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Asymmetric syntheses of *N*-substituted α-amino esters via dynamic kinetic resolution of α-haloacyl diacetone-D-glucose

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Abstract—Diacetone-D-glucose or D-allose mediated dynamic kinetic resolution of α-halo esters in nucleophilic substitution reaction has been investigated. Reactions with various amine nucleophiles in the presence of TBAI and DIEA can provide the *N*-substituted α-amino esters up to 99:1 dr. Stereochemical models of transition states, taking into account a hydrogen bonding, are proposed on the basis of the observed results. Also, application of this mild and simple methodology to stereoselective preparations of 1,1′-iminodicarboxylic acid derivatives is demonstrated.
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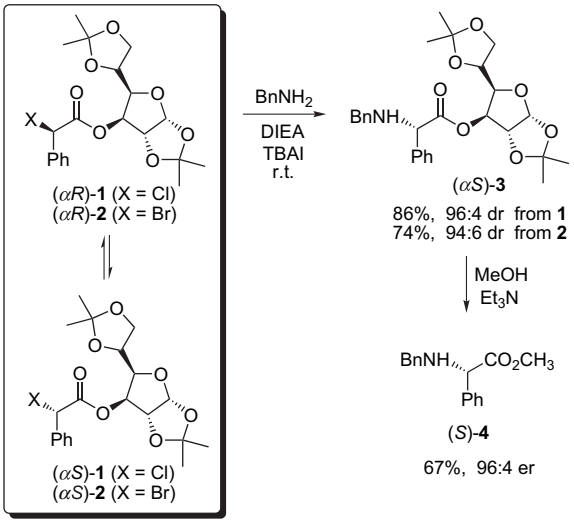
1. Introduction

During the last decade, intensive efforts have been devoted to develop the chiral auxiliary mediated dynamic resolution of α-halo esters or α-halo amides in nucleophilic substitution.[1] For asymmetric syntheses of α-amino acid derivatives, recent studies in our laboratory have focused on the development of a practical chiral auxiliary for dynamic resolution of α-haloacyl compounds under mild and simple reaction conditions amenable to easily scalable processes. Carbohydrates are readily available and inexpensive natural products in which numerous functional groups and stereogenic centers are present in a molecule. Despite their stereochemical and structural complexities, a large number of carbohydrate based templates have been systematically developed and used as chiral auxiliaries and chiral ligands for various stereoselective reactions.[2,3] Earlier we outlined our preliminary results in dynamic kinetic resolution of α-chloro-α-aryl esters using diacetone-D-glucose as a chiral auxiliary.[4] Herein we describe our recent progress to extend the scope of the methodology to various α-halo esters and to understand the mechanism of the asymmetric nucleophilic substitution. Application of this methodology to highly stereoselective preparation of 1,1′-iminodicarboxylic acid derivatives is also presented.

2. Results and discussion

We have previously reported that the treatment of α-chloro-α-phenyl acetate **1** with benzylamine (1.2 equiv), tetrabutylammonium iodide (1.0 equiv, TBAI), and diisopropylethylamine (1.0 equiv, DIEA) in CH_2Cl_2 at room temperature provided the substitution product **3** in 86% yield with 96:4 diastereomeric ratio (dr, α*S*:α*R*) as summarized pictorially in Scheme 1.[4] Subsequent removal of the chiral auxiliary with MeOH and Et_3N gave *N*-benzyl phenylglycinate (*S*)-**4** in 67% yield with 96:4 er. The chiral information of D-glucose is transferred to the substitution at α-chloro carbon



Scheme 1. Reactions of α-halo-α-phenylacetates **1** and **2**.

Keywords: Dynamic kinetic resolution; Asymmetric syntheses; Nucleophilic substitution; Carbohydrate; Chiral auxiliary.
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center via dynamic kinetic resolution in the nucleophilic substitution with benzylamine. The α-chloro stereogenic center of **1** undergoes rapid epimerization in the presence of DIEA and TBAI, and (α*R*)-**1** reacts with benzylamine preferentially to provide (α*S*)-**3**.[5]

In order to assess the effect of leaving group, TBAI and DIEA on yield and stereoselectivity, a series of reactions were examined as shown in Table 1. When α-bromo acetate **2** was treated with benzylamine in the presence of both TBAI and DIEA, the substitution provided **3** in 74% yield with almost same diastereoselectivity (95:5 dr) compared to the reactions of α-chloro acetate **1** (entry 1). Significant decrease in stereoselectivity was observed in the absence of TBAI (entry 2), while mild drop in stereoselectivity was observed in the absence of DIEA (entry 3). We speculate that the lowering of dr in the absence of TBAI or DIEA probably results from the slower epimerization of α-bromo-α-phenyl acetate **2**. In addition, the result in entry 4 suggests that the presence of both TBAI and DIEA is important for highly stereoselective substitution. Unlike the cases of α-bromo acetate **2**, the reaction of α-chloro acetate **1** in the absence of TBAI gave the substitution product **3** with almost same stereoselectivity (95:5 dr) compared to the reaction of **1** in the presence of both TBAI and DIEA (entry 5 and Scheme 1). On the other hand, mild drop of selectivity was observed in the absence of DIEA (entry 6). In both the reactions of α-chloro acetate **1** as shown in entries 5 and 6, the rate of the substitution was substantially decreased and the product **3** was obtained in 33% and 34% yields, respectively, after 24 h stirring at room temperature. In addition, in the absence of both TBAI and DIEA, the reaction did not produce **3** and most of starting material was recovered (entry 7). These results seem to indicate that both TBAI and DIEA are crucial for rate acceleration of the substitution of α-chloro-α-phenyl acetate **1**.

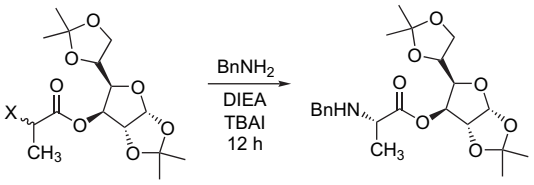
Table 1. Effects of leaving group, TBAI and DIEA in the reactions of **1** and **2**

Entry	S.M.[a]	Condition[b]	% Yield[c]	dr[d] (α*S*:α*R*)
1	**2**	TBAI, DIEA, $BnNH_2$	74 (**3**)	95:5
2	**2**	DIEA, $BnNH_2$	89 (**3**)	83:17
3	**2**	TBAI, $BnNH_2$	72 (**3**)	92:8
4	**2**	$BnNH_2$	67 (**3**)	74:26
5	**1**	DIEA, $BnNH_2$	34 (**3**)	95:5
6	**1**	TBAI, $BnNH_2$	33 (**3**)	92:8
7	**1**	$BnNH_2$	N.R.	—

[a] Initial drs of **1** and **2** were approximately 50:50.
[b] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[c] Isolated yields.
[d] The drs were determined by ^1H NMR of reaction mixture and confirmed by CSP-HPLC after removing the chiral auxiliary.

The scope of the observed dynamic kinetic resolution has been examined with various α-alkyl esters. Initial studies were carried out with the substitution reactions of α-chloro propionate **5** derived from diacetone-D-glucose and racemic α-chloro propionyl chloride. As shown in Table 2, entry 1, treatment of 69:31 diastereomeric mixture of **5** with $BnNH_2$ (1.2 equiv), TBAI (1.0 equiv), and DIEA (1.0 equiv) in CH_2Cl_2 for 24 h at room temperature gave **7** in 29% yield with 84:16 dr.[6] In an effort to improve the yield and the selectivity, we examined the substitutions of α-bromo propionate **6** under the same reaction condition. The reaction of α-bromo

Table 2. Reactions of α-halo-α-methyl acetates **5** and **6**



5 (X = Cl)
6 (X = Br)

7

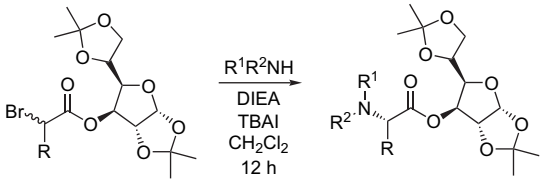
Entry[a]	X	dr of S.M.	Solvent	% Yield[b]	dr[c] (α*S*:α*R*)
1	Cl	69:31	CH_2Cl_2	29	84:16
2	Br	73:27	CH_2Cl_2	90	80:20
3	Br	55:45	CH_2Cl_2	91	80:20
4	Br	73:27	$CHCl_3$	99	76:24
5	Br	73:27	THF	87	80:20
6	Br	73:27	Ether	71	72:28
7	Br	73:27	DMF	73	72:28
8	Br	73:27	Hexane	93	69:31
9	Br	73:27	CH_3CN	99	76:24

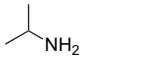
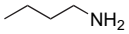
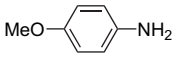
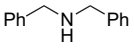
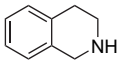
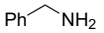
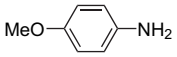
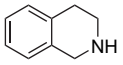
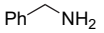
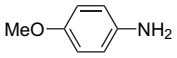
[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Isolated yields.
[c] The drs were determined by ^1H NMR of reaction mixture and confirmed by CSP-HPLC after removing the chiral auxiliary.

propionate **6** (73:27 dr) gave **7** in a better yield with a slightly lower dr[6] (entry 2). When **6** of 55:45 dr was treated with benzylamine in the presence of TBAI and DIEA, the reaction gave the product **7** with 80:20 dr as shown in entry 3.[6] Thus, the dr of product **7** is not dependent on the starting ratio of two epimers of α-bromo propionate **6**, which indicates that the primary pathway of the asymmetric induction is a dynamic kinetic resolution. In the reactions of α-bromo propionate **6**, none of other solvents explored gave better selectivities than CH_2Cl_2. As shown in entries 4–9, the substitution product **7** was obtained with 76:24 dr in $CHCl_3$, 80:20 dr in THF, 72:28 dr in ether, 72:28 dr in DMF, 69:31 dr in *n*-hexane, and 76:24 dr in CH_3CN. The faster reactions at 50 °C in various solvents did not give better selectivities compared to the reactions at room temperature.

Next, we examined six different amine nucleophiles in the reactions of **6** as shown in Table 3. We were pleased to observe that this methodology is efficient for some aromatic and cyclic amine nucleophiles such as *p*-anisidine and 1,2,3,4-tetrahydroisoquinoline, affording amino acid derivatives **10** and **12** with 91:9 dr and 97:3 dr, respectively, as shown in entries 3 and 6. Reactions of α-bromo propionate **6** with isopropylamine, butylamine, dibenzylamine, and benzylmethylamine gave moderate stereoselectivities. Encouraged by the high asymmetric induction in the reactions of α-bromo-α-methyl ester **6** with some amine nucleophiles, we examined two other α-bromo α-alkyl acetates **8** and **9** as shown in entries 8–12. When α-bromo-α-ethyl acetate **8** was treated with 1,2,3,4-tetrahydroisoquinoline in the presence of TBAI and DIEA for 24 h, the substitution provided the corresponding amino ester **18** in 49% yield with 95:5 dr, while the reactions of benzylamine and *p*-anisidine gave moderate stereoselectivities (entries 8–10). The reactions of α-bromo-α-butyl acetate **9** were also carried out with benzylamine and *p*-anisidine for the asymmetric syntheses of α-butyl-α-amino acid derivatives **19** and **20** as shown in entries 11 and 12. Limited results in Table 3 indicate that the size and nature of the amine nucleophiles

Table 3. Reactions of α-bromo-α-alkyl acetates **6**, **7** and **8**



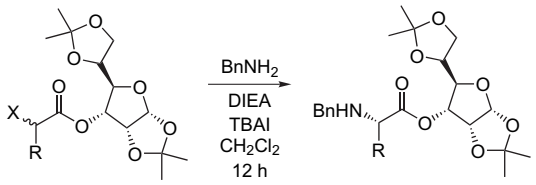
Entry[a]	R	R^1R^2NH	% Yield[b]	dr[c] (αS:αR)
1	Methyl (**6**)		70 (**10**)	80:20
2	Methyl (**6**)		80 (**11**)	77:23
3	Methyl (**6**)		85 (**12**)	91:9
4	Methyl (**6**)		48 (**13**)	69:31
5	Methyl (**6**)		91 (**14**)	75:25
6	Methyl (**6**)		92 (**15**)	97:3
8	Ethyl (**8**)		77 (**16**)	75:25
9	Ethyl (**8**)		99 (**17**)	70:30
10	Ethyl (**8**)		49 (**18**)	95:5
11	Butyl (**9**)		40 (**19**)	78:22
12	Butyl (**9**)		64 (**20**)	97:3

[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Isolated yields.
[c] The drs were determined by ^1H NMR of reaction mixture.

significantly affect the stereoselectivity of the nucleophilic substitution. No noticeable size effects of R group attached to the reacting center were recognized.

Our next concern was to examine the reactivity and the stereocontrolling ability of D-allofuranose template for the dynamic kinetic resolution of α-halo esters in nucleophilic substitution. Nucleophilic substitutions of **21** and **22** with benzylamine were conducted under the same reaction condition as that used for D-glucose derivatives **1** and **6**. Treatment of α-bromo propionate **21** with benzylamine, TBAI, and DIEA gave the substitution product **23** in 81% isolated yield with 71:29 dr (α*S*:α*R*) as shown in Scheme 2. Also, the reaction of α-chloro acetate **22** took place with high stereoselectivity, affording **24** in 69% isolated yield with 90:10 dr (α*S*:α*R*). The ratio of the diastereomeric mixture obtained from each nucleophilic substitution was determined by ^1H NMR analysis. The absolute configurations were assigned after removal of chiral auxiliary by chiral HPLC analysis of enantioenriched methyl *N*-benzyl alaninate and methyl *N*-benzyl phenylglycinate.

A plausible mechanistic rationale for the stereochemical outcomes observed in the nucleophilic substitutions of



Scheme 2. Stereoselective reactions of diacetone-D-allose derivatives **21** and **22**.

D-glucose derivatives and D-allose derivatives is speculated in Figure 1. We propose two transition state structures in which the R group adopts cis conformation relatively to the carbonyl group and hydrogen atom at C-3 of furanose eclipses the carbonyl group, based on the previous mechanistic studies of analogous reaction systems.[1f,h,i] With the shown conformational alignment, the nucleophilic attack of an amine nucleophile to sterically more hindered face could be aided by hydrogen bonding to basic oxygen atom of chiral auxiliary, thus explaining *S*-configurations of products observed in both reactions of D-glucose derivatives and D-allose derivatives. The proposed model by relying on hydrogen bonding is consistent with the poor stereoselectivities of the reactions with thiol nucleophiles and metalated nucleophiles, relatively poor hydrogen bond donor nucleophiles.[7]

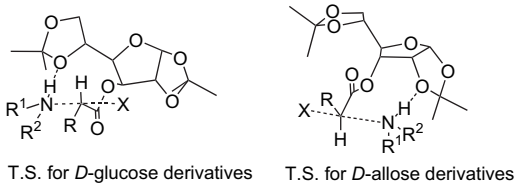
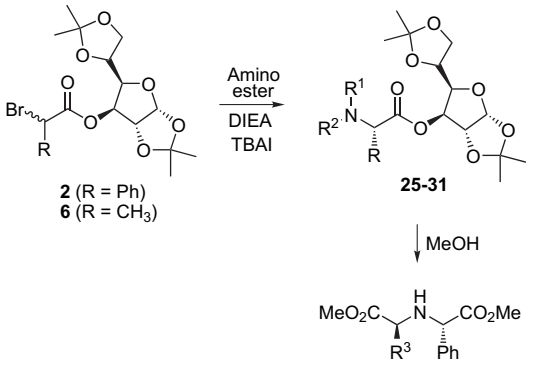


Figure 1. Proposed transition state structures.

Finally, we were pleased to demonstrate that this methodology is also efficient for the substitution with various amino ester nucleophiles, affording 1,1′-iminodicarboxylic acid derivatives **25–33** with high stereoselectivities as shown in Table 4. 1,1′-Iminodicarboxylic acid derivatives are pharmaceutically active as ACE-inhibitors and constitute interesting natural substance.[8] Substantial progress has been made toward the development of efficient methods for stereoselective preparation of these compounds.[9] As shown in Table 4, entry 1, treatment of α-bromo-α-phenyl acetate **2** with glycine methyl ester hydrochloride (1.2 equiv), TBAI (1.0 equiv), and DIEA (2.2 equiv) in CH_2Cl_2 at room temperature provided **25** in 36% yield with 92:8 dr (α*S*:α*R*). Interestingly, much higher stereoselectivities were obtained in the reactions with α-substituted amino ester nucleophiles to give the substituted products **26–31** as shown in entries 2–7. The reaction of **2** with L-alanine methyl ester afforded **26** in a ratio of 98:2 dr (α*S*:α*R*). When D-alanine methyl ester was used as a nucleophile, **27** was obtained in a 99:1 (α*S*:α*R*) ratio. Both L- and D-alanine ester nucleophiles gave the same chirality at the α-center (*S* configuration) and no notable double stereodifferentiation was observed. These results indicate

Table 4. Asymmetric syntheses of 1,1′-iminodicarboxylic acid derivatives



Entry[a]	Nucleophile	R	% Yield[b]	dr[c] (αS:αR)
1	MeO_2C NH_2	Ph	36 (**25**)	92:8
2	MeO_2C NH_2	Ph	55 (**26**)	98:2
3	MeO_2C NH_2	Ph	49 (**27**)	99:1
4	t-BuO_2C NH_2	Ph	67 (**28**)	98:2
5	MeO_2C NH_2	Ph	81 (**29**)	98:2
6	BnO_2C H N	Ph	60 (**30**)	99:1
7	BnO_2C H N	CH_3	32 (**31**)	99:1

[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Isolated yields.
[c] The drs were determined by ^1H NMR of reaction mixture.

that the stereochemistry of the major product is dominated by the asymmetry of diacetone-D-glucose auxiliary and not that of the incoming amino ester nucleophile. Furthermore, we attempted the substitution reaction of α-bromo propionate **6** with proline benzyl ester and found that **31** was afforded in 32% yield with 99:1 dr. The absolute configurations of (αS)-**26** and (αS)-**29** were determined after removing chiral auxiliary with MeOH and Et_3N, by comparison to the ^1H NMR of authentic epimers of (*S*)-**32** and (*S*)-**33** individually prepared from the substitution of methyl (*R*)-α-bromo α-methyl acetate or methyl (*R*)-α-bromo α-isobutyl acetate with L-phenylglycine methyl ester on the basis of inversion mechanism (S_N2). Those of **28**, **30**, and **31** were assigned by analogy to the formation of **26** and **29**. This convenient approach for asymmetric syntheses of 1,1′-iminodicarboxylic acid derivatives appears to offer a substantial advantage over previous methodologies.[9]

3. Conclusion

We have developed a novel and practical method for the asymmetric syntheses of *N*-substituted amino esters via dynamic kinetic resolution of α-halo esters using carbohydrates as a chiral auxiliary. The present results indicate that stereoselectivity is very dependent on both substrate and nucleophile and is also significantly influenced by epimerizing agents. Although the precise mechanism is still unclear, we propose the presence of hydrogen bonding interaction between an amine nucleophile and the chiral auxiliary in the transition state. The methodology has also been successful for highly asymmetric syntheses of 1,1′-iminodicarboxylic acid derivatives. The simple and mild protocol requires no special precautions and can be run on a multigram scale. In the longer term, application to highly stereoselective nucleophilic substitution with a variety of nucleophiles should see more general development and mechanistic analysis.

4. Experimental

4.1. General procedure for the preparation of α-halo esters 1, 2, 5, 6, 8, 9, 21, and 22

*For α-chloro esters **1**, **5**, and **22***: chiral auxiliary (1.0 equiv), racemic α-chloro α-phenyl (or methyl) acetyl chloride (1.0 equiv), and Et_3N (2.2 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature for 2 h. The mixture was treated with extractive work up and the organic phase was dried over $MgSO_4$. Filtration and concentration provided the crude product that was purified by column chromatography on silica gel.

*For α-bromo esters **2**, **6**, **8**, **9**, and **21***: chiral auxiliary (1.0 equiv), racemic α-bromo acid (1.0 equiv), DCC (1.0 equiv), Et_3N (2.2 equiv), and DMAP (0.2 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over $MgSO_4$, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel.

4.1.1. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-chloro-α-phenyl acetate (1). A colorless oil was obtained in 89% yield as a mixture of two diastereomers. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.51–7.36 (m, 5H), 5.85, 5.73 (d, J=3.6 Hz, 1H), 5.38, 5.37 (s, 1H), 5.34, 5.33 (d, J=2.9 Hz, 1H), 4.46, 4.32 (d, J=3.6 Hz, 1H), 4.04–4.13 (m, 2H), 3.88–3.91 (m, 2H), 1.50, 1.39, 1.34, 1.29, 1.26, 1.14 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, two diastereomers) 167.3, 167.2, 135.7, 135.6, 129.9, 129.3, 128.3, 128.2, 112.9, 109.8, 109.7, 105.5, 105.4, 83.4, 83.3, 80.5, 80.4, 78.1, 78.0, 72.5, 72.3, 67.8, 67.7, 59.5, 59.3, 27.2, 27.1, 27.0, 26.6, 25.5, 25.4; Anal. Calcd for $C_{20}H_{25}ClO_7$: C, 58.12; H, 6.05. Found: C, 58.18; H, 6.10.

4.1.2. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-bromo-α-phenyl acetate (2). A pale yellow oil was obtained in 54% yield as a mixture of two diastereomers. ^1H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.56–7.36 (m, 5H), 5.88, 5.83 (d, J=3.6 Hz, 1H), 5.38, 5.37 (s, 1H), 5.35, 5.34 (d, J=2.9 Hz, 1H), 4.48, 4.42 (d, J=3.6 Hz, 1H), 4.19–3.94 (m, 4H), 1.51, 1.39, 1.36, 1.30, 1.28, 1.26, 1.18 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, two diastereomers) 167.2, 135.5, 129.9, 129.3, 129.1, 112.9, 109.8, 105.5, 80.4, 78.1, 72.4, 67.7, 46.9, 28.2,

26.6, 25.5; Anal. Calcd for $C_{20}H_{25}BrO_7$: C, 52.53; H, 5.51. Found: C, 52.58; H, 5.64.

4.1.3. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-chloro propionate (5). A colorless oil was obtained in 74% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.91 (d, *J*=3.6 Hz, 1H), 5.33 (d, *J*=2.6 Hz, 1H), 4.51 (d, *J*=3.7 Hz, 1H), 4.43 (q, *J*=6.9 Hz, 1H), 4.24–4.20 (m, 2H), 4.14–4.10 (m, 1H), 4.00–3.97 (m, 1H), 1.72 (d, *J*=6.9 Hz, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diasteromer) 168.9, 112.8, 109.8, 105.5, 83.4, 80.4, 77.8, 72.7, 67.9, 52.6, 27.2, 27.1, 26.6, 25.5, 21.7; Anal. Calcd for $C_{15}H_{23}ClO_{77}$: C, 51.36; H, 6.61. Found: C, 51.30; H, 6.72.

4.1.4. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-bromo propionate (6). A pale yellow oil was obtained in 61% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.91 (d, *J*=3.6 Hz, 1H), 5.33 (d, *J*=2.8 Hz, 1H), 4.50 (d, *J*=3.8 Hz, 1H), 4.40 (q, *J*=6.9 Hz, 1H), 4.26–4.22 (m, 2H), 4.15–4.12 (m, 1H), 3.99–3.96 (m, 1H), 1.86 (d, *J*=6.9 Hz, 3H), 1.56 (s, 3H), 1.40 (s, 3H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 169.0, 112.8, 109.8, 105.5, 83.4, 80.5, 80.1, 72.6, 67.9, 39.9, 27.2, 27.1, 26.6, 25.6, 21.8; Anal. Calcd for $C_{15}H_{23}BrO$: C, 45.58; H, 5.87. Found: C, 45.51; H, 5.97.

4.1.5. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-bromobutyrate (8). A pale yellow oil was obtained in 45% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.91 (m, 1H), 5.34 (m, 1H), 4.49 (m, 1H), 4.22 (m, 4H), 3.99 (m, 1H), 2.04 (m, 2H), 1.53 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 168.5, 112.8, 109.8, 105.5, 83.3, 80.4, 77.8, 72.6, 67.0, 47.5, 28.6, 27.2, 26.6, 25.5, 24.7, 12.2; Anal. Calcd for $C_{16}H_{25}BrO_7$: C, 46.95; H, 6.16. Found: C, 46.96; H, 6.24.

4.1.6. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-bromohexanoate (9). A pale yellow oil was obtained in 49% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.90 (d, *J*=2.2 Hz, 1H), 5.33 (m, 1H), 4.49 (m, 1H), 4.23 (m, 3H), 4.13 (m, 1H), 4.01 (m, 1H), 2.10 (m, 2H), 1.53 (s, 3H), 1.32 (m, 13H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 168.6, 112.9, 109.8, 105.5, 83.3, 80.3, 77.7, 72.6, 67.9, 45.9, 34.8, 29.6, 27.2, 27.1, 26.6, 25.6, 22.4, 14.2; Anal. Calcd for $C_{18}H_{29}BrO_7$: C, 49.44; H, 6.68. Found: C, 49.52; H, 6.73.

4.1.7. (1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranos-3-*O*-yl) α-bromo propionate (21). A pale yellow oil was obtained in 98% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.86 (d, *J*=3.5 Hz, 1H), 4.87–4.86 (m, 2H), 4.43–4.41 (m, 1H), 4.33–4.32 (m, 1H), 4.19–4.18 (m, 1H), 4.11–4.07 (m, 1H), 3.95–3.92 (m, 1H), 1.86 (d, *J*=7.0 Hz, 3H), 1.55 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 169.6, 113.5, 110.4, 104.6, 78.0, 77.8, 75.3, 74.0, 66.0, 40.1, 29.2, 26.7, 25.4, 22.3, 21.9; Anal. Calcd for $C_{15}H_{23}BrO_7$: C, 45.58; H, 5.87. Found: C, 45.65; H, 5.81.

4.1.8. (1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranos-3-*O*-yl) α-chloro-α-phenyl acetate (22). A colorless oil was obtained in 99% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.52–7.37 (m, 5H), 5.83, 5.81 (d, *J*=3.8 Hz, 1H), 5.44–5.42 (s, 1H), 4.89–4.81 (m, 2H), 4.29–4.05 (m, 1H), 3.90–3.59 (m, 3H), 1.60–1.22 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 167.7, 135.9, 129.7, 129.2, 128.7, 113.6, 110.4, 104.8, 78.3, 75.5, 75.0, 74.3, 66.2, 59.1, 27.3, 26.7, 26.5, 25.5, 21.4; Anal. Calcd for $C_{20}H_{25}ClO_7$: C, 58.18; H, 6.10. Found: C, 58.21; H, 6.05.

4.2. General procedure for the asymmetric preparation of 3, 7, 10–20, 23–31

To a solution of α-halo ester (**1**, **2**, **5**–**9**, **21**, and **22**) in CH_2Cl_2 (ca. 0.1 M) at room temperature were added DIEA (1.0 equiv), TBAI (1.0 equiv), and a nucleophile (1.2 equiv). After the resulting reaction mixture was stirred at room temperature for 12 h, the solvent was evaporated and the crude material was purified by column chromatography to give a α-amino ester. The dr of the product was determined by ^{1}H NMR integration of anomeric or α-hydrogens of two diastereomers.

4.2.1. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-benzyl-(*S*)-phenylglycinate (3). A colorless oil was obtained in 86% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.38–7.25 (m, 10H), 5.56 (d, *J*=3.6 Hz, 1H), 5.33 (d, *J*=2.6 Hz, 1H), 4.41 (s, 1H), 4.18–3.97 (m, 5H), 3.76 (d, *J*=4.0 Hz, 2H), 2.34 (br, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.1, 139.8, 138.0, 129.2, 128.9, 128.8, 128.1, 127.8, 127.7, 112.8, 109.8, 105.4, 83.3, 80.3, 77.8, 76.8, 72.8, 67.7, 64.7, 51.8, 27.3, 27.2, 26.6, 25.7; HRMS (ESI) calcd for $C_{27}H_{34}NO_7$ (M^++1): 484.2335. Found: 484.2340.

4.2.2. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-benzyl-(*S*)-alaninate (7). A colorless oil was obtained in 90% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.33–7.25 (m, 5H), 5.86 (d, *J*=3.6 Hz, 1H), 5.39 (d, *J*=2.6 Hz, 1H), 4.42 (d, *J*=3.7 Hz, 1H), 4.21–4.18 (m, 2H), 4.11–4.07 (m, 1H), 4.03–4.00 (m, 1H), 3.81 (d, *J*=12.9 Hz, 1H), 3.68 (d, *J*=12.9 Hz, 1H), 3.44 (q, *J*=7.0 Hz, 1H), 1.81 (br, 1H), 1.53 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.29 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.8, 139.9, 128.9, 128.6, 127.6, 112.8, 109.9, 105.5, 83.9, 80.6, 76.4, 72.7, 67.9, 56.2, 52.3, 25.3, 27.2, 26.6, 25.7, 19.5; Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.86; H, 7.44; N; 3.12. For removal of chiral auxiliary, the mixture of **7** and Et_3N (15 equiv) in methanol (0.03 M) was stirred for 2 days. The solvent was evaporated and the crude material was purified by column chromatography to give methyl (*N*-benzyl) (*S*)-alaninate in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.32–7.23 (m, 5H), 3.80 (d, *J*=12.8 Hz, 1H), 3.72 (s, 3H), 3.67 (d, *J*=12.8 Hz, 1H), 3.39 (q, *J*=7.0 Hz, 1H), 1.85 (br, 1H), 1.32 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.6, 140.1, 128.8, 128.6, 127.5, 56.3, 52.4, 52.2, 19.5. Chiral HPLC: 79:21 er, t_R (*S*)-major enantiomer, 5.1 min;

t_R (*R*)-minor enantiomer, 5.6 min (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

4.2.3. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-isopropyl-(*S*)-alaninate (10). A colorless oil was obtained in 70% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.89 (d, *J*=3.5 Hz, 1H), 5.37 (d, *J*=2.0 Hz, 1H), 4.43 (d, *J*=3.7 Hz, 1H), 4.19–4.11 (m, 3H), 4.00 (m, 1H), 3.49 (q, *J*=7.0 Hz, 1H), 2.78 (m, 1H), 1.75 (br, 1H), 1.53 (s, 3H), 1.40 (s, 3H), 1.32 (m, 9H), 1.06, 1.02 (d, *J*=6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.3, 112.8, 109.8, 105.5, 83.8, 80.6, 76.3, 72.7, 68.0, 54.3, 47.1, 27.2, 26.6, 25.6, 24.2, 22.4, 22.3, 20.0; Anal. Calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.89; H, 8.50; N, 3.58.

4.2.4. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-butyl-(*S*)-alaninate (11). A colorless oil was obtained in 80% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 5.89 (d, *J*=3.5 Hz, 1H), 5.36 (d, *J*=2.6 Hz, 1H), 4.44 (d, *J*=3.7 Hz, 1H), 4.19 (m, 2H), 4.10 (m, 1H), 4.01 (m, 1H), 3.38 (q, *J*=7.0 Hz, 1H), 2.58 (m, 1H), 2.51 (m, 1H), 1.68 (br, 1H), 1.53 (s, 3H), 1.45 (m, 2H), 1.40 (s, 3H), 1.38–1.30 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.9, 112.8, 109.7, 105.6, 83.9, 80.5, 76.3, 72.7, 67.9, 57.0, 47.9, 32.7, 27.2, 27.1, 26.6, 25.6, 20.7, 19.4, 14.3; Anal. Calcd for $C_{19}H_{33}NO_7$: C, 58.90; H, 8.58; N, 3.61. Found: C, 58.88; H, 8.61; N, 3.51.

4.2.5. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-*p*-methoxyphenyl-(*S*)-alaninate (12). A colorless oil was obtained in 85% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 6.78 (d, *J*=8.8 Hz, 2H), 6.61 (d, *J*=8.9 Hz, 2H), 5.59 (d, *J*=3.6 Hz, 1H), 5.25 (d, *J*=1.8 Hz, 1H), 4.18 (m, 5H), 4.00 (m, 1H), 3.76 (m, 1H), 3.72 (s, 3H), 1.48 (m, 6H), 1.39 (s, 3H), 1.30 (s, 3H), 1.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.8, 153.4, 141.1, 115.7, 115.3, 112.7, 109.8, 105.5, 83.5, 80.2, 76.6, 72.8, 68.0, 56.1, 54.0, 27.2, 27.1, 26.4, 25.6, 19.1; Anal. Calcd for $C_{22}H_{31}NO_8$: C, 60.40; H, 7.14; N, 3.20. Found: C, 60.60; H, 7.09; N, 3.09.

4.2.6. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-dibenzyl-(*S*)-alaninate (13). A colorless oil was obtained in 48% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.39–7.23 (m, 10H), 5.84 (d, *J*=3.6 Hz, 1H), 5.35 (d, *J*=2.9 Hz, 1H), 4.42 (d, *J*=3.6 Hz, 1H), 4.20 (m, 2H), 4.09 (m, 1H), 4.05 (m, 1H), 3.84 (d, *J*=14.1 Hz, 2H), 3.68 (d, *J*=14.0 Hz, 2H), 3.55 (q, *J*=7.1 Hz, 1H), 1.53 (s, 3H), 1.44 (s, 3H), 1.24 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.9, 140.1, 140.0, 129.0, 128.7, 128.6, 127.5, 127.4, 112.8, 109.8, 105.5, 84.0, 80.4, 76.5, 72.8, 68.1, 56.8, 56.6, 54.7, 27.4, 27.2, 26.5, 25.7, 15.5; Anal. Calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.05; H, 7.15; N, 2.71.

4.2.7. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-benzyl-*N*-methyl-(*S*)-alaninate (14). A colorless oil was obtained in 91% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.34–7.24 (m, 5H), 5.87 (d, *J*=3.6 Hz, 1H), 5.34 (d, *J*=2.9 Hz, 1H), 4.45 (d, *J*=3.7 Hz, 1H), 4.21 (m, 2H), 4.11 (m, 1H), 4.01 (m, 1H), 3.75 (d, *J*=13.6 Hz, 1H), 3.64 (d, *J*=13.5 Hz, 1H), 3.49 (q, *J*=7.1 Hz, 1H), 2.30 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H), 1.35 (d, *J*=7.1 Hz, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.5, 139.7, 129.0, 128.7, 127.4, 112.8, 109.8, 105.5, 84.0, 80.5, 76.4, 72.8, 68.0, 61.1, 58.7, 38.1, 27.2, 27.1, 26.6, 25.6, 15.4; Anal. Calcd for $C_{23}H_{33}NO_7$: C, 63.43; H, 7.64; N, 3.22. Found: C, 63.43; H, 7.68; N, 3.13.

4.2.8. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-(3,4-dihydro-2(1*H*)-isoquinolinyl)propionate (15). A pale yellow oil was obtained in 92% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.11–6.98 (m, 4H), 5.88 (d, *J*=3.7 Hz, 1H), 5.34 (d, *J*=2.9 Hz, 1H), 4.47 (d, *J*=3.7 Hz, 1H), 4.23–4.17 (m, 2H), 4.13–4.09 (m, 1H), 4.01–3.97 (m, 1H), 3.85–3.83 (m, 2H), 3.57 (q, *J*=7.0 Hz, 1H), 3.03–3.01 (m, 1H), 2.88–2.82 (m, 3H), 1.52 (s, 3H), 1.43 (d, *J*=7.0 Hz, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.1, 135.1, 134.7, 129.2, 126.9, 126.5, 125.9, 112.8, 109.8, 105.5, 84.0, 80.5, 76.5, 72.8, 68.9, 62.5, 54.4, 47.6, 30.2, 27.2, 27.1, 26.6, 25.5, 15.4; Anal. Calcd for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.41; H, 7.54; N, 3.07.

4.2.9. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-(*N*-benzylamino)butyrate (16). A colorless oil was obtained in 77% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.34–7.25 (m, 5H), 5.85 (d, *J*=3.7 Hz, 1H), 5.40 (d, *J*=2.4 Hz, 1H), 4.41 (d, *J*=3.7 Hz, 1H), 4.21–4.17 (m, 2H), 4.11–4.08 (m, 1H), 4.03–4.00 (m, 1H), 3.83 (d, *J*=12.9 Hz, 1H), 3.63 (d, *J*=13.0 Hz, 1H), 3.23 (t, 1H), 1.70 (m, 2H), 1.53 (s, 3H), 1.42 (s, 3H), 1.32–1.26 (m, 6H), 0.94 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.5, 140.2, 128.8, 128.6, 127.5, 112.9, 109.9, 105.7, 83.9, 80.6, 76.6, 72.8, 68.2, 62.4, 52.6, 27.3, 27.2, 27.1, 26.7, 25.7, 10.7; Anal. Calcd for $C_{23}H_{33}NO_7$: C, 63.43; H, 7.64; N, 3.22. Found: C, 63.66; H, 7.56; N, 3.01.

4.2.10. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) α-(*N*-*p*-methoxyphenylamino)butyrate (17). A colorless oil was obtained in 99% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 6.78 (d, *J*=8.9 Hz, 2H), 6.62 (d, *J*=8.9 Hz, 2H), 5.57 (d, *J*=3.6 Hz, 1H), 5.26 (d, *J*=2.1 Hz, 1H), 4.16–4.09 (m, 3H), 4.02–3.97 (m, 3H), 3.75 (br, 1H), 3.72 (s, 1H), 1.87–1.84 (m, 2H), 1.48 (s, 3H), 1.39 (s, 3H), 1.29 (m, 3H), 1.22 (s, 3H), 1.05 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.1, 153.4, 141.3, 115.3, 115.2, 112.7, 109.8, 105.6, 83.5, 80.3, 76.5, 72.8, 67.9, 60.1, 56.1, 27.2, 27.1, 26.6, 26.3, 25.6, 10.6; Anal. Calcd for $C_{23}H_{33}NO_8$: C, 61.18; H, 7.37; N, 3.10. Found: C, 61.17; H, 7.44; N, 3.39.

4.2.11. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-(3,4-dihydro-2(1*H*)-isoquinolinyl)butyrate (18). A colorless oil was obtained in 49% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major

diastereomer) 7.26–6.98 (m, 4H), 5.86 (d, J=3.7 Hz, 1H), 5.35 (d, J=2.9 Hz, 1H), 4.45 (d, J=3.6 Hz, 1H), 4.24–4.12 (m, 3H), 4.01–3.98 (m, 1H), 3.90–3.78 (m, 2H), 3.35 (m, 1H), 3.06–3.03 (m, 1H), 2.88–2.76 (m, 3H), 1.82 (m, 2H), 1.52 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 0.98 (t, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.4, 135.4, 134.8, 129.2, 126.9, 126.5, 126.0, 110.1, 112.9, 105.5, 84.0, 80.6, 76.4, 72.7, 69.4, 68.2, 52.6, 47.4, 30.3, 27.2, 26.6, 25.5, 23.2, 23.1, 11.2; HRMS (ESI) calcd for $C_{25}H_{36}NO_7$ (M^++1): 462.2492. Found: 462.2492.

4.2.12. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-(*N*-benzylamino)hexanoate (19). A colorless oil was obtained in 40% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.33–7.24 (m, 5H), 5.85 (d, J=3.6 Hz, 1H), 5.39 (d, J=2.3 Hz, 1H), 4.41 (d, J=3.6 Hz, 1H), 4.20 (m, 2H), 4.09 (m, 1H), 4.02 (m, 1H), 3.81 (d, J=12.9 Hz, 1H), 3.64 (d, J=12.9 Hz, 1H), 3.27 (t, 1H), 1.77–1.53 (m, 6H), 1.42–1.27 (m, 12H), 0.88 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.7, 140.2, 128.8, 128.7, 127.5, 112.8, 109.9, 105.5, 83.8, 80.5, 76.7, 72.8, 68.1, 61.1, 52.4, 33.7, 28.3, 27.3, 26.7, 25.7, 22.9, 14.3; HRMS (ESI) calcd for $C_{25}H_{38}NO_7$ (M^++1): 464.2648. Found: 464.2646.

4.2.13. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-(*N*-*p*-methoxyphenylamino)hexanoate (20). A pale yellow oil was obtained in 64% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 6.76 (d, J=8.8 Hz, 2H), 6.61 (d, J=8.8 Hz, 2H), 5.54 (d, J=3.6 Hz, 1H), 5.25 (d, J=2.2 Hz, 1H), 4.24–3.98 (m, 6H), 3.72 (s, 3H), 1.78 (m, 2H), 1.47–1.34 (m, 4H), 1.46 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 1.21 (s, 3H), 0.92 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.7, 153.4, 141.4, 115.6, 115.3, 112.7, 109.8, 105.5, 83.4, 80.3, 76.5, 72.8, 67.9, 58.9, 56.1, 33.2, 28.2, 27.2, 27.1, 26.4, 25.6, 22.8, 14.3; Anal. Calcd for $C_{25}H_{37}NO_8$: C, 62.61; H, 7.78; N, 2.92. Found: C, 62.58; H, 7.86; N, 2.63.

4.2.14. (1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranos-3-*O*-yl) *N*-benzyl-(*S*)-alaninate (23). A colorless oil was obtained in 81% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.36–7.25 (m, 5H), 5.84 (d, J=3.6 Hz, 1H), 4.90 (m, 2H), 4.30 (m, 1H), 4.17 (m, 1H), 4.07 (m, 1H), 3.90 (m, 2H), 3.70 (d, J=12.9 Hz, 1H), 3.47 (q, J=7.0 Hz, 1H), 1.92 (br, 1H), 1.58 (s, 3H), 1.47 (s, 3H), 1.35 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.4, 140.2, 128.8, 128.7, 127.5, 113.4, 110.4, 104.6, 78.2, 75.5, 73.5, 66.2, 56.4, 55.8, 52.3, 27.2, 27.1, 26.7, 25.3, 19.2; Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.66; H, 7.57; N, 3.18.

4.2.15. (1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranos-3-*O*-yl) *N*-benzyl-(*S*)-phenylglycinate (24). A colorless oil was obtained in 69% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40–7.25 (m, 10H), 5.83 (d, J=3.9 Hz, 1H), 4.92–4.81 (m, 2H), 4.53 (s, 1H), 4.15–4.06 (m, 2H), 3.81 (m, 3H), 3.38 (m, 1H), 2.34 (br, 1H), 1.56 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.6, 139.9, 138.0, 129.1, 128.8, 128.7, 128.4, 128.1, 127.5, 113.4, 110.2, 104.8, 78.1, 77.9, 75.6, 73.8, 65.6, 64.4, 51.7, 27.3, 26.7, 26.4, 25.5; Anal. Calcd for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90. Found: C, 66.93; H, 7.08; N, 2.87.

4.2.16. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-[1-(methoxycarbonyl) methyl]-(*S*)-phenylglycinate (25). A colorless oil was obtained in 36% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.39–7.27 (m, 5H), 5.54 (d, J=3.7 Hz, 1H), 5.32 (d, J=2.4 Hz, 1H), 4.51 (s, 1H), 4.19–4.05 (m, 4H), 3.99–3.96 (m, 1H), 3.71 (s, 3H), 3.40 (d, J=3.6 Hz, 2H), 2.45 (br, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.6, 171.3, 137.3, 129.3, 129.0, 128.0, 112.8, 109.8, 105.4, 83.3, 80.3, 76.9, 72.8, 67.7, 64.9, 52.3, 48.4, 27.2, 27.1, 26.6, 25.6; HRMS (ESI) calcd for $C_{23}H_{32}NO_9$ (M^++1): 466.2077. Found: 466.2054.

4.2.17. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-[(*S*)-1-(methoxycarbonyl)ethyl]-(*S*)-phenylglycinate (26). A colorless oil was obtained in 55% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40–7.28 (m, 5H), 5.56 (d, J=3.6 Hz, 1H), 5.33 (d, J=2.2 Hz, 1H), 4.47 (s, 1H), 4.19–4.06 (m, 4H), 3.99–3.96 (m, 1H), 3.64 (s, 3H), 3.44 (q, J=6.4 Hz, 1H), 2.40 (br, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.32 (m, 6H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.5, 171.6, 137.7, 129.2, 128.9, 127.9, 112.7, 109.8, 105.4, 83.3, 80.3, 76.8, 72.8, 67.7, 64.9, 54.9, 52.3, 27.2, 27.1, 26.6, 25.6, 19.2; HRMS (ESI) calcd for $C_{24}H_{34}NO_9$ (M^++1): 480.2234. Found: 480.2225.

4.2.18. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-[(*R*)-1-(methoxycarbonyl)ethyl]-(*S*)-phenylglycinate (27). A colorless oil was obtained in 49% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.38–7.29 (m, 5H), 5.48 (d, J=3.6 Hz, 1H), 5.26 (d, J=2.4 Hz, 1H), 4.46 (s, 1H), 4.19 (m, 2H), 4.07 (m, 2H), 3.95 (m, 1H), 3.71 (s, 3H), 3.23 (q, J=7.0 Hz, 1H), 2.65 (br, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.33 (m, 6H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.7, 171.4, 137.8, 129.1, 128.8, 128.1, 112.8, 109.7, 105.3, 83.2, 80.1, 77.0, 72.8, 67.5, 63.8, 54.0, 52.3, 27.2, 27.1, 26.6, 25.6, 19.5; HRMS (ESI) calcd for $C_{24}H_{34}NO_9$ (M^++1): 480.2234. Found: 480.2220.

4.2.19. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-[(*S*)-1-(*tert*-butoxycarbonyl)ethyl]-(*S*)-phenylglycinate (28). A colorless oil was obtained in 67% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40–7.28 (m, 5H), 5.57 (d, J=3.6 Hz, 1H), 5.33 (d, 1H), 4.47 (s, 1H), 4.18–4.06 (m, 4H), 3.99 (m, 1H), 3.30 (q, J=6.8 Hz, 1H), 2.36 (br, 1H), 1.47–1.37 (m, 15H), 1.32–1.26 (m, 6H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.4, 171.6, 138.0, 129.2, 128.8, 127.9, 112.7, 109.7, 105.4, 83.3, 81.5, 80.3, 76.7, 72.8, 67.6, 64.3, 55.5, 28.4, 27.2, 27.1, 26.6, 25.6, 19.3; HRMS (ESI) calcd for $C_{27}H_{40}NO_9$ (M^++1): 522.2703. Found: 522.2692.

4.2.20. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) *N*-[(*S*)-1-(methoxycarbonyl)-3-methylbutyl]-(*S*)-phenylglycinate (29). A colorless oil was obtained in 81%

yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40–7.30 (m, 5H), 5.57 (d, J=3.6 Hz, 1H), 5.33 (d, J=2.0 Hz, 1H), 4.41 (s, 1H), 4.15 (m, 2H), 4.12 (m, 1H), 4.07 (m, 1H), 3.99 (m, 1H), 3.61 (s, 3H), 3.39 (t, J=7.1 Hz, 1H), 2.19 (br, 1H), 1.83 (m, 1H), 1.52–1.47 (m, 5H), 1.41 (s, 3H), 1.32 (s, 3H), 1.22 (s, 3H), 0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.9, 171.5, 138.1, 129.1, 128.9, 128.0, 112.7, 109.8, 105.4, 83.3, 80.3, 76.7, 72.8, 67.6, 64.6, 58.5, 52.0, 43.0, 27.2, 27.1, 26.6, 25.5, 25.2, 23.2, 22.5; HRMS (ESI) calcd for $C_{27}H_{40}NO_9$ (M^++1): 522.2703. Found: 522.2687.

4.2.21. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-[(*S*)-2-(benzoxycarbonyl)-1-pyrrolidinyl]-α-phenylacetate (30). A colorless oil was obtained in 60% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40–7.29 (m, 10H), 5.64 (d, J=3.6 Hz, 1H), 5.34 (d, J=2.8 Hz, 1H), 5.12 (d, J=12.6 Hz, 1H), 5.04 (d, J=12.3 Hz, 1H), 4.70 (s, 1H), 4.23 (d, J=3.6 Hz, 1H), 4.16 (m, 2H), 4.00 (m, 2H), 3.77 (m, 1H), 2.86 (m, 2H), 2.14 (m, 1H), 2.01 (m, 1H), 1.79 (m, 2H), 1.48 (s, 3H), 1.38 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.3, 170.6, 137.0, 136.3, 129.1, 129.0, 128.9, 128.7, 112.7, 109.7, 105.4, 83.4, 80.4, 76.5, 72.8, 68.5, 67.6, 66.7, 63.1, 49.9, 30.3, 27.2, 27.1, 26.6, 25.6, 24.0; HRMS (ESI) calcd for $C_{32}H_{40}NO_9$ (M^++1): 582.2703. Found: 582.2700.

4.2.22. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl) (*S*)-α-[(*S*)-2-(benzoxycarbonyl)-1-pyrrolidinyl]-propionate (31). A colorless oil was obtained in 32% yield as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.38–7.31 (m, 5H), 5.86 (d, J=3.7 Hz, 1H), 5.29 (d, J=2.4 Hz, 1H), 5.19 (d, J=12.7 Hz, 1H), 5.12 (d, J=12.7 Hz, 1H), 4.44 (d, J=3.6 Hz, 1H), 4.14 (m, 2H), 3.97 (m, 2H), 3.78 (q, J=7.2 Hz, 1H), 3.72 (dd, J=5.4, 8.8 Hz, 1H), 3.14 (m, 1H), 2.86 (q, J=7.9 Hz, 1H), 2.09 (m, 1H), 1.98 (m, 1H), 1.85 (m, 2H), 1.52 (s, 3H), 1.39 (d, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.5, 172.3, 136.4, 129.0, 128.6, 128.5, 112.7, 109.8, 105.5, 83.9, 80.4, 76.4, 72.8, 67.9, 66.7, 63.1, 57.7, 47.5, 30.1, 27.2, 27.1, 26.6, 25.5, 24.2, 17.4; HRMS (ESI) calcd for $C_{27}H_{38}NO_9$ (M^++1): 520.2547. Found: 520.2551.

4.3. General procedure for the removal of chiral auxiliary

The mixture of diisopropylidene-α-D-glucofuranosyl *N*-substituted α-amino ester and Et_3N (15 equiv) in methanol (0.03 M) was stirred for 2 days. The solvent was evaporated and the crude material was purified by column chromatography to give a product.

4.3.1. Methyl (*N*-benzyl)-(*S*)-phenylglycinate (4). A colorless oil was obtained in 67% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39–7.25 (m, 1H), 4.40 (s, 1H), 3.73 (s, 2H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.9, 139.9, 138.5, 129.1, 128.8, 128.7, 128.5, 128.0, 127.6. Chiral HPLC: 96:4 er t_R (*S*)-major enantiomer, 11.1 min; t_R (*R*)-minor enantiomer, 12.1 min (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

4.3.2. *N*-[(*S*)-2-Methoxy-2-oxoethyl-1-phenyl]-(*S*)-alanine methyl ester (32). A colorless oil was obtained in 99% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39–7.27 (m, 5H), 4.45 (s, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.39 (q, J=6.9 Hz, 1H), 2.45 (br, 1H), 1.34 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.6, 173.4, 138.1, 129.2, 128.7, 128.1, 64.1, 54.9, 52.7, 52.3, 19.1. HRMS (ESI) calcd for $C_{13}H_{18}NO_4$ (M^++1): 252.1236. Found: 252.1236.

4.3.3. *N*-((*S*)-2-Methoxy-2-oxoethyl-1-phenyl)-(*S*)-leucine methyl ester (33). A colorless oil was obtained in 88% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39–7.26 (m, 5H), 4.39 (s, 1H), 3.69 (s, 3H), 3.59 (s, 3H), 3.36 (t, J=7.2 Hz, 1H), 2.24 (br, 1H), 1.80 (m, 1H), 1.48 (m, 2H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.9, 173.3, 138.4, 129.1, 128.7, 128.1, 64.6, 58.5, 52.6, 52.1, 43.1, 25.2, 23.2, 22.6; HRMS (ESI) calcd for $C_{16}H_{24}NO_4$ (M^++1): 294.1705. Found: 294.1704.

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6. When we prepared diacetone-D-glucose bound α-halo esters from racemic α-halo carboxylic acid derivatives, we obtained **5** and **6** with 69:31 dr and 73:27 dr, respectively. Formation of anything other than a 1:1 mixture of diastereomers can be explained by dynamic resolution of α-halo acids in the ester bond formation with chiral auxiliary. Alternatively, the in situ preparation of a ketene from α-halo acid halides and its treatment with a chiral auxiliary can afford diastereomerically enriched α-halo esters. For examples, see: (a) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799; (b) Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1997**, *11*, 1877; (c) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2004**, *15*, 593. The 55:45 diastereomeric mixture of **6** is prepared by column chromatography with fractional collection.
7. When nucleophiles such as tritylthiol, sodium malonate, sodium 3,5-dimethoxyphenoxides, and potassium 6-flavonoxide were used for the reaction with **1** or **2**, the corresponding substitution products were obtained in 76–94% yields with diastereomeric ratios from 69:31 to 54:46.
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