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Tetrahedron
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Tetrahedron 61 (2005) 4341–4346

A new efficient and practical synthesis of 2-deoxy-L-ribose

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Received 27 January 2005; revised 1 March 2005; accepted 2 March 2005

Available online 19 March 2005

Abstract—An efficient and practical route for large-scale synthesis of 2-deoxy-L-ribose starting from L-ascorbic acid was developed in eight steps without chromatographic purification for all intermediates. Additionally, (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol, a versatile intermediate in carbohydrate synthesis, was also prepared readily in excellent yield as a key intermediate.

1. Introduction

The use of L-enantiomers of natural and modified nucleosides in medical application has increased dramatically due to their potent biological activity and lower toxicity compared to the corresponding D-nucleosides.[1–6] Among them, L-2′-fluoro-5-methylarabinofuranosyl uracil (L-FMAU),[2] L-thymidine (L-T),[3] L-3′-thiacytidine (L-3TC),[4] L-5-fluoro-3′-thiacytidine (L-FTC),[4a,5] L-2′,3′-dideoxycytidine (L-ddC),[6] and L-5-fluoro-2′,3′-dideoxycytidine (L-FddC)[6b,c] have been developed as excellent antiviral agents with greatly reduced toxicity. In addition, oligonucleotides composed of 2-deoxy-L-ribose (2-deoxy-L-*erythro*-pentose **1**) show resistance to digestion by certain nucleases.[7] Enantiomeric L-DNA and meso-DNA are, therefore, valuable tools for studying protein-DNA interactions and are promising antisense agents.[8] Recently, it was reported that 2-deoxy-L-ribose (**1**) and its analogs enhance apoptosis and suppress the growth of tumors by competitively inhibiting the activities of 2-deoxy-D-ribose and thus these analogs display promise for anti-tumor therapy.[9]

A great deal of effort, therefore, has been devoted to the synthesis of modified nucleosides with the unnatural L-configuration, which requires ready access to L-carbohydrates, especially L-ribose and its derivatives. For 2-deoxy-L-ribose (**1**), several syntheses have been published using naturally occurring carbohydrate starting materials such as L-arabinose[10] and L-ascorbic acid.[11] Even though L-ascorbic acid (**2**) has been used as a starting material, none of these methods, including our previous experience,[11a] have proved to be an efficient and practical procedure for the preparation of **1** in large quantities. We herein report an efficient and practical method for the large-scale synthesis of 2-deoxy-L-ribose (**1**) from cheap and commercially available L-ascorbic acid (**2**).

2. Results and discussion

Our synthesis of 2-deoxy-L-ribose (**1**) commenced with the protection of the 5,6-diol of L-ascorbic acid (**2**) (Scheme 1). Treatment of **2** with acetyl chloride in acetone according to the published procedure afforded 5,6-*O*-isopropylidene-L-ascorbic acid (**3**) in 95% yield.[12] Oxidation of **3** with hydrogen peroxide produced threonic acid sodium salt **4**,[13] which was then transformed to methyl ester **5** with dimethyl sulfate and sodium bicarbonate in water. At this point, we slightly altered the known procedure[13] for the preparation of **5**. Thus, without isolation of the oxidation product **4**, it was methylated in situ by slow addition of dimethyl sulfate to maintain the basic condition, which increased the yield of **5**. Treatment of the alcohol **5** with tosyl chloride in the presence of pyridine provided tosylate **6** in 95% yield, which was purified by recrystallization from cold (below −10 °C) isopropyl alcohol and hexane. Reduction of the ester **6** with sodium borohydride, and subsequent intramolecular S_N2 displacement of the tosylate by the alkoxide in the resulting primary alcohol using sodium methoxide smoothly gave the epoxide **7** in 98% yield. The fact that the key intermediate **7** was obtained in 69% overall yield from L-ascorbic acid (**2**) with no column chromatography clearly indicated that the present method

Keywords: L-Enantiomer; Large-scale synthesis; Epoxide-ring opening; Nitrile.
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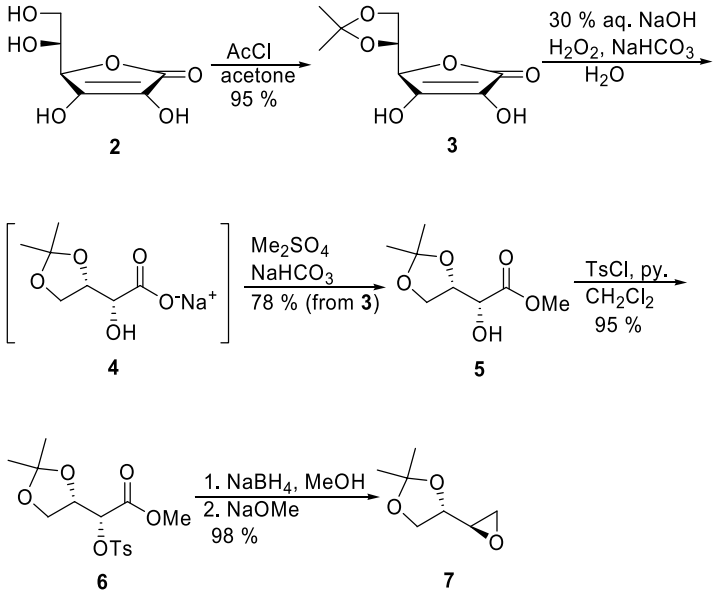
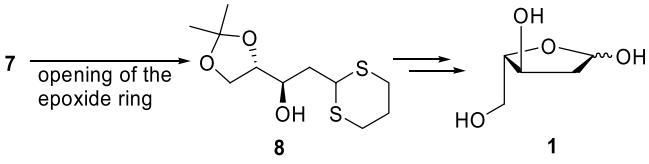
doi:10.1016/j.tet.2005.03.001



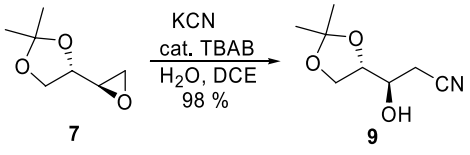
Scheme 1.

for the preparation of **7** is more efficient and suitable for the industrial application than the previously reported procedures.[13b,c,14]

In the previous reports, 2-deoxy-L-ribose (**1**) and its derivatives were synthesized by way of dithiane acetal **8**, which was prepared by the epoxide ring opening of **7** with dithiane anion (Scheme 2).[11a,15] Reaction employing dithiane anion and *n*-butyllithium, however, is difficult process to be applied for an industrial mass production. Therefore, we decided to utilize the cyanide as the source of one carbon extension and as the nucleophile for epoxide ring opening as well. Nucleophilic opening of the epoxide ring of the compound **7** with KCN in the presence of



Scheme 2.



Scheme 3.

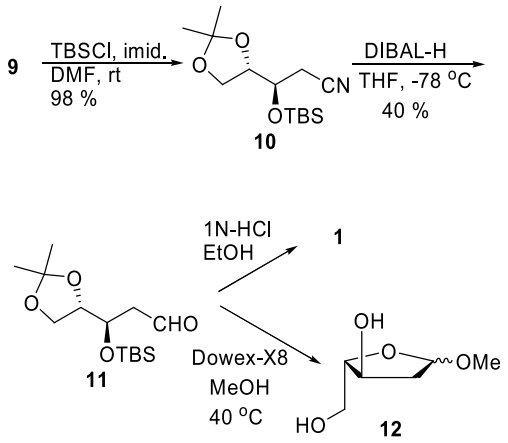
Table 1. Epoxide ring opening of **7** with cyanide under various conditions

Reagent	Solvent	Temparature (°C)	Yield (%)
Acetone cyanohydrin[16]	THF	40	18
Et_2AlCN[17]	Toluene	0	92
KCN	DMF	60	No reaction
KCN	MeOH	40	72
KCN, 18-crown-6[18]	CH_3CN	40	42
KCN, cat. TBAB[16]	H_2O/DCE	40	98

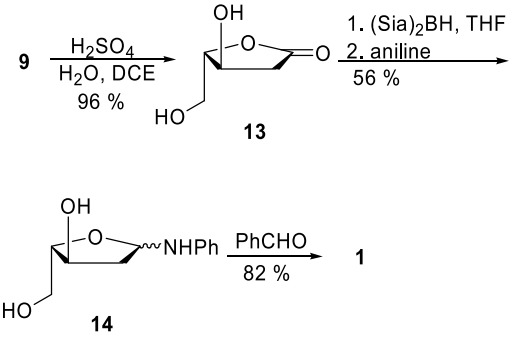
tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in dichloroethane (DCE) and water afforded almost quantitatively the desired nitrile **9** (Scheme 3, Table 1).[16] This method would also be very efficient for large scale mass production because only simple extraction is necessary for purification of the product **9** due to requirement of only 1 mol% of TBAB and the low partition coefficient of TBAB to Et_2O. On the other hand, the use of acetone cyanohydrin[16] as a cyanide source failed to open the epoxide ring of **7** effectively. Although the reaction with diethylaluminum cyanide (Et_2AlCN)[17] gave 92% conversion to **9** in our trial, its use is limited in industrial application due to toxicity and requirement of anhydrous condition. While reaction of **7** with KCN in DMF did not occur, those with KCN in MeOH and with KCN in the presence of 18-crown-6 in CH_3CN[18] furnished **9** in 72% and 42% yield, respectively.

Since attempts to convert directly the hydroxyl nitrile **9** into an aldehyde with DIBAL-H turned out to be futile, the hydroxyl group of **9** was protected with *t*-butyldimethylsilyl (TBS) chloride to afford compound **10** (Scheme 4). When the TBS protected alcohol **10** was subjected to the reduction with DIBAL-H at −78 °C, aldehyde **11** was obtained in 40% yield. Hydrolysis of both the isopropylidene group and the TBS group in **11** with 1 N HCl in ethanol afforded the crude **1**, but we were not able to purify the product **1** without column chromatography because of the inorganic salts generated from the addition of $NaOH/NaHCO_3$ to neutralize the reaction mixture. Instead of using HCl, hydrolysis of **11** using Dowex 50W-X8 resin[19] in MeOH afforded acetal **12**, while the same reaction in H_2O did not proceed.

The failure to obtain efficiently the pure **1** from **9** without column chromatography separation in the above procedure led us to consider another practical method. Compound **9** was deprotected, hydrolyzed, and lactonized successively at one-pot with conc. sulfuric acid in refluxing water and dichloroethane to give γ-lactone **13** in 96% yield (Scheme 5). Reduction of **13** by disiamylborane [$(Sia)_2BH$] in THF



Scheme 4.



Scheme 5.

followed by treatment the resulting hemiacetal with aniline in aqueous ethanol gave anilide **14** in 56% yield.[20] Finally, **14** was converted to 2-deoxy-L-ribose (**1**) by transamination using benzaldehyde in the presence of catalytic amount of benzoic acid.[21]

3. Conclusion

We have developed an efficient route to 2-deoxy-L-ribose (**1**) from inexpensive and commercially available L-ascorbic acid (**2**) in an overall 30% yield. The present method would be utilized as a practical and economical procedure for large-scale synthesis of **1** since no column chromatography is required for purification of any intermediates and reagents used in all steps are inexpensive and easy to handle. Furthermore, the epoxide **7**, which is a versatile intermediate in carbohydrate synthesis, was prepared readily and cleanly in large quantity from **2** in excellent yield.

4. Experimental

4.1. General

All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Thin-layer chromatography was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Melting points are uncorrected. IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. NMR spectra were recorded on a Bruker 250 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter.

4.1.1. 5,6-*O*-Isopropylidene-L-ascorbic acid (3)

A 10-L round bottomed flask, equipped with a mechanical stirrer and a reflux condenser, was charged with L-ascorbic acid (**2**, 1000 g, 5.68 mol) and acetone (2500 mL). To this solution was added acetyl chloride (440 mL, 6.19 mol). After being stirred for 2 h at 40 °C, the reaction mixture was cooled to −10 °C, then filtered and washed with cold acetone (1000 mL). The filtrate was dried in vacuum oven to afford 1166 g (95%) of the title compound **3** as a white solid: R_f=0.2 (EtOAc); mp 202.7–203.5 °C [lit.[13a] mp 218–219 °C]; ^{1}H NMR (250 MHz, D_2O) δ1.38 (s, 6H), 4.18 (dd, J=9.1, 5.0 Hz, 1H), 4.32 (dd, J=9.1, 7.2 Hz, 1H), 4.60 (ddd, J=7.2, 5.0, 2.2 Hz, 1H), 4.93 (d, J=2.2 Hz, 1H); ^{13}C NMR (63 MHz, D_2O) δ 25.7, 26.1, 65.1, 73.7, 74.5, 109.3, 118.4, 152.7, 170.5; IR (neat) 3238, 1758, 1670 cm^{-1}.

4.1.2. Methyl 3,4-*O*-isopropylidene-L-threonate (5)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with 5,6-*O*-isopropylidene-L-ascorbic acid (**3**, 887 g, 4.1 mol) and distilled water (4000 mL). To this suspended solution was added aqueous 30% NaOH (300 mL) and the reaction mixture was stirred to become a clear solution. To the clear solution was added $NaHCO_3$ (861 g, 10.3 mol), and then 35% hydrogen peroxide (800 mL, 8.2 mol) was added dropwise and the reaction mixture was stirred for further 1 h at room temperature. After sodium sulfite (62 g, 0.49 mol) and $NaHCO_3$ (517 g, 6.15 mol) were added to the reaction mixture at room temperature, the resulting solution was warmed to 40 °C and dimethylsulfate (1530 mL, 16.4 mol) was added dropwise at 40 °C. After being stirred for 4 h at 40 °C, the reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (4000 mL×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 611 g (78%) of the title compound **5** as a colorless oil: R_f=0.57 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.28 (s, 3H), 1.36 (s, 3H), 3.07 (d, J=8.1 Hz, 1H), 3.83 (s, 3H), 3.99–4.17 (m, 3H), 4.40 (td, J_t=6.7 Hz, J_d=2.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.3, 26.1, 52.8, 65.6, 70.3, 76.3, 110.0, 172.6; IR (neat) 3489, 2992, 1742 cm^{-1}.

4.1.3. Methyl 2-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-L-threonate (6)

A 6-L round bottomed flask, equipped with a mechanical stirrer, was charged with methyl 3,4-*O*-isopropylidene-L-threonate (**5**, 341 g, 1.79 mol) and CH_2Cl_2 (1790 mL). To this solution were added pyridine (555 mL, 7.17 mol) and *p*-toluenesulfonyl chloride (410 g, 2.15 mol) at 0 °C. After being stirred for 10 h at 0 °C, the reaction mixture was quenched with water (1790 mL). The resulting solution was stirred for further 10 min, then the organic layer was

separated and washed with 1 N HCl (1790 mL) and with brine (1790 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude syrub, which was crystallized from 20% 2-propanol in hexane to afford 587 g (95%) of the title compound **6**: R_f= 0.63 (hexane/EtOAc, 1:1); mp 58.3–59.1 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ1.29 (s, 3H), 1.30 (s, 3H), 2.45 (s, 3H), 3.70 (s, 3H), 3.96 (dd, J=9.0, 4.8 Hz, 1H), 4.05 (dd, J=9.0, 6.6 Hz, 1H), 4.44–4.49 (m, 1H), 4.84 (d, J=4.8 Hz, 1H), 7.19–7.81 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.7, 25.1, 25.9, 52.8, 65.1, 74.6, 77.6, 110.6, 128.2, 129.8, 132.8, 145.3, 166.9; IR (neat) 3002, 2991, 1763 cm^{-1}.

4.1.4. (2*S*,3*R*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (7)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with methyl 2-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-L-threonate (**6**, 825 g, 2.4 mol), CH_2Cl_2 (1200 mL), and MeOH (1200 mL). After the solution was cooled to −5 °C, sodium borohydride (136 g, 3.6 mol) was added portionwise. After stirring for 2 h at rt, sodium methoxide (155 g, 2.9 mol) was added. After being stirred for further 4 h at rt, the reaction mixture was quenched with water (2400 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2000 mL×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 339 g (98%) of the title compound **7** as a colorless oil: R_f=0.42 (hexane/EtOAc, 2:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.37 (s, 3H), 1.46 (s, 3H), 2.66 (dd, J= 4.9, 2.6 Hz, 1H), 2.85 (dd, J=4.8, 4.0 Hz, 1H), 3.00–3.05 (m, 1H), 3.83–3.95 (m, 2H), 4.13 (dd, J=8.1, 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.6, 25.8, 44.7, 51.2, 66.0, 75.7, 108.9; IR (neat) 2940, 2890, 1380, 1150, 1060 cm^{-1}.

4.1.5. (2*R*,3*S*)-1-Cyano-3,4-*O*-isopropylidenebutanetriol (9)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (**7**, 500 g, 3.45 mol), tetrabutylammonium bromide (33.5 g, 0.1 mol), and dichloroethane (2890 mL). To this solution was added a solution of potassium cyanide (903 g, 13.8 mol) in water (2890 mL). After being stirred for 20 h at 40 °C, the reaction mixture was cooled to room temperature. The organic layer was separated. The aqueous layer was extracted with Et_2O (3000 mL×2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 579 g (98%) of the title compound **9** as a white solid: R_f=0.32 (hexane/EtOAc, 2:1); $[\alpha]_D$= +9.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.35 (s, 3H), 1.42 (s, 3H), 2.58 (dd, J=16.8, 7.3 Hz, 1H), 2.75 (dd, J= 16.8, 3.7 Hz, 1H), 3.47 (m, 1H), 3.83 (m, 1H), 3.94–4.03 (m, 2H), 4.12 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.1, 24.9, 26.7, 66.5, 68.8, 77.3, 110.0, 117.9; IR (neat) 3475, 3000, 2878, 2250 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.13; H, 7.71; N, 8.12.

4.1.6. 2-Deoxy-L-*erythro*-pentono-1,4-lactone (13)

A 2-L round bottomed flask, equipped with a mechanical stirrer and a reflux condenser, was charged with (2*R*,3*S*)-1-cyano-3,4-*O*-isopropylidenebutanetriol (**9**, 105 g, 0.61 mol), dichloroethane (610 mL), and water (60 mL). After stirring to become a clear solution, 32.7 mL of concn sulfuric acid was added. The resulting solution was stirred for 1 h at 40 °C, heated to reflux for 5 h, and cooled to room temperature. After addition of THF (1200 mL) and $MgSO_4$ (150 g), the reaction mixture was stirred for further 1 h at rt. The resulting suspended solution was filtered and concentrated under reduced pressure to afford 78 g (96%) of the title compound **13** as a yellowish syrup: R_f=0.20 (EtOAc); ^{1}H NMR (250 MHz, D_2O) δ2.55 (dd, J=18.6, 2.6 Hz, 1H), 3.03 (dd, J=18.6, 6.7 Hz, 1H), 3.74 (dd, J= 12.9, 4.3 Hz, 1H), 3.80 (dd, J=12.9, 3.1 Hz, 1H), 4.49–4.57 (m, 2H); ^{13}C NMR (63 MHz, D_2O) δ 38.0, 61.2, 68.5, 89.2, 179.8; IR (neat) 3437, 1937, 1755, 1625 cm^{-1}.

4.1.7. 2-Deoxy-*N*-phenyl-L-*erythro*-pentofuranosylamine (14)

A dry, 5-L round bottomed flask, equipped with a thermometer and a magnetic stirring bar, was charged with borane-dimethylsulfide complex (2 M in THF, 926 mL). After the solution was cooled to 0 °C, 2-methyl-2-butene (490 mL, 4.6 mol) was added dropwise and the resulting solution was stirred for 2 h at 0 °C. To this solution was added dropwise a solution of 2-deoxy-L-*erythro*-pentono-1,4-lactone (**13**, 122 g, 0.92 mol) in THF (920 mL) at 0 °C via cannula. The reaction mixture was stirred for 20 h at 20 °C, quenched with water (560 mL) and 6 N hydrochloric acid (8 mL), and stirred for 1 h at rt. The aqueous layer was separated and the organic layer was extracted with water (560 mL). To the combined aqueous layers were added ethanol (1120 mL) and aniline (84 mL, 0.92 mol). The resulting solution was stirred for 3 h at 5 °C. After the solution was cooled to −10 °C, the precipitated solid was collected by filtration, washed with cold acetone, and dried under reduced pressure to afford 108 g (56%) of the title compound **14**: R_f=0.65 (MeOH/EtOAc, 1:5); ^{1}H NMR (250 MHz, DMSO-d_6) δ1.69–1.89 (m, 2H), 3.42 (d, J=12.0 Hz, 1H), 3.52 (m, 1H), 3.63–3.74 (m, 2H), 4.40 (d, J=3.8 Hz, 1H), 4.62 (td, J_t=9.0 Hz, J_d=2.0 Hz, 1H), 4.73 (d, J=5.6 Hz, 1H), 6.38 (d, J=8.9 Hz, 1H), 6.56–6.66 (m, 3H), 7.04–7.10 (m, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 34.7, 65.8, 66.8, 68.0, 80.0, 113.3, 117.0, 128.7, 146.5; IR (neat) 3330, 3255, 3062, 2910 cm^{-1}.

4.1.8. 2-deoxy-L-ribose (1)

A 2-L round bottomed flask was charged with 2-deoxy-*N*-phenyl-L-*erythro*-pentofuranosylamine (**14**, 35 g, 0.17 mol), benzaldehyde (35 mL, 0.2 mol), benzoic acid (3.7 g, 0.03 mol), and water (1070 mL). After being stirred for 24 h at rt, the reaction mixture was washed with Et_2O (1000 mL×3). The aqueous layer was concentrated under reduced pressure to afford 18.3 g (82%) of the title compound **1**: R_f=0.30 (MeOH/EtOAc, 1:5); $[\alpha]_D$= +58 (*c* 1.06, H_2O) [lit.[21] $[\alpha]_D$=+60 (*c* 1.06, H_2O)]; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.47 (m, 1H), 1.77 (m, 1H), 3.41–3.52 (m, 2H), 3.63 (dd, J=10.5, 2.4 Hz, 1H), 3.83 (m, 1H), 4.42–4.46 (m, 2H), 4.96 (m, 1H), 6.09 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz DMSO-d_6) δ 36.8, 63.5, 65.6, 67.9, 91.8. Anal. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.71; H, 7.55.

Acknowledgements

This work was supported by a grant from the Korea Science and Engineering Foundation through Center for Bioactive Molecular Hybrids (CBMH).

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