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Proline-catalyzed asymmetric assembly reactions: enzyme-like assembly of carbohydrates and polyketides from three aldehyde substrates†

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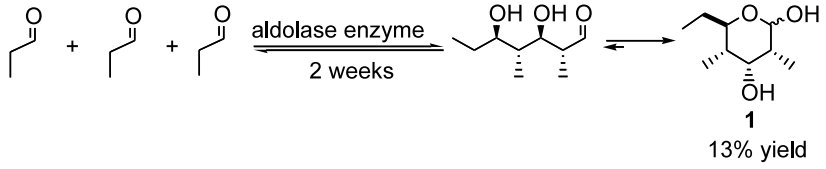
Abstract—Directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules like triketides has been described for the first time using L-proline catalyzed asymmetric double aldol reactions. The product pyranoses contain four asymmetric centers constructed under proline catalysis in a highly diastereoselective and modestly enantioselective fashion from three aldehyde molecules. These results suggest that the construction of complex products from simple starting materials is within the realm of organocatalysis involving the simple naturally occurring amino acid L-proline. Our successful assembly of pyranoses from simple aldehydes under proline catalysis suggests that this approach may warrant consideration as a prebiotic route to sugars and polyketides. © 2002 Elsevier Science Ltd. All rights reserved.

Polyketides are structurally diverse natural products possessing a broad range of biological activities.[1] Directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules like carbohydrates and polyketides has long been the purview of nature's enzymes.[2,3] Our approach to this problem began in 1997 when we embarked upon studies exploring the similarity between proline and aldolase antibody catalyzed reactions.[4] Recently, these studies have allowed us to describe the first direct organocatalytic asymmetric aldehyde additions in Michael, aldol, and Mannich-type reaction manifolds.[5] Aldehyde addition reactions are of particular significance to assembly strategies since the aldehyde functionality found in the products of these reactions provides a versatile chemical handle for further diversification, including the potential for additional aldol reactions. Encouraged by the pioneering studies of Wong concerning aldolase enzyme-catalyzed assembly reactions of aldehydes (Scheme 1),[2c] we recently reported the L-proline catalyzed asymmetric assembly of three acetaldehyde molecules to provide in a single step, (+)-5-hydroxy-(2*E*)-hexenal.[5b] Herein we describe L-proline catalyzed direct asymmetric assembly reactions involving three aldehyde components that provides for the remarkably simple preparation of polyketides in an enzyme-like assembly process.

In order to extend our studies of acetaldehyde assembly reactions to propionaldehyde, we treated propionaldehyde (1 M) with L-proline (10 mol%) in a variety of solvents.[6] DMF proved to be the most promising solvent and provided the trimeric aldol product **2** in 12% isolated yield, a yield similar to that obtained by Wong's enzyme-catalyzed assembly.[2c] The propionaldehyde aldol dimer was isolated as the major product in



Scheme 1. Aldolase-catalyzed self-aldolization of propionaldehyde.[2c]

Keywords: proline; aldehydes; aldol reaction; lactols; lactones.

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† Dedicated to Professor C.-H. Wong for his many contributions to the area of enzyme-catalyzed organic synthesis.

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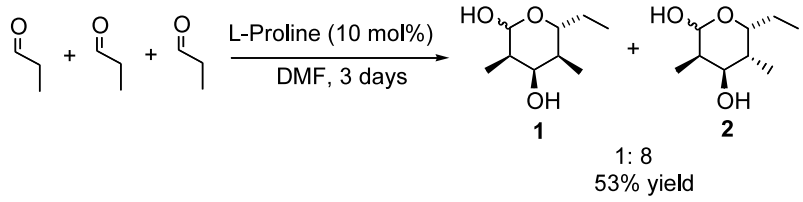
65% yield.[7] Upon consideration of the relative reactivities of propionaldehyde and its dimer, we performed the reaction by slowly adding propionaldehyde to the reaction in an attempt to improve the yield of the trimerized product. We were pleased to find that under these conditions, trimeric products **1** and **2** could be isolated in 53% yield as a 1:8 mixture of diastereomers with an anomeric ratio of 1:2 (α:β) (Scheme 2).

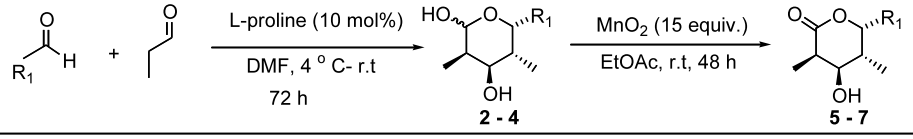
Encouraged by our studies involving propionaldehyde trimerization, we examined reactions involving nonequivalent aldehydes. When 2 equiv. of propionaldehyde was added slowly over 24 h to acceptor aldehydes such as isobutyraldehyde or isovaleraldehyde, the lactols **3** and **4** were formed as single diastereomers in moderate yields (Table 1, entries 2 and 3). Further, no condensation products derived from the trimers were formed in these reactions. The lactols were cleanly isolated as 1:2 mixtures of α/β anomers. To test the scalability of these types of assembly reactions, we performed the propionaldehyde trimerization reaction on a 10 g scale and found that the lactols could be obtained in crystalline form in 50% yield.

Provided the significance of triketides as key building blocks in natural products and drugs we were encouraged to convert our lactols to their corresponding δ-lactones. Polyketides are typically synthesized via biosynthetic assembly[3] or chemical methods founded on the aldol technology of Evans[8a] and Heathcock.[8b] For example, Staunton's expedient chemical syntheses via the aldol approach provide triketide δ-lactone products in seven steps.[8c] We found that we could readily convert lactols **2**–**4** to their corresponding δ-lactones **5**–**7** in quantitative yields using MnO_2 as the oxidant.[9] δ-Lactones **6** and **7** were isolated as single diastereomers and are thus assembled by proline in a very highly diastereoselective manner. With respect to enantioselectivity, δ-lactone **5**–**7** were obtained in very modest ee, 11–12% (entries 1–3).[6] When we performed the reaction at 4°C for 3 days, the product is formed in 30% yield with 33% ee. However, we found that the product **2** formed after 10 h shows 47% ee. Thus, a time-dependent decrease in the enantioselectivity of this aldol assembly reaction occurs. Nonetheless, the diastereoselective synthesis of δ-lactones from three simple aldehyde components could be achieved in only two chemical steps.



Scheme 2. Proline-catalyzed self-aldolization reaction of propionaldehyde.[14]

Table 1. L-Proline-catalyzed assembly of pyranoses and their conversion to δ-lactones[15–17]



entry	R_1	lactol	yield (%)	α:β[a]	lactone	ee[b]
1	Et	**2**	53[c]	1 : 2.2	**5**	11(47,[d] 33[e])
2	*i*-Pr	**3**	32	1 : 2	**6**	12
3	*i*-Bu	**4**	24	1 : 2.5	**7**	11

[a] Determined by 1H NMR. [b] The ee's of products were determined by chiral-phase HPLC analyses of 3,5-dinitrobenzoate derivative of lactones using chiralpak AD-RH column. Stereochemistry was assigned based on proline catalyzed Aldol reactions.
[c]Yield represents the combined yield of isolated diastereomers **1** & **2** after column chromatography. [d]ee of the product after 10 h at 4 °C.
[e]ee of the product after 3 days at 4 °C.

The stereochemistry of the lactols were determined by NMR experiments of lactone **5** and comparison with known compounds **1**, **8** and **9**.[2c,7] The positive NOE effect observed between C_3(H) and C_5(CH_3) groups in lactone **5** indicates the axial orientation of H and CH_3 groups on C_3 and C_5 carbons, respectively (Fig. 1). Hence, the stereochemical outcome of this self-aldolization assembly reaction is in accord with our previously proposed transition-state model for proline-catalyzed intermolecular aldol reactions.[10] In contrast to the aldolase enzyme-catalyzed assembly reaction of propionaldehyde, where primarily a single product is formed,[11] the proline-catalyzed reaction afforded lactols **1** and **2**, with **2** as the major product. The formation of **1** via **8** is readily explained by proline catalysis of two sequential aldol reactions.[2c,5b] Major product **2**, however, is formed from **9** through epimerization of the intermediate propionaldehyde dimer **8**. We verified this experimentally by incubating **8** with L-proline. This experiment confirmed that proline is capable of epimerizing the *anti* aldol dimer **8** to the corresponding *syn* diastereomer **9**.[12] Reaction of the third aldehyde substrate, the slowest step in this reaction sequence, with the *syn* aldol dimer provides lactol **2** as the major product. Pyrrolidine was also studied as a catalyst of this assembly reaction. In contrast to L-proline, pyrrolidine did not provide the products, confirming the role of L-proline in directing the chemistry and diastereoselectivity of these assembly reactions (Scheme 3).

In conclusion, we have demonstrated for the first time L-proline-catalyzed enzyme-like assembly of carbohydrates and polyketides. The product pyranoses contain four asymmetric centers constructed under proline catalysis with excellent diastereoselectivity and modest enantioselectivity (47% ee) from three aldehyde molecules. The identity of each aldehyde component can potentially be freely varied providing access to a wide range of molecules. This simple one-pot procedure provides direct access to carbohydrates and polyketides that are otherwise prepared using multi-step procedures. Furthermore, the reactions can be performed on a multi-gram scale under operationally simple and safe conditions. These results suggest that the assembly of complex products from simple starting materials is within the realm of organocatalysis involving the simple naturally occurring amino acid proline. Our successful assembly of pyranoses from simple aldehydes under proline catalysis suggests that this approach may warrant consideration as a prebiotic route to sugars and polyketides.[13] Further studies aimed at exploring the scope and increasing the enantioselectivity of these proline-catalyzed assembly reactions are ongoing.

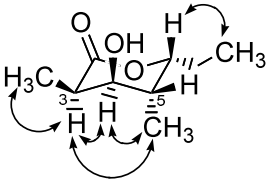
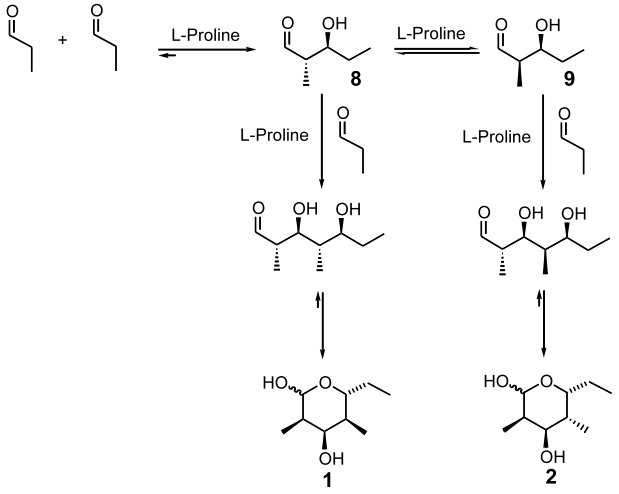


Figure 1. Selected NOEs for lactone **5**.



Scheme 3. Proposed reaction pathway for the proline-catalyzed assembly of pyranoses.

Acknowledgements

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6. Acetonitrile and dioxane are also good solvents for this reaction and the major product of the reaction was formed in these solvents with 15 and 11% ee, respectively. Significantly lower yields were obtained in THF, $CHCl_3$, toluene and DMSO.
7. This product was identical to that reported by MacMillan and co-workers during the course of these studies. Their report detailed their highly successful studies of proline-catalyzed direct cross-aldol reactions involving two aldehyde substrates: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.
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11. Epimerization of aldol intermediates has been observed in aldolase enzyme-catalyzed assembly reactions as well and these reactions are not typically 100% stereoselective. See Ref. 2b,c.
12. The ratio of dimers **8** and **9** in the proline-catalyzed self-aldol reaction of propionaldehyde varies with reaction time. For example the *anti*/*syn* ratio after 10, 13, 72, 96 h found to be 4, 2.5, 1.7 and 1, respectively.
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14. Typical experimental procedure for the catalytic asymmetric assembly of 6-ethyl-3,5-dimethyl-tetrahydropyran-2,4-diol (entry 1): A mixture of anhydrous DMF (2.5 mL), L-proline (10 mol%) and propionaldehyde (0.361 mL, 5 mmol) were stirred at 4°C for 10 h. To this propionaldehyde (0.18 mL, 2.5 mmol) was added slowly over 20 h and stirred at rt for an additional 42 h. Then, half saturated NH_4Cl solution and ether were added with vigorous stirring, the layers were separated and the aqueous phase was extracted thoroughly with ether followed by dichloromethane. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired pyranoses **1** in 6% yield (26 mg) and **2** in 47% yield (205 mg) with 11% ee as a mixture of anomers. **1**: R_f 0.42 (50% hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) (α:β = 1:3.2): δ 0.89 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.04 (d, J = 7.2 Hz), 1.08 (d, J = 6.8 Hz, 3H), 1.41 (m, 1H), 1.54 (m, 1H), 1.76 (m), 1.82 (m, 1H), 1.93 (m, 1H), 3.04 (bs, 1H), 3.20 (bs), 3.65 (bs, 1H), 3.71 (t, J = 2.8 Hz), 3.85 (ddd, J = 8.4, 6.4, 2.4 Hz), 4.08 (d, J = 6.4 Hz, 1H), 4.13 (dt, J = 6.8, 2.4 Hz, 1H), 4.72 (d, J = 6.0 Hz, α-CHOH), 4.98 (bs, 1H, β-CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) (α-anomer): δ 10.32, 10.41, 24.94, 37.09, 38.43, 74.00, 75.90, 97.16; (β-anomer): δ 0.14, 10.32, 13.21, 24.78, 32.15, 38.07, 65.67, 75.62, 96.46. **2**: R_f 0.32 (50% hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) (α:β = 1:2.2): δ 0.94 (m, 6H), 1.02 (d, J = 7.2 Hz, 3H), 1.48 (m, 2H), 1.63 (m, 2H), 2.09 (m, 1H), 2.19 (m), 2.56 (bs, 1H), 2.95 (ddd, J = 10.4, 8.0, 2.8 Hz), 3.01 (d, J = 6.0 Hz), 3.41 (dd, J = 11.2, 4.8 Hz, 1H), 3.54 (ddd, J = 10.8, 7.6, 2.8 Hz), 3.80 (dd, J = 10.0, 4.8 Hz, 1H), 4.76 (dd, J = 6.0, 2.0 Hz, α-CHOH), 5.10 (bs, β-CHOH); ^{13}C NMR (100 MHz, $CDCl_3$) (α-anomer): δ 4.32, 9.41, 13.02, 25.12, 35.69, 40.32, 75.20, 78.94, 95.81; (β-anomer): δ 9.18, 10.58, 13.18, 25.23, 36.41, 38.66, 71.19, 74.38, 97.00; HRMS for $C_9H_{18}O_3Na$ (MNa^+): calcd 197.1148, obsd 197.1147.
15. **6-Ethyl-4-hydroxy-3,5-dimethyl-tetrahydro-pyran-2-one (5)**: Lactol **2** (23 mg, 0.132 mmol) was dissolved in ethyl acetate (1.3 mL) and stirred with MnO_2 (172 mg, 1.981 mmol) at rt. After 48 h the reaction mixture was passed through a short column of silica gel with ethyl acetate. The eluate was concentrated to afford the desired lactone **5** in quantitative yield. R_f 0.32 (50% hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J = 7.2 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 7.2 Hz, 3H), 1.61 (m, 1H), 1.80 (m, 2H), 1.92 (bs, 1H), 2.67 (dq, J = 7.2, 3.6 Hz, 1H), 3.74 (t, J = 3.6 Hz, 1H), 3.76 (ddd, J = 10.8, 8.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.38, 11.15, 15.99, 26.11, 38.96, 41.78, 75.76, 82.61, 174.53; HRMS for $C_9H_{16}O_3Na$ (MNa^+): calcd 195.0992, obsd 195.0990; $[\alpha]_D = -12.0$ (c 1, $CHCl_3$). The enantiomeric excesses of the lactone **5** was determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate ester. The lactone **5** (20 mg, 0.116 mmol), 3,5-dinitrobenzoyl chloride (82.128 mg, 0.348 mmol) and DMAP (85 mg, 0.696 mmol) in dichloromethane (116 μL) were stirred at rt for 1 h to afford the corresponding 6-ethyl-4-(3′,5′-dinitrobenzoyloxy)-3,5-dimethyl-tetrahydro-pyran-2-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.6 Hz, 3H), 1.24 (d, J = 7.2 Hz, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.84 (m, 1H), 2.04 (m, 1H), 2.96 (dq, J = 7.2, 4.0 Hz, 1H), 3.90 (ddd, J = 10.8, 8.4, 2.8 Hz, 1H), 5.23 (dd, J = 3.8, 2.2 Hz, 1H), 9.07 (d, J = 2.4 Hz, 2H), 9.24 (t, J = 6.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.60, 14.61, 15.86, 19.83, 29.32, 36.67, 37.46, 80.21, 84.95, 122.80, 129.35, 133.01, 148.74, 162.05, 172.73; HRMS for $C_{16}H_{18}N_2O_8Na$ (MNa^+): calcd 389.0955, obsd 389.0958; $[\alpha]_D = 10.2$ (c 1, $CHCl_3$); HPLC (Daicel Chiralpak AD-RH, H_2O/MeCN = 52:48, 0.1% TFA, flow rate 0.8 mL/min, λ = 254 nm): t_R = 15.03 min (minor), t_R = 22.55 min (major).
16. Compound **6**: R_f 0.42 (50% hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.92 (m, 2H), 2.67 (dq, J = 6.8, 4.0 Hz, 1H), 3.73 (dd, J = 11.2, 2.0 Hz, 1H), 3.75 (t, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.18, 14.58, 16.06, 19.95, 29.23, 38.84, 39.43, 75.68, 85.32, 174.70; HRMS for $C_{10}H_{18}O_3Na$ (MNa^+): calcd 209.1148, obsd 209.1145; $[\alpha]_D = -5.2$ (c 1, $CHCl_3$). The enantiomeric excesses of the lactone **6** was determined by HPLC analysis of 6-isopropyl-4-(3′,5′-dinitrobenzoyloxy)-3,5-dimethyl-tetrahydro-pyran-2-one. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.96 (m, 1H), 2.16 (m, 1H), 2.95 (m, 1H), 3.87 (dd, J = 9.6, 2.4 Hz, 1H), 5.27 (t, J = 3.0 Hz, 1H), 9.07 (d, J = 2.4 Hz, 2H), 9.24 (t, J = 2.0,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.61, 14.61, 15.86, 19.85, 29.33, 36.68, 37.48, 80.23, 84.97, 122.83, 129.36, 133.03, 148.78, 162.08, 172.76; HRMS for $C_{17}H_{20}N_2O_8Na$ (MNa^+): calcd 403.1112, obsd 403.1120; HPLC (Daicel Chiralpak AD-RH, H_2O/MeCN = 52:48, 0.1% TFA, flow rate 1.0 mL/min, λ = 254 nm): t_R = 15.10 min (major), t_R = 18.90 min (minor).

17. Compound **7**: R_f 0.42 (50% hexanes/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 7.2 Hz, 3H), 1.34 (m, 1H), 1.65 (ddd, J = 14.0, 10.4, 3.2 Hz, 1H), 1.76 (m, 1H), 1.96 (m, 1H), 2.67 (dq, J = 7.2, 3.6 Hz, 1H), 3.74 (t, J = 3.2 Hz, 1H), 3.83 (dt, J = 9.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.19, 16.00, 21.23, 23.64, 23.95, 38.91, 42.85, 42.88, 75.80, 79.70, 174.49; HRMS for $C_{11}H_{20}O_3Na$ (MNa^+): calcd 223.1305, obsd 223.1305. HPLC (Daicel Chiralpak AD-RH, H_2O/MeCN = 60:40, 0.1% TFA, flow rate 0.8 mL/min, λ = 220 nm): t_R = 6.76 min (major), t_R = 8.92 min (minor).