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Peptide-Catalyzed Highly Asymmetric Cross-Aldol Reaction of Aldehydes to Biomimetically Synthesize 1,4-Dicarbonyls

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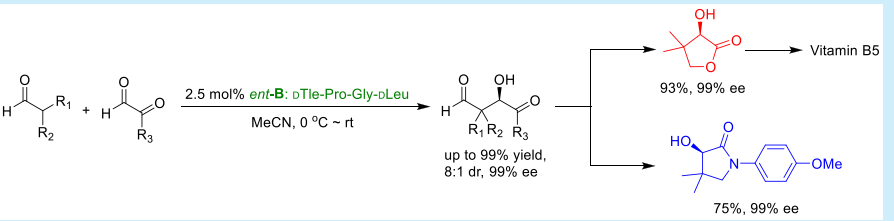

ABSTRACT: β-Turn tetrapeptides were demonstrated to catalyze asymmetric aldol reaction of α-branched aldehydes and α-carbonyl aldehydes, i.e. glyoxylates and α-ketoaldehydes, to biomimetically synthesize acyclic all-carbon quaternary center-bearing 1,4-dicarbonyls in high yield and excellent enantioselectivity under mild conditions. The spatially restricted environment of the tetrapeptide warrants high enantioselectivity and yield with broad substrates. Using this protocol, (*R*)-pantolactone, the key intermediate of vitamin B5, was readily accessed in a practical, efficient, and environmentally benign process from inexpensive starting materials.

Aldol reaction is commonly used in preparing diverse chiral bioactive compounds and thus has always been widely studied.[1] Catalytic asymmetric cross-aldol reaction of α-branched aldehydes and α-carbonyl aldehydes can directly produce chiral 2-hydroxy-3,3-disubstituted 1,4-dicarbonyls bearing an acyclic all-carbon quaternary center. These 1,4-dicarbonyl motifs are commonly found in natural products as well as biologically and pharmaceutically active compounds, such as extensively biologically and pharmaceutically active coenzyme **A** (**AC-1**, Figure 1) and glucocorticoids **AC-3** and **AC-4**.[2,3]

To the best of our knowledge, catalytically asymmetric preparation of these 1,4-dicarbonyls is rarely reported, except for the recently disclosed reaction of ethyl glyoxylate and limited α-branched aldehydes in insufficient enantioselectivity.[4,5] Mahrwald and co-worker made a seminal contribution in performing the cross-aldol reaction of ethyl glyoxylate with enolizable aldehydes, achieving good yields and enantioselectivity (85% yield and 79% ee) with 10% L-His as an organocatalyst.[4] Additionally, Hayashi's group employed diphenylprolinol silyl ether to catalyze the same reaction to construct all-carbon quaternary stereogenic centers in moderate to good enantioselectivity but with poor diastereoselectivity.[5] And notably, the reaction of α-branched aldehydes and α-ketoaldehydes for 1,4-dicarbonyls has not been disclosed to date. Therefore, it is highly anticipated to develop a new efficient strategy to synthesize highly enantioenriched 1,4-dicarbonyls by cross-aldol reaction of α-branched aldehydes with glyoxylates and especially with α-ketoaldehydes.

Synthetic short peptides are ideal surrogates of enzymes and have been utilized to biomimetically catalyze numerous highly enantioselective organic transformations.[6,7] In comparison to enzymes, peptides are more easily accessible, modifiable, and well compatible to varied conditions.[8] Although they reportedly catalyze asymmetric Aldol reactions, the successful substrates are mainly limited to acetone and cyclohexanone as

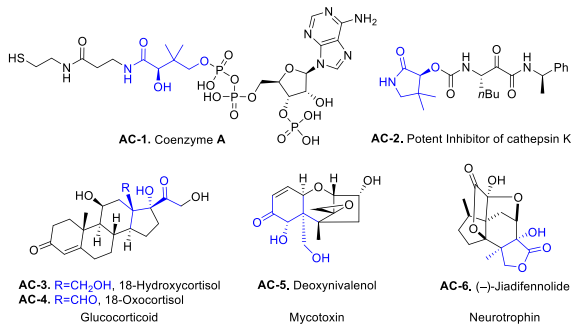

Figure 1. Bioactive compounds bearing 2-hydroxy-3,3-disubstituted 1,4-dicarbonyl motif.

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aldol donors.[9] Challengingly, the new arena of alkyl aldehydes, especially α-branched alkyl aldehydes, as aldol donors is expected to be explored with catalytic peptides. β-Turn tetrapeptides constitute a range of successful artificial enzymes in organic transformations.[10] X-ray analysis of a novel β-turn tetrapeptide, designed and synthesized by us based on our previous work,[11] shows that the catalytic terminal NH_2 and COOH groups both locate on the same side of the turn plane (Figure 2). The terminal bulky *i*-Bu and *t*-Bu groups position

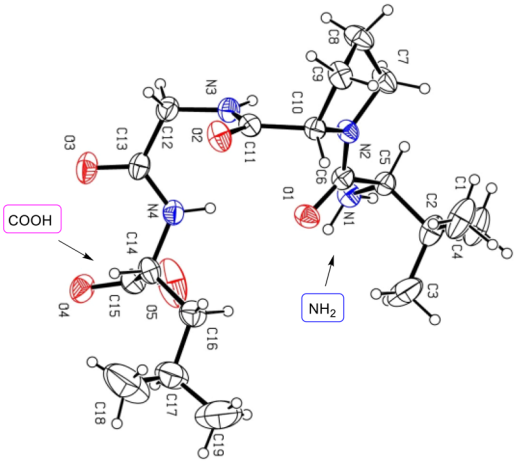
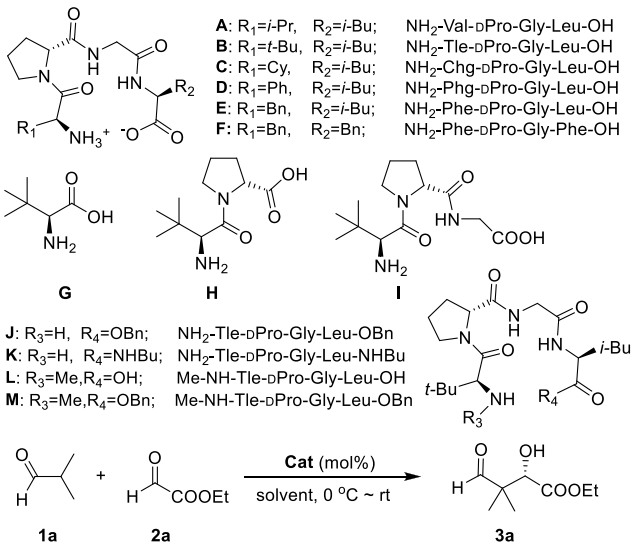


Figure 2. X-ray of a tetrapeptide (*ent*-**B**, NH_2-DTle-Pro-Gly-DLeu-OH, CCDC 1940092).

roughly on the same side as the NH_2 and COOH groups and effectively shade the two ends of the tetrapeptide. In the reaction of α-branched aldehydes and α-carbonyl aldehydes, the plane and the two bulky alkyl groups should form an idealistic spatially restricted chiral environment and thus largely limit the conformation freedom of the transition state complex and the attacking direction from the α-branched aldehyde nucleophile to the α-carbonyl aldehyde electrophile, probably enabling a highly asymmetric induction. Herein, we disclose our initial results of asymmetric cross-aldol reaction of α-branched aldehydes with glyoxylates and first with α-ketoaldehydes biomimetically catalyzed by low-loading β-turn tetrapeptides with excellent enantioselectivity and high yield.

The work was initiated with the typical reaction of isobutyraldehyde and ethyl glyoxylate at room temperature catalyzed by β-turn tetrapeptide **A** (Table 1, entry 1). The reaction proceeded smoothly with good yield and excellent enantioselectivity (74% yield and 94% ee), indicating the tetrapeptide was suitable for this reaction. Investigation of the loading of isobutyraldehyde revealed 2.0 equiv of isobutyraldehyde was ideal in view of the yield and enantioselectivity (entries 1−3). Subsequently, five other tetrapeptides **B**−**F** were tested. All of the peptides smoothly catalyzed the reaction with good to high enantioselectivity. Notably, self-aldol side-reaction of isobutyraldehyde was not detactable.[4a] Tetrapeptide **B**, bearing the largest *t*-Bu side chain group at the *N*-terminus, achieved the highest enantioselectivity (entries 2, 4−8), confirming our postulation about the positive effect of the bulky side chain group on the asymmetric induction. For the solvent, MeCN is optimal (entries 4, 9−14). Tetrapeptide **B** loading can be reduced to 2.5 mol % without erosion of the yield and enantioselectivity (entries 14−16).

Table 1. Optimization of Reaction Conditions[a]



entry	cat./ mol %	1a (mmol)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	**A**/5	2.0	CH_2Cl_2	72	74	94
2	**A**/5	1.0	CH_2Cl_2	72	79	94
3	**A**/5	0.5	CH_2Cl_2	72	70	89
4	**B**/5	1.0	CH_2Cl_2	72	85	97
5	**C**/5	1.0	CH_2Cl_2	72	80	91
6	**D**/5	1.0	CH_2Cl_2	72	59	75
7	**E**/5	1.0	CH_2Cl_2	72	80	91
8	**F**/5	1.0	CH_2Cl_2	72	84	84
9	**B**/5	1.0	PhMe	48	87	95
10	**B**/5	1.0	ClC_2H_4Cl	72	86	98
11	**B**/5	1.0	MeOH	48	91	86
12	**B**/5	1.0	THF	48	90	98
13	**B**/5	1.0	MeO*t*Bu	24	84	91
14	**B**/5	1.0	MeCN	24	98	99
15	**B**/2.5	1.0	MeCN	36	98	99
16	**B**/1	1.0	MeCN	48	77	95
17	**G**/5	1.0	MeCN	72	34	70
18	**H**/5	1.0	MeCN	48	43	48
19	**I**/5	1.0	MeCN	48	65	75
20	**J**/5	1.0	MeCN	24	50	93
21	**K**/5	1.0	MeCN	24	44	97
22	**L**/5	1.0	MeCN	120	26	78
23	**M**/5	1.0	MeCN	120	17	55

[a]Ethyl glyoxylate **2a** (0.5 mmol, 50% in toluene). [b]Isolated yield. [c]Determined with the *p*-nitrobenzoate of **3a** by chiral HPLC. The configuration was assigned by comparing the optical rotation direction of **3a** with its reported datum.[4a]

To demonstrate the structural superiority of tetrapeptide **B**, *tert*-leucine **G**, dipeptide **H**, and tripeptide **I** were investigated (Table 1, entries 14 vs 17−19). *tert*-Leucine made the reaction very sluggish and resulted in moderate enantioselectivity and a very low yield, with the self-aldol side-reaction of isobutyraldehyde detectable. Dipeptide **H** sharply decreased the enantioselectivity although it achieved a higher yield than *tert*-leucine **G**. Tripeptide **I** apparently displayed superior efficiency to *tert*-leucine and dipeptide **H** in view of the yield and enantioselectivity although its *C*-terminal amino acid residue is an achiral glycine.[12] But tripeptide **I** obtained a much lower yield and enantioselectivity than tetrapeptide **B**, probably

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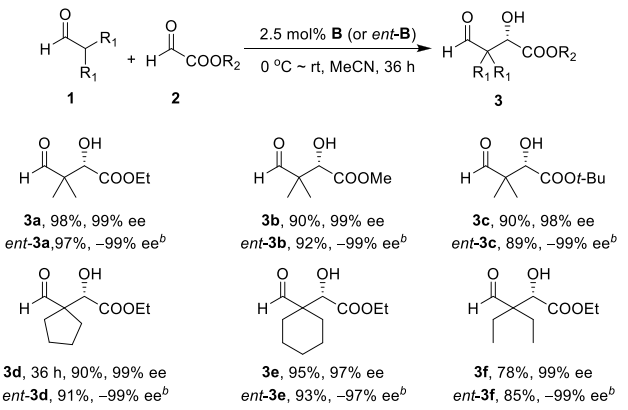
because tripeptide **I** cannot form a spatially restricted chiral environment like tetrapeptide **B**.

To investigate the roles of the terminal COOH and NH_2 groups of tetrapeptide **B**, tetrapeptides **J**−**M** were investigated (entries 14 vs 20−23). Tetrapeptide **J**, with *C*-terminal COOH protected by benzyl ester, similarly realized excellent 93% enantioselectivity but sharply decreased the yield. While the *C*-terminal COOH was changed into a secondary amide, tetrapeptide **K** slightly increased the enantioselectivity to 97%, but the yield was not accompanyingly increased. These two cases apparently reveal the indispensability of the *C*-terminal COOH in tetrapeptide **B** to the transformation.[13] Tetrapeptide **L**, with a *N*-terminal secondary amine group, abruptly decreased both the yield and enantioselectivity, unambiguously indicating the importance of the *N*-terminal NH_2 to both the yield and enantioselectivity. Tetrapeptide **M**, with a *N*-terminal secondary amine group and *C*-terminus benzyl ester, further diminished the yield and enantioselectivity in comparison with tetrapeptide **L**. Therefore, the *N*-terminus NH_2 and *C*-terminus COOH groups are both essential to high yield and enantioselectivity.

Under the optimized reaction conditions, the substrate scope was explored (Scheme 1). Clearly, this protocol is particularly suitable to this aldol reaction with very high enantioselectivity to all investigated aldehydes. While *ent*-**B** (the enantiomer of tetrapeptide **B**) was used, enantiomers of all the 1,4-dicarbonyl products were similarly realized with the same high yield and enantioselectivity. Thus, *ent*-**3a**−*ent*-**3c**, the intermediates of vitamin **B5** and coenzyme A, can be prepared in very high yield and enantioselectivity in an eco-friendly manner through a catalytic asymmetric reaction for the first time.

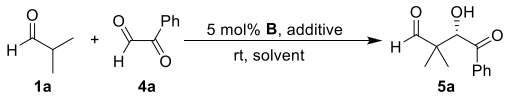
Scheme 1. Catalytic Enantioselective Aldol Reactions of Glyoxylates[a]



[a]1.0 mmol of **1** and 0.5 mmol of **2** were used. Isolated yield. Ee was determined with the *p*-nitrobenzoate of **3** by chiral HPLC. [b]The enantiomer of **B**, *ent*-**B**, was used.

While replacing the glyoxylate to α-ketoaldehydes (in monohydrate form), the reaction became slow and the yield was moderate despite very high enantioselectivity (Table 2, entry 1). Several additives were tested, and anhydrous Na_2SO_4 satisfactorily induced a remarkable effect on the yield (entries 2−4). An increase in Na_2SO_4 explicitly shortened the reaction time and enhanced the yield without changing the enantioselectivity (entries 4−5). Decreasing the tetrapeptide **B** loading did not decrease the enantioselectivity but slightly reduced the yield and prolonged the reaction time (entries 5 vs 6).

Table 2. Optimization of Aldol Reaction Conditions of Phenyl Glyoxal[a]

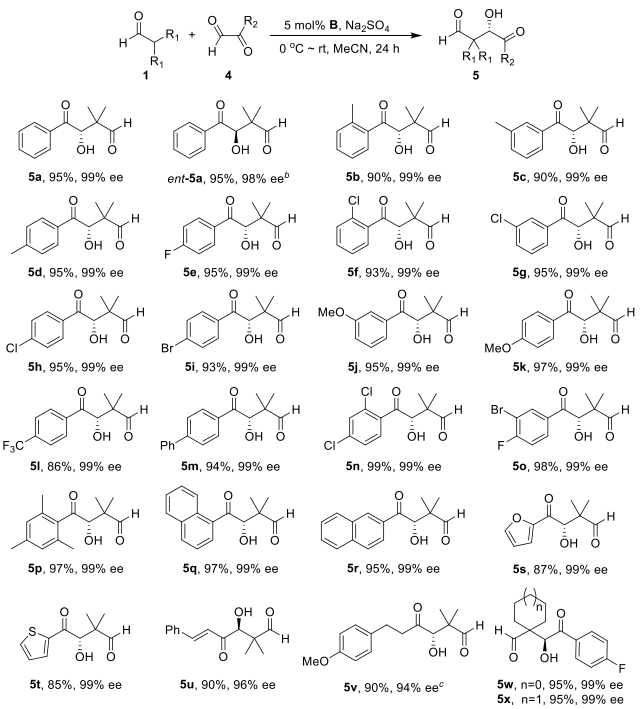


entry	additive (mg)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	–	MeCN	72	53	99
2	4 Å (50)	MeCN	48	60	99
3	$MgSO_4$ (50)	MeCN	48	55	99
4	Na_2SO_4 (50)	MeCN	24	85	99
5	Na_2SO_4 (100)	MeCN	12	95	99
6[d]	Na_2SO_4 (100)	MeCN	16	92	99

[a]1.0 mmol of **1a** and 0.5 mmol of **4a** were used. [b]Isolated yield. [c]Determined with the acetal of **5a** and 2,2-dimethyl-1,3-propanediol by chiral HPLC. [d]2.5 mol % **B** was used.

With this reoptimized reaction conditions, α-ketoaldehydes were extensively explored with symmetric α-branched aldehydes without a stereocenter (Scheme 2). Excitingly, the reaction is very idealistic for all of the investigated α-ketoaldehydes. All the aryl glyoxals uniformly realized 99% enantioselectivity (**5a**−**5t** and **5w**−**5x**), including two heteroaryl glyoxals (**5s**, **5t**). Even the alkenyl and alkyl glyoxals also achieved high yield and enantioselectivity (**5u**, **5v**). While using *ent*-**B** instead of **B**, high yield and enantioselectivity of the corresponding enantiomer of the 1,4-dicarbonyl were both

Scheme 2. Catalytic Enantioselective Aldol Reaction of α-Ketoaldehydes[a]



[a]1.0 mmol of **1**, 0.5 mmol of **4**, and 100 mg of anhydrous Na_2SO_4 were used. Isolated yield. Ee was determined with the acetal of **5** and 2,2-dimethyl-1,3-propanediol by chiral HPLC. [b]*ent*-**B** was used. [c]Ee was directly determined by chiral HPLC.

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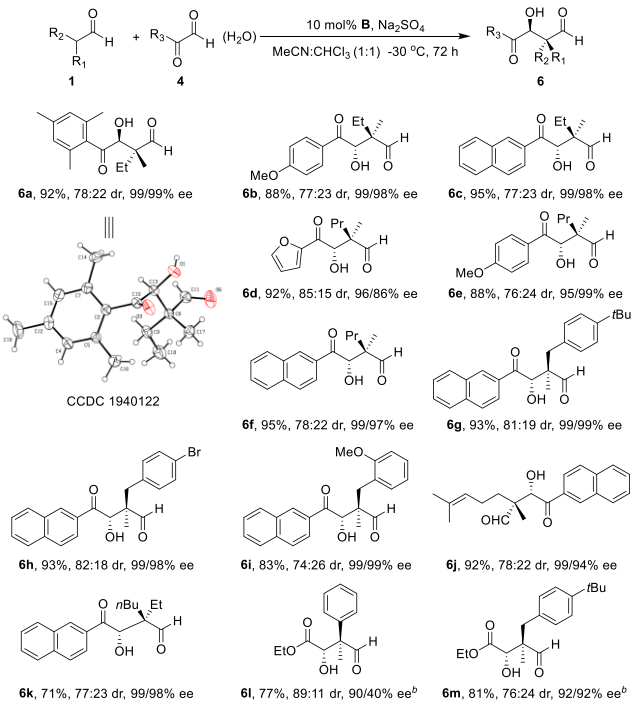
maintained (**5a** vs *ent*-**5a**). Therefore, pairs of highly enantiopure enantiomers of the 1,4-dicarbonyls should be readily accessible by simply switching two tetrapeptides with each other: **B** and its enantiomer *ent*-**B**.

Then, the reaction was extended to explore the asymmetric α-branched aldehyde with an α-carbon stereocenter to construct 1,4-dicarbonyls bearing an acyclic all-carbon quaternary stereocenter (Scheme 3). Highly enantioselective

Scheme 3. Catalytic Stereoselective Aldol Reaction of α-Branched Aldehydes and α-Carbonyl Aldehydes[a]

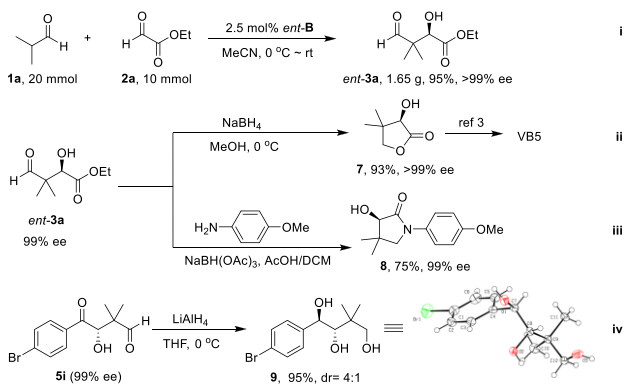


[a]1.0 mmol of **1**, 0.5 mmol of **4**, and 100 mg of anhydrous Na_2SO_4 were used. Isolated yield. Ee and dr value were determined by chiral HPLC, and the reported ee is anti/syn. [b]Ethyl glyoxylate was used.

construction of an acyclic all-carbon quaternary stereocenter is a big challenge for the numerous degrees of freedom of the molecule structure.[5,14] Under the reconstructed reaction conditions (for data for reoptimization of the reaction conditions, see p S4 in Supporting Information), all reactions proceeded smoothly and uniformly achieved excellent enantioselectivity. The predominant diastereomers are anti, determined by X-ray analysis of the crystal of **6a**. The diastereoselectivities are moderate to good. Methyl and ethyl groups are two alkyl groups that were the most difficult to differentiate at one carbon. Herein, 1,4-dicarbonyls bearing this motif achieved more than 3:1 diastereoselectivity (Scheme 3, **6a**–**6c**). While the ethyl group was replaced by a bulkier or longer alkyl group, the diastereoselectivity changed little and the highest dr value is higher than 4:1 for **6g** and **6h** (**6d**–**6k**). Notably, α-branched aldehydes bearing an alkenyl group similarly achieved excellent enantioselectivity and a high yield (**6j**). Finally, the diastereoselectivity can be raised to 8:1 with ethyl glyoxylate as the electrophile (**6l**–**6m**).

The model aldol reaction of isobutyraldehyde and ethyl glyoxylate was enlarged to gram scale without reduction in yield and ee with *ent*-**B** as the catalyst (i, Scheme 4). The product *ent*-**3a** was readily reduced into (*R*)-pantolactone (ii,

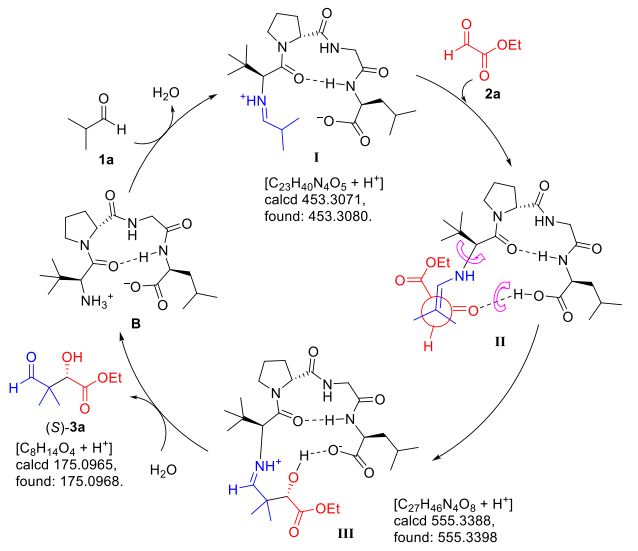
Scheme 4. Practicality Observation of the Transformation



Scheme 4),[8] the intermediate for synthesis of vitamin B5,[2d] (*R*)-panthenol and (*R*)-pantetheine.[15,16] Conventionally, highly enantiopure (*R*)-pantolactone is achieved by biological fermentation.[17] In addition, *ent*-**3a** can be transformed into the lactam **8** (iii, Scheme 4), the intermediate of the potent inhibitor of cathepsin K.[3a] The 1,4-dicarbonyl **5i** was readily reduced into triol **9**. X-ray analysis of the crystal of triol **9** (CCDC 1940111) enabled the absolute configuration of **5i** to be determined. Thus, the configuration of other 1,4-dicarbonyls **5** in Scheme 2 is deduced from **5i** (iv, Scheme 4).

Based upon our investigations in this work and previous reports, the speculated reaction mechanism is shown in Scheme 5.[9,18] The β-turn plane and two terminal bulky side

Scheme 5. Speculated Reaction Mechanism



chain groups of tetrapeptide **B** largely sterically constrain the rotation of both planes of the enamine from isobutyraldehyde with tetrapeptide **B** and the aldehyde group of ethyl glyoxylate in the transition state **II**. In this spatially constrained chiral environment, the attack only on the *Si*-face of ethyl glyoxylate is sterically admitted, leading to highly enantiopure (*S*)-**3a**. The intermediates were detected by HR-MS.

In summary, we first successfully demonstrated the peptide-catalyzed biomimetic cross-aldol reaction of α-branched aldehydes with glyoxylates and α-ketoaldehydes for enantioenriched 1,4-dicarbonyls bearing an acyclic all-carbon quaternary center in high yield, excellent enantioselectivity, and good

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diastereoselectivity under mild reaction conditions. This work can be used to efficiently synthesize extensively utilized and largely commercially demanded (*R*)-pantolactone in very high enantioselectivity and yield from inexpensive and green starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01407.

Reoptimization of reaction conditions for acyclic all-carbon quaternary stereocenter-bearing 1,4-dicarbonyls, peptides synthesis, experimental procedures, characterization of compounds, NMR and HPLC spectra for compounds (PDF)

Accession Codes

CCDC 1940092, 1940111, and 1940122 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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