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L-Proline catalyzed direct diastereoselective aldol reactions: towards the synthesis of *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine

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Abstract—L-Proline catalyzed direct diastereoselective aldol reactions of α-amino aldehydes with cyclic ketones have been described and utilized further for the stereoselective synthesis of the 2-amino-1,3,4-triol unit as the phytosphingosines base backbone. This leads to the formal synthesis of (2*S*,3*S*,4*S*)-*lyxo*-phytosphingosine.

1. Introduction

The asymmetric aldol reaction using 'directed processes,[1] for example, modified carbonyls' and 'direct processes,[2] for example, unmodified carbonyls', as carbanion equivalents is one of the most powerful and efficient methods for carbon–carbon bond formation. Due to its atom-economy, the direct process for asymmetric aldol reactions through an '*enamine*' intermediate using L-proline or its derivatives as organocatalysts, that mimic the '*enamine catalysis*' of class I aldolases,[3] has grown remarkably in the last few years.[4] Further exploitation of direct organocatalytic aldol reactions, along with other enantioselective transformations in asymmetric synthesis, has been reviewed very recently.[5] Enantiopure α-amino aldehydes are suitable precursors as acceptors in aldol reactions and valuable starting materials for the synthesis of biologically important compounds.[6] Recently, the diastereoselective aldol reaction of different *N*,*N*′-dibenzyl-α-amino aldehydes with ketones[7] and with dioxanone[8] catalyzed by proline has been developed. However, the direct diastereoselective aldol reaction of cyclic ketones with α-amino aldehydes needs to be explored further.

Stereoselective syntheses of amino-polyols are of major interest because of their existence in a variety of biologically active compounds and their utility as synthetic precursors for heterocyclic compounds. Sphingolipids contain long-chain amino diol and triol bases, which are essential membrane components and are involved in several cellular events such as the regulation of cell growth, differentiation, adhesion, neuronal repair and signal transduction.[9] Phytosphingosines consist of an aliphatic chain with a 2-amino-1,3,4-triol head and are important members of the sphingoids family (Fig. 1). Phytosphingosine itself is a bioactive lipid and its glycolated derivatives display promising antitumor and antivirus activities.[10] Due to their biological significance, several synthetic routes have been described in the literature:[11] most of the them are

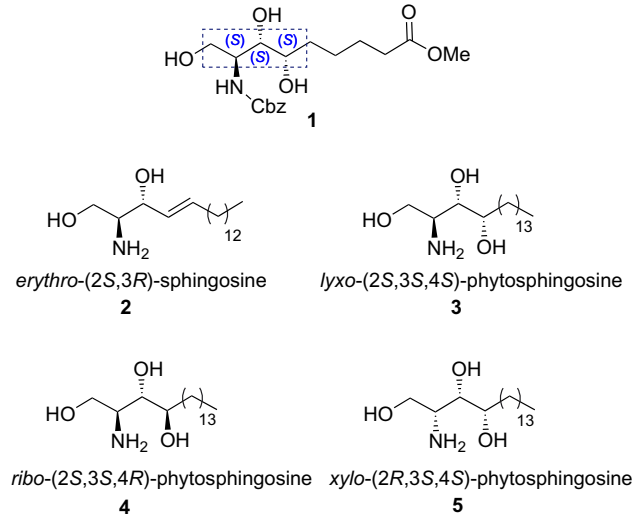

Figure 1.

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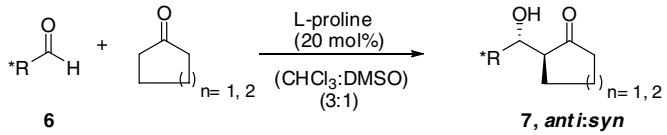
quite lengthy using carbohydrates and amino acids as starting materials, while asymmetric routes are rather rare.[12] Recently, Enders et al. reported a direct organocatalytic route for the asymmetric synthesis of D-*arabino*- and L-*ribo*-phytosphingosine.[13]

2. Results and discussion

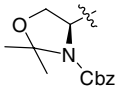
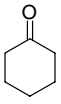
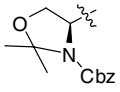
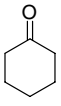
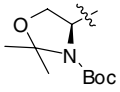
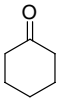
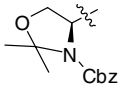
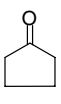
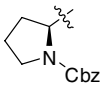
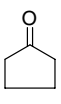
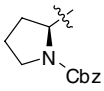
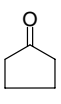
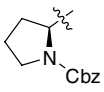
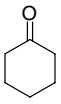
In continuation of our programme on the L-proline catalyzed direct inter- and intramolecular diastereoselective aldol reaction for the synthesis of amino-polyols and iminosugars,[14] we herein report the proline catalyzed diastereoselective aldol reaction of α-amino aldehydes with cyclic ketones and a new organocatalytic route for the synthesis of the sphingoid class of compounds, with the quick synthesis of the (2*S*,3*S*,4*S*)-*lyxo*-phytosphingosine backbone.

In our study, we first prepared the starting α-amino aldehydes **6** with a cyclic core structure from commercially available (*S*)-serine and (*S*)-proline by following literature procedures.[15] The direct diastereoselective aldol reaction of (*S*)-amino aldehydes was carried out with 2 mol equiv of cyclic ketones as donor in the presence of 20 mol % of (*S*)-proline at different temperatures in solvents $CHCl_3$–DMSO (3:1), and the results are summarized in Table 1. High levels of diastereoselectivities were obtained when the reactions were carried out at 20 °C for 48 h. A further improvement in the diastereoselectivity (>98%) was observed by carrying out the reactions at 5 °C for 60 h with yields of up to 85%. The enhancement in the diastereoselectivity at a lower temperature can be explained through better facial selection due to higher rigidity in the transition state. Similar observations were reported by Enders and Grondal for the direct diastereoselective aldol reaction of amino aldehydes **6** with dioxanone for the synthesis of carbohydrates.[8] They also established the matched/mismatched situation required for both proline catalysts and α-branched chiral aldehydes through kinetic-resolution in the transition states, which depends upon the steric requirement of chiral aldehydes. This assumption was further

Table 1. L-Proline catalyzed direct diastereoselective aldol reaction of α-amino aldehydes with cyclic ketones



6 **7**, ***anti*:*syn***

6	R*	Ketone[a]	Temperature (°C)	Time (h)	Yield[b] (%)	**7**, dr (*anti*:*syn*)[c]
a			20	48	78	83:17
b			5	60	81	>96:4
c			5	60	83	>98:not observed
d			5	60	78	>98:not observed
e			20	48	84	88:12
f			5	60	81	>95:5
g			5	60	86	>98:not observed

Abbreviations: Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl.

[a] General reaction conditions: 1.0 mmol of aldehyde, 2.0 mmol of cyclic ketone, 20 mol % L-proline, solvents $CHCl_3$–DMSO (3:1).

[b] Isolated yields of **7**.

[c] Determined by weighing separately after flash chromatography on silica gel.

supported by direct Mannich reaction for the synthesis of amino sugars and derivatives.[16a] The formation of *anti*-aldol products **7** consistent with the proline catalyzed aldol reactions,[8,17] which can be explained through the Houk–List model proposed for cyclic ketones,[18] where the cyclic enamine intermediate and an intermolecular hydrogen bonding play the critical role (Fig. 2).

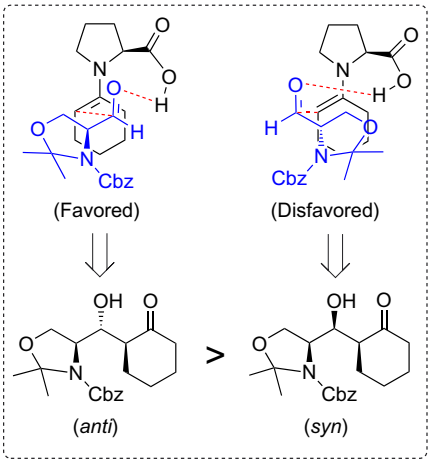


Figure 2. Houk–List model for direct diastereoselective aldol reaction of cyclic ketones with α-amino aldehydes catalyzed by L-proline.

Our next aim was to prepare the phytosphingosine base-backbone, which was carried out with *anti*-aldol product **7d** as almost pure diastereomer. This product **7d** was subjected to a Baeyer–Villiger oxidation by treating with 3 equiv of *m*-CPBA (55% activity) and 3 equiv of $NaHCO_3$ in dry CH_2Cl_2 for 4 h at rt and by adding another portion of the same amounts of *m*-CPBA and $NaHCO_3$ with additional stirring for 8 h at the same temperature to give the desired hydroxy-lactone compound **8** in 85% isolated yield. The hydroxy group of **8** was then protected with MOMCl (1.2 equiv) and diisopropylethyl amine (1.3 equiv) in dry CH_2Cl_2 at rt overnight to provide MOM-protected compound **9** in 87% yield. The delactonization of **9** was carried out by treating with K_2CO_3 (cat)/MeOH at rt and the progress of this reaction was monitored by TLC. After complete consumption of **9** within 2 h, this reaction was acidified with 2 M-HCl solution and additionally stirred for 2 h to deprotect the acetonide moiety. The solvent was evaporated and the crude material was passed through a small pad of column to give **1** as a white solid with 76% yield, which had the (2*S*,3*S*,4*S*)-2-amino-1,3,4-triol unit of *lyxo*-phytosphingosine **3**. The resulting compound **1** can be transformed into *lyxo*-phytosphingosine by converting the ester moiety in to a long chain carbon unit by using a similar method as reported by Lin and co-workers.[19] Our approach provides quick access to phytosphingosine backbones, which completes the formal synthesis of **3** (Scheme 1). All the new compounds were fully characterized by spectroscopic means.

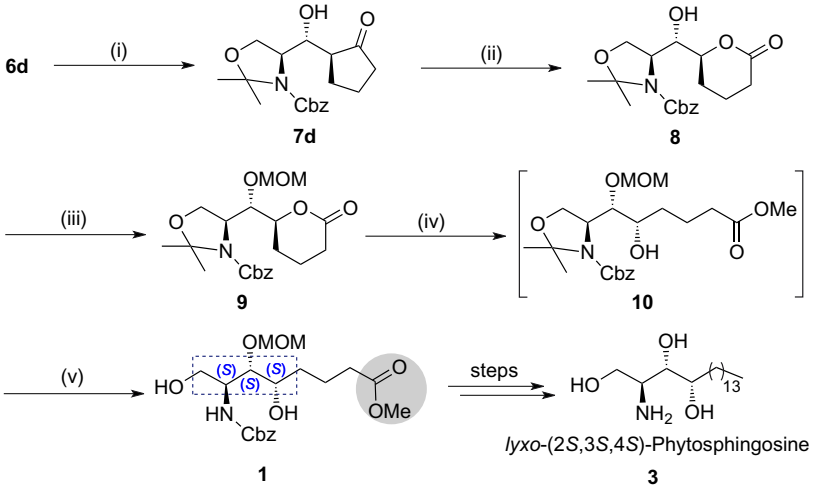
3. Conclusion

In conclusion, we have developed direct diastereoselective aldol reactions of different α-amino aldehydes with cyclic ketones using L-proline as an organocatalyst. This was further utilized for a quick organocatalytic route to the synthesis of the (2*S*,3*S*,4*S*)-*lyxo*-phytosphingosines backbone. This approach is very flexible and can be applied to the synthesis of other stereoisomers of the sphingoid family, since the organocatalyst and amino-aldehydes are easily available in both D and L-forms. Further study in this direction is currently underway and will be presented in the future.

4. Experimental

4.1. General methods

All reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under an argon atmosphere using oven-dried glassware. THF was distilled



Scheme 1. Reagents and conditions: (i) Cyclopentanone (2 mol equiv), L-proline (20 mol %), $CHCl_3$–DMSO (3:1), 5 °C, 60 h, 78%, dr > 98%; (ii) *m*-CPBA (55% activity, 6 equiv), $NaHCO_3$, (6 equiv), 12 h, rt, 85%; (iii) MOMCl (1.2 equiv), DIPEA (1.3 equiv), dry CH_2Cl_2, rt, overnight, 87%; (iv) K_2CO_3 (cat)/MeOH, rt, 2 h; (v) 2 M-HCl solution, rt, 2 h, 76% in two steps.

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 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 was recorded using electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under an 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 as rt.

4.2. General procedure for direct diastereoselective aldol reaction of α-amino aldehydes with ketones

To a stirred solution of α-amino aldehyde **6** (1 mmol) and cyclic ketone (2 mmol) in solvent $CHCl_3$–DMSO (3:1, 8 ml) was added 20 mol % (*S*)-proline at 5 °C and the reaction was stirred further for 60 h at the same temperature, followed by TLC. The reaction mixture was reduced in vacuo. The resulting residue EtOAc (30 ml) was taken and stirred with 10% $NaHCO_3$ solution (10 ml). The organic layer was separated and washed with brine solution, dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by flash chromatography on silica gel with hexane: ethyl acetate (8:2–7:3) to give the aldol product in good yield and diastereoselectivity, which was determined by weighing separately after chromatographic purification.

4.3. (*S*)-Benzyl 4-((*R*)-hydroxy-((*S*)-2-oxocyclohexyl)-methyl)-2,2-dimethyloxazolidine-3-carboxylate 7b

Yield 81%, **7b** (*anti*, major) $[\alpha]_D^{25} = -78.7$ (*c* 1, $CHCl_3$), **7b** (*syn*, minor) $[\alpha]_D^{25} = +10.8$ (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) for **7b** (*anti*): $\delta = 1.42$–1.62 (m, 8H), 1.72–2.05 (m, 5H), 2.27 (m, 1H), 2.43 (m, 1H), 3.32–3.48 (m, 1H), 3.89 (m, 1H), 4.10–4.25 (m, 2H), 4.90–5.20 (m, N–CH_2Ph, 2H), 7.34 (s, Ar, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.86$, 24.19, 25.20, 28.47, 32.97, 42.60, 50.63, 60.09, 64.87, 67.03, 73.40, 93.92, 127.76, 128.01, 128.35, 136.35, 153.70, 215.91. LC–MS (ESI-TOF): *m*/*z* for $C_{20}H_{27}NO_5$ $[M+H]^+$ 362.12, $[M+Na]^+$ 384.08. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.41; H, 7.58; N, 3.85.

4.4. (*S*)-*tert*-Butyl 4-((*R*)-hydroxy((*S*)-2-oxocyclohexyl)-methyl)-2,2-dimethoxazolidine-3-carboxylate 7c

Yield 83%, **7c** (*anti*): $[\alpha]_D^{25} = -119.7$ (*c* 0.85, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.38$–1.42 (m, 14H), 1.56–1.78 (m, 3H), 1.82–2.15 (m, 4H), 2.31–2.42 (m, 2H), 2.45–2.57 (m, 1H), 3.62–3.75 (m, 1H), 3.81–3.92 (m, 1H), 4.05–4.21 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.18$, 25.68, 27.88, 28.31, 28.72, 33.24, 43.06, 50.87, 59.61, 64.89, 73.60, 80.29, 93.72, 153.23, 216.21. LC–MS (ESI-TOF): *m*/*z* for $C_{17}H_{29}NO_5$ $[M+H]^+$ 328.22, $[M+Na]^+$ 350.21. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.32; H, 8.89; N, 4.31.

4.5. (*S*)-Benzyl 4-((*R*)-hydroxy-((*S*)-2-oxocyclopentyl)-methyl)-2,2-dimethyloxazolidine-3-carboxylate 7d

Yield 78%, **7d**, (*anti*): $[\alpha]_D^{25} = -66.5$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.42$–1.63 (m, 8H), 1.81–2.28 (m, 5H), 3.85–4.02, (m, 2H), 4.12–4.25 (m, 2H), 5.15 (s, 2H), 7.34 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.22$, 23.16, 25.51, 26.67, 37.97, 50.63, 59.59, 63.18, 66.77, 70.78, 94.43, 127.94, 128.11, 128.35, 136.01, 152.04, 216.23. LC–MS (ESI-TOF): *m*/*z* for $C_{19}H_{25}NO_5$ $[M+H]^+$ 348.27, $[M+Na]^+$ 370.26. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.62; H, 7.31; N, 4.09.

4.6. (*S*)-Benzyl 2-((*R*)-hydroxy-((*S*)-2-oxocyclopentyl)-methyl)pyrrolidine-1-carboxylate 7f

Yield 81%, **7f**, (*anti*): $[\alpha]_D^{25} = -99.5$ (*c* 1, $CHCl_3$), (*syn*): $[\alpha]_D^{25} = +18.5$ (*c* 1, $CHCl_3$),^{1}H NMR (200 MHz, $CDCl_3$): for **7f** (*anti*): $\delta = 1.62$–1.85 (m, 4H), 1.94–2.25 (m, 6H), 2.28–2.31, (m, 1H), 3,38–3.61 (m, 2H), 3.75–4.02 (m, 1H), 4.11–4.28 (m, 1H), 5.12 (dd, $J = 11.6$ Hz, 2H), 7.34 (s, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.46$, 23.71, 24.45, 26.24, 37.99, 46.86, 50.72, 59.96, 66.32, 71.67, 127.49, 127.62, 128.20, 136.74, 154.79, 216.09. LC–MS (ESI-TOF): *m*/*z* for $C_{18}H_{23}NO_4$ $[M+H]^+$ 318.01, $[M+Na]^+$ 339.98. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.19; H, 7.25; N, 4.49.

4.7. (*S*)-Benzyl 2-((*R*)-hydroxy-((*S*)-2-oxocyclohexyl)-methyl)pyrrolidine-1-carboxylate 7g

Yield 86%, **7g**, (*anti*): $[\alpha]_D^{25} = -90.9$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): for **7f** (*anti*): $\delta = 1.50$–2.02 (m, 10H), 2.14 (m, 1H), 2.34, (m, 1H), 2.45 (m, 1H), 3.38 (m, 1H), 3.40–3.71 (m, 2H), 4.07 (m, 1H), 5.09 (s, 2H), 7.33 (s, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.80$, 24.99, 25.65, 28.18, 31.87, 42.68, 46.94, 52.11, 59.70, 66.57, 72.91, 127.63, 127.77, 128.34, 136.98, 155.50, 215.68. LC–MS (ESI-TOF): *m*/*z* for $C_{19}H_{25}NO_4$ $[M+H]^+$ 332.10, $[M+Na]^+$ 354.07. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.71; H, 7.55; N, 4.29.

4.8. (*S*)-Benzyl 4-((*S*)-hydroxy((*S*)-6-oxotetrahydro-2*H*-2-pyran-2-yl)methyl)-2,2-dimethyloxazolidin-3-carboxylate 8

To a stirred solution of compound **7d** (700 mg, 2.02 mmol) in dry CH_2Cl_2 (30 ml) at 0 °C were added *m*-CPBA (55% activity; 1.0 g, 6 mmol) and $NaHCO_3$ (508 mg, 6 mmol), and then stirred at room temperature for 4 h after which was added another portion of the same amounts of *m*-CPBA and $NaHCO_3$ with stirring for an additional 8 h. After completion of the reaction, the excess *m*-CPBA was quenched with aq $Na_2S_2O_3$. The insoluble material was removed by filtration and washed with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were washed with satd $NaHCO_3$, brine solutions and dried over Na_2SO_4 and concentrated under reduced pressure, the resulting pasty mass was purified by column chromatography (pet ether–EtOAc, 3:2) and gave

8 (625 mg, 85% yield) as a colourless pasty liquid. $[\alpha]_D^{25} = 14.2$ (*c* 0.70, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.42$–1.75 (m, 8H), 1.75–2.01 (m, 2H), 2.52 (m, 2H), 3.41–3.62 (m, 3H), 2.98–3.105 (m, 1H), 3.63–3.84 (m, 3H), 4.06 (m, 1H), 4.27 (m, 1H),5.13 (dd, $J = 12.5$, 2H), 7.35 (s, 25H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.33$, 22.83, 24.25, 26.33, 29.48, 60.13, 63.45, 67.10, 78.94, 81.29, 93.70, 128.13, 128.22, 128.51, 135.97, 152.59, 170.62. LC–MS (ESI-TOF): *m/z* $C_{19}H_{25}NO_6$ $[M+H]^+$ 364.18, $[M+Na]^+$ 386.01. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.77; H, 6.89; N, 3.91.

4.9. (*S*)-Benzyl-4-((*S*)-(methoxymethoxy)((*S*)-6-oxotetrahydro-2*H*-2-pyran-2-yl)methyl)-2,2-dimethyloxazolidin-3-carboxylate 9

To a stirred solution of compound **8** (0.6 g, 1.65 mmol) and diisopropylethyl amine (DIPEA) (0.27 g, 2.14 mmol) in dry CH_2Cl_2 (8 ml) was added MOMCl (0.16 g, 1.98 mmol) at 0 °C. The resulting reaction mixture was stirred further overnight at rt. After completion of the reaction, the solvent was evaporated and the residue was chromatographed over silica gel to give compound **9** (0.58 g, 87% yield) as a colourless pasty liquid. $[\alpha]_D^{25} = -5.85$ (*c* 0.6, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.41$–1.65 (m, 10H), 2.28–2.62 (m, 2H), 3.37 (s, 3H), 3.85–4.15 (m, 3H), 4.20–4.48 (m, 2H), 4.69 (dd, J=6.5 Hz, 2H), 5.15 (s, 2H), 7.35 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.43$, 22.93, 24.35, 25.96, 29.59, 56.42, 58.62, 63.56, 67.20, 79.05, 80.96, 93.80, 98.55, 128.23, 128.32, 128.61, 136.08, 152.54, 170.72. LC–MS (ESI-TOF): *m/z* $C_{21}H_{29}NO_7$ $[M+H]^+$ 408.05, $[M+Na]^+$ 430.03. Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N, 3.44. Found: C, 61.97; H, 7.14; N, 3.49.

4.10. (5*S*,6*S*,7*S*)-Methyl 7-(benzyloxycarbonylamino)-5,8-dihydroxy-6-(methoxymethoxy)octanoate 1

To a solution of compound **9** (0.5 g, 1.23 mmol) in MeOH (10 ml), was added K_2CO_3 in a catalytic amount and stirred at rt. The reaction reached to completion in about 2 h, monitored by TLC. This reaction was quenched with an excess of dilute HCl and additionally stirred for 2 h at the same temperature. The solvent was evaporated under a reduced pressure and passed through a small pad of column to give white solid compound **1** (0.37 g, 76% yield) after two steps. $[\alpha]_D^{25} = -6.6$ (*c* 0.7, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3/D_2O$): $\delta = 1.45$–1.78 (m, 4H), 2.15–2.30 (m, 2H), 3.36 (s, 3H,) 3.68 (s, 3H), 3.75–4.02 (m, 2H), 4.10–4.45 (m, 3H), 4.65–4.75 (m, 2H), 5.18 (s, 2H), 7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3/D_2O$): $\delta = 18.33$, 30.93, 33.78, 50.35, 53.35, 56.31, 63.45, 67.10, 68.99, 86.90. 98.44, 128.05, 128.22, 128.51, 135.97, 153.56, 173.55. Anal. Calcd for $C_{19}H_{29}NO_8$: C, 57.13; H, 7.32; N, 3.51. Found: C, 57.18; H, 7.29; N, 3.59.

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