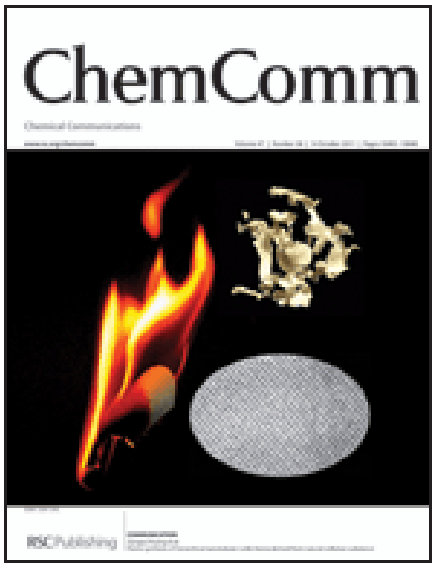

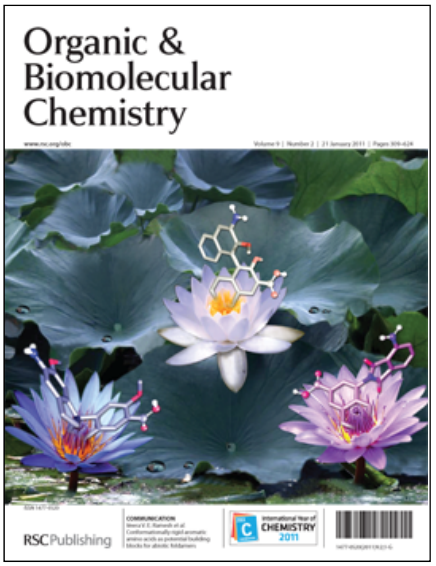

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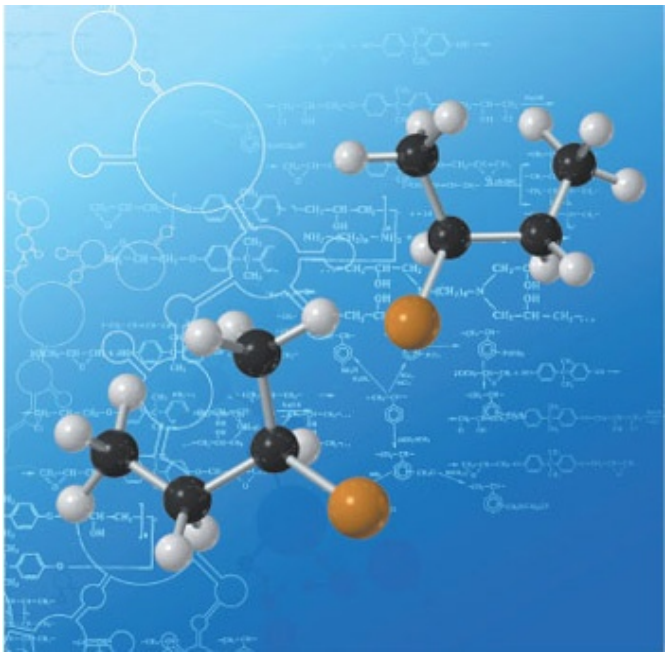

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PAPER

Aminohydroxyacetone synthons: versatile intermediates for the organocatalytic asymmetric aldol reaction†‡

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A practical method for the synthesis of 1,3-aminohydroxyacetone synthons was developed, and their utility in the organocatalytic asymmetric aldol reaction was demonstrated in a short synthesis of aza-sugars.

Introduction

Protected 1,3-dihydroxyacetone compounds are versatile intermediates for the synthesis of biologically interesting natural products with polyhydroxylated functionality.[1] The key structural unit of 1,3-amino alcohol is very relevant to this chemistry, and has been found in many antibiotics and other biologically active natural products.[2] In addition, 1,3-amino alcohols and their derivatives can play an important role in asymmetric synthesis as chiral ligands, as chiral auxiliaries, as resolving agents, and as phase-transfer catalysts.[3] Hence, there are considerable synthetic challenges to constructing these frameworks by the use of several strategies, but most of these are based on diastereoselective or enantioselective reduction of β-amino ketones or β-hydroxy imines/oximes.[4] There are therefore still some limitations in the direct and efficient methods for the construction of these valuable species.

Organocatalytic asymmetric transformations have recently attracted a great deal of attention from synthetic chemists as powerful and fascinating tools because of their mildness, high efficiencies, and environmentally friendly characteristics.[5] In our extensive efforts in this field,[6] we were particularly interested in the development of new designer aminohydroxyacetone synthons as analogs of 1,3-dihydroxyacetone derivatives. To our surprise, however, a search of the literature revealed that there is no precedent regarding the preparation of these molecules.

In this paper, we describe a new practical method for the synthesis of 1,3-aminohydroxyacetone synthons and their use in organocatalytic asymmetric aldol reactions.

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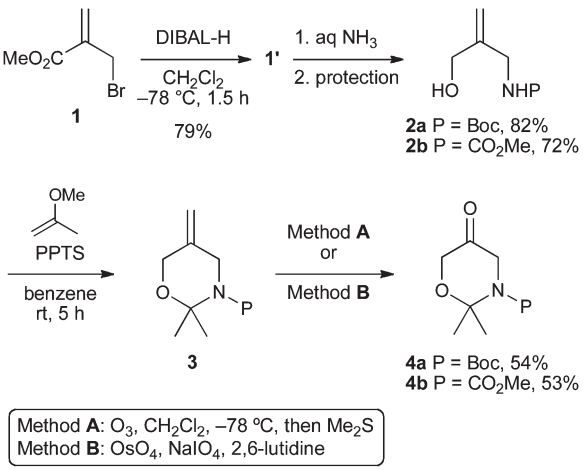
Results and discussion

Our synthetic strategy is outlined in Scheme 1.

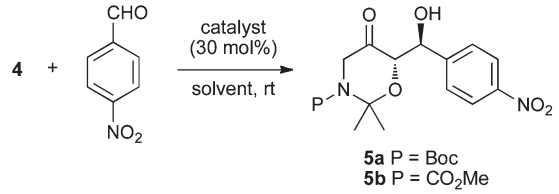


Scheme 1 Synthesis of protected aminohydroxyacetones.

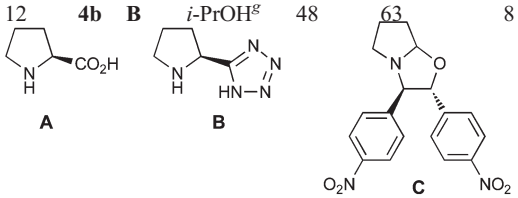
First, we started with the known allyl bromide **1**,[7] DIBAL-H reduction of the ester followed by exposure to an excess of aqueous ammonia and subsequent protection of the primary amine as *tert*-butyl carbamate or methyl carbamate gave **2a** or **2b** in good yield. Next, treatment of this substrate with 2-methoxypropene in the presence of a catalytic amount of PPTS smoothly gave the corresponding acetonide **3**. Finally, conversion to the target molecule **4** was achieved *via* oxidative cleavage of the double bond under either ozonolysis (Method **A** for **4a**) or Lemieux–Johnson conditions (Method **B** for **4b**). This overall process is easy for a multi-gram-scale preparation and for the attachment of other nitrogen protective groups such as benzyl carbamate.

Next, we examined the aldol reaction of **4** with 0.5 equiv of *p*-nitrobenzaldehyde using L-proline (30 mol%) in dimethyl sulfoxide (DMSO) at room temperature. Unfortunately, however, no

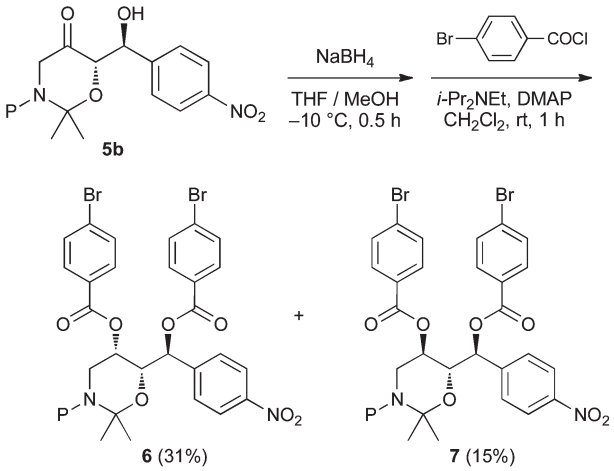
Table 1 Organocatalytic asymmetric aldol reaction of **4**: optimization study[a]



Entry	4	Cat.	Solvent	Time (h)	Yield[b] (%)	*syn* : *anti*[c]	ee[d] (%)
1	**4a**	**A**	DMSO	168	0	—	—
2	**4a**	**A**[e]	DMSO	5	0[f]	—	—
3	**4b**	**A**	DMSO	168	0	—	—
4	**4a**	**B**	*i*-PrOH	120	81	2 : 98	90
5	**4a**	**B**	MeCN	120	71	11 : 89	97
6	**4b**	**B**	DMSO	168	14	3 : 97	94
7	**4b**	**B**	DMF	120	66	1 : 99	96
8	**4b**	**B**	NMP	72	69	4 : 96	96
9	**4b**	**B**	$MeNO_2$	72	50	7 : 93	98
10	**4b**	**B**	MeCN	96	71	15 : 85	98
11	**4b**	**B**	*i*-PrOH	72	73	5 : 95	98
12	**4b**	**B**	*i*-PrOH[g]	48	63	8 : 92	79



[a] Conditions: **4** (1 mmol), *p*-nitrobenzaldehyde (0.5 mmol) in the solvent (2.5 mL) in the presence of 30 mol% of the catalyst. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis using a Chiralcel OD-H after converting to the corresponding acetate. [e] 100 mol% of the catalyst was used. [f] 1,3-Oxazolidine **C** was isolated in 40% yield. [g] 500 mol% of H_2O was added as an additive.



Scheme 2 Derivatization of **5b** (P = CO_2Me).

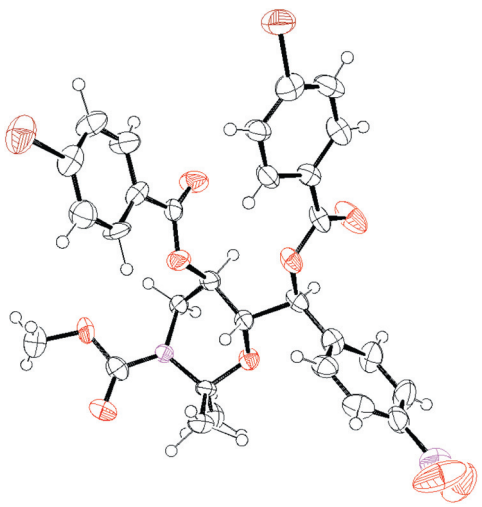


Fig. 1 Structure of the dibenzoate stereoisomer **7** by X-ray analysis.

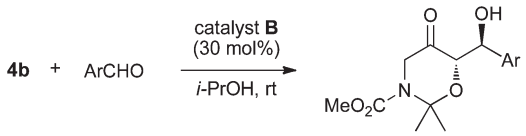
reaction was observed even after 1 week (Table 1, entries 1 and 3). The use of 100 mol% of L-proline caused the parasitic reaction of L-proline,[8] and gave bicyclic 1,3-oxazolidine **C** in 40% yield (based on L-proline) (Table 1, entry 2). Instead, the use of L-proline-derived tetrazole **B**[9] as a catalyst was found to be favorable for our purpose. Thus, the reaction of **4a** with 0.5 equiv of *p*-nitrobenzaldehyde using 30 mol% of catalyst **B** in *i*-PrOH at room temperature gave the adduct **5a** in 81% yield with excellent diastereoselectivity (*syn* : *anti* = 2 : 98) and high enantioselectivity (90% ee), but the reaction required 5 days to reach completion (Table 1, entry 4). Interestingly, the reaction was rather sensitive to the solvent used, and the reaction rates were relatively slow in DMSO, DMF, and MeCN (Table 1, entries 5–7, 10). After screening, we found that the reaction with **4b** in *i*-PrOH was the best in terms of reaction time, product yield, and diastereo- and enantioselectivity (Table 1, entry 11). In contrast to our previous observations regarding proline-catalysis,[10] the addition of water significantly decreased the enantioselectivity (Table 1, entry 12).

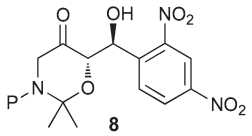
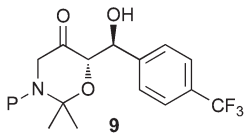
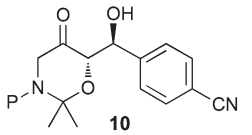
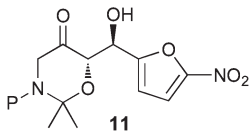
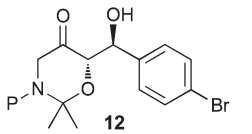
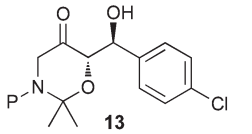
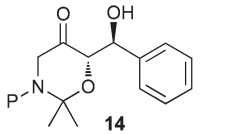
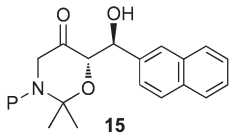
At this stage, the regiochemistry of the reaction course and the absolute configuration of the major diastereomer of **5** were both unknown. To solve these problems, **5b** was reduced with $NaBH_4$ in THF–MeOH followed by esterification using 2.5 equiv of *p*-bromobenzoyl chloride–*i*-Pr_2NEt in CH_2Cl_2 (Scheme 2). Fortunately, one of the dibenzoate stereoisomers, **7**, was obtained as a crystalline substance (mp 170–172 °C) and its structure was unambiguously determined by X-ray crystallographic analysis (Fig. 1).[11]

As evident from this result, carbon–carbon bond-formation was highly regioselective, and the reaction took place only at the oxygen-containing α-side of aminohydroxyacetone **4**. On the other hand, the absolute stereochemical sequence exactly dictates well-established enamine-based asymmetric organocatalysis.[12] Consequently, in the present system, enamine formation *via* deprotonation at the α-carbon might be considered to be facilitated by the enhanced acidity due to the presence of an electronegative oxygen atom.

With the optimal conditions in hand, we then examined a variety of aromatic and heteroaromatic aldehydes to establish the general utility of this synthetic methodology. All reactions were performed in *i*-PrOH at room temperature in the presence of 30 mol% of catalyst **B** (Table 2).[13,14]

Table 2 Organocatalytic asymmetric aldol reaction of **4b**: generality[a]



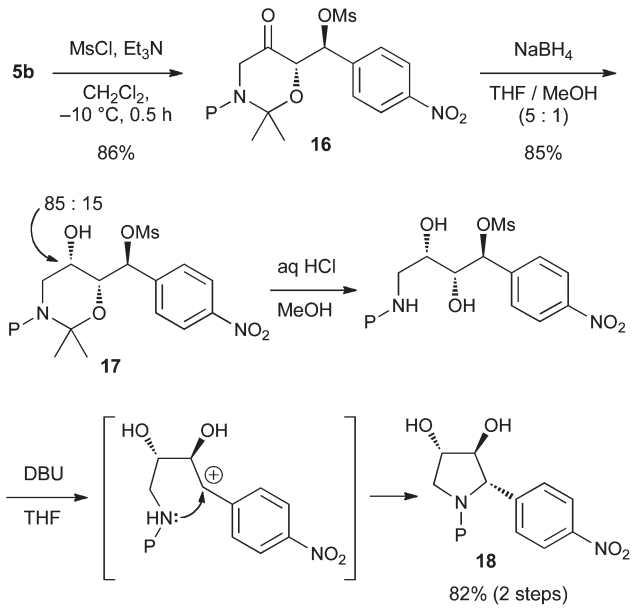
Entry	Product (P = CO_2Me)	Time (h)	Yield[b] (%)	*syn* : *anti*[c]	ee[d] (%)
1	 **8**	48	93	14 : 86	89
2	 **9**	24	60	5 : 95	97
3	 **10**	120	70	8 : 92	94
4[e]	 **11**	72	70	21 : 79	80
5	 **12**	120	41	4 : 96	94
6	 **13**	120	31	2 : 98	96
7	 **14**	168	17	17 : 83	91
8	 **15**	120	29	7 : 93	89

[a] Conditions: **4b** (1 mmol), ArCHO (0.5 mmol) in *i*-PrOH (2.5 mL) in the presence of 30 mol% of the catalyst. [b] Isolated yield. The absolute configuration of the products was surmised by analogy. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis using a Chiralcel OD-H after converting to the corresponding acetate. [e] MeCN was used as the solvent.

Various aldehydes reacted smoothly with **4b** in moderate yields (up to 93%) with excellent diastereo- (up to *syn* : *anti* = 2 : 98) and enantioselectivity (up to 97%) (Table 2, entries 1–8). This method is particularly useful for reactive aldehydes bearing electron-withdrawing groups, with a good level of chemical yield (Table 2, compare entries 1–4 with entries 5–8).

To demonstrate the synthetic value of this organocatalytic asymmetric protocol, polyhydroxylated pyrrolidine alkaloids were targeted, since these molecules have attracted considerable attention as mimics of sugars and as potential pharmaceutical drugs.[15] Our four-step sequence is outlined in Scheme 3.

Mesylation of **5b** by treatment with MsCl–Et_3N followed by reduction with $NaBH_4$ in THF–MeOH provided monoalcohol **16** in good yield with high stereoselectivity (85 : 15). After deprotection of an acetonide function, intramolecular cyclization was affected by exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene

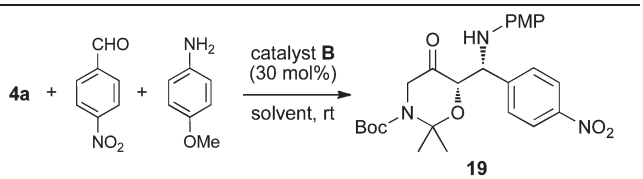


Scheme 3 Short synthesis of aza-sugar **18** (P = CO_2Me).

(DBU) in THF at room temperature to afford the desired pyrrolidine derivative **18** with an almost complete retention of stereochemistry (60% total yield). The relative configuration of this product was assigned by NOESY experiments, suggesting at the final stage in this reaction sequence the S_N1-type pyrrolidine-ring cyclization at the benzylic position.

Finally, we briefly examined the applicability of **4** to the three-component Mannich-type reaction using *p*-nitrobenzaldehyde and *p*-anisidine (Table 3). In this case, the use of **4a** as a donor in DMF was most favorable, and the expected 1,4-diamine derivative **19** was obtained in 63% yield with high diastereo- (*syn* : *anti* = 84 : 16) and enantioselectivity (88% ee) (Table 3, entry 2).[13,16]

Table 3 Organocatalytic asymmetric synthesis of Mannich adduct **19**[a]



Entry	Solvent	Time (h)	Yield[b] (%)	*syn* : *anti*[c]	ee[d] (%)
1	DMSO	72	71	68 : 32	68
2	DMF	96	63	84 : 16	88
3	NMP	96	55	75 : 25	88
4	THF	96	23	81 : 19	ND[e]

[a] Conditions: **4a** (0.75 mmol), *p*-nitrobenzaldehyde (0.5 mmol), *p*-anisidine (0.5 mmol) in the solvent (1.7 mL) in the presence of 30 mol % of the catalyst. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC analysis using a Chiralpak AD after deprotection of an acetonide function followed by mono-acetylation. [e] Not determined.

Conclusions

In conclusion, we have developed a new practical method for the synthesis of aminohydroxyacetone synthons, and demonstrated their versatile utility in organocatalytic asymmetric aldol and Mannich reactions. In addition, this methodology was successfully applied to the short synthesis of aza-sugars in optically active forms. We believe that this method should provide an expeditious route to a significant class of 1,3-amino alcohol derivatives. Further studies to extend the scope of this method are now in progress.

Experimental section

2-(Bromomethyl)prop-2-en-1-ol (1′)

To a solution of **1** (5.23 g, 29.4 mmol) in CH_2Cl_2 (200 mL) was added at −78 °C DIBAL-H (1.03 M in hexane; 60 mL, 61.8 mmol) over 0.5 h. After stirring for 1 h, the mixture was allowed to warm to 0 °C and quenched by addition of MeOH. Subsequent addition of saturated Rochelle's solution produced a gelatin-like solid, which was stirred at room temperature until the slurry was re-dissolved and a separation of the layers was observed. The aqueous layer was separated and extracted thoroughly with CH_2Cl_2. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–Et_2O = 2 : 1) to afford the bromoalcohol **1′** (3.5 g, 79%) as a colorless oil; FTIR (KBr) ν 3366, 1210, 1059, 1027, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (1H, br), 4.05 (2H, s), 4.29 (2H, s), 5.26 (1H, m), 5.31 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.8, 63.2, 115.6, 144.6; Anal. Calcd for C_4H_9BrO: C, 31.82; H, 4.67. Found: C, 32.20; H, 4.43.

tert-Butyl 2-(hydroxymethyl)allylcarbamate (2a)

To a solution of 28% aq NH_3 (60 mL) was added dropwise a solution of **1′** (2.8 g, 18.7 mmol) in MeOH (9 mL) at 0 °C over 10 min. After stirring for 1 h, the mixture was concentrated under reduced pressure. The residue was re-dissolved in a mixture of 1,4-dioxane–H_2O (40 mL, 3 : 1), and Boc_2O (4.5 g, 20.5 mmol) and Et_3N (5.2 mL, 37.3 mmol) were added at room temperature. After stirring for 1 h, H_2O was added and the mixture was extracted with AcOEt. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 2 : 1) to afford **2a** (2.87 g, 82%) as a colorless oil; FTIR (KBr) ν 3352, 1694, 1524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s), 3.02 (1H, br), 3.80 (2H, d, J = 6.1 Hz), 4.10 (2H, d, J = 2.4 Hz), 4.87 (1H, br), 4.99 (1H, s), 5.06 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4 (×3), 42.8, 64.0, 79.9, 112.2, 146.2, 156.8; Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.08; H, 9.53; N, 7.58.

Methyl 2-(hydroxymethyl)allylcarbamate (2b)

To a solution of 28% aqueous NH_3 (60 mL) was added dropwise a solution of **1′** (3.1 g, 20.7 mmol) in MeOH (9 mL) at 0 °C

over 10 min. After stirring for 1 h, the mixture was concentrated under reduced pressure. The residue was re-dissolved in a mixture of 1,4-dioxane–H_2O (40 mL, 3 : 1), and $ClCO_2Me$ (1.91 mL, 22.7 mmol) and Et_3N (5.75 mL, 41.3 mmol) were added at room temperature. After stirring for 1 h, the solvent was removed under reduced pressure and the residue was extracted with AcOEt. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 1 : 1) to afford **2b** (2.11 g, 72%) as a colorless oil; FTIR (KBr) ν 3337, 1706, 1541, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.19 (1H, br), 3.69 (3H, s), 3.85 (2H, d, J = 6.1 Hz), 4.11 (2H, d, J = 3.9 Hz), 5.02 (1H, s), 5.10 (1H, s), 5.26 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.1, 52.3, 63.9, 112.2, 145.6, 157.7; Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.49; H, 8.02; N, 9.75.

tert-Butyl 2,2-dimethyl-5-methylen-1,3-oxazinane-3-carboxylate (3a)

To a solution of **2a** (2.01 g, 11.3 mmol) in benzene (56 mL) were added 2-methoxypropene (4.2 mL, 45.2 mmol) and PPTS (284 mg, 1.13 mmol) at room temperature, and the mixture was stirred for 9 h. After quenching by addition of 1 N NaOH, the mixture was extracted with AcOEt. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford **3a** (2.46 g, 96%) as a colorless oil, which was used for the next reaction without further purification; FTIR (KBr) ν 1696, 1384, 1366, 1245, 1164, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.61 (6H, s), 4.09 (2H, s), 4.35 (2H, m), 4.77 (1H, m), 4.93 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (×2), 28.4 (×3), 44.7, 63.0, 79.9, 88.1, 106.4, 142.7, 153.5; Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.80; H, 9.54; N, 6.17.

Methyl 2,2-dimethyl-5-methylen-1,3-oxazinane-3-carboxylate (3b)

To a solution of **2b** (3.0 g, 21 mmol) in benzene (100 mL) were added 2-methoxypropene (7.7 mL, 83 mmol) and PPTS (1.04 g, 4.1 mmol) at room temperature, and the mixture was stirred for 5 h. After quenching by addition of 1 N NaOH, the mixture was extracted with AcOEt. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated to afford **3b** (3.79 g, 99%) as a colorless oil, which was used for the next reaction without further purification; FTIR (KBr) ν 1705, 1441, 1376, 1244, 1223, 1085 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5 (×2), 44.9, 52.1, 63.0, 88.2, 106.7, 142.2, 154.3; Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.41; H, 8.55; N, 7.43.

tert-Butyl 2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (4a)

A solution of **3a** (1.95 g, 8.58 mmol) in CH_2Cl_2 (120 mL) was stirred with bubbling of gaseous ozone at −78 °C. After stirring for 0.5 h, the excess of ozone was removed by passing through nitrogen for 5 min. Then Me_2S (3 mL) was added, and the mixture was allowed to warm to room temperature. After stirring for 5 h, the mixture was concentrated under reduced pressure, and the residue was recrystallized from hexane–AcOEt to afford **4a** (1.65 g, 84%) as colorless prisms; Mp 110–113 °C (from hexane–AcOEt); FTIR (KBr) ν 1753, 1699, 1387, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (9H, s), 1.69 (6H, s), 4.13 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3 (×2), 28.3 (×3), 50.3, 67.0, 81.1, 88.5, 153.3, 206.3; Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.86; H, 8.61; N, 6.17.

Methyl 2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (4b)

To a solution of **3b** (3.79 g, 20 mmol) in 1,4-dioxane–H_2O (100 mL, 3 : 1) were added at room temperature 2,6-lutidine (4.77 mL, 41 mmol), OsO_4 (2.8% in H_2O, 3.72 g, 0.4 mmol), and $NaIO_4$ (17.5 g, 82 mmol), and the mixture was stirred for 1 h. After dilution by addition of H_2O, the mixture was extracted with CH_2Cl_2. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 5 : 1) to afford **4b** (2.9 g, 76%) as a colorless solid; Mp 29–31 °C; FTIR (KBr) ν 1753, 1709, 1446, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (6H, s), 3.70 (3H, s), 4.15 (2H, s), 4.17 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (×2), 50.2, 52.6, 66.9, 88.7, 154.3, 205.6; Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.53; H, 7.27; N, 7.58.

General procedure for the aldol reaction of 4

To a solution of **4** (0.5 mmol) in *i*-PrOH (1.25 mL) were added aldehyde (0.25 mmol) and catalyst (0.075 mmol), and the mixture was stirred at room temperature. After completion of the reaction, the mixture was diluted with H_2O, and extracted with AcOEt. The combined extracts were washed with saturated NH_4Cl and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane–AcOEt) to afford the desired product as summarized in Table 1.

After acetylation (Ac_2O, pyridine, room temperature, overnight), the major product was isolated in a pure form and its ee value was determined by chiral HPLC analysis using a Chiralcel OD-H. The results are summarized in Tables 1 and 2.

tert-Butyl (6*S*,1′*S*)-6-(acetoxy(4-nitrophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (5a-Ac)

Pale yellow oil; $[\alpha]_D^{18}$ −38.0 (c 1.64, $CHCl_3$); FTIR (KBr) ν 1752, 1700, 1525, 1370, 1348, 1230, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.53, 1.73, 2.16 (each 3H, s), 3.40 (1H, dd, J = 17.6, 1.0 Hz), 4.39 (1H, d, J = 17.6 Hz), 4.63 (1H, dd, J = 4.0, 1.0 Hz), 6.25 (1H, d, J = 4.0 Hz), 7.55 (2H, d, J = 8.8 Hz), 8.17 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.4 (×2), 28.3 (×3), 50.4, 72.4, 76.2, 81.4, 89.4, 123.1 (×2), 129.2 (×2), 142.4, 147.9, 153.0, 169.5, 203.7; HRMS Calcd for $C_{20}H_{26}N_2O_8$ 422.1689, Found 422.1684. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 90 : 10, 0.5 mL min^{-1}): t_R 14.57 (minor) and t_R 20.79 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(4-nitrophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (5b-Ac)

Pale yellow oil; $[\alpha]_D^{18}$ −37.7 (*c* 0.82, $CHCl_3$); FTIR (KBr) *ν* 1752, 1709, 1524, 1373, 1348, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.55, 1.76, 2.15 (each 3H, s), 3.46 (1H, dd, *J* = 17.5, 1.0 Hz), 3.67 (3H, s), 4.40 (1H, br d, *J* = 17.5 Hz), 4.64 (1H, dd, *J* = 4.0, 1.0 Hz), 6.24 (1H, d, *J* = 4.0 Hz), 7.54 (2H, d, *J* = 9.0 Hz), 8.17 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 20.9, 23.8, 24.3, 50.4, 52.7, 72.4, 76.2, 89.6, 123.1 (×2), 129.2 (×2), 142.2, 147.8, 154.1, 169.5, 203.1; HRMS Calcd for $C_{17}H_{20}N_2O_8$ + H 381.1298, Found 381.1288. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 90 : 10, 0.5 mL min^{-1}): t_R 31.65 (minor) and t_R 44.90 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(2,4-dinitrophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (8-Ac)

Pale yellow oil; $[\alpha]_D^{24}$ −25.2 (*c* 0.30, $CHCl_3$); FTIR (KBr) *ν* 1755, 1709, 1607, 1539, 1446, 1372, 1350, 1226 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.58, 1.69, 2.19 (each 3H, s), 3.68 (3H, s), 3.87 (1H, br d, *J* = 17.0 Hz), 4.49 (1H, br d, *J* = 17.0 Hz), 4.56 (1H, br d, *J* = 4.5 Hz), 6.74 (1H, d, *J* = 4.5 Hz), 7.92 (1H, d, *J* = 8.5 Hz), 8.47 (1H, dd, *J* = 8.5, 2.5 Hz), 8.88 (1H, d, *J* = 2.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 20.7, 23.7, 24.4, 50.7, 52.8, 69.8, 75.1, 90.1, 120.2, 127.2, 130.5, 138.6, 147.5, 147.9, 169.0, 202.9; HRMS Calcd for $C_{17}H_{19}N_3O_{10}$ + H 426.1149, Found 426.1137. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 80 : 20, 0.5 mL min^{-1}): t_R 38.45 (minor) and t_R 63.25 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(4-trifluoromethylphenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (9-Ac)

Colorless oil; $[\alpha]_D^{18}$ −45.2 (*c* 1.11, $CHCl_3$); FTIR (KBr) *ν* 1752, 1712, 1374, 1327, 1231, 1169, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.56, 1.74, 2.13 (each 3H, s), 3.46 (1H, dd, *J* = 17.1, 1.5 Hz), 3.66 (3H, s), 4.37 (1H, br d, *J* = 17.1 Hz), 4.63 (1H, dd, *J* = 4.2, 1.5 Hz), 6.21 (1H, d, *J* = 4.1 Hz), 7.50 (2H, d, J_{AB} = 8.3 Hz), 7.58 (2H, d, J_{AB} = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 20.9, 23.7, 24.4, 50.5, 52.6, 72.8, 76.3, 89.5, 119.9, 122.6, 124.8 (5), 124.8(9), 124.9(3), 124.9(7), 125.3, 128.0, 128.6 (×2), 130.1, 130.4, 130.7, 131.0, 139.1, 154.1, 169.5, 203.2; HRMS Calcd for $C_{18}H_{20}F_3NO_6$ + H 404.1321, Found 404.1321. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 95 : 5, 0.5 mL min^{-1}): t_R 20.35 (minor) and t_R 28.52 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(4-cyanophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3- carboxylate (10-Ac)

Colorless oil; $[\alpha]_D^{18}$ −34.5 (*c* 1.04, $CHCl_3$); FTIR (KBr) *ν* 2229, 1750, 1709, 1373, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.55, 1.74, 2.14 (each 3H, s), 3.45 (1H, dd, *J* = 17.2, 2.0 Hz), 3.67 (3H, s), 4.39 (1H, br d, *J* = 17.2 Hz), 4.61 (1H, br d, *J* = 4.0 Hz), 6.19 (1H, d, *J* = 4.0 Hz), 7.48 (2H, d, J_{AB} = 7.6 Hz), 7.62 (2H, d, J_{AB} = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 20.9, 23.8, 24.3, 50.4, 52.7, 72.6, 76.2, 89.6, 112.4, 118.5, 129.0 (×2), 131.8 (×2), 140.3, 154.2, 169.5, 203.2; HRMS Calcd for $C_{18}H_{20}N_2O_6$ + H 361.1400, Found 361.1403. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 90 : 10, 0.5 mL min^{-1}): t_R 56.74 (major) and t_R 81.77 (minor) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(5-nitro-2-furyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (11-Ac)

Yellow oil; $[\alpha]_D^{23}$ −20.4 (*c* 0.96, $CHCl_3$); FTIR (KBr) *ν* 1758, 1709, 1537, 1504, 1372, 1358, 1226 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.58, 1.80, 2.16 (each 3H, s), 3.70 (3H, s), 3.83 (1H, d, *J* = 17.5 Hz), 4.55 (1H, br d, *J* = 17.5 Hz), 4.74 (1H, d, *J* = 5.0 Hz), 6.24 (1H, d, *J* = 5.0 Hz), 6.61 (1H, d, *J* = 3.5 Hz), 7.25 (1H, d, *J* = 3.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 20.7, 23.7, 24.3, 50.4, 52.8, 66.4, 74.1, 90.1, 111.9, 113.0, 151.8 (×2), 157.7, 169.2, 202.2; HRMS Calcd for $C_{15}H_{18}N_2O_9$ + H 371.1091, Found 371.1084. The ee was determined by chiral HPLC (hexane–i-PrOH = 80 : 20, 0.5 mL min^{-1}): t_R 38.45 (minor) and t_R 63.25 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(4-bromophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (12-Ac)

Colorless oil; $[\alpha]_D^{17}$ −28.4 (*c* 1.21, $CHCl_3$); FTIR (KBr) *ν* 1751, 1710, 1373, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.56, 1.73, 2.11 (each 3H, s), 3.45 (1H, dd, *J* = 17.1, 1.2 Hz), 3.66 (3H, s), 4.34 (1H, br d, *J* = 17.1 Hz), 4.59 (1H, dd, *J* = 4.2, 1.2 Hz), 6.11 (1H, d, *J* = 4.2 Hz), 7.25 (2H, m), 7.44 (2H, m); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 21.2, 23.9, 24.7, 50.6, 52.8, 73.0, 76.5, 89.6, 122.8, 130.2 (×2), 131.3 (×2), 134.3, 154.3, 169.8, 203.6; HRMS Calcd for $C_{17}H_{20}BrNO_6$ + H 414.0552, Found 414.0531. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 95 : 5, 0.5 mL min^{-1}): t_R 21.99 (minor) and t_R 28.85 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(4-chlorophenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (13-Ac)

Colorless oil; $[\alpha]_D^{17}$ −37.3 (*c* 0.77, $CHCl_3$); FTIR (KBr) *ν* 1750, 1710, 1373, 1232 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.56, 1.73, 2.12 (each 3H, s), 3.44 (1H, dd, *J* = 17.0, 1.5 Hz), 3.66 (3H, s), 4.34 (1H, br d, *J* = 17.0 Hz), 4.58 (1H, br d, *J* = 4.0 Hz), 6.12 (1H, d, *J* = 4.0 Hz), 7.26–7.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 21.3, 24.0, 24.8, 50.8, 52.9, 73.1, 76.7, 89.7, 128.5 (×2), 130.0 (×2), 134.0, 134.7, 154.4, 169.9, 203.7; HRMS Calcd for $C_{17}H_{20}ClNO_6$ + H 370.1057, Found 370.1037. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 95 : 5, 0.5 mL min^{-1}): t_R 23.14 (minor) and t_R 28.06 (major) min.

Methyl (6*S*,1′*S*)-6-(acetoxy(phenyl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (14-Ac)

Colorless oil; $[\alpha]_D^{18}$ −88.8 (*c* 0.66, $CHCl_3$); FTIR (KBr) *ν* 1751, 1709, 1373, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.56, 1.71, 2.12 (each 3H, s), 3.44 (1H, dd, *J* = 17.0, 1.0 Hz), 3.65 (3H, s), 4.31 (1H, br d, *J* = 17.0 Hz), 4.60 (1H, dd, *J* = 4.0, 1.0 Hz), 6.14 (1H, d, *J* = 4.0 Hz), 7.29–7.31 (3H, m), 7.35–7.37 (2H, m); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 21.1, 23.7, 24.6,

50.5, 52.6, 73.6, 76.6, 89.3, 128.0 (×2), 128.2 (×2), 128.5, 135.1, 169.7, 203.5 (carbamate carbon is missing); HRMS Calcd for $C_{17}H_{21}NO_6$ + H 336.1447, Found 336.1447. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 95 : 5, 0.5 mL min^{-1}): t_R 24.94 (minor) and t_R 35.08 (major) min.

Methyl (6*S*,1′*S*)-(acetoxy(naphthalen-2-yl)methyl)-2,2-dimethyl-5-oxo-1,3-oxazinane-3-carboxylate (15-Ac)

Colorless oil; $[\alpha]_D^{18}$ −16.2 (*c* 0.98, $CHCl_3$); FTIR (KBr) *ν* 1750, 1709, 1372, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.56, 1.74, 2.14 (each 3H, s), 3.42 (1H, dd, *J* = 16.8, 1.4 Hz), 3.63 (3H, s), 4.31 (1H, br d, *J* = 16.8 Hz), 4.70 (1H, dd, *J* = 4.2, 1.2 Hz), 6.33 (1H, d, *J* = 4.2 Hz), 7.45–7.50 (2H, m), 7.53 (1H, dd, *J* = 8.5, 1.7 Hz), 7.78–7.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 21.0, 23.7, 24.5, 50.5, 52.5, 73.6, 76.7, 89.3, 125.7, 126.1, 126.3, 127.5, 127.6, 127.8, 128.2, 132.6, 132.7, 133.2, 154.1, 169.7, 203.5; HRMS Calcd for $C_{21}H_{23}NO_6$ + H 386.1604, Found 386.1597. The ee was determined by chiral HPLC (hexane–*i*-PrOH = 95 : 5, 0.5 mL min^{-1}): t_R 27.35 (minor) and t_R 33.88 (major) min.

Derivatization of 5b to the corresponding dibenzoate esters 6 and 7

To a solution of **5b** (32 mg, 0.094 mmol) in THF–MeOH (1.8 mL, 5 : 1) was added at −10 °C $NaBH_4$ (6.8 mg, 0.178 mmol), and the mixture was stirred at this temperature for 0.5 h. After quenching by addition of ice-water, the aqueous layer was extracted with AcOEt. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL), and *i*-Pr_2NEt (36.4 mg, 0.282 mmol), 4-dimethylaminopyridine (4.6 mg, 0.038 mmol), and *p*-bromobenzoyl chloride (51.9 mg, 0.235 mmol) were added at room temperature, and the mixture was stirred for 1 h. After quenching by addition of saturated $NaHCO_3$, the mixture was extracted with AcOEt. The combined extracts were washed with saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 4 : 1) to afford **6** (21 mg, 31%) as an oil and **7** (10 mg, 15%) as colorless crystals.

Compound 6

Colorless oil; $[\alpha]_D^{24}$ +22.3 (*c* 1.30, $CHCl_3$); FTIR (neat) *ν* 1727, 1607, 1590, 1525 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.31, 1.54 (each 3H, s), 3.43 (1H, dd, *J* = 14.0, 6.5 Hz), 3.64 (3H, s), 4.33 (1H, dd, *J* = 14.0, 6.5 Hz), 4.35 (1H, dd, *J* = 10.0, 4.0 Hz), 5.61 (1H, dt, *J* = 6.5, 4.0 Hz), 6.10 (1H, d, *J* = 10.0 Hz), 7.50–7.54 (4H, m), 7.63 (2H, d, *J* = 8.5 Hz), 7.67 (2H, d, *J* = 8.0 Hz), 7.74 (2H, d, *J* = 8.5 Hz), 8.20–8.22 (2H, m); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 22.8, 25.0, 42.8, 52.5, 68.0, 71.9, 72.5, 89.7, 123.5 (×2), 127.5, 127.8, 128.1 (×2), 128.7, 128.9, 130.9 (×2), 131.1 (×2), 131.7 (×2), 131.8 (×2), 144.9, 147.8, 154.7, 163.9, 164.7; HRMS Calcd for $C_{29}H_{26}Br_2N_2O_9$ + H 705.0083, Found 705.0074.

Compound 7

Mp 170–172 °C (from Et_2O); $[\alpha]_D^{21}$ −86.0 (*c* 0.10, $CHCl_3$); FTIR (KBr) *ν* 1722, 1700, 1590, 1525 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.50, 1.71 (each 3H, s), 3.33 (1H, dd, *J* = 14.5, 3.0 Hz), 3.61 (3H, s), 4.14 (1H, d, *J* = 14.5 Hz), 4.27 (1H, t, *J* = 6.0 Hz), 5.35 (1H, m), 6.17 (1H, d, *J* = 5.5 Hz), 7.47 (2H, m), 7.58 (2H, m), 7.67 (2H, m), 7.76 (2H, m), 7.79 (2H, m), 8.20 (2H, m); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 23.4, 24.7, 43.3, 52.4, 71.1, 73.2, 75.0, 89.6, 123.5 (×2), 127.8, 128.0, 128.4 (×2), 128.8, 128.9, 131.0 (×4), 131.8 (×4), 143.2, 147.9, 154.8, 164.3, 164.8; HRMS Calcd for $C_{29}H_{26}Br_2N_2O_9$ + H 705.0083, Found 705.0076.

Mesylation of 5b

To a solution of **5b** (111 mg, 0.33 mmol) in CH_2Cl_2 (6.7 mL) were added at −10 °C Et_3N (57 mg, 0.56 mmol) and MsCl (56 mg, 0.50 mmol), and the mixture was stirred at this temperature for 0.5 h. After quenching by addition of H_2O, the mixture was extracted with $CHCl_3$. The combined extracts were washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 1 : 4) to afford **16** (117 mg, 86%) as a pale yellow solid; $[\alpha]_D^{21}$ −15.3 (*c* 0.29, $CHCl_3$); FTIR (KBr) *ν* 1752, 1708, 1525, 1446, 1369, 1350 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.56, 1.80, 3.00 (each 3H, s), 3.48 (1H, dd, *J* = 18.0, 1.0 Hz), 3.68 (3H, s), 4.44 (1H, br d, *J* = 18.0 Hz), 4.76 (1H, dd, *J* = 4.0, 1.0 Hz), 6.05 (1H, d, *J* = 4.0 Hz), 7.60 (2H, d, *J* = 8.5 Hz), 8.22 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 23.9, 24.2, 39.1, 50.4, 52.8, 77.2, 78.4, 90.0, 123.5 (×2), 129.3 (×2), 140.4, 148.3, 154.1, 202.3; HRMS Calcd for $C_{16}H_{20}N_2O_9S$ + H 417.0968, Found 417.0954.

Reduction of 16

To a solution of **16** (244 mg, 0.585 mmol) in THF–MeOH (6 mL, 5 : 1) was added at −10 °C $NaBH_4$ (27 mg, 0.71 mmol), and the mixture was stirred at this temperature for 0.5 h. After quenching by addition of ice-water, the mixture was extracted with AcOEt. The combined extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt = 1 : 2) to afford **17** (208 mg, 85%) as an amorphous solid; $[\alpha]_D^{21}$ +35.9 (*c* 0.50, $CHCl_3$); FTIR (KBr) *ν* 3424, 1695, 1525, 1451, 1389, 1350, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.54, 1.62 (each 3H, s), 2.59 (1H, d, *J* = 7.6 Hz), 2.92 (3H, s), 3.43 (1H, br t, *J* = 8.8 Hz), 3.69 (4H, br s), 3.89 (1H, m), 4.44 (1H, ddd, *J* = 9.4, 6.8, 2.8 Hz), 5.56 (1H, d, *J* = 8.8 Hz), 7.65, 8.29 (each 2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 24.3, 26.0, 39.0, 46.4, 52.3, 71.9, 77.2, 80.6, 94.7, 123.9 (×2), 128.5 (×2), 143.0, 148.3, 152.8; HRMS Calcd for $C_{16}H_{21}N_2O_9S$ + H 419.1124, Found 419.1133.

Conversion of 17 to aza-sugar 18

To a solution of **17** (50 mg, 0.12 mmol) in MeOH (5 mL) was added at room temperature HCl in MeOH (0.5 mL), and the

mixture was stirred for 12 h. After completion of the reaction, the solvent was removed *in vacuo*, and the residue was diluted with THF (1 mL) and then DBU (2 drops) was added at room temperature. After stirring for 10 min, the mixture was concentrated under reduced pressure and purified by silica-gel column chromatography (eluted with AcOEt) to afford **18** (28 mg, 82%) as colorless crystals; mp 105–108 °C; $[\alpha]_D^{24}$ +48.0 (*c* 1.09, MeOH); FTIR (KBr) *ν* 3322, 1687, 1604, 1549, 1518, 1351 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, H–H and C–H COSY, NOESY) *δ* 2.98 (1H, br d, *J* = 4.5 Hz; NCH(Ar)C***H***OH), 3.15 (1H, dd, *J* = 13.5, 6.5 Hz; C***H***H′N), 3.27 (1H, dd, *J* = 13.5, 6.5 Hz; CH***H′***N), 3.49 (3H, s; $NCO_2C\boldsymbol{H_3}$), 3.58 (1H, dt, *J* = 6.5, 4.5 Hz; $NCH_2C\boldsymbol{H}OH$), 3.89 (1H, br s; NCH(Ar)C***H***OH), 7.40 (2H, d, *J* = 8.0 Hz; 2-C***H₂*** of C_6H_4–4-NO_2), 8.10 (2H, d, *J* = 8.0 Hz; 3-C***H₂*** of C_6H_4–4-NO_2). ^{13}C NMR (125.8 MHz, CD_3OD, C–H COSY) *δ* 45.0 (***C***H_2N), 52.6 ($NCO_2\boldsymbol{C}H_3$), 55.8 (N***C***HAr), 65.7 (NCH(Ar)***C***HOH), 71.3 ($NCH_2\boldsymbol{C}$HOH), 124.6 (×2) (aromatic ***C***H), 127.7 (×2) (aromatic ***C***H), 146.4 (quaternary aromatic ***C***), 149.1 (quaternary aromatic ***C***), 159.6 (N***C***O_2CH_3); HRMS Calcd for $C_{12}H_{15}N_2O_6$ + H 283.0903, Found 283.0933.

Typical procedure for the Mannich reaction

To a solution of *p*-nitrobenzaldehyde (43.8 mg, 0.29 mmol) and *p*-anisidine (35.8 mg, 0.29 mmol) in DMF (1 mL) were added the catalyst (12.2 mg, 0.09 mmol) and **4a** (100 mg, 0.436 mmol), and the mixture was stirred at room temperature for 96 h. Then H_2O and AcOEt were added with vigorous stirring, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with saturated NH_4Cl and saturated NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluted with hexane–AcOEt–$CHCl_3$ = 4 : 1 : 1) to afford **19** (88 mg, 63%; *syn* : *anti* = 84 : 16) as an inseparable mixture of diastereomers; amorphous solid; FTIR (KBr) *ν* 1749, 1698, 1605, 1515, 1369, 1347, 1243, 1153 cm^{-1}.

Syn-adduct (major product)

^1H NMR (400 MHz, $CDCl_3$) *δ* 1.45 (9H, s), 1.54 (3H, s), 1.67 (3H, s), 3.67 (3H, s), 3.71 (1H, dd, *J* = 16.8, 1.2 Hz), 4.39 (1H, br s), 4.48 (1H, d, *J* = 16.8 Hz), 5.11 (1H, d, *J* = 2.2 Hz), 6.53 (2H, m), 6.68 (2H, m), 7.52(4) (2H, d, *J* = 8.8 Hz), 8.16 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 24.3, 24.8, 28.2(3) (×3), 50.7, 55.5, 57.4, 78.3, 81.4, 89.2(9), 114.8 (×2), 115.6 (×2), 123.6 (×2), 128.1 (×2), 139.2, 145.5, 147.4(3), 147.3(3), 152.8 (6), 204.9.

Anti-adduct (minor product)

^1H NMR (400 MHz, $CDCl_3$) *δ* 1.43 (9H, s), 1.61 (3H, s), 1.74 (3H, s), 3.19 (1H, dd, *J* = 16.8, 1.2 Hz), 3.69 (3H, s), 4.31 (1H, d, *J* = 16.8 Hz), 4.65 (1H, d, *J* = 3.9 Hz), 5.00 (1H, d, *J* = 3.9 Hz), 6.57 (2H, m), 6.70 (2H, m), 7.52(1) (2H, d, *J* = 8.8 Hz), 8.11 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 24.3, 24.8, 28.2 (0) (×3), 50.4, 55.5, 57.7, 77.5, 81.4, 89.3(3), 114.8 (×2), 116.0 (×2), 123.1 (×2), 129.6 (×2), 139.1, 145.5, 147.3(9), 147.4(3), 152.9(3), 205.4.

Derivatization of 19 to the corresponding mono-acetate

To a solution of **19** (310 mg, 0.64 mmol) in MeCN (5 mL) was added 1 N HCl (15 drops) at room temperature, and the mixture was stirred for 24 h. After dilution by addition of CH_2Cl_2, the mixture was dried (K_2CO_3) and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and Ac_2O (0.25 mL) and pyridine (0.5 mL) were added at room temperature. After stirring for 9 h at room temperature, the reaction was quenched by addition of H_2O and extracted with AcOEt. The combined extracts were washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane–acetone–$CHCl_3$) to afford the mono-acetate **19-Ac** (176 mg, 57%); yellowish oil; $[\alpha]_D^{24}$ +14.4 (*c* 0.175, $CHCl_3$); FTIR (neat) *ν* 3381, 1739, 1708, 1515, 1367, 1347, 1231 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 1.45 (9H, s), 2.11 (3H, s), 3.68 (3H, s), 4.05 (1H, dd, *J* = 20.0, 5.0 Hz), 4.25 (1H, dd, *J* = 20.0, 5.0 Hz), 5.16 (1H, br s), 5.19 (1H, m), 5.52 (1H, d, *J* = 3.0 Hz), 6.50 (2H, m), 6.69 (2H, m), 7.50 (2H, d, *J* = 8.5 Hz), 8.18 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) *δ* 20.4, 28.3 (×3), 48.7, 55.6, 58.4, 79.1, 80.4, 114.9 (×2), 115.4 (×2), 124.0 (×2), 127.9 (×2), 138.9, 145.8, 147.6, 153.1, 155.5, 169.4, 201.4; HRMS Calcd for $C_{24}H_{28}N_3O_8$ + H 487.1955, Found 487.1947; The ee was determined by chiral HPLC using a Chiralpak AD (hexane–*i*-PrOH = 90 : 10, 0.8 mL min^{-1}): t_R 39.42 (minor) and t_R 44.62 (major) min.

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