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Organocatalytic *anti*-Mannich Reactions with Dihydroxyacetone and Acyclic Dihydroxyacetone Derivatives: A Facile Route to Amino Sugars

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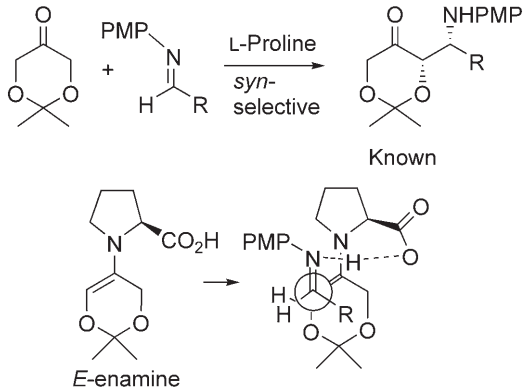
Abstract: The first primary amine-containing amino acid-catalyzed *anti*-Mannich reactions of dihydroxyacetone and acyclic dihydroxyacetone derivatives with a variety of imines have been developed. This approach complements proline-based strategies in the preparation of amino sugars.

Keywords: acyclic dihydroxyacetone derivatives; *anti*-Mannich reaction; dihydroxyacetone; primary amine-containing amino acids

Amino and imino sugars are of significant interest not only for use as tools in glycobiology but also for the treatment of a range of human diseases ranging from HIV-1 and hepatitis C infections to genetic disorders like Gaucher's disease and other inborn errors of metabolism. Consequently, there has been significant interest in the development of efficient syntheses of these types of compounds.[1,2] Typically, these sugars require multistep syntheses.[3] The most expedient *de novo* syntheses use aldolase enzymes or organocatalytic aldol reactions involving dihydroxyacetone (DHA) derivatives.[4] Although aldol-based DHA routes are efficient, this approach is limited with respect to the placement of the amino functionality within the target sugar. Enzyme-based strategies based on DHA are limited to the aldol reaction since the enzymes do not accept Mannich imine acceptors.

Direct catalytic asymmetric Mannich reactions have emerged as a powerful class of C–C bond-forming reactions that provide access to optically enriched nitrogen-containing compounds. The use of DHA and DHA derivatives as C_3 synthons in organocatalytic Mannich reactions promise efficient syntheses of amine-containing sugars.[5,6] Despite considerable attention afforded to the catalytic asymmetric aldol reactions of DHA and DHA derivatives,[4] these substrates are not well explored in organocatalytic Mannich and Mannich-type reactions. Highly enantioselective Mannich reactions of dioxanone catalyzed by proline or its derivative were recently achieved; however, only *syn*-Mannich products were produced in those reactions (Scheme 1).[5,6] In addition, these reactions are limited in scope to the single DHA derivative 2,2-dimethyl-1,3-dioxane-5-one. Herein, we disclose a significant elaboration of our organocatalytic carbohydrate strategy as we describe the first organocatalytic *anti*-Mannich reactions of protected and unprotected DHA derivatives with a variety of aromatic and aliphatic aldehyde-derived imines.

As one part of our ongoing program to meet the stereochemical challenges in Mannich chemistry that are not addressed with proline and its derivatives, we have recently developed efficient *anti*-Mannich strategies.[7,8] In our previous *anti*-Mannich studies, we demonstrated an efficient route to highly enantiomerically enriched *anti*-1,2-amino alcohols by employing unmodified hydroxyacetone and proposed the intermediacy of a hydrogen bond-stabilized (*Z*)-enamine



Scheme 1.

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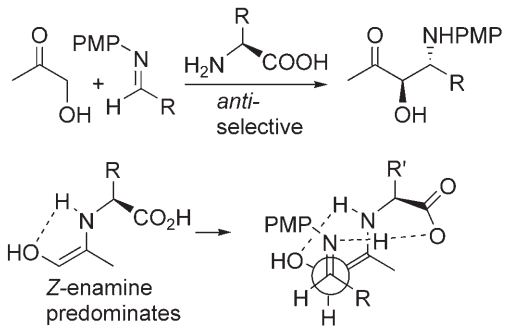
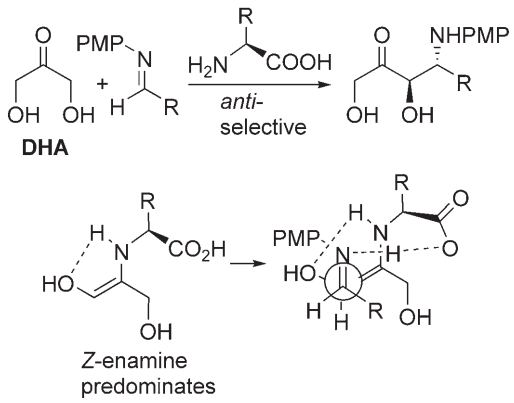


Scheme 2.

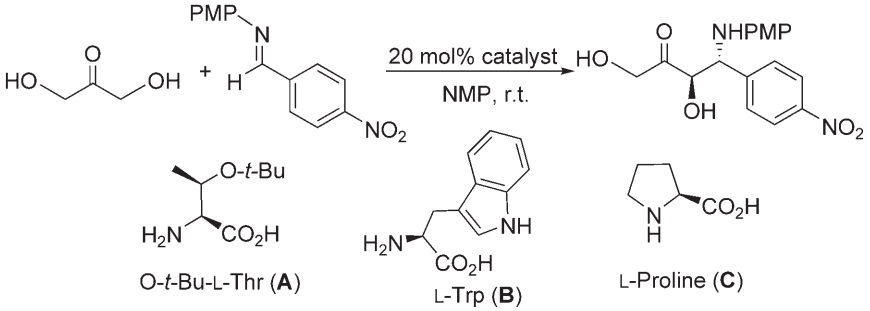


Scheme 3.

in the transition state (Scheme 2).[7] In accord with this design principle, we reasoned that the *anti*-Mannich product of unprotected DHA should be selectively formed under primary amine-based amino acid catalysis (Scheme 3). The DHA derivative 2,2-dimethyl-1,3-dioxane-5-one can only form an (*E*)-enamine, which leads to the *syn*-Mannich product (Scheme 1). A strategy based on unprotected DHA as a Mannich donor would be a more economical route to amino sugars than that using 2,2-dimethyl-1,3-dioxane-5-one as a donor.

We first investigated the Mannich reaction between unprotected DHA and a preformed imine of nitrobenzaldehyde in the presence of the amino acid L-tryptophan (L-Trp) or O-*t*-Bu-L-threonine (O-*t*-Bu-L-Thr) (Table 1). In the presence of 20 mol% O-*t*-Bu-L-Thr in *N*-methylpyrrolidinone (NMP) at ambient temperatue, we obtained the *anti*-Mannich product **1** with a *dr* of 4:1 and 85% *ee* (Table 1, entry 1). We found that the *dr* and *ee* of **1** could be significantly increased to 99:1 and 97%, respectively, by simple recrystallization. Further optimization revealed that the addition of 5-methyl-1*H*-tetrazole[9] enhanced both reaction rate and enantioselectivity (compare entries 1 and 2). In contrast to our *syn*-aldol reaction with Bn-protected DHA, addition of 3 vol% of water significantly slowed the reaction although the *ee* increased (com-

Table 1. Mannich reaction of unprotected DHA and *p*-nitrobenzaldehyde preformed imine.[a]



Entry	Catalyst	Time [days]	Yield [%][b]	*dr* (*anti*:*syn*)[c]	*ee* (*anti*/*syn*) [%][d]
1	**A**	1	68	4:1 (99:1)[i]	85/- (97)[i]
2[e]	**A**	0.8	77	4:1	90/64
3[f]	**A**	1	23	2:1	89/67
4[e,g]	**A**	3	55	3:1	92/-
5[e]	**B**	1	50	3:1	79/30
6[e,h]	**C**	0.8	73	1:1.8	51/49

[a] See Supporting Information.
[b] Isolated yields.
[c] Determined by HPLC or NMR.
[d] Determined by chiral-phase HPLC.
[e] With additive 5-methyl-1*H*-tetrazole.
[f] 3 vol% H_2O.
[g] At 4 °C.
[h] 40 mol% of L-proline.
[i] After recrystallization.

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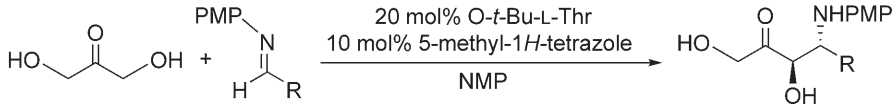
Table 2. Scope of the *anti*-Mannich reaction of unprotected DHA with various acceptors.[a]



Entry	R	Product	Time [h]	Yield [%][b]	*dr* (*anti*:*syn*)[c]	*ee* (*anti*/*syn*) [%][d]
1	*p*-$NO_2C_6H_4$	**1**	21	77	4:1	90
2	*p*-CNC_6H_4	**2**	24	75	3:1	88
3	*p*-BrC_6H_4	**3**	24	78	2:1	78
4[e]	*p*-$CF_3C_6H_4$	**4**	24	71	3:1	81
5[f]	Cyclohexyl	**5**	72	70	1.5:1	66
6[f]	CH_2CH_2Ph	**6**	60	65	2:1	72
7[e]	$CH(OCH_3)_2$	**7**	18	72	1:1	71
8[g]	CO_2Et	**8**	17	53	1:1	28

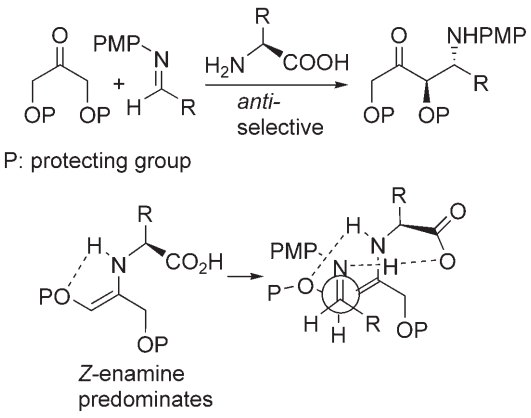
[a] See Supporting Information.
[b] Isolated yield containing *anti* and *syn* diastereomers.
[c] Determined by ^1H NMR or HPLC.
[d] Determined by chiral-phase HPLC.
[e] Three-component reaction: ketone (1 mmol, 2.0 equiv.), aldehyde (0.5 mmol, 1.0 equiv.), $PMPNH_2$ (0.55 mmol, 1.1 equiv.), catalyst (0.1 mmol, 0.2 equiv., 20 mol% to aldehyde), and 5-methyl-1*H*-tetrazole (0.05 mmol, 0.1 equiv., 10 mol% to aldehyde).
[f] Three-component reaction: ketone (1 mmol, 2.0 equiv.), aldehyde (0.5 mmol, 1.0 equiv.), $PMPNH_2$ (0.5 mmol, 1.0 equiv.).
[g] Without additive 5-methyl-1*H*-tetrazole.

pare entries 1 and 3). Lowering the reaction temperature was not a benefit (entry 4). O-*t*-Bu-L-Thr catalysis proved to be superior to L-Trp catalysis with respect to both *dr* and *ee* (entry 5). Interestingly, when using 40 mol% proline and 5-methyl-1*H*-tetrazole, **1** could be prepared in good yield, albeit with moderate *ee* and *syn*-favored selectivity (entry 6). We believe this to be the only known proline-catalyzed Mannich reaction involving unprotected DHA.

The scope of the reaction was then studied using unprotected DHA and various aromatic and aliphatic acceptors under the optimized conditions (Table 2). Results of the reaction with preformed imines as acceptors are shown in entries 1–3 and 8 and those from the traditional three-component Mannich process in entries 4–7. Electron-deficient aromatic imines generally gave good selectivities (entries 1–4), whereas aliphatic imines gave lower diastereo- and enantioselectivities (entries 5 and 6). Aryl imines bearing electron-donating groups were also substrates for this reaction, albeit with less favorable outcomes. The O-*t*-Bu-L-Thr catalyzed three-component Mannich reaction of DHA with dimethoxyacetaldehyde and *p*-anisidine afforded Mannich product **7** with the *dr* of almost 1:1. The reaction of DHA and glyoxylate imine proceeded smoothly without additive;[10] however, the product was obtained in poor *ee* and *dr* (entry 8).

Mannich products **7** and **8** are very useful synthons for the synthesis of aza-sugars[1,2,5,6] and polyoxamic acid[11], respectively. Development of *anti*-Mannich reactions with imino esters or α-oxygen-bearing aldehyde-derived imines is of considerable importance. The α-oxygen-bearing acceptors and glyoxylate imine are poor substrates for this reaction. In previous studies, we found that the Mannich reaction of protected monohydroxyacetone with *p*-nitrobenzaldehyde afforded the *anti*-Mannich product in high yield and high enantioselectivity under primary amine-containing amino acid catalysis.[12] Thus, we reasoned that protected forms of DHA should also form a (*Z*)-enamine in the transition state (Scheme 4).

Thus, we studied the Mannich reaction of Bn-protected DHA with ethyl glyoxylate imine.[13] To our delight, O-*t*-Bu-L-Thr catalyzed the Mannich-type reaction of Bn-protected DHA with ethyl glyoxylate imine, affording high enantioselectivity (Table 3,



Scheme 4.

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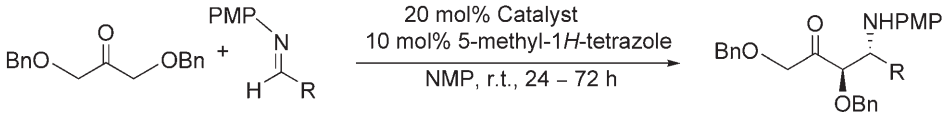
Table 3. Bn-protected DHA as donor in the *anti*-Mannich reactions.[a]

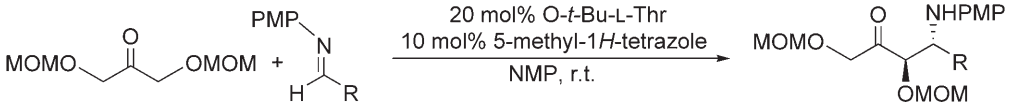


Entry	R	Product	Catalyst	Yield [%][b]	*dr* (*anti*:*syn*)[c]	*ee* (*anti*/*syn*) [%][d]
1	CO_2Et	**9**	**A**	65	2:1	87/37
2[e,f]			**A**	78	2:1	89/68
3[e,f]			**B**	76	3:1	91/63
4[g]	$CH(OCH_3)_2$	**10**	**A**	68	2.3:1	81/19
5			**B**	73	2:1	79/21
6	*p*-$NO_2C_6H_4$	**11**	**A**	91	4:1	97/77
7[f,h]			**B**	78	4:1	92/54
8	*p*-$CF_3C_6H_4$	**12**	**A**	77	4:1	94/84
9	*p*-BrC_6H_4	**13**	**A**	85	4:1	88/57
10[f]				-	3:1	85/38
11[g]	$CH(CH_3)_2$	**14**	**A**	73	2:1	73/7

[a] See Supporting Information.
[b] Isolated yield containing *anti* and *syn* diastereomers.
[c] Determined by ^1H NMR or HPLC.
[d] Determined by chiral-phase HPLC.
[e] 2-PrOH as solvent.
[f] Without additive 5-methyl-1*H*-tetrazole.
[g] Three-component reaction: ketone (1 mmol, 2.0 equiv.), aldehyde (0.5 mmol, 1.0 equiv.), $PMPNH_2$ (0.55 mmol, 1.1 equiv.), catalyst (0.1 mmol, 0.2 equiv., 20 mol% to aldehyde), and 5-methyl-1*H*-tetrazole (0.05 mmol, 0.1 equiv., 10 mol% to aldehyde).
[h] 30 mol% of L-Trp.

entry 1). In the absence of additive, higher diastereo- and enantioselectivity were observed when L-Trp was employed as catalyst rather than O-*t*-Bu-L-Thr (entry 3). The three-component Mannich reaction of Bn-protected DHA with dimethoxyacetaldehyde and *p*-anisidine afforded the *anti*-isomer as the major product with 81% *ee* in the presence of O-*t*-Bu-L-Thr. Bn-protected DHA was also a suitable donor for aromatic and aliphatic aldehyde-derived imines, giving *anti*-selective Mannich products in good yields and with high enantioselectivities (Table 3). To briefly examine protecting group tolerability of the reaction, we studied methoxymethyl (MOM) and TBS since these protecting groups are readily removed under mild conditions. As expected, reactions involving MOM-protected DHA furnished the desired *anti*-major Mannich products in good yield (Table 4). Significantly, the three-component Mannich reaction of

Table 4. MOM-protected DHA as donor in the *anti*-Mannich reactions.[a]



Entry	R	Product	Yield [%][b]	*dr* (*anti*:*syn*)[c]	*ee* [%] *anti*[d]
1	*p*-$NO_2C_6H_4$	**15**	75	2.5:1	90
2	*p*-$CF_3C_6H_4$	**16**	71	2:1	87
3[e]	CH_2OBn	**17**	61	1.5:1	72

[a] See Supporting Information.
[b] Isolated yield containing *anti* and *syn* diastereomers.
[c] Determined by HPLC or NMR.
[d] Determined by chiral-phase HPLC.
[e] Three-component reaction: ketone (0.5 mmol, 2.0 equiv.), aldehyde (0.25 mmol, 1.0 equiv.), $PMPNH_2$ (0.275 mmol, 1.1 equiv.), catalyst (0.05 mmol, 0.2 equiv., 20 mol% to aldehyde), and 5-methyl-1*H*-tetrazole (0.025 mmol, 0.1 equiv., 10 mol% to aldehyde).

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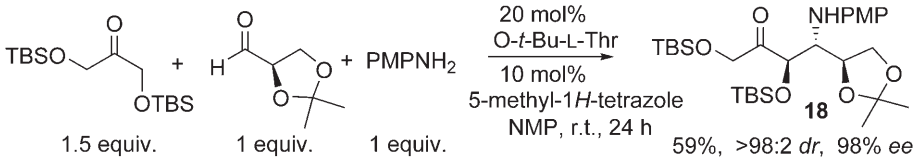

Scheme 5. Synthesis of protected 4-amino-4-deoxy-D-psicose **18**.

TBS-protected DHA with the acetonide of D-glyceraldehyde and *p*-anisidine under our standard conditions successfully afforded the protected 4-amino-4-deoxy-D-psicose **18** in virtually stereoisomerically pure form (>98:2 *dr*, 98% *ee*) (Scheme 5). Since protecting groups have considerable strategic value in synthetic chemistry, our strategy of employing acyclic protected DHA as donors should facilitate the development of *anti*-selective direct asymmetric Mannich reaction of DHA derivatives for the synthesis of amino sugars.

The absolute configuration of *anti*-**1** was determined to be 3*R*,4*R* (see Supporting Information); these results are in accord with our previous results in which monohydroxyacetone was employed as a donor. The absolute configurations of the other products were assigned by analogy.

In summary, we have demonstrated the first direct catalytic asymmetric Mannich reactions that involve unprotected dihydroxyacetone and acyclic protected dihydroxyacetones with a variety of aromatic and aliphatic aldehyde-derived imines. These reactions generated *anti*-polyhydroxylated amino alcohols and amino sugars; these new syntheses complement proline-based strategies and should find use in the synthesis of amine-containing carbohydrates.

Experimental Section

General Procedure for Two-Component Mannich-Type Reactions of DHA

To a solution of *N*-PMP-protected preformed imine (0.5 mmol, 1 equiv.) in anhydrous 1-methyl-2-pyrrolidinone (NMP, 0.5 mL) was added 1,3-dihydroxyacetone dimer (0.5 mmol, 1 equiv.; 2 equiv. as monomer) followed by O-*t*-Bu-L-Thr (0.1 mmol, 0.2 equiv.) and 5-methyl-1*H*-tetrazole (0.05 mmol, 0.1 equiv.) at room temperature. The reaction was stirred at room temperature for the time as indicated in Table 1 and Table 2. The reaction mixture was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The organic layers were washed with water and brine, dried over Na_2SO_4, filtered, concentrated under vacuum, and purified by flash column chromatography (AcOEt/hexane) to afford the corresponding Mannich adducts as an *anti*/*syn* mixture. Racemic standards were prepared using (±)-tryptophan and phenylphosphinic acid.

Acknowledgements

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[9] Solvent and additive screening at room temperature showed that NMP and 5-methyl-1*H*-tetrazole were the best choices considering the reaction rate, yield, and selectivity (data not shown). 5-Methyl-1*H*-tetrazole acts as an acid co-catalyst.

[10] According to Westermann, no reaction could be observed with DHA and glyoxylate imine under the conditions: 30 mol% proline, DMSO, room temperature. See ref.[5]

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[12] Mannich reaction of methoxyacetone to *p*-nitrobenzaldehyde in the presence of 30 mol% L-Trp in DMF at room temperature affording the desired *anti*-major product in 93% yield; 4.4:1 *dr* (*anti*:*syn*), 93% *ee* for *anti*, and 83% *ee* for *syn*. Similar work was done by Lu et al., see ref.[8e]

[13] Poor enantioselectivity was observed in the β-proline catalyzed Mannich reaction with Bn-protected DHA and ethyl glyoxylate imine; *dr* 1.4:1 (*anti*:*syn)* and 45% *ee* (*anti*); see ref.[8c]

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