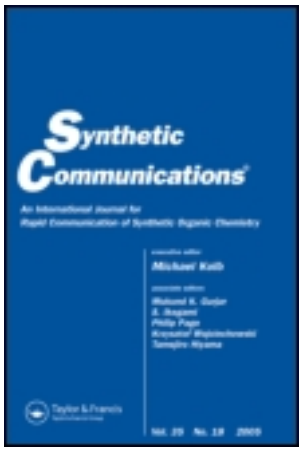

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SYNTHETIC COMMUNICATIONS, 31(18), 2849–2854 (2001)

A PROTECTED FORM OF (1*S*,2*R*,3*S*,4*R*)-4-AMINOCYCLOPENTANE-1,2,3-TRIOL, A USEFUL PRECURSOR TO 5′-NOR CARBOCYCLIC NUCLEOSIDES

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ABSTRACT

5′-Nor carbocyclic nucleosides have been found to possess a variety of meaningful biological properties. One of the building blocks for this class of compounds is (1*S*,2*R*,3*S*,4*R*)-4-aminocyclopentane-1,2,3-triol. To date, the reported routes to this compound are not particularly facile. Thus, a convenient route to this triol in its protected isopropylidene form (**2**) from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate. This will facilitate the preparation of new 5′-nor carbocyclic nucleosides in the "D-ribo-like" configuration. This method is also adaptable to the "L-like" series and the 2′- and 3′-deoxy analogs.

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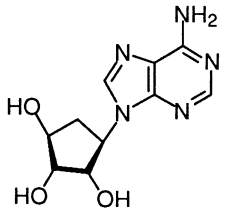
INTRODUCTION

Reports on the biological activity of both enantiomers of 5′-noraristeromycin[2,3] (**1**, as the (−)-antipode) and related derivatives[4,5] have prompted considerable interest in the 5′-nor carbocyclic series of nucleosides[6] as potential medicinal agents[2–5] and oligomer building blocks.[7,8] We recently sought a facile route to other derivatives in this series that possessed bases other than the standard naturally occurring purines and pyrimidines. For this purpose, a convenient preparation of the protected cyclopentylamine (**2**), which could be employed in a *de novo* type process[6b,9] to the new analogs, was desired.



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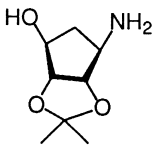

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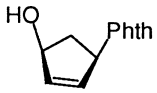

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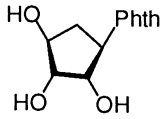

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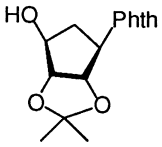

5

A review of the literature showed that a racemic[10] and a chiral[11] synthesis of **2** were available. However, since chiral **2** was needed for our studies, the numerous steps in one literature procedure[11a] and limited flexibility in another[11b] to this material led to developing a procedure more adaptable to modification in the cyclopentyl ring and to scale-up. This route is described here.

RESULTS

Beginning with (+)-(1*S*,4*R*)-4-phthalimidyl-2-cyclopenten-1-ol (**3**)[12] (available from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate[13]) near quantitative glycolization using standard conditions (*N*-methylmorpholine

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N-oxide, osmium tetroxide) led to **4**.[14] Protection of the 2,3-dihydroxy groups of **4** as an isopropylidene unit (**5**) was followed by removal of the phthalyl group (with methylamine) to give **2** in 48% overall yield from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate. The properties of **2** compared favorably with those reported.[10,11]

Compound **3** is also a convenient precursor to the 2′- and 3′-deoxy 5′-nor carbocyclic nucleoside series[15] whereas the enantiomer of **3** would avail a means to the "L-like" derivatives.[3,4]

EXPERIMENTAL

General Methods

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA. ^{1}H spectra were recorded on a Bruker AC 250 spectrometer, referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols *s* (singlet), *d* (doublet), *t* (triplet), *m* (multiplet) and *br* (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, 60 Å and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

(+)-(1*S*,4*R*)-4-Phthalimidyl-2-cyclopenten-1-ol (3). To a solution of the potassium salt of phthalimide (3.84 g, 20.5 mmol) in anhydrous (DMSO (20 mL) were added triphenylphosphine (300 mg, 6 mol%) and *tetrakis*(triphenylphosphine)palladium (800 mg, 4 mol%). The mixture was stirred for 5 min and a solution of (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate[13] (2.84 g, 20 mmol) in freshly distilled THF (100 mL) was added to the above mixture. The flask containing this new mixture was immediately transferred to an oil bath preheated at 50°C and the mixture was stirred for 16 h. The solvents were removed under reduced pressure and the residue slurried in CH_2Cl_2 (200 mL) and filtered. The clear filtrate was washed with brine (150 mL), dried (Na_2SO_4) and filtered. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using the solvent systems in the following order: hexane–AcOEt (20 : 1), hexane–AcOEt (10 : 1), and hexane–AcOEt (5 : 1). Removal of the final solvent mixture afforded **3** (3.2 g, 70%) as a light yellow solid, mp 63–64°C (lit.[12] 69–71°C); ^{1}H NMR (DMSO-d_6) δ 1.92 (dt, $J = 12.5$ and 5 Hz, 1H),

2.61 (dt, $J = 12.5$ and 7.5 Hz, 1H), 4.65 (m, 1H), 5.00 4.62 (m, 1H), 5.20 (dt, $J = 7.5$ Hz, 1H), 5.88 (dd, $J = 5$ Hz, 14 Hz, 1H), 5.96 (dd, $J = 7.5$ Hz, 14 Hz, 1H), 7.84 (s, 4H). Anal. calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.97; H, 4.81; N, 6.20.

(1*S*,2*R*,3*S*,4*R*)-4-(*N*-Phthalimidyl)cyclopentane-1,2,3-triol (4). A mixture of **3** (1.71 g, 7.5 mmol), *N*-methylmorpholine *N*-oxide (3 mL of 50% aq. solution, 14 mmol), and a catalytic amount of OsO_4 (60 mg) were stirred in acetone (20 mL) at room temp. for 2.5 h during which time the reaction was complete as judged by tlc (CH_2Cl_2-MeOH, 4:1) analysis. Removal of the solvent under reduced pressure gave a residue to which 10% $NaHSO_3$ solution (20 mL) was added. The mixture was acidified to pH 2–3 using 5% H_2SO_4 and then extracted several times with AcOEt. The extracts were combined, dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated to a small volume. The new residue was collected and washed with hexane-AcOEt (8:1) and dried (P_2O_5) to give **4** (1.75 g, 88%) as a white powder, mp 176–178°C; ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 1H, H-5), 2.15 (m, 1H, H-5), 3.70–4.54 (m, 4H, H-1, H-2, H-3, H-4), 4.66 (d, $J = 3.7$ Hz, 1H, OH), 4.90 (d, $J = 5$ Hz, 1H, OH), 4.96 (d, $J = 2.5$ Hz, H, OH), 7.85 (s, 4H, aromatic). Anal. calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.18; H, 5.00; N, 5.34.

(1*S*,2*R*,3*S*,4*R*)-4-(*N*-Phthalimidyl)-2,3-*O*-isopropylidenecyclopentane-1,2,3-triol (5). To a solution of **4** (2 g, 0.76 mmol) in dry acetone (60 mL) and 2,2-dimethoxypropane (5 mL) in a 100 mL round-bottom flask was added a small crystal of *p*-toluenesulfonic acid under N_2. This mixture was stirred at room temp. overnight and was then passed through a pad of silica gel. The resulting solution was evaporated under reduced pressure and the residue extracted with AcOEt (2×50 mL). The combined extracts were dried (Na_2SO_4), filtered, and the filtrate concentrated *in vacuo* to provide a residue that was triturated with hexane to afford **5** (1.95 g, 84%) as an off-white powder, mp 90–92°C; ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 3H, Me), 1.43 (s, 3H, Me), 2.08–2.30 (m, 2H, H-5), 3.96–4.48 (m, 3H, H-2, H-3, H-4), 4.96–5.01 (m, 2H, H-1 and OH), 7.86 (s, 4H, aromatic). Anal. calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.29; H, 5.63; N, 4.62.

(1*S*,2*R*,3*S*,4*R*)-4-Amino-2,3-*O*-isopropylidenecyclopentane-1,2,3-triol (2). A 33% solution of methylamine in absolute EtOH (60 mL) was added to a stirred suspension of **5** (1.5 g) in absolute EtOH (40 mL). After stirring for 5 min at room temp. the mixture was refluxed for 2 h during which time the reaction was complete (tlc analysis, 4:1 CH_2Cl_2-MeOH). The mixture was cooled to room temp. and the solvent evaporated on a rotary evaporator. The residue was adsorbed on silica gel (2 g); this was then loaded onto a silica gel column and, in turn, eluted (15 : 1, CH_2Cl_2 : MeOH) to remove the target compound. Evaporation of the solvent followed by trituration of the

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residue using hexane yielded **2** (800 mg, 92%) as a white powder; mp 126–127°C (lit.[11] 126–127°C); ^{1}H NMR (DMSO-d_6) δ 1.19 (s, 3H, Me), 1.25 (s, 3H, Me), 1.35 (m, 1H, H-5), 1.50 (m, 1H, H-5), 1.95 (m, 3H, NH_2, OH), 3.22 (d, $J = 5$ Hz, 1H, H-4), 3.89 (d, $J = 2.5$ Hz, 1H, H-1), 4.38 (d, $J = 5$ Hz, 1H, H-2), 4.45 (d, $J = 5$ Hz, 1H, H-3). Anal. calcd for $C_8H_{15}NO_3 \cdot 0.1$ MeOH: C, 55.18, H, 8.75; N, 7.94. Found: C, 54.98; H, 8.48; N, 7.77.

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