7	97.5	>99	(*R*)
3	2	40.1	96.4	>99	(*R*)
4	3	43.0	95.7	>99	(*R*)
5	4	40.8	95.4	>99	(*R*)

[a] At 5 °C; molar ratio of amino alcohol/HCS = 1:0.49.
[b] Reclaimed times.
[c] Isolated yield based on the amount of racemates.
[d] Reclaim proportion of HCS.
[e] Determined by HPLC using a Chiralcel OD-H columns.

hydrolytic decomposition of the corresponding oxazolidines with a high yield (>95.0%) without any decrease of the resolving ability. The results of an investigation on the resolving effect of β-amino alcohol **1** using reclaimed HCS are displayed in Table 3.

3. Conclusions

In conclusion, the novel C-12 higher carbon sugar derived from naturally occurring sucrose was employed to probe the non-enzymatic kinetic resolution reaction of a series of β-amino alcohols. This protocol was carried out under very mild conditions and the results were excellent (ee >99%). More importantly, the chiral auxiliary could be efficiently recovered in a reusable form, without any decrease in the resolving ability. Owing to its high efficiency and convenience, this method will lead to many new applications in the synthesis of chiral drugs. Further investigations to broaden the scope and synthetic application of this new enantioselective NKR are under progress.

4. Experimental

4.1. General

All chemicals were used as received unless otherwise noted. Reagent grade solvents were distilled prior to use. All reported NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as the internal reference. Infrared spectra were recorded on Nicolet IR200 instrument using KBr disks in the 400–4000 cm^{-1} regions. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof Micro™ instrument using the ESI technique. Melting points were determined using a XT5A apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter at 20 °C in MeOH. Single crystal structure was carried out on a Rigaku R-AXIS-IV area detector. Enantiomeric excess was determined by chiral HPLC at room temperature using Syltech 500 pump equipped with a UV 500 version 4.1 ultra-violet detector with Chiralcel OD-H (4.6 mm × 250 mm) column.

4.2. Preparation and characterization of β-amino alcohols

4.2.1. General procedure for the preparation of β-amino alcohols 1, 2, and 3. Racemic amino alcohol **1** was prepared from the reaction of ammonia with glycidphenylether. Racemic amino alcohols **2** and **3** were prepared from epichlorohydrin via two steps as shown in Scheme 2. The corresponding substituted phenol (0.1 mol) was added to a solution of epichlorohydrin (0.5 mol) in the presence of K_2CO_3 (0.2 mol) in acetone (100 ml) with stirring. The mixture was heated and kept at reflux for 6–10 h followed by filtration and then concentration under vacuum pressure to dryness. The residue was then mixed with superfluous 25–28% NH_3 aq and the reaction mixture was further stirred for 10–15 h at 0–10 °C. Water and excess NH_3 were then removed under vacuum. The residue was dissolved with ethanol after which water was added, subsequently, a lot of white deposition appears. The mixture was filtered and then pure racemic amino alcohols were obtained by recrystallization from ethyl acetate or ethanol in 72–80% yields.

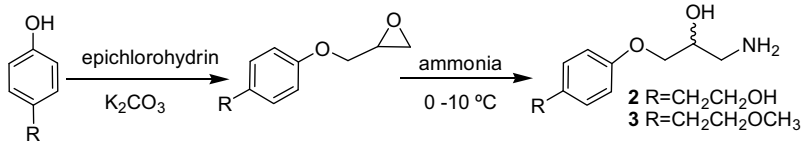
4.3. Characterization of amino alcohols

4.3.1. 1-Amino-3-(4-(2-hydroxyethyl)phenoxy)propan-2-ol 2. Mp 102–103 °C IR (KBr): 3325, 3041, 2938, 2881, 1610, 1512, 1425, 1046 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.18 (d, 2H, $J = 8.6$ Hz, H-3 and H-5, Ph), δ 6.92 (d, 2H, $J = 8.6$ Hz, H-2 and H-6, Ph), 4.21 (m, 1H, $NH_2CH_2CHCH_2$), 4.08 (dd, 1H, $J = 3.9$, 10.3 Hz, CH_aH_b-O–Ph), 4.03 (dd, 1H, $J = 5.5$, 10.2 Hz, CH_aH_bO–Ph), 3.73 (t, 2H, $J = 6.6$ Hz, $HOCH_2CH_2Ph$), 3.23 (dd, 1H, $J = 3.8$, 13.2 Hz, $NH_2CH_aH_bCH$), 3.11 (dd, 1H, $J = 8.3$, 13.2 Hz, $NH_2CH_aH_bCH$), 2.74 (t, $J = 6.6$ Hz, $HOCH_2CH_2Ph$) ^{13}C NMR (100.6 MHz, D_2O): δ 156.8 (C-1 Ph), 132.6 (C-4 Ph), 130.6 (C-3,5 Ph), 115.2 (C-2,6 Ph), 70.1 (CH_2O–Ph), 66.6 ($NH_2CH_2CHCH_2$), 63.0 ($HOCH_2CH_2Ph$), 42.2 ($CHCH_2NH$), 37.3 ($HOCH_2CH_2Ph$); HRMS: calcd for $C_{11}H_{17}NO_3$: 211.1208. Found: 212.1265 $[M+H]^+$.

4.3.2. 1-Amino-3-(4-(2-methoxyethyl)phenoxy)propan-2-ol 3. Mp 98–99 °C IR (KBr): 3355, 2926, 2871, 1582, 1513, 1119 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.12 (d, 2H, $J = 8.3$ Hz, H-3 and H-5, Ph), δ 6.84 (d, 2H, $J = 8.4$ Hz, H-2 and H-6, Ph), 3.91 (dd, 1H, $J = 3.9$, 10.3 Hz, CH_aH_bO–Ph), 3.84 (dd, 1H, $J = 5.5$, 10.2 Hz, CH_aH_bO–Ph), 3.73 (m, 1H, $NH_2CH_2CHCH_2$), 3.47 (t, 2H, $J = 6.9$ Hz, $HOCH_2CH_2Ph$), 3.23 (s, 1H, CH_2OCH_3), 3.17 (m 2H, NH_2CH_2CH), 2.72 (t, $J = 6.8$ Hz, $HOCH_2$-CH_2Ph) ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 158.0 (C-1 Ph), 131.7 (C-4 Ph), 130.5 (C-3,5 Ph), 115.1 (C-2,6 Ph), 73.9 (CH_2O–Ph), 71.2 ($NH_2CH_2CHCH_2$), 71.1 ($HOCH_2$-CH_2Ph), 58.6 (CH_3OCH_2), 45.6 ($CHCH_2NH$), 35.3 ($HOCH_2CH_2Ph$); HRMS: calcd for $C_{12}H_{19}NO_3$: 225.1365. Found: 226.2901 $[M+H]^+$.

4.4. Preparation and characterization of oxazolidine derivatives 4, 5, and 6

4.4.1. Preparation and characterization of oxazolidine 4. To a solution of HCS (2.82 g, 9.8 mmol) in methanol (40 ml), racemic amino alcohol **1** (1-amino-3-phenyloxy-2-propanol) (20.0 mmol) was added (a catalytic amount



Scheme 2. Preparation of amino alcohols **2** and **3**.

of *p*-TsOH was also added). The mixture was stirred at 5 °C for 20 h, followed by concentration and purification by crystallization from isopropanol or ethanol, giving compound **4** as white solids in 98.5% yield (determined based on HCS). Mp 121–123 °C, $[\alpha]_D^{20} = +58.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3407, 3285, 2925, 2880, 1632, 1596, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 2H, H-3 and H-5, Ph), 6.98 (t, 1H, $J = 7.4$ Hz, H-4, Ph), 6.92 (d, 2H, $J = 8.4$ Hz, H-2 and H-6, Ph), 4.67 (t, 1H, $J = 4.4$ Hz, H-10), 4.65 (d, 1H, $J = 6.4$ Hz, H-3), 4.45 (t, 1H, $J = 6.0$ Hz, H-4), 4.39 (m, 1H, C*H*CH_2OPh), 4.31 (dd, 1H, $J = 6.0$, 11.6 Hz, H-11), 4.26 (d, 1H, $J = 4.4$ Hz, H-9), 4.18 (d, 1H, $J = 10.6$ Hz, H-1a), 4.14 (dd, 1H, $J = 5.2$, 9.6 Hz, H-5), 4.13 (d, 1H, $J = 10.6$ Hz, H-1b); 4.08 (dd, 1H, $J = 5.6$, 9.6 Hz, C$H_a$$H_b$O–Ph), 4.08 (s, 1H, H-7), 4.00 (dd, 1H, $J = 6.4$, 9.4 Hz, H-12a), 3.98 (dd, 1H, $J = 5.6$, 9.6 Hz, $CH_a$$H_b$O–Ph), 3.93 (dd, 1H, $J = 4.8$, 9.4 Hz, H-6b), 3.85 (dd, 1H, $J = 4.8$, 9.4 Hz, H-6a), 3.64 (dd, 1H, $J = 6.4$, 9.4 Hz, H-12b), 3.30 (dd, 1H, $J = 7.2$, 12.0 Hz, HNC$H_a$$H_b$CH), 3.22 (dd, 1H, $J = 4.0$, 12.0 Hz, HNC$H_a$$H_b$CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (C-1 Ph), 129.5 (C-3,5 Ph), 121.3 (C-4 Ph), 114.5 (C-2,6 Ph), 105.1 (C-8), 85.3 (C-9), 84.0 (C-3), 82.1 (C-7), 81.6 (C-4), 81.2 (C-10), 79.5 (C-2), 77.2 (C-1), 75.5 (*C*HCH$_2$OPh), 75.3 (C-12), 73.7 (C-6), 72.7 (C-5), 70.8 (C-11), 68.5 (–*C*H$_2$OPh), 47.3 (CH*C*H$_2$NH); HRMS: calcd for $C_{21}H_{27}NO_9$: 437.1686. Found: 438.1740 $[M+H]^+$.

4.4.2. Preparation and characterization of oxazolidine 5. The same process as for the preparation of **4** was carried out. Compound **5** was obtained as a white solid (yield 96.3%). Mp 156–157 °C, $[\alpha]_D^{20} = +67.3$ (*c* 1.00, CH_3OH); IR (KBr): 3469, 3408, 3287, 2934, 2874, 1614, 1512, 1421, 1235, 1083, 1043 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.13 (d, 2H, $J = 8.5$ Hz, H-3 and H-5, Ph), 6.83 (d, 2H, $J = 8.5$ Hz, H-2 and H-6, Ph), 4.60 (d, 1H, $J = 5.4$ Hz, H-9), 4.54 (t, 1H, $J = 4.5$ Hz, H-4), 4.35 (m, 1H, HNCH$_2$C*H*CH$_2$), 4.26 (m, 2H, H-3, H-10), 4.25 (dd, 1H, H-5, $J = 5.2$, 9.3 Hz), 4.11 (m, 1H, H-11), 3.99 (dd, 1H, $J = 3.4$, 10.2 Hz, $CH_a$$H_b$O–Ph), 3.97 (s, 1H, H-7), 3.90 (dd, 1H, $J = 3.4$, 10.2 Hz, C$H_a$$H_b$O–Ph), 3.89 (d, 1H, $J = 8.5$ Hz, H-1b), 3.87 (m, 1H, H-6b) 3.84 (d, 1H, $J = 8.5$ Hz, H-1a), 3.81 (dd, 1H, $J = 6.0$, 8.5 Hz, H-12b), 3.65 (t, 2H, $J = 6.6$ Hz, HOCH_2CH$_2$Ph), 3.42 (dd, 1H, $J = 6.0$, 8.5 Hz, H-12b), 3.41 (m, 1H, H-6a), 3.09 (dd, 1H, $J = 7.4$, 12.4 Hz, HNC$H_a$$H_b$CH), 3.03 (dd, 1H, $J = 4.2$, 12.4 Hz, HNC$H_a$$H_b$CH), 2.66 (t, $J = 6.6$ Hz, HOCH$_2$CH_2Ph); ^{13}C NMR (100 MHz, D_2O): δ 156.3 (C-1 Ph), 131.9 (C-4 Ph), 130.1 (C-3,5 Ph), 115.0 (C-2,6 Ph), 104.6 (C-8), 85.5 (C-9), 83.6 (C-10), 81.0 (C-3), 80.8 (C-2), 80.7 (C-7), 80.6 (C-4), 75.3 (*C*HCH$_2$OPh), 74.6 (C-1), 72.0 (C-5), 71.2 (C-6), 70.8 (C-12), 70.5 (C-11), 69.2 (–*C*H$_2$OPh), 62.5 (HO*C*H$_2$CH$_2$Ph), 45.6 (CH*C*H$_2$NH), 36.8 (HOCH$_2$*C*H$_2$Ph); HRMS: calcd for $C_{23}H_{31}NO_{10}$: 481.1948. Found: 482.2026 $[M+H]^+$.

4.4.3. Preparation and characterization of oxazolidine 6. The same process as for the preparation of **4** was carried out and compound **6** was obtained as a white solid (yield 94.0%). Mp 135–136 °C, $[\alpha]_D^{20} = +25.6$ (*c* 0.8, CH_3OH); IR (KBr): 3417, 2932, 2878, 1611, 1512, 1243, 1114, 1050 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.15 (d, 2H, $J = 8.4$ Hz, H-3 and H-5, Ph), 6.88 (d, 2H, $J = 8.5$ Hz, H-2 and H-6, Ph), 4.65 (d, 1H, $J = 4.2$ Hz, H-9), 4.59 (t, 1H, $J = 4.5$ Hz, H-4), 4.35 (m, 1H, HNCH$_2$C*H*CH$_2$), 4.30 (m, 2H, H-3, H-10), 4.29 (m, 1H, H-5), 4.15 (m, 1H, H-11), 4.00 (s, 1H, H-7), 3.99 (m, 1H, $CH_a$$H_b$O–Ph), 3.96 (d, 1H, $J = 8.5$ Hz, H-1b), 3.95 (m, 1H, H-6b), 3.93 (dd, 1H, $J = 4.3$, 6.9 Hz, C$H_a$$H_b$O–Ph), 3.91 (d, 1H, $J = 8.5$ Hz, H-1a), 3.85 (dd, 1H, $J = 6.6$, 8.4 Hz, H-12b), 3.59 (t, 2H, $J = 6.6$ Hz, HOCH_2CH$_2$Ph), 3.50 (dd, 1H, $J = 6.6$, 8.4 Hz, H-12b), 3.49 (m, 1H, H-6a), 3.23 (s, 3H, CH_2OCH_3), 3.13 (dd, 1H, $J = 7.3$, 12.3 Hz, HNC$H_a$$H_b$CH), 3.08 (dd, 1H, $J = 4.2$, 12.3 Hz, HNC$H_a$$H_b$CH), 2.74 (t, $J = 6.5$ Hz, HOCH$_2$CH_2Ph); ^{13}C NMR (100 MHz, D_2O): δ 156.9 (C-1 Ph), 132.3 (C-4 Ph), 130.4 (C-3,5 Ph), 115.2 (C-2,6 Ph), 105.0 (C-8), 86.0 (C-9), 84.1 (C-10), 81.6 (C-3), 81.5 (C-2), 81.3 (C-7), 81.1 (C-4), 75.7 (*C*HCH$_2$OPh), 75.2 (C-1), 73.5 (CH_2OCH_3), 72.4 (C-5), 71.7 (C-6), 71.3 (C-12), 71.0 (C-11), 69.6 (–*C*H$_2$OPh), 58.1 (HO*C*H$_2$CH$_2$Ph), 46.2 (CH*C*H$_2$NH), 34.4 (HOCH$_2$*C*H$_2$Ph); HRMS: calcd for $C_{23}H_{31}NO_{10}$: 495.5195. Found: 518.2002 $[M+Na]^+$.

4.5. Liberation of (*R*)-isomers of amino alcohols 1, 2, 3 from compounds 4, 5, and 6

4.5.1. General method. 1 mmol of the crystals of oxazolidine derivatives obtained was dissolved in 20 ml of methanol after which 5.0 mmol *c*. HCl aq was added. After the evaporation of methanol, 10 ml of water was added and the mixture was stirred for 30 min, then HCS was recovered by extracting using toluene or ethyl acetate. Then 2.5 mmol NaOH was added in the water layer (pH 10), after which the amino alcohols were extracted using toluene. The toluene solution was dried over Na_2SO_4 and removed by filtration. The solvent was removed to yield the resoluted β-amino alcohols recrystallized from ethyl acetate or ethanol.

4.5.2. HPLC conditions of resolved amino alcohols

4.5.2.1. HPLC conditions for amino alcohol 1. *n*-Hexane/isopropanol/diethylamine = 70:30:0.05, OD-H, 0.3 ml/min, 254 nm.

(*S*)-**1**, $[\alpha]_D^{25} = -3.9$ (*c* 1.0, methanol), >99% ee, $t_S = 35.7$.

(*R*)-**1**, $[\alpha]_D^{25} = +3.9$ (*c* 1.0, methanol), >99% ee, $t_R = 16.2$.

4.5.2.2. HPLC conditions for amino alcohol 2 and 3. *n*-Hexane/isopropanol/diethylamine = 60:40:0.05, OD-H, 0.5 ml/min, 254 nm.

(*S*)-**2**, $[\alpha]_D^{25} = -4.0$ (*c* 1.0, methanol), >99% ee, $t_S = 16.7$.

(*R*)-**2**, $[\alpha]_D^{25} = +4.0$ (*c* 1.0, methanol), >99% ee, $t_R = 13.3$.

(*S*)-**3**, $[\alpha]_D^{25} = -6.8$ (*c* 1.0, methanol), >99% ee, $t_S = 19.1$.

(*R*)-**3**, $[\alpha]_D^{25} = +6.8$ (*c* 1.0, methanol), >99% ee, t_R=15.8.

4.5.3. Effect of temperature on the NKR of β-amino alcohols in a ratio of 1:0.49 of β-amino alcohols and HCS. See Table 4.

Table 4. Effect of temperature on the NKR of β-amino alcohols[a] in a ratio of 1:0.49 of β-amino alcohols and HCS

Entry	Amino alcohols	*T* (°C)	Time (h)	Yields[b] of (*R*) (%)	ee[c] of (*R*) (%)
1	1	0	40	44.5	95
2	1	5	20	44.2	>99
3	1	25	6	40.5	>99
4	1	50	3	38.5	53
5	2	0	45	46.0	96
6	2	5	30	44.3	>99
7	2	25	9	39.5	>99
8	2	50	5	35.0	42
9	3	0	46	45.0	93
10	3	5	35	42.6	>99
11	3	25	10	39.0	>99
12	3	50	5	37.8	51

[a] Molar ratio of amino alcohol/HCS = 1:0.49.
[b] Isolated yield based on the amount of racemates.
[c] Determined by HPLC using a Chiralcel OD-H columns.

4.5.4. X-ray crystallographic data of compounds 4 and 5. Crystals of compounds **4** and **5** suitable for X-ray analysis were obtained by recrystallization from methanol at room temperature. Crystallographic data (excluding structure factors) for the structure reported in this paper have been checked using the CheckCIF utility on the Web at http://checkcif.iucr.org/ and there were no syntax errors (Fig. 1).

Crystallographic data for **4** and **5** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-622932 and CCDC-670555. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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14. Specific rotations we have obtained are (*R*)-**1** $[\alpha]_D^{25} = +3.9$ (*c* 1.0, methanol), (*S*)-**1**: $[\alpha]_D^{25} = -3.9$ (*c* 1.0 methanol).
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