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A facile access to 2-deoxy-L-ribose

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Abstract—The title compound was prepared in five steps starting from *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one **1** via *syn*-dihydroxylation of its double bond, regioselective tosylation of the 2-OH group in the thus obtained diol **2** followed by selective deoxygenation of that position.

1. Introduction

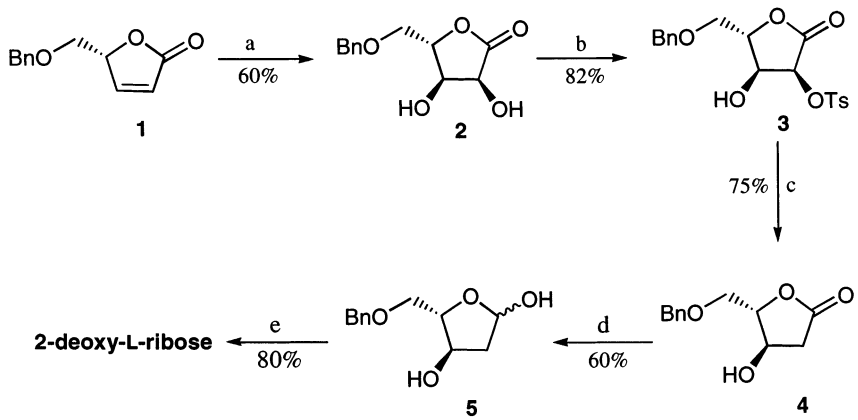
Selectively protected derivatives of L-configured riboses constitute central building blocks for L-enantiomers of natural and chemically modified nucleosides, several of which are highly valuable anti-viral agents[1] and are useful in cancer[2] and malaria[3] therapy. Thus, L-thymidine (L-T), L-3′-thiacytidine (L-3-TC, 'Lamivudine'), L-5-fluoro-3′-thiacytidine (L-FTC), L-2′,3′-dideoxy-cytidine (L-ddC), L-5-fluoro-2′,3′-dideoxy-cytidine (L-5-FddC) have shown excellent antiviral activities with greatly reduced toxicities in mammalian systems as compared to the corresponding D-nucleosides. As a great advantage for therapeutic applications and in contrast to the corresponding D-oligodeoxynucleotides (D-DNA) such enantiomeric L-DNA oligomers display considerably enhanced resistance towards the action of nucleases.[4]

Recently we reported a novel synthesis of the title compound[5] starting from *R*-(+)-5-benzyloxymethyl-5*H*-furan-2-one **1**, which in turn was obtained (a) in six steps from L-ascorbic acid[5,6] or (b) in three steps from (*R*)-benzyl glycidol.[7] The key step was the diastereoselective introduction of a 'masked' hydroxyl group ($PhMe_2Si$-) using Fleming chemistry,[8] followed by conversion of the resulting intermediate into **4** with retention of configuration.

Although this route leads to the title compound with high enantiomeric excess, the method has a number of drawbacks: the silyl reagent $(PhMe_2Si)_2Cu(CN)Li_2$ has to be prepared directly prior to use, it is also employed in a two-fold excess and thus, the route is not very economical.

2. Results and discussion

On this basis we explored the possibility of introducing diastereoselectively two hydroxy groups at the double bond of **1**, followed by regioselective deoxygenation of the 2-OH group (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) $KMnO_4$, dicyclohexano-18-crown-6, dichloromethane, –42°C, 2 h; (b) *p*-TsCl, Et_3N, dichloromethane, –20°C, 18 h; (c) aq. NH_2NH_2, Br_2, THF, 0°C–rt, 30 min; (d) disiamylborane, THF, rt, 24 h; (e) HCOOH, Pd/C 10%, MeOH, rt, 1 h.

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Syn-dihydroxylation[9] of **1** was carried out in dichloromethane at −42°C using $KMnO_4$ as oxidant in the presence of dicyclohexano-18-crown-6 as phase transfer catalyst. (3*S*,4*S*,5*S*)-(−)-5-Benzyloxymethyl-3,4-dihydroxy-dihydro-furan-2-one **2** was obtained in 60% yield as single diastereoisomer (^{13}C NMR). Regioselective protection[10] of the 2-OH group in **2** was achieved successfully by tosylation (*p*-TsCl, Et_3N, CH_2Cl_2) leading to **3** in 82% yield. Deoxygenation of the tosylate function in **3** using an 80% aqueous solution of N_2H_4[11] and Br_2 in THF at 0°C afforded **4** in 75% yield. As reported earlier, **4** can be converted into the title compound by: (a) selective reduction of the carbonyl function using disiamylborane leading to **5** and (b) removal of the benzyl protecting group (HCO_2H, 10% Pd/C).[5]

In comparison to the previously reported method for the synthesis of the title compound we feel that the above route has several advantages using: (a) simpler procedures, (b) commercially available reagents and (c) being faster. The only remaining drawback is the requirement for one additional step and a lower overall yield (18%) as compared to the silyl based procedure (28%). This is, in our opinion, more than compensated by the above rapid and facile procedure.

3. Experimental

3.1. General

Reagents were obtained from commercial suppliers and used without further purification. Dichloromethane was dried over P_2O_5. Merck silica gel 60 (70–230 mesh) was used for column chromatography. TLC analyses were run on SiO_2 $60F_{254}$ (Merck), detection with UV and Vaniline/H_2SO_4 reagent. ^1H and ^{13}C NMR spectra were measured at 400 MHz (Bruker). Chemical shifts are reported relative to $CDCl_3$ at 7.27 ppm. IR spectra were measured with a Perkin–Elmer Infrared Spectrophotometer 1420; optical rotations with a Perkin–Elmer 241 (thermostated at +20°C, chloroform stabilized with 1% ethanol). Mass spectra were measured with a Variant MAT 311 A (EI, 70 eV). Elemental analyses were carried out with an Elementar Vario EL. Melting points are uncorrected.

3.2. (3*S*,4*S*,5*S*)-(−)-5-Benzyloxymethyl-3,4-dihydroxy-dihydro-furan-2-one 2

To a vigorously stirred solution of **1** (500 mg, 2.45 mmol) and dicyclohexano-18-crown-6 (91.2 mg, 0.24 mmol, 0.1 equiv.) in dry dichloromethane (15 mL, under argon, at −42°C (CH_3CN/CO_2 bath) was added $KMnO_4$ (465 mg, 2.94 mmol, 1.2 equiv.) in several portions over 30 min. The mixture was stirred for 2 h at −42°C and then transferred into a separatory funnel. Solid Na_2SO_3 (2 g) was added followed by the dropwise addition of 1 M aqueous H_2SO_4 under shaking until complete decolorization was observed. The mixture was filtered by suction in order to remove any remaining solids and the aqueous phase was extracted with dichloromethane (2×20 mL). The collected organic phases were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel using as eluent AcOEt/*n*-hexane (2/1). The diol **2** was obtained in 60% yield (291 mg) based on **1** and taking into account the recovered **1** (85 mg). Recrystallization from AcOEt/*n*-hexane gave **2** in form of white needles; mp 106–107°C; R_f: 0.25 AcOEt/*n*-hexane (2/1). $[\alpha]_D^{20} = -23$ (*c* 0.9, acetone). ^1H NMR (acetone-d_6): δ 7.36–7.23 (m, 5H, Ph), 4.62 (br, 2OH), 4.59 (d, $J = 5.59$ Hz, 1H, CO-CH), 4.52 (s, 2H, $PhCH_2$), 4.46 (t, $J = 3.05$ Hz, 1H, $BnOCH_2$-CH), 4.36 (d, $J = 5.59$ Hz, 1H, COCHOH-CH), 3.75 (dd, $J = 11.08$ Hz, $J = 3.05$ Hz, 1H, $BnOCH_a$), 3.71 (dd, $J = 10.92$ Hz, $J = 3.12$ Hz, 1H, $BnOCH_b$). ^{13}C NMR (acetone-d_6): δ 177.02 (C=O), 139.57 (C_{ar}), 129.85 (C_{ar}), 129.14 (C_{ar}), 129.05 (C_{ar}), 84.99 ($BnOCH_2$-CH), 74.65 ($PhCH_2$), 71.64 (CO-CH), 70.93 ($BnOCH_2$), 70.44 (COCHOH-CH). IR (KBr, cm^{-1}) 3474 (OH), 3298 (OH), 2923 (-CH_2-$_{asym}$), 2864 (-CH_2-$_{sym}$), 1756 (C=O). MS *m*/*z* 238 (M^+), 107 ($PhCH_2O^+$), 91 (tropyllium ion). Anal. calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.14; H, 5.45%.

3.3. (3*S*,4*S*,5*S*)-(+)-5-Benzyloxymethyl-4-hydroxy-3-(4-methylbenzenesulfonate)-dihydro-furan-2-one 3

To a solution of **2** (280 mg, 1.17 mmol) in dry dichloromethane (10 mL) was added Et_3N (248 μl, 1.76 mmol, 1.5 equiv.) at 0°C followed by the addition of solid *p*-TsCl (224 mg, 1.17 mmol, 1 equiv.). The mixture was allowed to stand in a freezer at −20°C for 18 h without stirring and then diluted with dichloromethane (10 mL). The organic layer was washed with 1N aqueous HCl, brine and then dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel using as eluent AcOEt/*n*-hexane (1/1) and **3** was isolated as a pale yellow oil (363 mg, 82%). R_f: 0.38 AcOEt/*n*-hexane (1/1). $[\alpha]_D^{20} = +37$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.80 (d, $J = 8.14$ Hz, 2H, $CHCCHSO_3$), 7.40–7.22 (m, 7H, 1Ph+CH_3CHCCH), 5.34 (d, $J = 5.09$ Hz, 1H, COCH), 4.62 (d, $J = 5.09$ Hz, 1H, COCHOTsCH), 4.59 (m, $BnOCH_2CH$), 4.53 (d, $J = 11.69$ Hz, 1H, $PhCH_a$), 4.48 (d, $J = 11.69$ Hz, 1H, $PhCH_b$), 3.73 (t, $J = 2.03$ Hz, 2H, $BnOCH_2$), 2.56 (br, 1OH), 2.45 (s, 3H, CH_3Ph). ^{13}C NMR ($CDCl_3$): δ 169.27 (C=O), 145.88 (C_{ar}), 136.79 (C_{ar}), 131.56 (C_{ar}), 130.01 (C_{ar}), 128.62 (C_{ar}), 128.28 (C_{ar}), 127.97 (C_{ar}), 127.70 (C_{ar}), 83.61 ($BnOCH_2CH$), 74.30 (COCH), 73.85 ($PhCH_2$), 70.15 (COCHOTsCH), 68.86 ($BnOCH_2$), 21.70 (CH_3Ph). IR (film, cm^{-1}) 3508 (OH), 2924 (-CH_2-$_{asym}$), 2870 (-CH_2-$_{sym}$), 1797 (C=O), 1370 (-SO_3-). MS *m*/*z* 392 (M^+), 237 ($M^+-CH_3PhSO_2$), 220 ($C_{12}H_{12}O_4^+$), 155 ($CH_3PhSO_2^+$), 107 ($PhCH_2O^+$), 91 (tropyllium ion). Anal. calcd for $C_{19}H_{20}O_7S$: C, 58.15; H, 5.14; S, 8.17. Found: C, 58.01; H, 5.07; S, 8.05%.

3.4. (4*R*,5*S*)-(−)-5-Benzyloxymethyl-4-hydroxy-dihydro-furan-2-one 4

To a stirred solution of **3** (300 mg, 0.79 mmol) in THF (5 mL) at 0°C, hydrazine (80% aq. solution, 370 μl, 3.96

mmol, 5 equiv.) was added and the mixture stirred for 30 min at rt. The mixture was cooled to 0°C and Br_2 (304 μl, 5.92 mmol, 7.5 equiv.) was added dropwise until no more N_2 evolution was observed. The organic solvent was removed under vacuum and the remaining aqueous solution diluted with water (10 mL). The pH was adjusted to $\cong 7$ and the aqueous phase was extracted with dichloromethane (3×10 mL). Chromatographic purification on silica gel using as eluent *n*-hexane/AcOEt (1/1) yielded **4** as an oil (132 mg, 75%), R_f: 0.26 hexane/AcOEt (1/1). $[\alpha]_D^{20} = -5$ (*c* 1.4, $CHCl_3$). All spectroscopic data were consistent to those reported earlier (see Ref. 5).

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