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Note

Improved synthesis of dicyclohexylidene protected quebrachitol and its use in the synthesis of L-*chiro*-inositol derivatives

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Abstract—A modified synthesis of 1L-1,2:3,4-di-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositol has been accomplished that improves the overall procedure, yield, and environmental aspects of its formation. Several inositol analogues have been prepared from this intermediate for testing as biosynthetic inhibitors of glycosyl-phosphatidylinositol (GPI) anchor formation.

Keywords: Inositol protection; Quebrachitol; 1L-1,2:3,4-Di-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositol; *chiro*-Inositol derivatives

Quebrachitol is a versatile cyclitol from the chiral pool that has received considerable attention as a starting material for the synthesis of natural products and bioactive materials.[1,2] An important derivative of quebrachitol is dicyclohexylidene acetal **1**, which has been used in the synthesis of inositol phosphates,[3,4] natural products,[5–7] and as a chiral auxiliary.[8] However, the usual preparation of **1** from quebrachitol is an unattractive procedure involving treatment with cyclohexanone in benzene followed by extraction with chloroform.[9–11] The yield for this procedure is a reported 55–72% using recrystallized quebrachitol, and in the course of our work yields below this range were obtained. Large amounts of the cyclohexanone aldol condensation by-product were also formed,[10] complicating the purification. Because we required a significant amount of **1** for subsequent use, we began by designing a more environmentally friendly synthesis involving treatment of quebrachitol, without prior recrystallization, with dimethoxy cyclohexane acetal (Scheme 1). A 24 h reaction time was followed by dilution in ethyl acetate, washing with water, and crystallization of the crude material from hexanes to give pure **1** in good yield. The mono-cyclohexylidene derivative **2**, formed as a by-product, was found to be isolable by simple concentration of the aqueous fractions followed by purification. This preparation of **1** is a highly robust procedure that has been reproduced on the 65 g scale (isolated **1**), thus allowing for large-scale formation of this important intermediate.

Inositol is an essential precursor for the formation of glycosyl-phosphatidylinositol (GPI) anchors found in the majority of surface molecules in organisms. In addition, it has an essential role in the phoshatidylinositol signal transduction pathways that controls many cell cycle events. Examples that we are interested in include protozoan flagellates[12,13] and yeast cells such as *Candida albicans*.[14] Quebrachitol derivatives have been shown to have small substrate recognition activity in these two species,[15,16] therefore, the synthesis of several new substrates from inositol **1** were undertaken for additional studies. Synthesis of inositols **5** and **6**[17] involved standard chemistry. Initial protection of the remaining hydroxyl in **1** as either the methyl ether or the benzoyl ester gave **3** and **4**, respectively, in excellent yields. Subsequent removal of the cyclohexylidene protecting groups under typical conditions[18,19] gave **5** and **6** as diprotected *chiro*-inositol derivatives (Scheme 2).

Synthesis of mono-methoxy inositol **7** was achieved as shown in Scheme 3 via demethylation of **1**, using a slight

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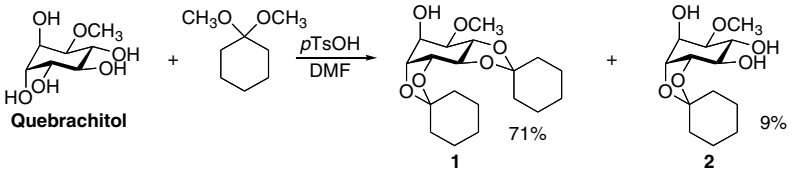
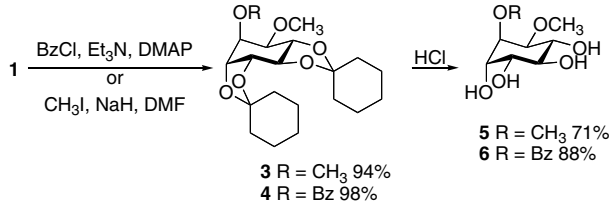


Scheme 1.



Scheme 2.

modification of Shima's procedure.[4,6,7] It was envisioned that subsequent treatment of diol **8** with *tert*-butyldimethylsilyl chloride (TBSCl) would preferentially give **9**. Although an acceptable yield of **9** was obtained, a 2:1 ratio of isomers **9** and **10** was generated. The regiochemistry of this reaction was determined by benzoylation of a portion of the product mixture to give a mixture of **11** and **12**, which simplified the determination of the regioisomeric ratio due to a downfield shift of the signal attributed to the proton adjacent to the OBz group. In the ^{1}H NMR spectrum of the product mixture, a doublet of doublets at 5.58 ppm ($J_{eq-eq} = 4.94$, $J_{ax-eq} = 3.5$ Hz) was attributed to the equatorial proton vicinal to the OBz group in the major product **11**, and a doublet of doublets at 5.41 ppm ($J_{ax-ax} = 9.6$, $J_{ax-eq} = 4.4$ Hz) was attributed to the axial proton vicinal to the OBz group in the isomeric product **12**. The 2:1 ratio of **11**:**12**, and hence 2:1 ratio of **9**:**10** was obtained from the ratio of the integrals of those two signals. Separation via flash chromatography gave predominantly **9** with approximately 20% of **10** still present, which could be completely removed following the subsequent transformation. Alternative mono-protection using tin chemistry, for example, has not been attempted to date.

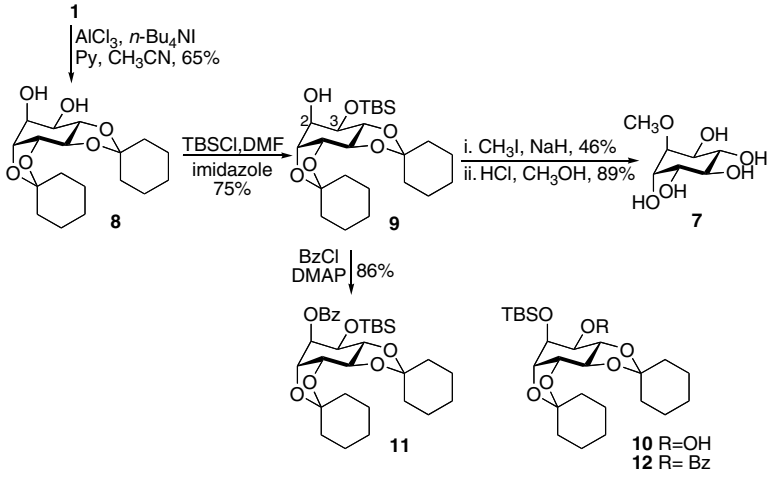
Inositol **7** was obtained by methylation of **9** followed by removal of the silyl and cyclohexylidene protecting groups. Comparison of the ^{1}H NMR spectrum of **7**, which contains an axial methoxy group, to that of quebrachitol containing an equatorial methoxy, further established the regioselectivity in the formation of **9**. Improving the yield of the methylation reaction with alternative reagents has also not been attempted at this point.

In conclusion, an improved synthesis of 1L-1,2:3,4-di-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositol (**1**) has been achieved involving benign reagents and a straightforward purification. This procedure would be amenable to the large-scale preparation of **1**. Using inositol **1**, several new derivatives of quebrachitol have been synthesized for biological testing. Results of the biological activity will be presented elsewhere.

1. Experimental

1.1. General methods

Unless otherwise stated, the following conditions apply: All reactions were performed under argon in oven-dried



Scheme 3.

glassware using standard syringe techniques. CH_2Cl_2, Et_3N, CH_3CN, and CH_3OH were distilled from calcium hydride. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich Chemical company and used without further purification. All other reagents were of commercial quality and distilled prior to use if necessary. Reaction progress was monitored using aluminum-backed TLC plates pre-coated with silica UV254 and visualized by UV radiation (254 nm), ceric ammonium molybdate dip or anisaldehyde dip. Purification of products via flash column chromatography was conducted using a column packed with Silica Gel 60 (220–240 mesh) with the solvent systems as indicated. ^1H and ^{13}C spectra were recorded on a Varian Inova at 300 and 75 MHz, respectively. Spectra were referenced to solvent peaks (^1H: residual $CHCl_3$, DMSO, or acetone; ^{13}C: $CDCl_3$, DMSO-d_6, or acetone-d_6). Infrared spectra were obtained on a Biorad FTS-7 or a Bruker Tensor 27 FTIR spectrometer. High-resolution mass spectroscopy was recorded using a Mariner electrospray time of flight spectrometer. Optical rotations were measured using a Perkin–Elmer 241 polarimeter.

1.2. 1L-1,2:3,4-di-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositol (1)

To a stirred suspension of quebrachitol (50 g, 0.25 mol) in DMF (400 mL) and dimethoxycyclohexane (320 mL, 2.06 mol), under argon, was added *p*-TsOH·H_2O (8.0 g, 0.04 mol) at rt. The mixture was then heated to 85 °C and stirred for 18 h, and then to 105 °C for a further 4.5 h. The reaction was cooled, treated with Et_3N (7 mL, 0.05 mol), and diluted with EtOAc (1 L). The solution was washed with H_2O (3 × 500 mL), and the combined H_2O washings were extracted with Et_2O (2 × 300 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$), and the solvents removed in vacuo to yield a yellow solid, which was recrystallized from petroleum ether (ca. 500 mL) to yield a first crop of **1** as white crystals (45.5 g). Two further crystallizations from petroleum ether gave a total yield of 64.8 g (71%) of **1**: mp 117–119 °C (lit.:[9] mp 117–119 °C); $[\alpha]_D$ −18 (*c* 0.1, CH_2Cl_2, lit.:[9] $[\alpha]_D$ −18 (*c* 0.1, CH_2Cl_2)); ^1H NMR (300 MHz, $CDCl_3$) δ 3.80–4.24 (m, 3H), 3.71–3.56 (m, 3H), 3.56 (s, 3H), 2.80 (s, 1H) 1.76–1.32 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.7, 110.6, 79.3, 79.0, 78.3, 76.4, 75.9, 69.5, 58.2, 38.0, 36.7, 34.9, 25.2, 24.1, 23.9, 23.8, 23.7; IR (neat) 3499, 2940, 1468, 1336, 1098, 1040, 973, 902, 769, 648 cm^{-1}; ESIMS *m*/*z* calcd for $C_{19}H_{31}O_6$ [M+H^+]: 355.2115. Found: 355.2106.

Also isolated, by concentration of the aqueous portions, EtOAc extraction, and crystallization, was 9% of the mono-acetal 1L-1,2-*O*-cyclohexylidene-5-*O*-methyl-*chiro*-inositol **2**.

1.3. 1L-3,4:5,6-Di-*O*-cyclohexylidene-1,2-di-*O*-methyl-*chiro*-inositol (3)

To a solution of **1** (460 mg, 1.30 mmol) in anhydrous DMF (6 mL) at 0 °C under argon was added NaH (80% in mineral oil, 60 mg, 1.95 mmol). The resulting suspension was stirred for 30 min after which time CH_3I (405 μL, 6.5 mmol) was added. The solution was then warmed to rt and allowed to stir overnight. The reaction was quenched by the addition of H_2O, and the mixture was extracted with Et_2O (2×). The combined organic fractions were then washed with 5% $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and the solvents removed under reduced pressure. The residues were purified by gradient flash column chromatography (1:10→1:5, EtOAc/petroleum ether) to yield **3** as an oil that solidified upon standing, 450 mg (94%): $[\alpha]_D$ −50 (*c* 0.18, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.39–4.26 (m, 2H), 3.83 (dd, 1H, $J = 4.1$, 3.8 Hz), 3.74–3.68 (m, 2H), 3.59 (dd, 1H, $J = 8.0$, 1.5 Hz), 3.54 (s, 3H), 3.52 (s, 3H), 1.84–1.32 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.0, 110.4, 79.0, 78.6, 78.2, 76.2, 76.1, 75.6, 59.5, 57.8, 37.6, 36.3, 36.2, 34.5, 24.8 (2C), 23.7, 23.5, 23.4, 23.3; IR (neat) 2934, 2860, 1449, 1279, 1100, 907, 830, 727 cm^{-1}; ESIMS *m*/*z* calcd for $C_{20}H_{33}O_6$ [M+H^+]: 369.2272. Found: 369.2267.

1.4. 1L-1,2-Di-*O*-methyl-*chiro*-inositol (5)

A solution of **3** (250 mg, 0.68 mmol) was stirred overnight at rt under air in 3 mL of 10% aq HCl in CH_3OH. After this time, solid $NaHCO_3$ was added until effervescence was no longer observed, and the solvents then removed under reduced pressure. The residue was purified by flash column chromatography (1:6, CH_3OH/CH_2Cl_2) to yield **5**, 120 mg (71%), as an oil which crystallized upon standing: mp 138–140 °C; $[\alpha]_D$ −56 (*c* 0.06, CH_3OH);[20] ^1H NMR (300 MHz, DMSO) δ 4.86 (d, 1H, $J = 3.9$ Hz), 4.60 (d, 1H, $J = 4.2$ Hz), 4.55 (d, 1H, $J = 3.7$ Hz), 4.45 (d, 1H, $J = 4.7$ Hz), 3.80 (m, 1H), 3.53 (m, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 3.26 (m, 3H), 3.15 (dd, 1H, $J = 9.3$, 2.7 Hz); ^{13}C NMR (75 MHz, DMSO) δ 81.3, 78.6, 73.5, 72.7, 71.0, 69.1, 58.9, 57.7; IR (neat) 1340, 2932, 2854, 1448, 1365, 1278, 1105, 1026, 927, 907 cm^{-1}; ESIMS *m*/*z* calcd for $C_8H_{17}O_6$ [M+H^+]: 209.1019. Found: 209.1009.

1.5. 1L-1-*O*-Benzoyl-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol (4)

Benzoyl chloride (260 μL, 2.32 mmol) and DMAP (7 mg, 0.06 mmol) were added to a solution of **1** (412 mg, 1.16 mmol) in CH_2Cl_2 (5.5 mL) and Et_3N (645 μL, 4.66 mmol) at 0 °C under argon, and then stirred for five days at rt. H_2O was then added and the mixture extracted with CH_2Cl_2 (3×). The combined organic fractions were

washed with brine, dried ($MgSO_4$), and the solvents removed under reduced pressure to yield an orange oil that was purified by flash chromatography (1:15, EtOAc/petroleum ether) to yield **4** as a white solid, 522 mg (98%): mp 79–81 °C; $[\alpha]_D$ −8.3 (*c* 0.1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 5.82 (dd, 1H, $J = 3.7$, 3.2 Hz), 4.42 (m, 2H), 3.90–3.68 (m, 3H), 3.46 (s, 3H), 1.85–1.35 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 133.3, 129.9, 129.5, 128.4, 112.6, 111.0, 79.2, 77.9, 76.4, 76.0, 75.7, 70.0, 58.2, 37.9, 36.5, 36.3, 34.8, 25.0, 24.9, 23.9, 23.6 (2C), 23.5; IR (neat) 2936, 2860, 1724, 1450, 1269, 1107, 1070, 908, 731 cm^{-1}; ESIMS *m*/*z* calcd for $C_{26}H_{35}O_7$ $[M+H^+]$: 459.2377. Found: 459.2383.

1.6. 1L-1-*O*-Benzoyl-2-*O*-methyl-*chiro*-inositol (6)

To a solution of **4** (80 mg, 0.18 mmol) in wet acetone (1 mL) at rt under air was added aqueous HCl (four drops) and the reaction stirred for 2 days, when TLC analysis revealed 100% conversion. Solid $NaHCO_3$ (50 mg) was added, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (1:10, CH_3OH/CH_2Cl_2) to yield **6**, 46 mg (88%) as a crystalline solid: mp 144–149 °C. $[\alpha]_D$ −48 (*c* 0.06, CH_3OH or acetone);[†] ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 8.00 (m, 2H), 7.64 (m, 1H), 7.51 (m, 2H), 5.63 (m, 1H), 4.65 (d, 1H, $J = 3.4$ Hz), 4.32 (br s, 1H), 4.24 (br s, 1H), 4.15 (br s, 1H), 4.06 (m, 1H), 3.66 (m, 3H), 3.47 (dd, 1H, $J = 9.5$, 3.2 Hz), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 165.6, 133.9, 130.8, 130.2, 129.3, 80.5, 74.1, 73.8, 72.4, 70.6, 70.5, 58.1; IR (neat) 3336, 2928, 1699, 1450, 1178, 1096, 1070, 1025, 751, 708 cm^{-1}; ESIMS *m*/*z* calcd for $C_{14}H_{19}O_7$ $[M+H^+]$: 299.1125. Found: 299.1133.

1.7. 1L-1,2:3,4-Di-*O*-cyclohexylidene-*chiro*-inositol (8)

Dicyclohexylidene quebrachitol **1** (1.00 g, 2.82 mmol) was dissolved in anhydrous CH_3CN (25 mL) and cooled to 0 °C. Pyridine (2.3 mL, 28.2 mmol), *n*-Bu_4NI (7.0 g, 19.0 mmol), and $AlCl_3$ (3.8 g, 28.2 mmol) were then added in that order. The mixture was heated to 62 °C overnight, cooled to rt, quenched by careful addition of H_2O (60 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The organic fractions were combined and washed with brine, dried ($MgSO_4$), and the solvents removed under reduced pressure to yield a white solid, which was subsequently re-dissolved in a minimum amount of CH_2Cl_2. To this solution was added Et_2O (100 mL) and the resulting white precipitate removed by vacuum filtration. The filtrate was reduced in vacuo to yield an oil that was purified by gradient flash chromatography (1:10→1:3, EtOAc/petroleum ether,) to give 624 mg (65%) of **8** as an amorphous white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (m, 2H), 4.19 (m, 1H), 4.13 (m, 1H), 3.78–3.63 (m, 2H), 2.77 (d, 1H, $J = 2.9$ Hz), 2.73 (d, 1H, $J = 2.4$ Hz), 1.85–1.36 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.1, 110.9, 78.7, 78.1, 77.3, 75.9, 71.0, 70.1, 38.0, 36.7 (2C), 34.8, 25.2, 25.1, 24.2, 23.9, 23.8, 23.7; IR (neat) 3460, 2937, 2857, 1368, 1270, 1095, 1046, 909, 730 cm^{-1}; ESIMS *m*/*z* calcd for $C_{18}H_{29}O_6$ $[M+H^+]$: 341.1959. Found: 341.1973.

1.8. 1L-1,2:3,4-Di-*O*-cyclohexylidene-5-*O*-(*tert*-butyldimethylsilyloxy)-*chiro*-inositol (9)

To a solution of the diol **8** (130 mg, 0.38 mmol) in DMF (650 μL) at 0 °C were added imidazole (52 mg, 0.76 mmol) and TBSCl (63 mg, 0.42 mmol). The solution was then allowed to warm to rt and stir overnight, after which it was diluted with Et_2O, washed with satd aq $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and the solvents removed under reduced pressure. The product **9** was isolated by flash column chromatography (1:5, EtOAc/petroleum ether) as an oil, 130 mg (75%, as a mixture of **9** and **10**). Further gradient flash chromatography (1:20→1:5, EtOAc/petroleum ether) allowed partial separation of the isomers, to yield **9** contaminated with 20% of the isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 4.38–4.28 (m, 2H), 4.11 (m, 1H), 4.01 (dd, 1H, $J = 8.3$, 5.6 Hz), 3.60–3.53 (m, 2H), 2.99 (br s, 1H), 1.72–1.35 (m, 20H), 1.91 (s, 9H), 1.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.0, 110.1, 78.7, 78.0, 76.5, 75.7, 71.6, 71.2, 37.8, 36.8, 36.0, 34.6, 25.7 (3C), 25.0, 24.9, 23.8, 23.7, 23.5, 23.4, 18.4, −3.9, −4.6; IR (neat) 3544, 2932, 2856, 1449, 1211, 1099, 1084, 935, 907, 837, 779, 731 cm^{-1}; ESIMS *m*/*z* calcd for $C_{24}H_{43}O_6Si$ $[M+H^+]$: 455.2829. Found: 455.2822.

1.9. 1L-1-*O*-Methyl-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-(*tert*-butyldimethylsilyloxy)-*chiro*-inositol

To a solution of **9** (40 mg, 0.09 mmol, containing ca. 20% of the isomer **10**) in DMF (0.5 mL) was added NaH (80% in mineral oil, 10 mg, 0.29 mmol). The resulting suspension was stirred for 10 min after which time CH_3I (50 μL, 0.80 mmol) was added. The solution was then warmed to rt and allowed to stir for 20 h. H_2O was added and the mixture was extracted with Et_2O (3×). The combined organic fractions were washed with 5% $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (1:20, EtOAc/petroleum ether) to yield 19 mg (46%) of the desired methoxylated inositol an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.32–4.25 (m, 2H), 4.60 (dd, 1 H $J = 9.0$, 4.2 Hz), 3.68–3.60 (m, 2H), 3.53 (s, 3H), 3.49 (m, 1H),

[†] The optical rotation for this compound, which has been checked on multiple occasions, is in disagreement with published data[17] (+50.1); we suggest that the +50.1 is a typographical error.

1.70–1.30 (m, 20H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.6, 110.3, 81.3, 79.3, 77.1, 76.9, 76.4, 75.9, 71.6, 60.6, 37.9, 36.8, 36.0, 34.9, 25.8 (3C), 25.1, 25.0, 23.9, 23.8, 23.6, 23.5, 18.4, −4.5, −5.0; IR (neat) 2933, 2856, 1449, 1366, 1252, 1104, 907, 837, 778, 731 cm^{-1}; ESIMS *m*/*z* calcd for $C_{25}H_{45}O_6Si$ [M+H$^+$]: 469.2979. Found: 469.2973.

1.10. 1L-1-*O*-Methyl-*chiro*-inositol (7)

The fully protected L-*chiro*-inositol derivative above (45 mg, 0.10 mmol) was dissolved in 2 mL of 10% HCl in CH_3OH and stirred at rt for 4 h. The solvents were then removed under reduced pressure and the residue purified by washing with hexanes and EtOAc and then purified by flash column chromatography (1:3→1:2, CH_3OH/CH_2Cl_2) to yield 17 mg (89%) of **7**: $[\alpha]_D$ −57 (*c* 0.05, D_2O);[21] ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.76 (d, 1H, $J = 3.9$ Hz), 4.49 (d, 1H, $J = 4.1$ Hz), 4.47 (d, 1H, $J = 3.9$ Hz), 4.41 (d, 1H, $J = 3.9$ Hz), 4.39 (d, 1H, $J = 3.4$ Hz), 3.77 (dd, 1H, $J = 6.7$, 3.4 Hz), 3.53–3.43 (m, 1H), 3.33–3.16 (m, 4H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 82.9, 73.5, 73.3, 71.2, 70.8, 69.4, 59.2 cm^{-1}; ESIMS *m*/*z* calcd for $C_7H_{18}O_6N$ [M + NH_4^+]: 212.1129. Found: 212.1126.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.04.030.

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