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Stereoselective synthesis of 2-amino-1,3,5-hexane triols using L-proline catalyzed aldol reaction

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Abstract—An efficient synthesis of the 2-amino-1,3,5-hexane triol pattern has been achieved by a diastereoselective aldol reaction of an amino aldehyde with acetone catalyzed by L-proline.

1. Introduction

The aldol reaction is an important and concise method for C–C bond formation, because of the importance of β-hydroxyl carbonyl compounds in organic chemistry. Over the past half decade, rapid progress has been made in the development of asymmetric aldol reactions using 'preformed and stereo defined stable enolates'[1] and 'in situ generated labile enalote synthons'.[2] In part, the efficiency and applicability of amino acids, especially proline catalyzed aldol reactions, have been established recently.[3] Highly efficient syntheses of carbohydrates and polyhydroxy amino acids can be achieved in one to two steps by using L-proline catalyzed aldol reaction of suitably protected ketones or α-oxyaldehydes with different aldehydes.[4] However this catalytic reaction still requires investigation in order to achieve its application in natural product synthesis.

Stereoselective synthesis of amino polyols or poly hydroxy amino acids have been the focus of major interest because of their occurrence in the complex nucleoside antibiotics that exhibit a variety of biological activities.[5] For example, sphingolipids are widely distributed in *mammalian membranes*, and all have most commonly (2*S*,3*R*,4*E*)-2-amino-4-ene-1,3-diol **2** defined as a '*sphingoid base*' backbone. The anticancer activity of sphingosine **2** and other sphingolipids, particularly against colon cancer lines has been established recently.[6] The sphingoid base with 5-hydroxy-(3*E*)-sphingenine **3** occurs naturally and is significantly more effective than **2** in inhibiting the breast tumor cell line (Fig. 1).[7] Amino polyols are also important synthetic precursors for various nitrogenated heterocycles, accessible through cyclization of an activated hydroxyl group (Fig. 2).

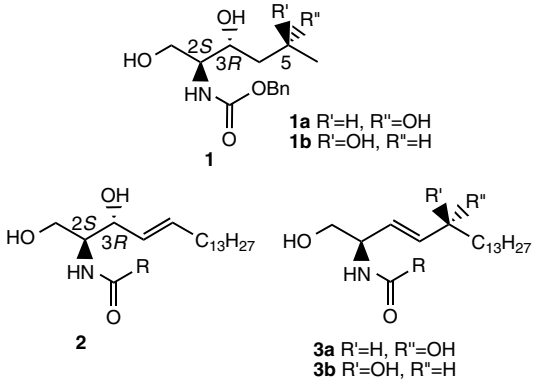

Figure 1.

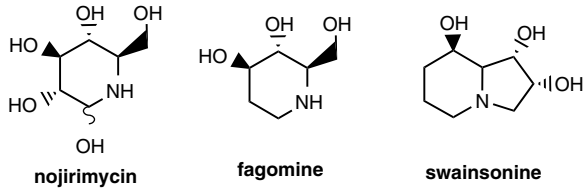

Figure 2.

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The significance of the 2-amino-1,3,5-triol **1** unit relies upon the fact that it is wide spread in natural products and synthetic drugs.

2. Results and discussion

As a part of our ongoing programme[8] on L-proline catalyzed asymmetric aldol reactions towards the development of new procedures for the synthesis of natural products, we have been pursuing a simple and straightforward route to the synthesis of 2-Cbz-amino-1,3,5-hexane triol pattern **1**, in which the stereogenic integrity at C-5 was altered using different reduction conditions. The key features of our proposed route involves: (1) the highly diastereoselective aldol reaction catalyzed by L-proline; (2) diastereoselective reduction of 3-hydroxy ketone **6** using different reaction conditions; (3) all reaction materials are readily available, thus making this method practical.

The first diastereo- and enantioselective organocatalytic aldol reaction of amino aldehyde **4** with dioxanone was reported by Enders et al.[9a] Furthermore the proline catalyzed diastereoselective aldol reaction of several amino aldehydes with different ketones has also been studied recently.[9b] In our study, (*S*)-3-(benzyloxy-carbonyl)-4-formyl-2,2-dimethyloxazolidine **4** was easily obtained through the reported procedure from L-serine.[10] Amino aldehyde **4** was subjected to the aldol reaction in acetone/DMSO at 20 °C for 50 h using 20 mol % L-proline as a catalyst, to afford β-hydroxy ketone **6** in 85% yield (Scheme 1). The minor diastereoisomer was not detected by ^{1}H and ^{13}C NMR analysis, implying that its diastereomeric purity is over 90%. The formation of (*R*)-benzyl 4-((*R*)-1-hydroxy-3-oxobutyl)-2,2-dimethyl oxazolidine-3-carboxylate **6** can be explained through the Houk–List model[11] for L-proline catalyzed aldol reactions (Fig. 3).

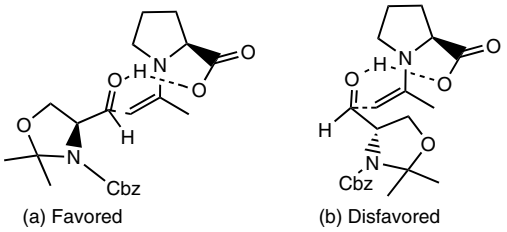
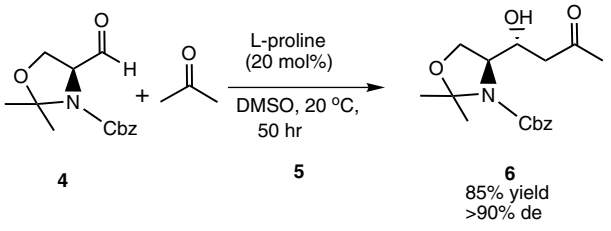


Figure 3.

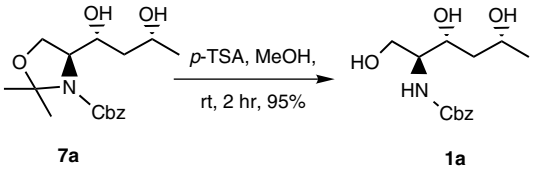
Our next aim was to propagate the existing stereocentres created in the diastereoselective aldol reaction through successive highly diastereoselective transformations. The β-hydroxyl ketone **6** obtained was diastereoselectively reduced to 3,5-*syn*-diol **7a** (dr = 95:5) using $Et_2B(OMe)/NaBH_4$ in dry THF/MeOH at −78 °C with combined 89% yield[12] and similarly 3,5-*anti*-diol **7b** (dr = 20:80) was obtained in 82% combined yield using NaBH $(OAc)_3$/acetic acid/CH_3CN at room temperature,[13] respectively (Scheme 2).

The diastereomeric ratio of the stereoselective reduction was determined by weighing separately, after purification, by column chromatography.

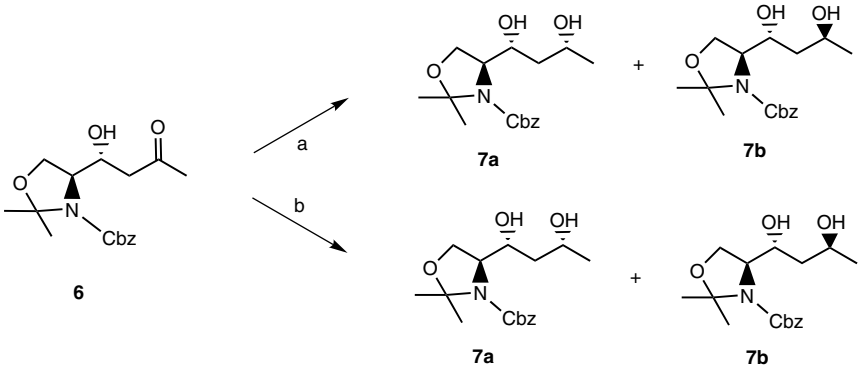
The 2-amino-1,3,5-triol **1** pattern was achieved by deprotection of acetonide (Scheme 3). To this end, **7a** was treated with *p*-TSA/MeOH at room temperature



Scheme 1.



Scheme 3.



Scheme 2. Reagents and conditions: (a) $Et_2B(OMe)/NaBH_4$, dry THF/MeOH, −78 °C, 5 h, 89% (dr, **7a**/**7b** 95:5); (b) NaBH $(OAc)_3$/acetic acid/CH_3CN, rt, 4 h, 82% (dr, **7a**/**7b** 20:80).

for 2 h to afford the **1a** amino triol unit as a white solid in 95% yield. In the same manner, **7b** was transformed to **1b**. All the new compounds were fully characterized by spectroscopic means.

3. Conclusion

In conclusion, we have described L-proline catalyzed highly diastereoselective aldol reaction of acetone with α-amino aldehyde **4**. The potential of this reaction has been further demonstrated in the synthesis of the versatile 2-Cbz-amino-1,3,5-hexane triol pattern. Further studies in the direction of the synthesis of sphingolipids analogues using the same strategy is currently underway and will be reported in due course.

4. Experimental

4.1. General methods

All reagents were used as supplied. The reactions involving hygroscopic reagents were carried out, under argon, using oven-dried glassware. THF was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on a Perkin–Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^{1}H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^{1}H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC–MS were recorded using electrospray ionization technique. All organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100–200 and 230–400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred to as rt.

4.2. (*R*)-Benzyl 4-((*R*)-1-hydroxy-3-oxobutyl)-2,2-dimethyloxazolidine-3-carboxylate 6

To a stirred solution of amino aldehyde **4** (263 mg, 1 mmol) in 10 ml acetone and 2 ml DMSO at 20 °C, L-proline (23 mg, 20 mol %) was added. The reaction mixture was stirred further for 50 h at the same temperature, followed by TLC. The reaction mixture was reduced in vacuo. The resulting residue was taken in EtOAc (30 ml) and stirred with 10% $NaHCO_3$ solution (10 ml). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography, eluting with (20% EtOAc/pet. ether) to give a slightly yellow oil **6** (272 mg, 85% yield): $[\alpha]_D = +5.7$ (*c* 1, $CHCl_3$); TLC (20% EtOAc/pet. ether), $R_f = 0.32$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (s, 6H), 2.14 (s, 3H), 2.40–2.65 (m, 2H), 3.80–4.15 (m, 4H), 5.15 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 26.7, 30.7, 45.9, 61.0, 64.8, 67.4, 68.7, 94.3, 127.9, 128.1, 128.4, 135.8, 154.2, 209.3. LC–MS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{23}NO_5$ $[M+H]^+$ 321.15, found $[M+H]^+$ 321.48.

4.3. (*R*)-Benzyl 4-((1*R*,3*R*)-1,3-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate 7a

To a stirred solution of β-hydroxy ketone **6** (321 mg, 1 mmol) in dry THF (8 ml) and anhydrous methanol (2 ml) at −78 °C under argon, was added dropwise Et_2-B(OMe) (1.1 mmol). The solution was stirred for 20 min and then $NaBH_4$ (42 mg, 1.1 mmol) was added. The resulting mixture was stirred further for 5 h at the same temperature. The reaction was quenched with 1 ml of acetic acid. The reaction was warmed to rt and solvent was removed in vacuo. The crude mass was taken in EtOAc (25 ml) and stirred with saturated $NaHCO_3$ (8 ml) for 2 h. The organic layer was separated, washed with brine and dried over Na_2SO_4 after which it was concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with (15% EtOAc/5% acetone/pet. ether) to give **7a** (272 mg, $R_f = 0.35$, *syn*) TLC (15% EtOAc/5% acetone/pet ether) and **7b**, in combined 85% yield. Compound **7a**: $[\alpha]_D = -13.2$ (*c* 1, $CHCl_3$), FT-IR (cm^{-1}): 3423, 1698, 1413, 1362, 1089, 757. ^{1}H NMR (200 MHz $CDCl_3$): δ 1.15 (d, $J = 7$ Hz 3H), 1.3–1.6 (m, 8H), 2.4–2.8 (br s, 2H, OH), 3.75–4.20 (m, 5H), 5.13 (s, 2H), 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 24.3, 26.3, 40.4, 61.1, 62.3, 64.6, 67.5, 69.1, 94.4, 128.0, 128.1, 128.4, 135.6, 154.5. LC–MS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{25}NO_5$ $[M+H]^+$ 323.17, found $[M+H]^+$ 323.18.

4.4. (*R*)-Benzyl 4-((1*R*,3*S*)-1,3-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate 7b

To a stirred solution of $NaBH(OAc)_3$ (1.899 g, 9 mmol) (freshly prepared) in dry CH_3CN (6 ml) and glacial acetic acid (3 ml), was added β-hydroxy ketone **6** (321 mg, 1 mmol) in CH_3CN dropwise. The combined reaction mixture was stirred for a further 4 h at rt. The solvent was removed in vacuo. Similar workup procedure and flash column chromatography gave **7b** (212 mg, $R_f = 0.28$, *anti*) TLC (15% EtOAc/5% acetone/pet. ether) and **7a** in combined 82% yield. Compound **7b**: $[\alpha]_D = -9.7$ (*c* 1, $CHCl_3$), FT-IR (cm^{-1}): 3423, 1698, 1413, 1362, 1089, 757. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.14 (d, $J = 7$ Hz 3H), 1.3–1.7 (m, 8H), 2.6–3.0 (br s, 2H, OH), 3.75–4.20 (m, 5H), 5.14 (s, 2H), 7.34 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.4, 24.3, 26.3, 40.4, 61.1, 62.3, 64.6, 67.5, 69.1, 94.4, 128.0, 128.1, 128.4, 135.6, 154.5. LC–MS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{25}NO_5$ $[M+H]^+$ 323.17, found $[M+H]^+$ 323.20.

4.5. Benzyl (2*R*,3*R*,5*R*)-1,3,5-trihydroxyhexan-2-ylcarbamate 1a

To a solution of **7a** (200 mg, 0.62 mmol) in MeOH (8 ml) at rt, was added *p*-TSA (catalytic amount) and the mixture was further stirred for 2 h. Small amount of solid K_2CO_3 was added and the solvent was removed in vacuo. The residue was dissolved in diethyl ether and the precipitated material was filtered. Organic solvent was dried over Na_2SO_4 and concentrated to gave a white

solid material **1a** (167 mg, 95% yield): $[\alpha]_D = +2.25$ (*c* 0.5, MeOH), FT-IR (cm^{-1}): 3452, 3317, 2958, 2884, 1686, 1470, 1238, 1049. ^1H NMR (200 MHz, $CDCl_3/D_2O$ exchange): δ 1.13 (m, 3H), 1.58 (m, 2H), 3.45–3.70 (m. 3H), 3.8–4.0 (m, 2H), 5.05 (s, 2H), 7.29 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 40.5, 60.7, 61.8, 63.5, 66.2, 68.8, 128.2, 128.5, 128.8, 135.4, 155.1. LC–MS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{21}NO_5$ $[M+H]^+$ 283.14, found $[M+H]^+$ 284.12.

4.6. Benzyl (2*R*,3*R*,5*S*)-1,3,5-trihydroxyhexan-2-ylcarbamate 1b

In the similar way, **7b** was converted into **1b**: $[\alpha]_D = +6.6$ (*c* 0.5, MeOH), FT-IR (cm^{-1}): 3452, 3317, 2958, 2884, 1686, 1470, 1238, 1049. ^1H NMR (200 MHz, $CDCl_3/D_2O$): δ 1.13 (m, 3H), 1.58 (m, 2H), 3.45–3.70 (m, 3H), 3.8–4.0 (m, 2H), 5.05 (s, 2H), 7.29 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 40.5, 60.7, 61.8, 63.5, 66.2, 68.8, 128.2, 128.5, 128.8, 135.4, 155.1. LC–MS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{21}NO_5$ $[M+H]^+$ 283.14, found $[M+H]^+$ 284.17.

Acknowledgements

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References

1. (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432; (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917.
2. Saito, S.; Yamamoto, H. *Chem.-Eur. J.* **1999**, *5*, 1959.
3. (a) Groger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529; (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548; (c) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
4. (a) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152; (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752; (c) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696; (d) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343; (e) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Reyes, E.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (f) Reyes, E.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 6605; (g) Córdova, A.; Engqvist, M.; Ibrahem, I.; Casas, J.; Sundn, H. *Chem. Commun.* **2005**, 2047.
5. (a) Isono, K. *J. Antibiot.* **1998**, *41*, 1711; (b) Isono, K. *Pharm. Ther.* **1991**, *52*, 269; (c) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.
6. Symolon, H.; Schmelz, E. M.; Dillehay, D. L.; Merrill, A. H., Jr. *J. Nutr.* **2004**, *134*, 1157.
7. Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355.
8. Kumar. I.; Rode. C. V. *Communicated*.
9. (a) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210; Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079; (b) Pan, Q.; Zou, B.; Wang, Y.; Ma, D. *Org. Lett.* **2004**, *6*, 1009.
10. Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1996**, *61*, 581.
11. (a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16; (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475.
12. Chen, K.-M.; Hardtmann, G. E.; Prashad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
13. Evans, D. A.; Chapmann, K. T.; Careers, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.