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ARTICLE

Synthesis of sialic acid derivatives based on chiral substrate-controlled stereoselective aldol reactions using pyruvic acid oxabicyclo[2.2.2]octyl orthoester

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The synthesis of sialic acids and their analogs was accomplished based on substrate-controlled asymmetric aldol reactions between sterically complicated aldehydes easily prepared from commercially available carbohydrates and a novel pyruvic acid oxabicyclo[2.2.2]octyl orthoester. Systematic aldol reaction studies using chiral aldehydes revealed that α,β,γ-benzyloxy-substituted aldehydes with an α,β-*anti* relative configuration preferentially provided the Felkin products with 4,5-*anti* configuration with high diastereoselectivity. The relative β,γ-configuration in the α,β,γ-benzyloxy-substituted aldehydes with an α,β-*syn* arrangement exerted a secondary effect on the diastereoselectivity of the stereogenic center formed in the aldol reactions, and α,β-*syn*-β,γ-*anti* benzyloxyaldehyde exhibited superior diastereoselectivity to yield the Felkin products than α,β-*syn*-β,γ-*syn* benzyloxyaldehyde.

Introduction

Sialic acids are a family of monosaccharides containing a common 3-deoxy-2-ulosonic acid structure of which more than 50 natural derivatives have been identified, including *N*-acetylneuraminic acid (Neu5Ac, **1**), 3-deoxy-D-glycero-D-galacto-2-nonulosonic acid (KDN, **2**), and 3-deoxy- D-manno-2-octulosonic acid (KDO, **3**) (Figure 1). Neu5Ac, which is the most common sialic acid, is frequently observed at the α-ketosidically linked nonreducing terminal end of glycoconjugates such as glycoproteins, glycolipids, and oligosaccharides, in the cell membranes of various living organism, and plays a vital role in numerous biological processes including cell-to-cell recognition, neurobiological functions, tumor metastasis, and viral infections.[1] The most abundant sialic acid, Neu5Ac, is synthesized in vivo from *N*-acetylmannosamine-6-phosphate and phosphoenolpyruvate by *N*-acetylneuraminic acid 9-phosphate synthase (Neu5Ac-9-P synthase), followed by *N*-acetylneuraminic acid 9-phosphate phosphatase (Neu5Ac-9-P phosphatase).[1-3]

Owing to their biological and medical significance coupled with their polyfunctionalized molecular structures, this unique class of carbohydrate and its analogs are recognized as highly attractive and important targets for chemical synthesis.[4-21] In this context, one of the most straightforward synthetic approaches toward sialic acids such as Neu5Ac, KDN, and KDO is the direct carbon–carbon bond forming reaction at the C4 position between an electrophilic six- or five-carbon moiety

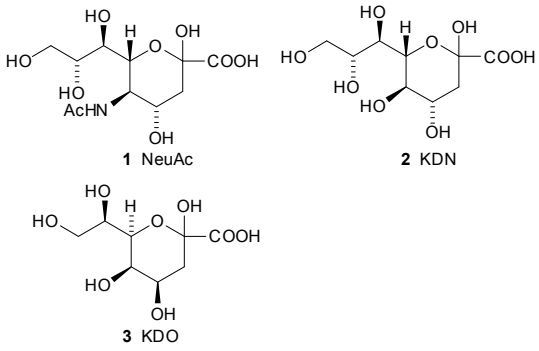

Figure 1 Representative natural octulo- and nonulosonic acids.

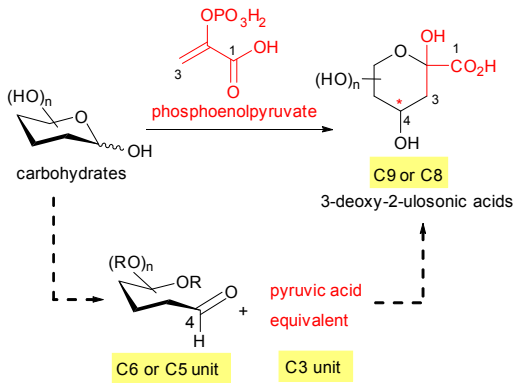

Figure 2 Biomimetic synthetic approach to 3-deoxy-2-ulosonic acids.

derived from hexose or pentose, and a nucleophilic pyruvate equivalent such as an oxobutanedioic acid derivative,[5] an α-(bromomethyl)acrylic acid derivative,[6-8] a 2-acetylthiazole derivative,[9,10] propargyl bromide,[11] and pyruvaldehyde

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dimethyl acetal,[12,13] among others[14] (Figure 2). However, despite much pioneering work, the reaction yield and the stereoselectivity at the C4 position induced by addition of a pyruvate equivalent remain problematic. Moreover, lengthy synthetic routes involving multiple protective group manipulations are often necessary both for the preparation of an electrophilic coupling partner derived from aldose, and/or the transformations of the coupling product to the desired sialic acid through selective oxidation of the C1 position to a carboxylic acid. Very recently, Kanai and Shimizu *et al.* reported the highly efficient synthesis of sialic acids via the chiral copper catalyst-controlled stereoselective propargylation of unprotected aldoses and subsequent stepwise oxidations of the carbon–carbon triple bond at the C1 and C2 position.[15]

We herein describe a versatile synthesis of sialic acids, the key step of which is based on a substrate-controlled stereoselective aldol reaction between the chiral aldehydes easily prepared from commercially available carbohydrates and a novel pyruvate equivalent.

Results and discussion

We began our preliminary investigations on the aldol reaction between the chiral aldehyde **14e** prepared from D-mannose and commercially available ethyl pyruvate **4** or pyruvaldehyde dimethyl acetal **5** under strong basic conditions using lithium hexamethyldisilazane (LiHMDS) in THF at −78 °C (Figure 3). However, the use of ethyl pyruvate as a nucleophilic pyruvate equivalent resulted in the recovery of aldehyde **14e**, and the desired aldol adduct is not obtained. This result suggests the occurrence of the retro-aldol reaction by the coupling products under basic conditions due to the strong electron-withdrawing property of the α-keto ester structure in ethyl pyruvate. Conversely, the aldol reaction of pyruvaldehyde dimethyl acetal **5** (in which the α-keto ester structure is masked) with aldehyde **14e** partially proceeded, but the yield of aldol adduct **6** was very low (28% yield, dr = 6:1) and 42% of the pyruvaldehyde dimethyl acetal **5** was consumed by the formation of the self-aldol product **7**.

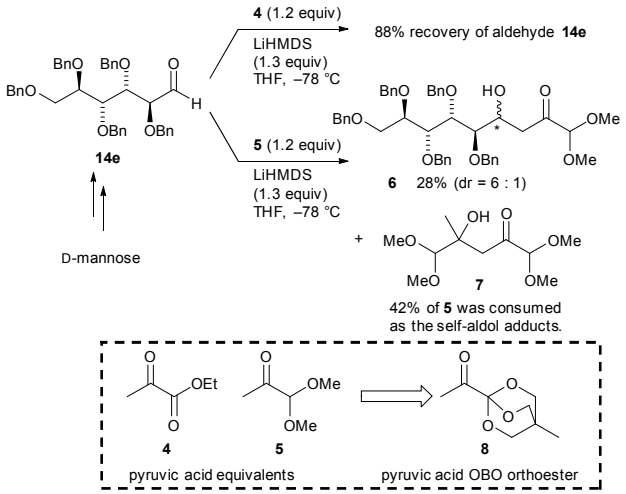
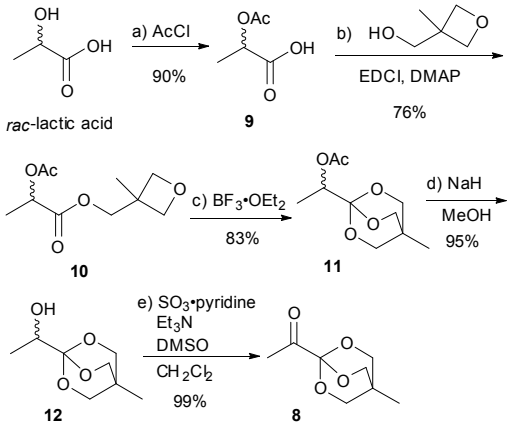


Figure 3 Aldol reactions between the chiral aldehyde **14e** and pyruvic acid equivalents **4** or **5**.



Scheme 1 Synthesis of pyruvic acid orthoester **8**. Reagents and conditions: a) AcCl (2.0 equiv), THF (0.1 M), 0 °C to rt, 1 h, 90%; b) 3-methyl-3-oxetanemethanol (1.2 equiv), EDCI (1.1 equiv), DMAP (0.10 equiv), CH_2Cl_2 (0.5 M), 0 °C to rt, 4 h, 76%; c) $BF_3{\cdot}Et_2O$ (0.1 equiv), CH_2Cl_2 (0.4 M), 0 °C to rt, 4 h, 83%; d) NaH (0.1 equiv), MeOH (0.3 M), 0 °C to rt, 3 h, 95%; e) $SO_3{\cdot}$pyridine (4.0 equiv), Et_3N (12 equiv), DMSO (4.0 equiv), CH_2Cl_2 (0.6 M) 0 °C to rt, 1.5 h, 99%.

To overcome these problems, we designed pyruvic acid oxabicyclo[2.2.2]octyl (OBO) orthoester **8** as a novel pyruvate equivalent. We predicted that the existence of the highly electron-donating and more stable OBO orthoester adjacent to the carbonyl carbon (instead of the ethoxycarbonyl group) would not only suppress the retro-aldol reaction but also inhibit the formation of the self-aldol product (derived from the ketone as a nucleophile) owing to the steric hindrance of the OBO structure. Additionally, installation of the orthoester, which is in the same oxidation state with carboxylic acid, avoids the need for troublesome oxidative transformations after the aldol coupling reaction.

The preparation of pyruvic acid OBO orthoester **8** is shown in Scheme 1. The protection of the hydroxy group of *rac*-lactic acid as the acetate[22] followed by the esterification of the carboxylic acid with 3-hydroxymethyl-3-methyloxetane using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC•HCl) afforded ester **10** in high yield, which on treatment with 0.1 equivalent of $BF_3{\bullet}OEt_2$,[23] yielded the OBO orthoester **11** in 83% yield. The deprotection of the acetate in **11** using NaOMe and subsequent Parikh–Doering oxidation provides pyruvic acid OBO orthoester **8** as nonhygroscopic, stable, and storable powder.

The synthesis of the aldehyde **14b** as a coupling partner for pyruvic acid OBO orthoester **8** in the aldol reaction is shown in Scheme 2.[24] Considering both the short-step syntheses of aldehydes from commercially available carbohydrates and the removal step of the hydroxy-protecting groups to yield a highly polar product after the aldol coupling reaction, we decided to protect all the hydroxy groups as benzyl ethers. The aldehydes **14a**–**14f** were easily prepared from the corresponding carbohydrate in three steps via the temporary masking of the aldehyde group with *O*-methylhydroxylamine, benzyl

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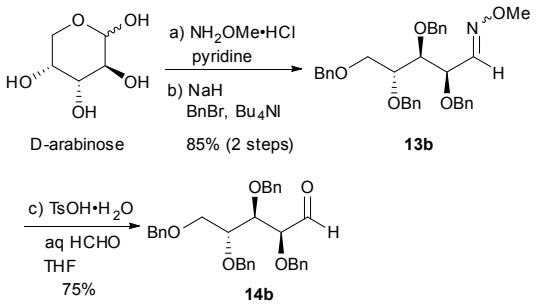
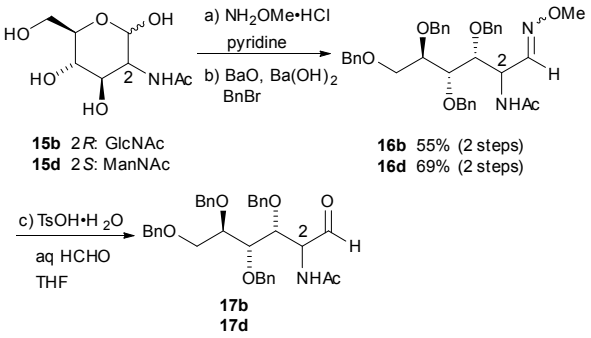


Scheme 2 Synthesis of *O*-benzyl-protected aldehydes **14b**. Reagents and conditions: (a) $NH_2OMe{\cdot}HCl$ (1.2 equiv), pyridine (0.7 M), rt to 70 °C, 12 h; (b) NaH (7.0 equiv), BnBr (6.0 equiv), Bu_4NI (0.1 equiv), DMF (0.1 M), 0 °C to rt, 18 h, 85 % (two steps); (c) $TsOH{\cdot}H_2O$ (1.0 equiv), aq HCHO–THF (1:2.5, 0.1 M), rt, 12 h, 75%.



Scheme 3 Synthesis of *O*-benzyl-protected *N*-acetylaldehydes **17b** and **17d**. Reagents and conditions: (a) $NH_2OMe{\cdot}HCl$ (1.2 equiv), pyridine (0.7 M), rt to 70 °C, 12 h; (b) BaO (9.4 equiv), $Ba(OH)_2$ (3.2 equiv), BnBr (13 equiv), DMF (0.2 M), 0 °C to rt, 24 h, 55% for **16b** (two steps), 69% for **16d** (two steps); (c) $TsOH{\cdot}H_2O$ (1.0 equiv for **16b**, 18 equiv for **16d**), aq HCHO–THF (1:2.5, 0.1 M), rt, 15 min. The crude product was passed through a short silica gel column before the aldol reaction.

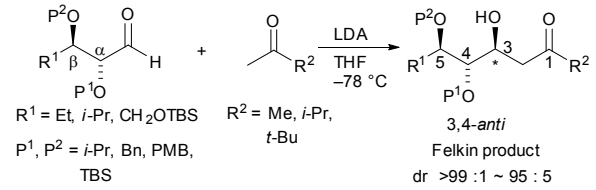


Figure 4 Studies on asymmetric induction in methyl ketone aldol additions to α,β-bisalkoxy aldehydes by Evans *et al.* (Ref. 25).

protection of the hydroxy groups, and regeneration of the aldehyde by trans-oximation. The preparation of *N*-acetyl α-amino aldehydes **17b** and **17d**, which were precursors for Neu5Ac and its analogs, was also achieved through similar transformations (Scheme 3).[24]

Concerning asymmetric induction in diastereoselective aldol reactions, Evans *et al*. have reported systematic studies on π-face selectivity in the addition of lithium enolates prepared from methyl ketones to α,β-bisalkoxy aldehydes, and concluded that *anti*-α,β-bisalkoxy aldehydes exhibit superior diastereoselectivity relative to *syn*-α,β-bisalkoxy aldehydes to afford the 3,4-*anti* diastereomer (Felkin product) as the major product, according to the Cornforth–Evans transition-state model (Figure 4).[25] However, stereoselectivity in substrate-controlled aldol reactions between more stereochemically complicated chiral aldehydes and pyruvate equivalents, which is the key reaction to synthesize biologically and medicinally valuable sialic acids and their analogs, remains to be achieved.

Our investigation into the aldol reaction between the chiral aldehydes **14a**–**14f** and pyruvic acid OBO orthoester **8** are presented in Table 1. The reaction of α,β-*syn*-β,γ-*syn* benzyloxyaldehyde **14a** with the Li enolate prepared from pyruvic acid OBO orthoester **8** and LiHMDS[26] in THF at −78 °C provided aldol **18a** as a 2:1 diastereomeric mixture of the 4,5-*anti* and 4,5-*syn* adducts in 58% yield (entry 1). Under the same conditions, the aldol reaction of α,β-*syn*-β,γ-*anti* benzyloxyaldehyde **14b** with pyruvic acid OBO orthoester **8** resulted in increased diastereoselectivity (4,5-*anti*:4,5-*syn* = 7:1) and a 67% yield (entry 3). The addition of $ZnCl_2$ to the aldol reaction of α,β-*syn*-β,γ-*anti* benzyloxy-substituted aldehyde **14b** improved the diastereoselectivity to 4,5-*anti*:4,5-*syn* = 11:1 in 60% yield (entry 4), whereas low conversion was observed in the case of α,β-*syn*-β,γ-*syn* benzyloxyaldehyde **14a** (entry 2). Conversely, the use of α,β-*anti* benzyloxyaldehydes **14c** and **14d** in the aldol reaction with pyruvic acid OBO orthoester **8** provided the 4,5-*anti* aldol adduct (Felkin product) as the major product with excellent diastereoselectivity (4,5-*anti*:4,5-*syn* = >20:1) and in good yields (entries 5–8).

These results indicate that the major controlling factor for the diastereoselectivity is the relative configuration of the α- and β-positions in the aldehydes (entries 1 and 3 *vs* 5 and 7). That is to say, α,β-*anti* benzyloxyaldehydes exhibit higher diastereoselectivity than α,β-*syn* benzyloxyaldehydes in the aldol reaction with pyruvic acid OBO orthoester **8** to preferentially afford the Felkin products. This is in good agreement with the previous work by Evans.[25] In addition, our systematic examination indicates that the relative configuration of the β- and γ-positions in the aldehydes exerts as a secondary influence on the π-face selectivity in the aldol reaction, and aldehydes with β,γ-*anti* configuration are more favorable as substrates to provide the Felkin product with higher diastereoselectivity than those with β,γ-*syn* configuration (entry 1 *vs* 2). The reactions of the more stereochemically complicated aldehydes **14e** and **14f** with the Li enolate from pyruvic acid OBO orthoester **8** afforded the aldol adducts **18e** and **18f** in good yields and acceptable diastereoselectivity (4,5-*anti*:4,5-*syn* = 7:1 for aldehyde **14e**, 4,5-*anti*:4,5-*syn* = 11:1 for aldehyde **14f**) favoring the Felkin products (entries 9 and 11). Furthermore, the use of 1.3 equivalents of $ZnCl_2$ as an additive provided the 4,5-*anti* aldol product with excellent diastereoselectivity (4,5-*anti*:4,5-*syn* = >20:1 for aldehydes **14e** and **14f**) (entries 10 and 12).

We next examined the aldol reactions of chiral α-acetylaminoaldehydes **17a**–**17d** with pyruvic acid OBO orthoester **8** for the syntheses of Neu5Ac and its analogs (Table 2). The treatment of α,β-*syn* α-acetylamino-β-benzyloxyaldehyde **17a** with the Li enolate prepared from 2.2

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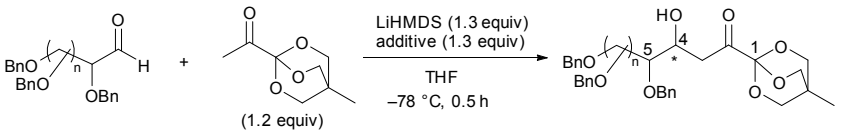
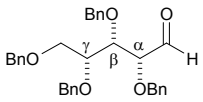
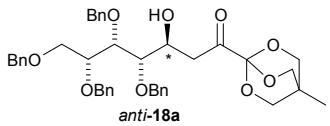
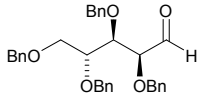
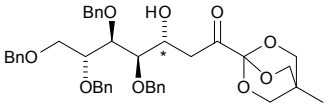
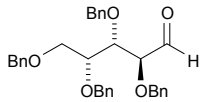
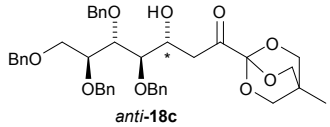
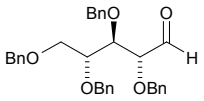
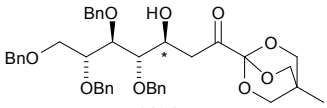
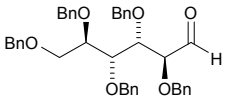
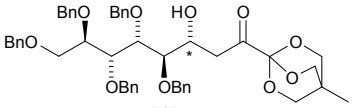
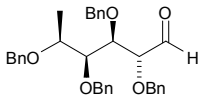
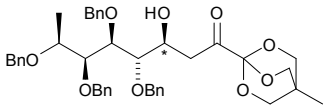
Table 1 The chiral substrate-controlled diastereoselective aldol reaction of *O*-benzyl-protected aldehydes **14a–14f** with pyruvate orthoester **8**.



14a–14f **8** **18a–18f**

Entry	Aldehyde	Additives	Major adduct (Felkin product)	Yield (%)	dr (4,5-*anti* : 4,5-*syn*)
1	 **14a**	—	 *anti*-**18a**	58	2 : 1
2		$ZnCl_2$		< 10	2 : 1
3	 **14b**	—	 *anti*-**18b**	67	7 : 1
4		$ZnCl_2$		60	11 : 1
5	 **14c**	—	 *anti*-**18c**	54	> 20 : 1
6		$ZnCl_2$		50	> 20 : 1
7	 **14d**	—	 *anti*-**18d**	51	> 20 : 1
8		$ZnCl_2$		52	> 20 : 1
9	 **14e**	—	 *anti*-**18e**	62	7 : 1
10		$ZnCl_2$		58	> 20 : 1
11	 **14f**	—	 *anti*-**18f**	51	11 : 1
12		$ZnCl_2$		47	> 20 : 1

equivalents of pyruvic acid OBO orthoester **8** and 2.3 equivalents of LiHMDS in THF at −78 °C afforded the aldol adduct **19a** in 65% yield with a moderate diastereomeric ratio (entry 1, dr = 2:1). Low diastereoselectivity was also observed in the aldol reaction using the more stereochemically complicated α,β-*syn* α-acetylamino-β-benzyloxyaldehyde **17b** (entry 2, 4,5-*anti*:4,5-*syn* = 3.5:1). Conversely, when α,β-*anti* α-acetylamino-β-benzyloxyaldehyde **17c** or **17d** was used as a substrate, the aldol reactions proceeded with good to high diastereoselectivity, furnishing the *anti*-Felkin product as the major diastereomer (entry 3, 4,5-*anti*:4,5-*syn* = 1:6; entry 4, 4,5-*anti*:4,5-*syn* = 1:>20). It should be noted that a reversal C=O face selectivity was observed between the aldol reactions of α,β-*anti* α-acetylamino-β-benzyloxyaldehydes and those of α-benzyloxyaldehydes.

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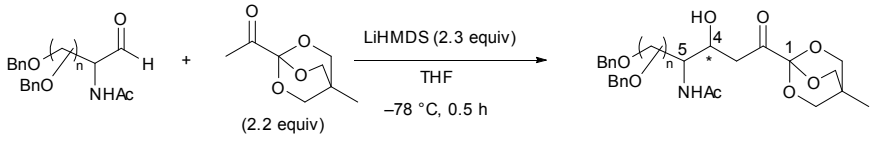
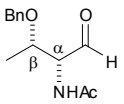
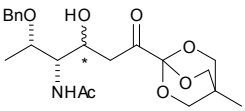
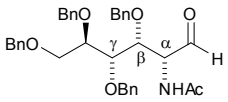
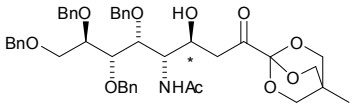
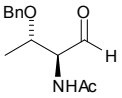
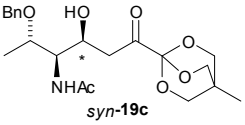
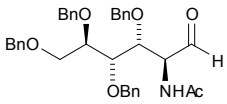
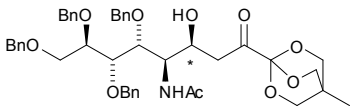
Table 2 The chiral substrate-controlled diastereoselective aldol reaction of *O*-benzyl-protected α-*N*-acetylaminoaldehydes **17a**-**17d** with pyruvate orthoester 8.



17a–17d **8** **19a–19d**

Entry	Aldehyde	Major adduct	Yield (%)	dr (4,5-*anti* : 4,5-*syn*)
1	 **17a**	 **19a**	65	(2 : 1) [a]
2	 **17b**	 *anti*-**19b**	76	3.5 : 1
3	 **17c**	 *syn*-**19c**	71	1 : 6
4	 **17d**	 *syn*-**19d**	82	1 : > 20

[a] The stereochemistry of the newly formed stereogenic center C4 position of major aldol adducts was not determined.

Having established the utility of substrate-controlled diastereoselectivity using chiral aldehydes and pyruvic acid OBO orthoester **8**, we examined the transformation of the aldol adducts to the desired sialic acids and their analogs. Deprotection of the benzyl ether groups and the hemi ketalization of aldol adduct **18b** by treatment with wet-type Pd–C in THF under hydrogen atmosphere, followed by hydrolysis of the ester under mild basic conditions, afforded the triethylammonium salt **21b**. The purification of the product was performed by recrystallization from H_2O–EtOH of the corresponding ammonium salts **22b** (Scheme 4).[6a] Other aldol adducts **19c** and **19d** were also converted to triethylammonium salts **23c** and **25d** by a sequence of hydrogenolysis and hydrolysis, and the characterizations of these products were performed using the corresponding methyl esters **24c** and **26d** (Scheme 5).

Conclusion

In summary, we have developed a synthetic strategy for sialic acids and their analogs based on the substrate-controlled asymmetric aldol reactions between sterically complicated aldehydes easily prepared from commercially available carbohydrates, and pyruvic acid OBO orthoester **8**, which was employed as a novel pyruvic acid equivalent. Systematic studies on the aldol reaction using chiral aldehydes derived from pentoses revealed that α,β,γ-benzyloxy-substituted aldehydes with an α,β-*anti* relative configuration preferentially provided the Felkin products with 4,5-*anti* configuration in high diastereoselectivity. In addition, the relative β,γ-configuration in the α,β,γ-benzyloxy-substituted aldehydes with an α,β-*syn* arrangement exerted a secondary effect on the diastereoselectivity of the stereogenic center formed in the aldol reactions with pyruvic acid OBO orthoester **8**, and α,β-*syn*-β,γ-*anti*

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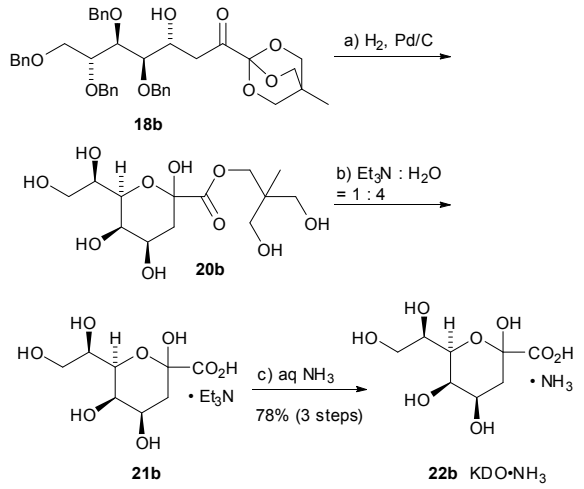
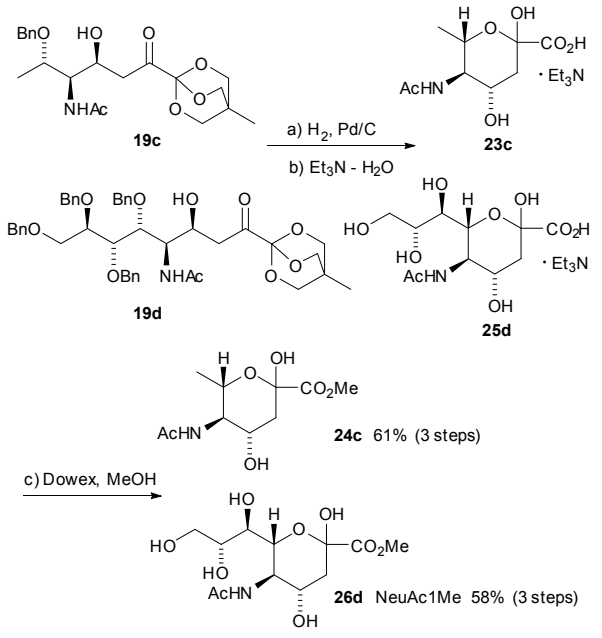
benzyloxyaldehyde exhibited superior diastereoselectivity to yield the Felkin products (which could be further improved by the addition of $ZnCl_2$) than α,β-*syn*-β,γ-*syn* benzyloxyaldehyde. Conversely, we also found that the aldol reactions of α,β-*anti* α-acetylamino-β-benzyloxy-substituted aldehydes with pyruvic acid OBO orthoester **8** preferentially afforded *anti*-Felkin products with 4,5-*syn* configuration. Moreover, some of the obtained aldol adducts could be transformed to sialic acids and their analogs in three steps without the need for oxidation reactions. The chiral substrate-controlled stereoselective aldol reaction described here will provide not only a convenient synthetic method for sialic acid derivatives but also a guiding principle for asymmetric induction in aldol reactions using stereochemically complicated aldehydes.



Scheme 4 Transformation of the aldol adduct **18b** to the KDO ammonium salt **22b**. Reagents and conditions: a) H_2, 10% wet-type Pd/C (50% w/w), THF (0.1 M), rt, 1.5 h; b) Et_3N:H_2O = 1:4 (0.2 M), rt, 2 h; c) aq 28% NH_3, rt, 1 min, 78% (three steps) after recrystallization.



Scheme 5 Transformation of the aldol adducts **19c** and **19d** to the ulosonic acids **24c** and **26d**. Reagents and conditions: a) H_2, 10% wet-type Pd/C (50% w/w), THF (0.1 M), rt, 1.5 h; b) Et_3N:H_2O = 1:4 (0.2 M), rt, 2 h; c) Dowex 50WX8, MeOH, 61% (three steps) for **24c**, 58% (three steps) for **26d**.

Experimental

(3-Methyloxetan-3-yl)methyl 2-acetoxypropanoate (10)

To a stirred solution of 3-methyl-3-oxetanemethanol (5.86 g, 57.4 mmol, 1.2 equiv), EDCI (10.1 g, 52.6 mmol, 1.1 equiv) and DMAP (584 mg, 4.78 mmol, 0.10 equiv) in CH_2Cl_2 (96 mL, 0.50 M) at 0 °C was added dropwise a solution of *rac*-2-acetoxypropanoic acid **9**[22] (6.31g, 47.8 mmol) in CH_2Cl_2 (30 mL, 1.6 M) under N_2 atmosphere. After the mixture was stirred for 4 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The resulting mixture was extracted with $CHCl_3$ (3 x 100 mL). The combined organic phases were washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 4 : 1) to give **10** (7.85 g, 36.3 mmol, 76% yield) as colorless oil. Rf value on TLC 0.62 (Hexane : AcOEt = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.10 (q, *J* = 6.8 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.21 (d, *J* = 11.2 Hz, 1H), 2.13 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 79.3, 79.3, 69.1, 68.6, 39.1, 21.0, 20.6, 16.9; IR (neat) 2965, 2944, 2874, 1744, 1451, 1382, 1374, 1238, 1202, 1132, 1100, 1052, 984 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{16}NaO_5$ $[M+Na]^+$ 239.0895, found 239.0886.

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethyl acetate (11)

To a stirred solution of **10** (7.83 g, 36.2 mmol, 1.0 equiv) in CH_2Cl_2 (91 mL, 0.40 M) at 0 °C under N_2 atmosphere was added dropwise $BF_3{\cdot}OEt_2$ (0.447 mL, 3.62 mmol, 0.10 equiv). After 4 h at room temperature, the reaction was quenched with Et_3N (0.756 mL, 5.43 mmol, 0.15 equiv) at 0 °C and the mixture was stirred for 15 min. The resulting mixture was diluted with H_2O (100 mL) and extracted with $CHCl_3$ (3 x 200 mL). The combined organic phases were washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 6 : 1) to give **11** (6.49 g, 30.0 mmol, 83% yield) as white solid. Mp 79–81 °C; Rf value on TLC 0.61 (Hexane : AcOEt = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.99 (q, *J* = 6.4 Hz, 1H), 3.92 (s, 6H), 2.09 (s, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.81 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1, 107.6, 72.7, 69.9, 30.6, 21.3, 14.5, 14.3; IR (KBr) 2993, 2970, 2946, 2883, 1729, 1478, 1457, 1432, 1402, 1383, 1373, 1357, 1259, 1214, 1194, 1105, 1081, 1051, 1027, 1007, 982 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{16}NaO_5$ $[M+Na]^+$ 239.0895, found 239.0888.

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-ol (12)

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To a stirred solution of **11** (6.47 g, 29.9 mmol, 1.0 equiv) in MeOH (100 mL, 0.30 M) at 0 °C was added portionwise NaH (55% dispersion in oil, 131 mg, 2.99 mmol, 0.10 equiv), and the mixture was stirred for 3 h at room temperature. After the solvent was removed under reduced pressure, the obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 4 : 1 contained 1% Et_3N) to give **12** (4.95 g, 28.4 mmol, 95%) as white solid. Mp 63–66 °C; Rf value on TLC 0.28 (Hexane : AcOEt = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 6H), 3.73 (q, *J* = 6.4 Hz, 1H), 2.13 (br s, 1H, -OH), 1.19 (d, *J* = 6.4 Hz, 3H), 0.81 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 108.3, 72.7, 69.4, 30.6, 16.2, 14.3; IR (KBr) 3529, 2992, 2969, 2943, 2884, 1475, 1458, 1399, 1363, 1281, 1195, 1132, 1077, 1048, 1023, 958 cm^{-1}; HRMS (ESI) m/z calcd for $C_8H_{14}NaO_4$ $[M+Na]^+$ 197.0790, found 197.0790.

1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (8)

To a stirred solution of **12** (4.95 g, 28.4 mmol, 1.0 equiv), DMSO (8.10 mL, 114 mmol, 4.0 equiv) and Et_3N (47.5 mL, 341 mmol, 12 equiv) in CH_2Cl_2 (47 mL, 0.60 M) at 0 °C was added portionwise SO_3·Py (18.1 g, 114 mmol, 4.0 equiv). After the mixture was stirred at room temperature for 1.5 h under N_2 atmosphere, the reaction was quenched with H_2O (100 mL). The resulting mixture was extracted with AcOEt (3 x 200 mL). The combined organic phases were washed with H_2O (2 x 200 mL) and brine (2 x 200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 5 : 1) to give **8** (4.84 g, 28.1 mmol, 99% yield) as white solid. Mp 105–114 °C; Rf value on TLC 0.54 (Hexane : AcOEt = 1 : 1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 6H), 2.23 (s, 3H), 0.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.5, 103.2, 73.0, 30.8, 24.4, 14.1; IR (KBr) 2975, 2960, 2941, 2920, 2892, 1737, 1480, 1459, 1424, 1369, 1351, 1329, 1301, 1190, 1135, 1061, 1024, 982 cm^{-1}; HRMS (ESI) m/z calcd for $C_8H_{12}NaO_4$ $[M+Na]^+$ 195.0633, found 195.0639.

***N*-((2*R*,3*R*,4*S*,5*R*,*Z*)-3,4,5,6-tetrakis(benzyloxy)-1-(methoxyimino)hexan-2-yl)acetamide (16d)**

A solution of *N*-acetyl-D-mannosamine **15d** (1.00 g, 4.52 mmol, 1.0 equiv) and *O*-methylhydroxylamine hydrochloride (453 mg, 5.42 mmol, 1.2 equiv) in pyridine (6.5 mL, 0.70 M) was stirred for 12 h at 70 °C under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give colorless oil. To a stirred solution of the above crude product in DMF (23 mL, 0.20 M) at 0 °C was successively added BnBr (7.01 mL, 59.2 mmol, 13.1 equiv), BaO (6.52 g, 42.5 mmol, 9.4 equiv) and $Ba(OH)_2$·$8H_2O$ (4.57 g, 14.5 mmol, 3.2 equiv). After stirred at 0 °C for 6 h and then at room temperature for 18 h under N_2 atmosphere, the mixture was filtered through a Celite pad® by rinsing with $CHCl_3$. After the filtrate was concentrated under reduced pressure, the resulting residue was dissolved in AcOEt (100 mL) and washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 6 : 1) to give **16d** (1.91 g, 3.13 mmol, 69% in 2 steps) as pale yellow oil. Rf value on TLC 0.32 (Hexane : AcOEt = 2 : 1); $[\alpha]_D^{24}$ +3.23 (*c* 0.50, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.22 (m, 21H), 6.40 (d, *J* = 8.0 Hz, 1H, -NH), 5.02 (dt, *J* = 8.0, 4.8 Hz, 1H), 4.74 (d, *J* = 10.8 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.54 (s, 2H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 3.97 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.94–3.90 (m, 3H), 3.85 (s, 3H), 3.75–3.70 (m, 1H), 1.66 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.7, 147.4, 138.4, 138.2, 137.9, 137.8, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.7, 127.7, 127.6, 127.6, 80.1, 79.0, 74.3, 73.4, 72.9, 72.3, 69.1, 61.8, 49.5, 23.0; IR (neat) 3086, 3063, 3030, 3004, 2938, 2901, 2869, 2817, 1676, 1661, 1497, 1454, 1370, 1305, 1210, 1103, 1069, 1043, 1027, 907 cm^{-1}; HRMS (ESI) calcd for $C_{37}H_{42}N_2NaO_6$ $[M+Na]^+$ 633.2941, found 633.2934.

***N*-((2*S*,3*R*,4*S*,5*R*)-3,4,5,6-tetrakis(benzyloxy)-1-oxohexan-2-yl)acetamide (17d)**

To a stirred solution of **16d** (600 mg, 0.982 mmol, 1.0 equiv) in THF and 36-38% aqueous HCHO (2.5 : 1, 9.8 mL, 0.10 M) at room temperature was added TsOH·H_2O (3.37 g, 17.7 mmol, 18 equiv). The progress of the reaction was checked by TLC analysis ever 5 min.[27] After the mixture was stirred for 15 min at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with AcOEt (2 x 50 mL). The combined organic phases were washed with H_2O (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was passed through a short column of silica gel using as an eluent (Hexane : AcOEt = 1 : 1). The obtained product **17d** (593 mg, pale yellow oil) was used for next reaction without further purification.[28]

***N*-((3*S*,4*R*,5*R*,6*S*,7*R*)-5,6,7,8-tetrakis(benzyloxy)-3-hydroxy-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-1-oxooctan-4-yl)acetamide (19d)**

To a stirred solution of LiHMDS (1.0 M in THF solution, 1.69 mL, 1.69 mmol, 2.3 equiv) in THF (7.4 mL) at –78 °C was added dropwise a solution of **8** (279 mg, 1.62 mmol, 2.2 equiv) in THF (1.8 mL) under N_2 atmosphere. After 30 min at –78 °C, a solution of **17d** (428 mg, 0.736 mmol, 1.0 equiv) in THF (1.8 mL) was added, and the resulting mixture was furthermore stirred for 30 min at –78 °C. The reaction was quenched with phosphate buffer (pH 6.86, 10 mL), and the mixture was allowed to gently warm up to room temperature. The resulting mixture was extracted with AcOEt (3 x 50 mL). The combined organic phases were washed with H_2O (2 x 100 mL) and brine (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified by silica gel column chromatography (Hexane : AcOEt = 1 : 2) to give **19d** (452 mg, 0.600 mmol, 82% yield, *anti* : *syn* = 1 : >20) as colorless oil. Rf value on TLC 0.30 (Hexane : AcOEt = 1 : 2); $[\alpha]_D^{27}$ +7.35 (*c* 0.25, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 20H), 5.99 (d, *J* = 9.2 Hz, 1H, -NH), 4.73 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 10.4 Hz, 1H), 4.65 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.49–4.46 (m, 1H), 4.10 (ddd, *J* = 9.2, 6.0, 1.2 Hz, 1H), 3.96 (s, 6H), 3.91–3.82 (m, 4H), 3.72 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.34 (br s, 1H, -OH), 2.78 (dd, *J* = 18.4, 8.8 Hz, 1H), 2.70 (dd, *J* = 18.4, 3.6 Hz, 1H), 1.74 (s, 3H), 0.83 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.1, 170.3, 138.5, 138.3, 138.2, 138.0, 128.4, 128.3, 128.3, 128.3, 128.3, 128.1, 127.9, 127.8,

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127.7, 127.6, 127.5, 127.5, 103.2, 79.1, 79.0, 79.0, 74.2, 73.3, 73.0, 72.2, 69.1, 65.7, 53.0, 41.6, 30.8, 23.2, 14.1; IR (neat) 3401, 3086, 3064, 3030, 2922, 2881, 1746, 1659, 1496, 1454, 1371, 1209, 1082, 1032, 998 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{51}NNaO_{10}$ $[M+Na]^+$ 776.3411, found 776.3394.

Methyl (4*S*,5*R*,6*S*)-5-acetamido-2,4-dihydroxy-6-((1*R*,2*R*)-1,2,3-trihydroxypropyl)tetrahydro-2*H*-pyran-2-carboxylate (26d)

A mixture of **19d** (300 mg, 0.398 mmol, 1.0 equiv) and wet-type Pd-C (10% on carbon, 150 mg, 50% w/w) in THF (4.0 mL, 0.10 M) was strongly stirred for 1.5 h under H_2 atmosphere. The reaction mixture was filtered through a filter paper by rinsing with MeOH. The combined filtrate was concentrated under reduced pressure to give the crude product as colorless amorphous. A solution of the above crude product in H_2O and Et_3N (4 : 1, 2.0 mL, 0.20 M) was stirred for 1.5 h at room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was passed through a column of silica gel ($CHCl_3$: MeOH = 30 : 1 then only MeOH) to remove 1,1,1-tris(hydroxymethyl)ethane. The obtained product was used for next reaction without purification. A solution of the above product in anhydrous MeOH (4.0 mL, 0.10 M) was treated with Dowex®50WX8 (400% w/w) at room temperature for 2 h. The mixture was filtered through a cotton filter, and concentrated under reduced pressure to give **26d** (74.7 mg, 0.231 mmol, 58% yield) as white solid. The physical data of the synthesized compound **26d** were good agreement with those reported in the references.[29, 30] Mp 179–180 °C; Rf value on TLC 0.30 ($CHCl_3$: MeOH : AcOH : H_2O = 60 : 30 : 3 : 5); $[\alpha]_D^{25}$ –24.3 (*c* 0.5, MeOH); ^{1}H-NMR (400 MHz, MeOD) δ 4.07–3.96 (m, 2H), 3.85–3.78 (m, 2H), 3.78 (s, 3H), 3.72–3.68 (m, 1H), 3.62 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.48 (dd, *J* = 8.8, 1.2 Hz, 1H), 2.22 (dd, *J* = 12.8, 5.2 Hz, 1H), 2.01 (s, 3H), 1.89 (dd, *J* = 12.8, 11.2 Hz, 1H); ^{13}C-NMR (100 MHz, MeOD) δ 175.1, 171.8, 96.7, 72.1, 71.7, 70.2, 67.9, 64.9, 54.3, 53.1, 40.7, 22.6; IR (KBr) 3386, 2959, 2936, 1749, 1742, 1701, 1686, 1654, 1638, 1627, 1560, 1542, 1509, 1490, 1475, 1458, 1438, 1375, 1311, 1279, 1127, 1069, 1035, 946 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{21}NNaO_9$ $[M+Na]^+$ 346.1114, found 346.1120.

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