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A straightforward route to the asymmetric synthesis of 3,4-diepipolyoxamic acid and its isomers

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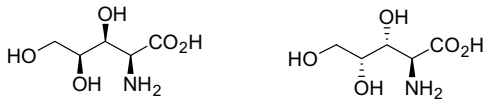
Abstract—The shortest route at present for the asymmetric synthesis of 3,4-diepipolyoxamic acid **2** and the isomer of polyoxamic acid **5** has been developed *via* the diastereoselective aldol reaction of camphor-based tricyclic iminolactones **3** and **4** with good stereoselectivities (dr: 12:1 and 9:1) and high yields.

1. Introduction

The 1,2-amino alcohol fragment is found in many natural products, in particular as a central moiety of non-proteingenic acids and amino polyols. An important example of the above class is polyoxamic acid **1** (Fig. 1), which is the key component amino acid of the polyoxins usually as nucleoside antibiotics.[1] Sphingofungins, which inhibit serinepalmitoyl transferase,[2] also consist of polyhydroxy amino acid **2** head groups. Interests in the field of chemistry and biology have led to the development of a number of syntheses of polyoxamic acid and its derivatives over the past several years.[3]

Recently, we have accomplished an efficient asymmetric syntheses of α-amino acids[4] using our chiral templets, tricyclic iminolactones **3** and **4**, which were synthesized from natural (1*R*)-(+)-camphor in over 50% total yield,



1 [(+)-Polyoxamic acid] **2**

Figure 1.

as the glycine equivalents for the asymmetric synthesis of α-amino acids. Herein, we targeted polyhydroxy amino acids **2** and **5**, which associate with a program on the asymmetric synthesis of sphingofungin. The key features of our proposed route involve: (1) the diastereoselective aldol reaction to afford the primary amino alcohols (2*S*,3*R*,4*R*)-**7** and (2*R*,3*S*,4*R*)-**8**, with structured two stereocenters in one step; (2) *endo*-products which were only obtained because of the rigid skeleton of our templet iminolactones **3** and **4**. Thus, only two compounds from four isomers were found in good ratios between these two epimers; (3) chiral auxiliaries (2-*exo*-hydroxyepicamphor[4a] and 3-*exo*-hydroxycamphor[4b]) can be recycled quantitatively; and (4) all reaction materials are inexpensive, readily available with the method being practical, and the shortest one at present.

2,3-*O*-(Isopropylidene)-D-glyceraldehyde **6** was easily obtained through two steps from D-mannitol.[5] Aldol reactions were performed by **3** and **4** with LDA in THF at −78 °C (Scheme 1). Lithium chloride as an additive can improve the stereoselectivity (Table 1). The polyhydroxy amino acid derivatives were obtained.[6] The optical rotations and melting point of compounds **7** and **8** are as follows: (2*S*,3*R*,4*R*)-**7**, mp 144–145 °C, $[\alpha]_D^{22}$ = +51.0 (*c* 1.0, CH_2Cl_2) and (2*S*,3*S*,4*R*)-**7** (*epi*-**7**), mp 63–64 °C, $[\alpha]_D^{22}$ = +111 (*c* 1.0, CH_2Cl_2); (2*R*,3*S*,4*R*)-**8**, mp 71–72 °C, $[\alpha]_D^{22}$ = −10.0 (*c* 0.7, CH_2Cl_2) and (2*R*,3*R*,4*R*)-**8** (*epi*-**8**), mp 120–121 °C, $[\alpha]_D^{22}$ = −188 (*c* 1.0, CH_2Cl_2).

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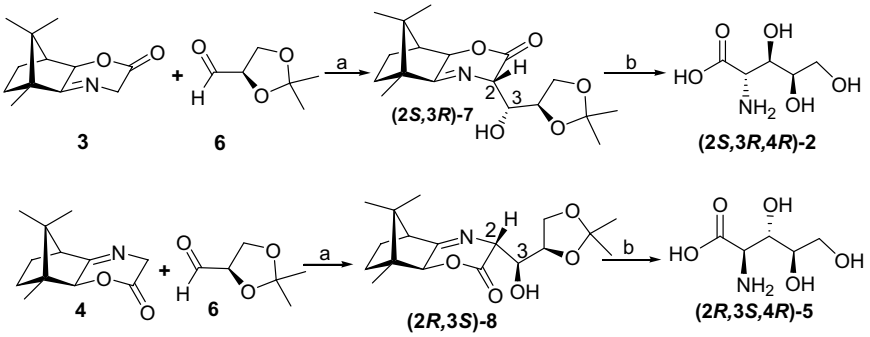

Scheme 1. Reagents and conditions: (a) LDA, THF, additive, −78 °C; (b) (1) 4 M HCl, rt, 2 h; (2) 0.6 M $NH_3{\cdot}H_2O$, Dowex 50W X8 (H^+).

Table 1. Aldol reaction of iminolactones **3** and **4** with **6**

Substrate	Additive	Dr[a]	Yield[b] (%)
3	—	(2*S*,3*R*):(2*S*,3*S*):(2*R*,3*S*):(2*R*,3*R*) = 4:1:0:0	88
3	LiCl (3 equiv)	(2*S*,3*R*):(2*S*,3*S*):(2*R*,3*S*):(2*R*,3*R*) = 12:1:0:0	85
4	—	(2*R*,3*S*):(2*R*,3*R*):(2*S*,3*S*):(2*S*,3*R*) = 3:1:0:0	85
4	LiCl (3 equiv)	(2*R*,3*S*):(2*R*,3*R*):(2*S*,3*S*):(2*S*,3*R*) = 9:1:0:0	83

[a] The ratios were measured by ^{1}H NMR of the crude products on a Varian Mercury-400 MHz.
[b] The reported yields were isolated total yields.

The mechanism of the stereoselective aldol reactions can be rationalized to form six-membered ring in the presence of lithium ion by taking into account two possible transition state models (Fig. 2). For substrate **3**, transition state **I** (attacked from the *Si* face) would bear steric interaction between the 1,2-*O*-(isopropylidene)-ethyleneglycol group and the ring of the tricyclic iminolactone. The orientation of the aldehyde is dictated by the steric interactions and favors attack at the *Re* face of the carbonyl (**TSII**). For substrate **4**, the favored attack of the carbanion is from the *Si* face of the carbonyl (**TSIII**). The primary products (2*S*,3*R*,4*R*)-**7** and (2*R*,3*S*,4*R*)-**8**, were performed, respectively. X-ray structure of (2*S*,3*R*,4*R*)-**7**[7] proved the favored transition state model and that the hydroxyl group of these products is at the *endo* position of iminolactones (Fig. 3). The absolute configuration was also confirmed by the specific rotations of their hydrolyzed products by comparison with known compounds. (2*R*)-**7** and (2*S*)-**8** were not obtained. This is in agreement with our former results, because the C_{12}-methyl group of camphor should be able to block the top face in the aldol step and thus exhibiting good diastereoselectivity in that tricyclic skeleton is more rigid than a monocyclic system.

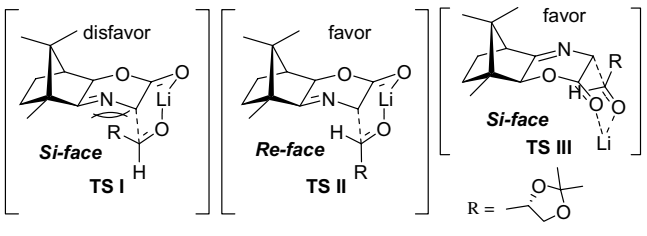

Figure 2. Possible transition states.

Treatment of (2*S*,3*R*,4*R*)-**7** with 4 M HCl in methanol solvent at room temperature for 2 h and then concentration under reduced pressure with the residue dissolved in aqueous ammonium hydroxide (0.6 M, 4 mL), and chromatographed through a column of Dowex 50W X8 (H^+) gave (2*S*,3*R*,4*R*)-polyhydroxy amino acid **2** (3,4-diepipolyoxamic acid), mp 145–150 °C (dec), $[\alpha]_D^{21}$ = −18.0 (*c* 0.43, H_2O) {lit.[3l] mp 148–152 °C (dec), $[\alpha]_D^{27}$ = −17.9 (*c* 0.24, H_2O)}. Analogously, the epimer of **2** (*epi*-**2**, 4-epipolyoxamic acid), mp 182–195 °C (dec), $[\alpha]_D^{21}$ = +4.5 (*c* 0.74, H_2O) {lit.[3o] $[\alpha]_D$ = +5.0 (*c* 0.2, H_2O)}, (2*R*,3*S*,4*R*)-3,4,5-trihydroxy-2-amino pentanoic acid **5**, (2,4-diepipolyoxamic acid), mp 162–166 °C (dec), $[\alpha]_D^{21}$ = −2.3 (*c* 0.42, H_2O) {lit.[3o] $[\alpha]_D$ = −2.7 (*c* 0.2, H_2O)} and the epimer of **5** [*epi*-**5**, (−)-polyoxamic acid], mp 178–185 °C (dec), $[\alpha]_D^{21}$ = −5.0 (*c* 1.0, H_2O) {lit.[3r] mp 163–171 °C (dec), $[\alpha]_D^{23}$ = −5.1 (*c* 1.0, H_2O)} were obtained in high yields (90–95%).

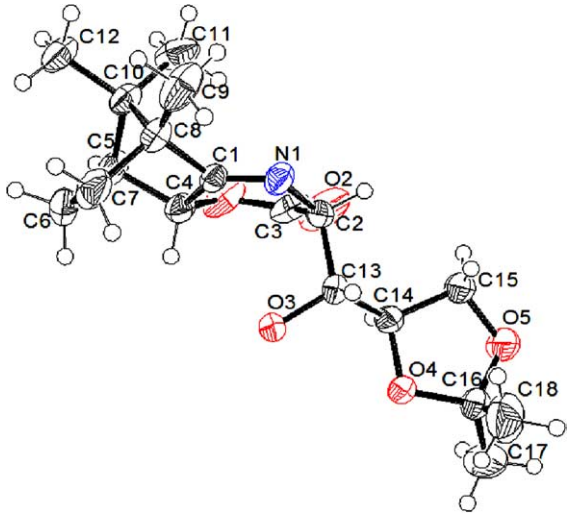

Figure 3. X-ray structure of (2*S*,3*R*,4*R*)-**7**.

2. Conclusion

In summary, we have reported a practical and convenient new asymmetric synthesis for polyhydroxy amino acids utilizing camphor-based tricyclic iminolactones **3** and **4**. Two stereocenters can be constructed with good distereoselectivity in one step via an asymmetric aldol reaction by the use of the chiral templet **3** and **4**, which possess the characteristic rigid framework. Deprotection of the chiral auxiliary and isopropylidene can be carried out in one step and high yield (90–95%). Using a similar protocol, the synthesis of sphingofungins and polyoxins in our laboratory is currently in progress.

Acknowledgments

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6. Spectral data of key compounds: (2*R*,3*S*,4*R*)-**7** mp 144–145 °C; $[\alpha]_D^{20}$ = +51.0 (*c* 1.0, CH_2Cl_2), FT-IR (cm^{-1}): 3415, 2988, 2967, 2935, 2878, 1740, 1696, 1377, 1254, 1217.3, 1075, 1044, 848. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.86 (s, 1H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.38–4.34 (m, 1H), 4.21 (dd, *J* = 6.4, 8.4 Hz, 1H), 3.88–3.83 (m, 2H), 2.70 (d, *J* = 2.0 Hz, 1H), 2.21 (d, *J* = 4.4 Hz, 1H), 2.08–2.02 (m, 1H), 1.81–1.74 (m, 1H), 1.67–1.61 (m, 1H), 1.43–1.37 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.07 (s, 3H), 0.97 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 169.4, 109.9, 80.3, 76.9, 74.6, 66.0, 64.2, 53.0, 48.4, 47.6, 29.1, 26.8, 25.9, 25.3, 20.1, 19.5, 10.1. MS *m/z* (%): 337 (M^+, 3.9), 322 (8.2), 309 (2.6), 236 (4.8), 207 (15.9), 192 (12.4), 178 (15.5), 162 (10.6), 131 (17.8), 123 (17.5), 110 (15.1), 101 (100), 59 (40.7), 55 (25.2), 43 (85.1), 41 (42.5). HRMS *m/z* calcd for $C_{18}H_{27}NO_5$: $[M+H]^+$ 338.1962. Found: $[M+H]^+$ 338.1962. (2*S*,3*R*,4*R*)-**8** mp 71–72 °C; $[\alpha]_D^{22}$ = −10 (*c* 0.7, CH_2Cl_2), FT-IR (cm^{-1}): 3544, 3239, 2911, 2962, 1749, 1720, 1674, 1482, 1456, 1377, 1255, 1221, 1154, 1071, 850. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.66 (d, *J* = 4.0 Hz, 1H), 4.64 (s, 1H), 4.20 (dd, *J* = 6.4, 11.2 Hz, 2H), 4.09–4.05 (m, 2H), 3.97 (dd, *J* = 5.6, 8.8 Hz, 1H), 3.37 (br s, 1H), 2.41 (d, *J* = 4.4 Hz, 1H), 2.00–1.95 (m, 1H), 1.89–1.82 (m, 1H), 1.60–1.53 (m, 1H), 1.40 (s, 3H), 1.39–1.34 (m, 1H), 1.34 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.0, 169.3, 109.5, 82.1, 75.9, 73.9, 65.6, 64.0, 53.9, 49.5, 48.3, 34.5, 26.6, 25.0, 21.4, 19.9, 19.2, 9.6. MS *m/z* (%): 337 (M^+, 5.3), 322 (21), 309 (5.4), 294 (11.7), 236 (13.7), 207 (60.5), 192 (27.3), 162 (28.9), 101 (100). HRMS *m/z* calcd for $C_{18}H_{27}NO_5$: $[M+H]^+$ 338.1962. Found: $[M+H]^+$ 338.1971.
7. Crystal data of (2*S*,3*R*,4*R*)-**7**: $C_{18}H_{26}NO_5$, *M* = 336.41, orthorhombic, space group $P2_12_12_1$, *a* = 10.446(3), *b* = 25.759(9), *c* = 6.656(2), *V* = 1791(2) Å^3, *Z* = 4, *D*c = 1.247 mg/m^3, *F*(000) = 724. A colorless prism crystal of the dimensions 0.25 × 0.2 × 0.10 mm (from ethyl acetate/hexane) was measured at 173.2 K on Rigaku/MSC Mercury CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Absorption was neglected (μ = 0.090 mm^{-1}). Theta range for data collection = 3.1–27.5°, limiting indices = $-13 \leqslant h \leqslant 13$, $-22 \leqslant h \leqslant 33$, $-8 \leqslant h \leqslant 8$; reflections collected/unique 14223/4108 [$R_{(int)}$ = 0.027]; completeness to theta = 27.49, 99.62%, absorption correction = semi-empirical from equivalents; max. and min. transmission = 0.991 and 0.861, refinement method = full-matrix least-squares on *F*2; data/parameters 3777/218; Goodness-of-fit on *F*2 = 1.212, final *R* indices [$F^2 > 2.0\sigma(F^2)$] *R*1 = 0.0523, *wR*2 = 0.0649, absolute structure parameter = 0.0(9), largest diff. peak and hole = 0.36 and −0.2 eÅ^{-3}. CCDC No. 257848 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: (Internet) +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk.