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Convenient Synthesis of 4-C-Branched Lactones and 3'-C-Branched 2',3'-Dideoxynucleosides

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CONVENIENT SYNTHESIS OF 4-C-BRANCHED LACTONES AND 3'-C-BRANCHED 2',3'-DIDEOXYNUCLEOSIDES

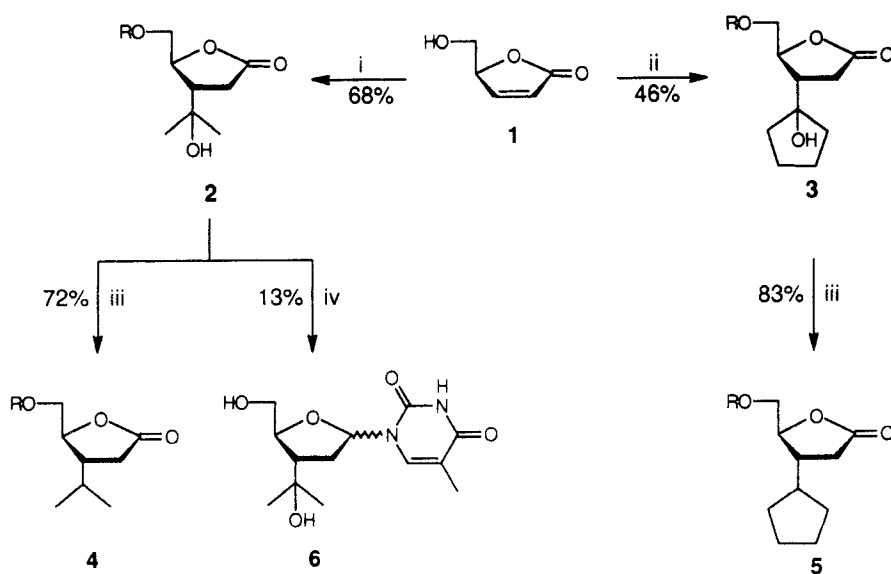
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Abstract: The regio- and stereoselective photocatalysed addition of 2-propanol and cyclopentanol to (5*S*)-hydroxymethylfuran-2(5*H*)-one (**1**) gave 4-*C*-branched lactones **2** and **3** after selective silylations. The lactones **2** and **3** were radically deoxygenated affording lactones **4** and **5**, respectively. As an example, compound **2** was transformed without purification of the intermediates into an anomeric mixtures of deprotected 3'-*C*-branched 2',3'-dideoxynucleosides **6** by the following reaction sequence: silylation, reduction, acetylation, coupling with silylated thymine and desilylation.

In the search of novel biologically active nucleoside^{1,2} and oligonucleotide³ analogues, we became interested in 3'-*C*-alkylated 2',3'-dideoxynucleosides. Recently, John Mann and co-workers⁴⁻⁷ have reported a photocatalysed method for stereo- and regioselective addition of alcohols to (5*S*)-hydroxymethylfuran-2(5*H*)-ones to give *erythro*-configured intermediates used for synthesis of *e.g.* 2',3'-dideoxy-3'-*C*-hydroxymethylnucleosides.⁶ Stimulated by this work, we here report synthesis of lactones **2** and **3** and their subsequent free radical deoxygenation to give lactones **4** and **5**, respectively. In addition, lactone **2** was converted into an anomeric mixture of the novel β-*D-erythro*-configured⁸ 3'-*C*-branched 2',3'-dideoxynucleoside analogue **6**. This conversion was achieved without column chromatographic purification of the intermediates. Thus, this method should enable straightforward synthesis of a large number of 3'-*C*-branched 2',3'-dideoxynucleosides to be biologically tested as anomeric mixtures.

The syntheses are outlined in the scheme. The key synthons (4*S*,5*S*)-5-(*tert*-butyldiphenylsilyl)oxymethyl-4-*C*-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one (**2**) and the



Scheme

Reagents: **i.** a) 2-propanol, benzophenone, irradiation, b) TBPSCl, imidazole, DMF; **ii.** a) cyclopentanol, benzophenone, irradiation, b) TBPSCl, imidazole, DMF; **iii.** a) DMAP, ClCOCO₂CH₃, CH₃CN, b) Bu₃SnH, AIBN, toluene; **iv.** a) ETSA, TBAF·3H₂O, b) DIBAL, toluene, c) Ac₂O, Et₃N, DMAP, d) silylated thymine, TMS-triflate, CH₃CN, e) TBAF, THF. R = TBDPS.

corresponding 4-*C*-(1-hydroxycyclopentyl)tetrahydrofuran-2-one **3** were prepared by irradiation of (5*S*)-hydroxymethylfuran-2(5*H*)-one (**1**) with 2-propanol⁹ and cyclopentanol, respectively, in the presence of benzophenone followed by selective protection of the primary hydroxyl by reaction with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF. In both cases, the reactions proceeded with complete regio- and stereoselectivity to give analytically pure **2** (68% yield) and **3** (46% yield) after column chromatographic purifications. The configuration of lactones **2** and **3** were confirmed by ¹H NOE NMR experiments to be *erythro* (4*S*,5*S*) in accordance with the results obtained earlier in similar reactions.⁴⁻⁷ Thus, mutual key NOE contacts were observed between H-5 and protons in the 4-*C*-substituent (the methyl protons in **2** and the cyclopentyl

protons in **3**). To evaluate the possibility of free radical deoxygenation of the 3-C-substituent *via* the corresponding methoxalylesters,¹⁰ **2** and **3** were treated with methoxalyl chloride and dimethylaminopyridine (DMAP). Subsequent free radical deoxygenation using tributyltin hydride in the presence of α,α' -azobisisobutyronitrile (AIBN) proceeded smoothly to give lactones **4** (72% yield) and **5** (83% yield).

Lactone **2** was transformed to the corresponding nucleoside derivative **6** without purification of the intermediates by the following reaction sequence: a) Trimethylsilyl protection of the tertiary hydroxyl by reaction with ethyl trimethylsilylacetate (ETSA) in the presence of tetrabutylammonium fluoride (TBAF);¹¹ b) Reduction of the protected lactones to the corresponding hemiacetals with diisobutylaluminium hydride (DIBAL) in anhydrous toluene;¹² c) Acetylation to give the anomeric acetates;¹² d) Condensation of the anomeric acetates with silylated thymine¹³ in anhydrous acetonitrile in the presence of trimethylsilyl trifluoromethanesulfonate (TMS-triflate)^{14,15} to give an anomeric mixture of protected nucleosides; e) Desilylation by reaction with TBAF in THF at room temperature. After column chromatographic purification, an anomeric mixture of unprotected 3'-C-branched 2',3'-dideoxynucleosides **6** ($\alpha:\beta \sim 1:1$ according to ¹³C NMR) was obtained in a yield of 13% (from lactone **2**). Although the non-optimised transformation of lactone **2** to nucleosides **6** was low-yielding, a sufficient amount of material for biological testing was obtained,¹⁶ and analogous reactions on lactones **3-5** should be possible.

In summary, an anomeric mixture of a novel 3'-C-branched 2',3'-dideoxynucleoside has been conveniently synthesised from α,β -unsaturated lactone **1** by photocatalysed stereoselective addition of 2-propanol followed by direct conversion of the addition product into the target nucleosides. Starting *e.g.* from lactones **2-5**, this reaction sequence should be applicable for rapid synthesis of a large number of 2',3'-dideoxynucleoside analogues for biological testing.

EXPERIMENTAL

The ¹³C and ¹H NMR spectra were recorded on a Bruker AC 250 FT spectrometer with TMS as internal standard. Mass spectra (MS) were recorded using Electron Ionization (EI) on a Varian Mat 311A spectrometer or Fast Atom Bombardment (FAB)

on a Kratos MS 50 RF spectrometer. Analytical TLC was performed on precoated TLC sheets (Merck silica gel 60 F₂₅₄ 0.2 mm). The silica gel (0.040 - 0.063 mm) used for column chromatography was purchased from Merck.

(4S,5S)-5-(tert-Butyldiphenylsilyl)oxymethyl-4-C-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one (2). Lactone **1** (1.5 g, 13.1 mmol) was dissolved in 2-propanol (100 ml) and the solution was placed in a Pyrex vessel. Benzophenone (100 mg, 0.5 mmol) was added and the mixture was degassed by N₂ for 1 h. The solution was irradiated by a medium-pressure mercury 125 W lamp for 18 h. The solvent was removed *in vacuo*. The ¹H and ¹³C NMR data of the crude intermediate (4S,5S)-5-hydroxymethyl-4-C-(1-hydroxy-1-methylethyl)tetrahydrofuran-2-one were identical with those previously reported.⁶ The crude photoadduct was dissolved in anhydrous DMF (75 ml), and imidazole (7.7 g, 113 mmol) and *tert*-butyldiphenylsilyl chloride (TBDPSCl, 4.0 ml, 15.4 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, diluted with CH₂Cl₂ (150 ml), washed successively with an ice cold aqueous solution of 2 M HCl (3 x 50 ml) and water (50 ml), dried (Na₂SO₄) and evaporated *in vacuo*. Purification by silica gel column chromatography (0-1.5 % MeOH in CH₂Cl₂, v/v) afforded compound **2** as a clear oil (3.7 g, 68% yield). Anal. calcd. for C₂₄H₃₂O₄Si: C 69.87; H 7.82; Found: C 70.21; H 7.82. EI MS *m/z* (%): 413 (4, M⁺). ¹H NMR (CDCl₃, 250 MHz): δ 1.06 (9H, s, C(CH₃)₃), 1.16 (3H, s, CH₃), 1.17 (3H, s, CH₃), 2.40-2.51 (2H, m, H-3a, H-4), 2.74 (1H, dd, J = 11.4, 19.1 Hz, H-3b), 3.67 (1H, dd, J = 2.9, 11.4 Hz, H-6a), 3.93 (1H, dd, J = 3.1, 11.3 Hz, H-6b), 4.57 (1H, m, H-5), 7.25-7.68 (10H, m, Ar). ¹³C NMR (CDCl₃, 62.9 MHz): δ 19.16 (C(CH₃)₃), 26.36 (CH₃), 26.79 (C(CH₃)₃), 27.72 (CH₃), 31.23 (C-4), 46.77 (C-3), 65.93 (C-6), 70.97 (C-OH), 81.26 (C-5), 127.88, 129.93, 132.47, 132.94, 135.54, 135.65 (Ar), 176.94 (C=O).

(4S,5S)-5-(tert-Butyldiphenylsilyl)oxymethyl-4-C-(1-hydroxycyclopentyl)tetrahydrofuran-2-one (3). The same procedure as described for preparation of **2** was used. Amounts: Lactone **1** (2.0 g, 17.5 mmol), cyclopentanol (100 ml), benzophenone (100 mg, 0.55 mmol), anhydrous DMF (100 ml), imidazole (10.9 g, 160 mmol) and TBDPSCl (5.7 ml, 21.9 mmol). Reaction times: Photoaddition 24 h; silylation 13 h. Purification by silica gel column chromatography (0-0.5 % MeOH in CH₂Cl₂, v/v)

afforded compound **3** as a clear oil (3.7 g, 46%). Anal. calcd. for $C_{26}H_{34}O_4Si \cdot H_2O$: C 68.39; H 7.95; Found: C 68.71; H 7.67. 1H NMR ($CDCl_3$, 250 MHz): δ 1.07 (9H, s, $C(CH_3)_3$), 1.44-1.83 (8H, m, cyclopentyl), 2.47-2.64 (2H, m, H-3a, H-4), 2.74 (1H, dd, J = 11.7, 19.3 Hz, H-3b), 3.69 (1H, dd, J = 3.2, 11.3 Hz, H-6a), 3.94 (1H, dd, J = 3.2, 11.4 Hz, H-6b), 4.56 (1H, m, H-5), 7.26-7.68 (10H, m, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 19.20 ($C(CH_3)_3$), 23.57, 23.83 (cyclopentyl), 26.84 ($C(CH_3)_3$), 31.54 (C-4), 38.08, 38.29 (cyclopentyl), 45.30 (C-3), 65.64 (C-6), 82.11, 82.70 (C-OH, C-5), 127.86, 129.94, 132.57, 133.03, 135.57, 135.69 (Ar), 177.29 (C=O).

(4S,5S)-5-(tert-Butyldiphenylsilyl)oxymethyl-4-C-(1-methylethyl)tetrahydrofuran-2-one (4). To compound **2** (518 mg, 1.26 mmol) dissolved in anhydrous CH_3CN (10 ml) was added dimethylaminopyridine (DMAP, 336 mg, 2.75 mmol) and methoxalyl chloride (0.25 ml, 2.7 mmol). After stirring at r.t. for 1.5 h, the mixture was diluted with EtOAc (25 ml), washed successively with a saturated aqueous solution of $NaHCO_3$ (15 ml), water (15 ml) and brine (15 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was dried by coevaporation with anhydrous toluene (2 x 5 ml) and the residue was dissolved in anhydrous toluene (15 ml). α,α' -Azobisisobutyronitrile (AIBN, 21 mg, 0.13 mmol) and Bu_3SnH (0.60 ml, 2.2 mmol) were added and the reaction mixture was refluxed for 3.5 h. After cooling to r.t., the mixture was evaporated *in vacuo* and the residue was purified on a silica gel column (20-30 % EtOAc in petroleum ether, v/v) to afford compound **4** as a clear oil (360 mg, 72% yield). Anal. calcd. for $C_{24}H_{32}O_3Si$: C 72.68; H 8.13; Found: C 72.88; H 8.24. EI MS m/z (%): 396 (100, M^+). 1H NMR ($CDCl_3$, 250 MHz): δ 0.87-0.91 (6H, m, 2 x CH_3), 1.06 (9H, s, $C(CH_3)_3$), 1.61-1.76 (1H, m, $(CH_3)_2CH$), 2.24-2.36 (2H, m, H-3a, H-4), 2.72 (1H, dd, J = 11.2, 19.2 Hz, H-3b), 3.65 (1H, dd, J = 3.4, 11.4 Hz, H-6a), 3.89 (1H, dd, J = 3.1, 11.2 Hz, H-6b), 4.31 (1H, m, H-5), 7.25-7.68 (10H, m, Ar). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 19.02, 19.17, 19.59 ($C(CH_3)_3$, 2 x CH_3), 26.77 ($C(CH_3)_3$), 30.93, 32.19 ($C(CH_3)_2$, C-4), 42.27 (C-3), 65.54 (C-6), 83.15 (C-5), 127.81, 129.88, 132.60, 133.00, 135.54, 135.64 (Ar), 177.02 (C=O).

(4S,5S)-5-(tert-Butyldiphenylsilyl)oxymethyl-4-C-(cyclopentyl)tetrahydrofuran-2-one (5). The same procedure as described for preparation of **4** was used. Amounts:

Compound **3** (1.09 g, 2.4 mmol), anhydrous CH_3CN (20 ml), DMAP (610 mg, 5.0 mmol), methoxalyl chloride (0.35 ml, 3.8 mmol), EtOAc (50 ml), anhydrous toluene (25 ml), AIBN (33 mg, 0.20 mmol) and Bu_3SnH (0.95 ml, 3.5 mmol). Reaction times: acylation 2.5 h; deoxygenation 20 h. After purification on a silica gel column (20 % EtOAc in petroleum ether, v/v), compound **5** was obtained as a clear oil (842 mg, 83%). Anal. calcd. for $\text{C}_{26}\text{H}_{34}\text{O}_3\text{Si}$: C 73.89; H 8.11; Found: C 73.68; H 7.95. FAB MS (CHCl_3 , 3-nitrobenzyl alcohol m/z (%): 423 (35, $\text{M}+\text{H}^+$). ^1H NMR (CDCl_3 , 250 MHz): δ 1.06 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.52-1.88 (8H, m, cyclopentyl), 2.24-2.40 (2H, m, H-3a, H-4), 2.76 (1H, dd, $J = 8.6, 17.0$ Hz, H-3b), 3.66 (1H, dd, $J = 3.5, 11.5$ Hz, H-6a), 3.86 (1H, dd, $J = 3.2, 11.4$ Hz, H-6b), 4.29 (1H, m, H-5), 7.25-7.68 (10H, m, Ar). ^{13}C NMR (CDCl_3 , 62.9 MHz): δ 19.10 ($\text{C}(\text{CH}_3)_3$), 24.82 (cyclopentyl), 26.69 ($\text{C}(\text{CH}_3)_3$), 31.54 (C-4), 30.24, 30.29 (cyclopentyl), 33.83 (C-3), 41.14, 43.55 (cyclopentyl, C-4), 65.14 (C-6), 84.50 (C-5), 127.72, 129.79, 132.55, 132.94, 135.47, 135.57 (Ar), 176.89 (C=O).

1-(2,3-Dideoxy-3-C-(1-hydroxy-1-methylethyl)- α,β -D-erythro-pentofuranosyl)thymine (6). To a stirred solution of compound **2** (865 mg, 2.1 mmol) in anhydrous THF (5 ml) was added TBAF·3 H_2O (13 mg, 0.04 mmol) and ethyl trimethylsilylacetate (ETSA, 0.90 ml, 4.9 mmol). After 1 h, the reaction mixture was diluted with petroleum ether (5 ml), washed successively with a saturated aqueous solution of NaHCO_3 (3 x 5 ml) and water (5 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The resulting crude yellow oil was dissolved in anhydrous toluene (40 ml), cooled to -78°C and DIBAL (1.5 M solution in toluene, 1.45 ml, 2.2 mmol) was added during 1 h. Additional DIBAL (0.50 ml, 0.75 mmol) was added and the reaction mixture was stirred for 5 h. The reaction was quenched with CH_3OH (0.5 ml) and the temperature was allowed to rise (to r.t.). A saturated aqueous solution of NaHCO_3 (3 ml) was added and the mixture was stirred for 1 h. Powdered Na_2SO_4 (15 g) was added and the mixture was stirred for 2 h. The solid was filtered off and washed with EtOAc and the filtrate was concentrated *in vacuo*. The crude product was redissolved in CH_2Cl_2 (5 ml), Ac_2O (0.40 ml, 4.2 mmol), Et_3N (0.55 ml, 3.9 mmol) and a catalytical amount of DMAP were added and stirring was continued for 8 h. The reaction mixture was diluted with CH_2Cl_2 (8 ml) and washed successively with water (5 ml), brine (5 ml) and water (5 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the crude product was dried by coevaporation with

anhydrous CH_3CN (2 x 5 ml) and redissolved in CH_3CN (5 ml). The mixture was added to a solution of bis(trimethylsilyl)thymine¹³ (610 mg, 2.50 mmol) in CH_3CN (5 ml) and the mixture was cooled to $-30\text{ }^\circ\text{C}$ and TMS-triflate (0.2 ml, 1.0 mmol) was added dropwise during 15 min. After stirring for 15 min, the reaction mixture was diluted with EtOAc (10 ml), washed successively with a saturated aqueous solution of NaHCO_3 (2 x 10 ml) and water (10 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Deprotection of the crude nucleosides was done by adding a 1.1 M solution of TBAF in THF (2.4 ml, 2.6 mmol) to a stirred solution of the nucleosides in anhydrous THF (10 ml). After 18 h, the solvent was removed *in vacuo* and the residue was purified on a silica gel column (1-7 % CH_3OH in CH_2Cl_2 , v/v) to give the anomeric mixture **6** (26 mg, 13% yield). ^1H NMR (CD_3OD , 250 MHz): δ 1.38 (s, CH_3), 1.47 (s, CH_3), 1.55 (s, CH_3), 1.59 (s, CH_3), 2.03 (d, $J = 1.0$ Hz, CH_3), 2.04 (d, $J = 1.0$ Hz, CH_3), 2.20-2.44 (m, H-2', H-3'), 2.55-2.84 (m, H-2'), 3.34-3.65 (m, H-5'), 3.75-3.81 (m, H-4'), 3.86-3.93 (m, H-4'), 6.15-6.21 (m, H-1'), 7.59 (d, $J = 1.1$ Hz, H-6), 7.82 (d, $J = 1.1$ Hz, H-6). ^{13}C NMR (CD_3OD , 62.9 MHz): δ 12.82, 14.20 (CH_3), 23.78, 25.07 (CH_3), 28.80, 29.95 (C-2'), 33.81, 35.32 (C-3'), 66.72, 66.83 (C-5'), 71.54, 71.67 (C-3''), 85.13, 85.31, 85.51, 85.78 (C-1', C-4'), 111.37, 111.47 (C-5), 137.88, 138.27 (C-6), 152.62, 152.78 (C-2), 166.72 (2xC-4).

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