Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Rajiv Sharma & Victor E. Marquez (1994) Rapid Synthesis of 5-O-(tert-Butyldiphenylsilyl)-2-deoxy-L-ribonolactone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:13, 1937-1945, DOI: 10.1080/00397919408010201

To link to this article: http://dx.doi.org/10.1080/00397919408010201

SYNTHETIC COMMUNICATIONS, 24(13), 1937-1945 (1994)

RAPID SYNTHESIS OF 5-*O*-(*tert*-BUTYLDIPHENYLSILYL)-2-DEOXY-*L*-RIBONOLACTONE

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Abstract. A convenient, four-step synthesis of the title compound (**1**) in 21% overall yield from *L*-arabinose is described. Selective formation of the 2-*O*-phenoxythiocarbonyl derivative **6** and its tributyltin hydride/azobis(isobutyronitrile) deoxygenation performed in the presence of an unprotected hydroxyl group are highlighted.

5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-*L*-ribonolactone (**1**) is a key intermediate for the synthesis of 3-*O*-tetradecanoyl-2-deoxy-*L*-ribonolactone (**3**).[1] Compound **3** was designed as a conformationally constrained analogue of

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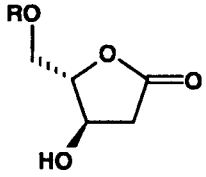
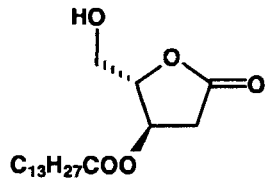
diacylglycerol and as such it behaved as a potent inhibitor (K_i = 2.5 μM) of the binding of [20-^{3}H] phorbol-12,13-dibutyrate to protein kinase C (PK-C).[1] During the course of a study designed to investigate the effect of various 3-*O*-acyl substituents on the biological activity of the 2-deoxy-*L*-ribonolactone template,[2] we required a rapid and efficient access to intermediate **1**. Our original synthesis of **1**[1] from *L*-



1, R = Me_3CPh_2Si

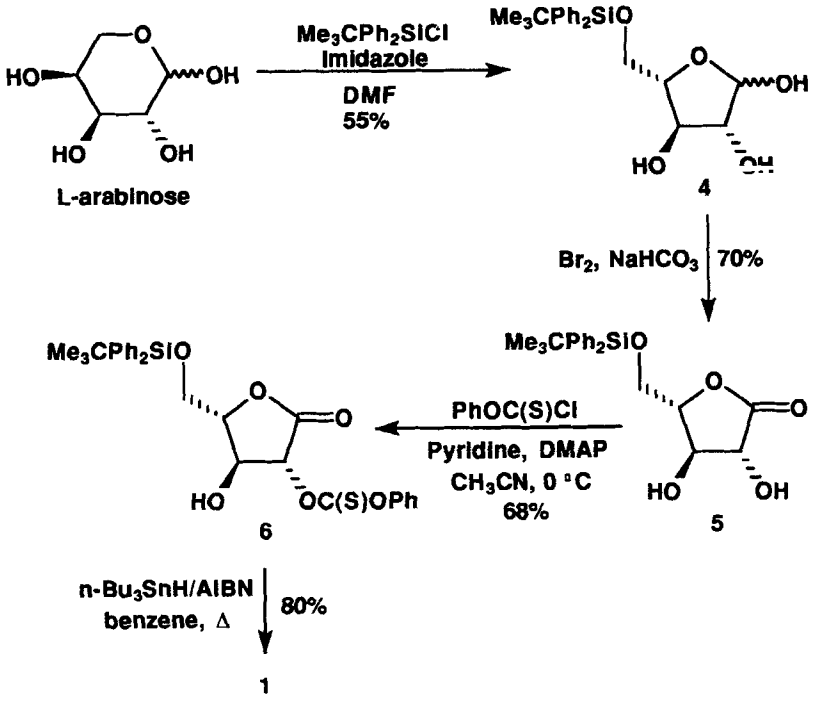
2, R = Ph_3C



3

ascorbic acid was rather lengthy, and another recently devised seven-step preparation[3] required a relatively expensive starting material such as (*R*)-(-)5-oxo-2-tetrahydrofuran-carboxylic acid. Additionally, a seven-step synthesis for the related 5-*O*-trityl-2-deoxy-*L*-ribonolactone (**2**)[4] has been reported from *L*-arabinose but the overall yield was rather low. Herein, we report a facile synthesis of **1** in four simple steps from *L*-arabinose.

Scheme



Treatment of *L*-arabinose with *tert*-butyldiphenylchlorosilane and imidazole in DMF[5] afforded a 55% yield of protected 5-*O*-*tert*-butyldiphenylsilyl-*L*-arabinofuranose (**4**) (Scheme). Selective oxidation at C-1 with bromine/water/$NaHCO_3$[6] produced the corresponding lactone, 5-*O*-tert-butyldiphenylsilyl-*L*-arabino-1,4-lactone (**5**) in 70% yield. An attempted α-deoxygenation of **5** to give **1** directly

via the recently developed SmI_2-ethylene glycol/HMPA procedure[7] resulted only in the recovery of starting material. However, selective acylation at C-2 (68% yield) with phenylchlorothionoformate, followed by radical deoxygenation with tri-*n*-butyltin hydride/AIBN [azobis(isobutyronitrile)] in refluxing benzene provided the title compound **1** in 80% yield (21% overall yield from *L*-arabinose). An important feature of this method is the tolerance of a free hydroxyl group under free radical deoxygenation conditions.

In summary, a concise and practical synthesis of **1** in 21% overall yield was achieved from the inexpensive and relatively abundant starting material *L*-arabinose.

EXPERIMENTAL

5-*O*-*tert*-Butyldiphenylsilyl-*L*-arabino-1,4-lactone (**5**). A freshly prepared bromine solution [60 mL, 2 M in EtOH/H_2O (9/1), 120 mmol] was added dropwise during the course of 1 h to a stirred suspension of 5-*O*-*tert*-butyldiphenylsilyl-*L*-arabinofuranose[5] (**4**, 5.673 g, 14.6 mmol) and $NaHCO_3$ (61.35

g, 0.73 mol) in 80 mL of ethanol/H_2O (9/1) at room temperature. The reaction mixture was then stirred at room temperature for a total of 6 h more, quenched with solid sodium thiosulfate until colorless, and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 X 50 mL) and washed with H_2O (50 mL). Removal of the solvent gave a crude material (6.02 g) which was column chromatographed on silica gel 60 (230-400 mesh) using ethyl acetate/hexane (1/1) as eluant to give **5** (R_f = 0.44) as a colorless solid (3.36 g, 70 % based on 15% recovered starting material after further elution); mp 120-121 °C (EtOAc/ hexane); $[\alpha]_D^{25}$ = –27.43 (*c* 1.17,$CHCl_3$); IR (KBr) 3463, 3200, 3047, 1779, 1472, 1427, 1331, 1194 cm^{-1}; ^1H NMR ($CDCL_3$) δ 1.05 (s, 9 H, $C(C\underline{H}_3)_3$), 2.46 (d, 1 H, *J* = 3.6 Hz, O<u>H</u>, D_2O exchangeable), 2.90 (d, 1 H, *J* = 2.8 Hz, O<u>H</u>, D_2O exchangeable), 3.88 (dd,1 H, *J* = 11.8, 3.3 Hz, $H5_a$), 3.98 (dd, 1 H, *J* = 11.8, 3.4 Hz, $H5_b$), 4.20 (m, 1 H, H4), 4.40-4.55 (m, 2 H, H2, H3), 7.40-7.70 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ 19.18, 26.69, 61.59, 73.43, 74.83, 80.98, 127.84, 129.93, 132.41, 132.72,

135.48, 135.60, 174.80. Anal. Calcd for $C_{21}H_{26}O_5Si$: C, 65.26; H, 6.78. Found: C, 65.31; H, 6.78.

5-*O*-*tert*-Butyldiphenylsilyl-2-*O*-phenoxythiocarbonyl-*L*-arabino-1,4-lactone (**6**). A stirred solution of **5** (1.379 g, 3.57 mmol) in dry acetonitrile (35 mL) containing pyridine (0.43 mL, 5.35 mmol) and *N,N*-dimethylaminopyridine (87 mg, 0.71 mmol) at 0 °C was treated dropwise with phenylchlorothionoformate (0.864 g, 5 mmol) while maintained under a blanket of argon. After 5 h, the reaction was quenched with water (4 mL), concentrated under vacuum, extracted into EtOAc (3 X 20 mL), washed successively with 1M HCl (2 X 15 mL), water (15 mL), saturated $NaHCO_3$ (15mL) and water (15mL). The organic extract was dried (Na_2SO_4) and concentrated. The crude oil obtained (1.73g) was flash chromatographed on silica gel 60 (230-400 mesh) and eluted with hexane/EtOAc (9/1). Compound **6** (1.274 g, 68 %) was obtained as a gum which solidified on standing, mp 98.5-100.0 °C (EtOAc/ hexane); $[\alpha]_D^{25}$ = -60.18 (*c* 1.08, $CHCl_3$); IR (KBr)

3464, 3071, 1782, 1590, 1490, 1287 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (s, 9 H, $C(CH_3)_3$), 3.08 (d, 1 H, *J* = 9.5 Hz, OH, D_2O exchangeable), 3.87 (dd,1 H, *J* = 11.9, 2.9 Hz, $H5_a$), 4.00 (dd, 1 H, *J* = 11.9, 2.8 Hz, $H5_b$), 4.40 (m, 1 H, H4), 4.86 (dt, 1 H, *J* = 6.6, 2.9 Hz, H3), 6.03 (d, 1H, *J* = 6.7 Hz, H2), 7.10-7.70 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.18, 19.24, 26.70, 61.89, 72.52, 81.86, 82.99, 121.52, 127.08, 127.93, 129.75, 130.05, 132.13, 132.69, 135.51, 135.66, 153.52, 168.10, 195.54. Anal. Calcd for $C_{28}H_{30}O_6SSi$: C, 64.35; H, 5.79; S, 6.12. Found: C, 64.14; H, 6.13; S, 6.19.

5-*O*-(*tert*-Butyldiphenylsilyl)-2-deoxy-*L*-ribonolact-one (**1**). A solution of **6** (1.254 g, 2.34 mmol), tri-*n*-butyltin hydride (0.837 g, 2.88 mmol) and AIBN (50 mg) in anhydrous benzene (42 mL) was refluxed with stirring under argon for 1.5 h. The reaction mixture was concentrated under vacuum and the residual oil was column chromatographed on silica gel 60 (230-400 mesh) eluting with hexane/EtOAc (3/1) to give **1** [R_f = 0.13, hexane/EtOAc (4/1)] as an oil (0.709 g, 80 %); $[\alpha]_D^{25}$ =

-24.65 (*c* 1.27, $CHCl_3$); {lit.[1] $[\alpha]_D^{25}$ = -24.37 (*c* 1.26, $CHCl_3$)}. This material was identical in every respect (IR, ^1H NMR, and ^{13}C NMR) to compound **1** which was synthesized earlier in this laboratory by a different method.[1]

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(Received in the USA 03 December 1993)