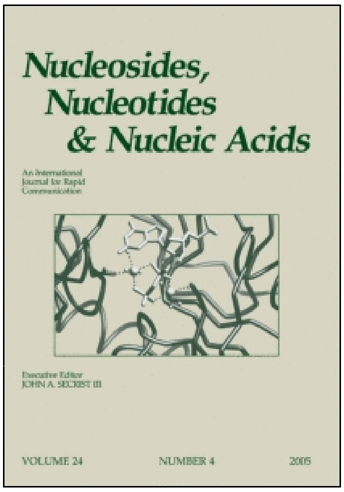


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Jesper Wengel[a]; Kirsten Østergaard[a]; Anders Hager[a]
[a] Department of Chemistry, Odense University, Odense M, Denmark

To cite this Article Wengel, Jesper , Østergaard, Kirsten and Hager, Anders(1996) 'Convenient Synthesis of 4-*C*-Branched Lactones and 3'-*C*-Branched 2',3'-Dideoxynucleosides', Nucleosides, Nucleotides and Nucleic Acids, 15: 7, 1361 — 1368
To link to this Article: DOI: 10.1080/07328319608002436
URL: http://dx.doi.org/10.1080/07328319608002436

NUCLEOSIDES & NUCLEOTIDES, 15(7&8), 1361-1368 (1996)

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

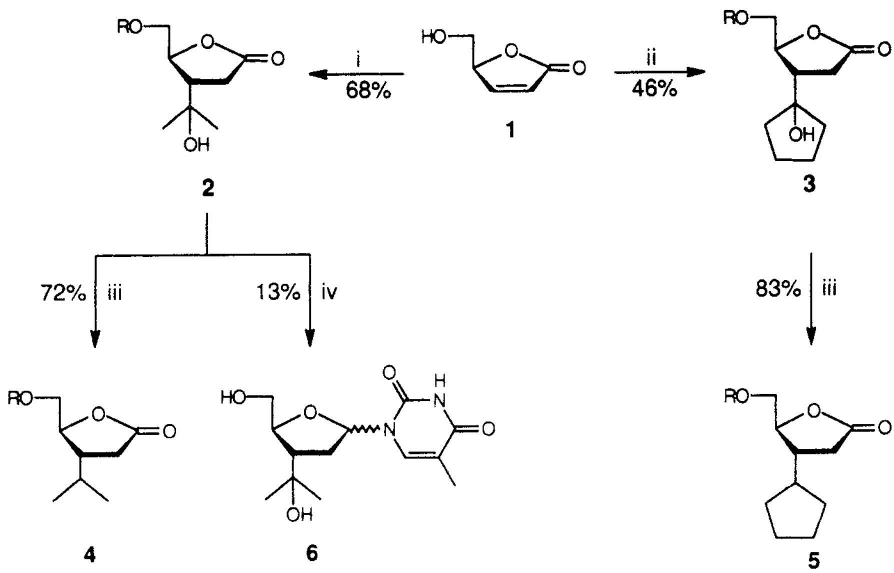
Jesper Wengel,* Kirsten Østergaard and Anders Hager

Department of Chemistry, Odense University, DK-5230 Odense M, Denmark

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 oligonucleotide[3] analogues, we became interested in 3'-*C*-alkylated 2',3'-dideoxynucleosides. Recently, John Mann and co-workers[4-7] have reported a photocatalysed method for stereo- and regioselective addition of alcohols to (5*S*)-hydroxymethylfuran-2(5*H*)-ones to give *erythro*-configurated 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*-configurated[8] 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, $ClCOCO_2CH_3$, CH_3CN, b) Bu_3SnH, AIBN, toluene; **iv**. a) ETSA, TBAF·$3H_2O$, b) DIBAL, toluene, c) Ac_2O, Et_3N, DMAP, d) silylated thymine, TMS-triflate, CH_3CN, 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-propanol[9] 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 ^{1}H 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 thymine[13] 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** (α:β ~ 1:1 according to ^{13}C 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 ^{13}C and ^{1}H 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 F_{254} 0.2 mm). The silica gel (0.040 - 0.063 mm) used for column chromatography was purchased from Merck.

(4*S*,5*S*)-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 N_2 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 ^{1}H and ^{13}C NMR data of the crude intermediate (4*S*,5*S*)-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 CH_2Cl_2 (150 ml), washed successively with an ice cold aqueous solution of 2 M HCl (3 x 50 ml) and water (50 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by silica gel column chromatography (0-1.5 % MeOH in CH_2Cl_2, v/v) afforded compound **2** as a clear oil (3.7 g, 68% yield). Anal. calcd. for $C_{24}H_{32}O_4Si$: C 69.87; H 7.82; Found: C 70.21; H 7.82. EI MS *m/z* (%): 413 (4, M^+). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.06 (9H, s, $C(CH_3)_3$), 1.16 (3H, s, CH_3), 1.17 (3H, s, CH_3), 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). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 19.16 ($C(CH_3)_3$), 26.36 (CH_3), 26.79 ($C(CH_3)_3$), 27.72 (CH_3), 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).

(4*S*,5*S*)-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 CH_2Cl_2, 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. ^{1}H 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 ($C(\mathit{C}H_3)_3$), 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).

(4*S*,5*S*)-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^+). ^{1}H 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, $(CH_3)_2C\mathit{H}$), 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 ($C(\mathit{C}H_3)_3$), 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).

(4*S*,5*S*)-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 $C_{26}H_{34}O_3Si$: C 73.89; H 8.11; Found: C 73.68; H 7.95. FAB MS ($CHCl_3$, 3-nitrobenzyl alcohol) *m/z* (%): 423 (35, $M+H^+$). ^1H NMR ($CDCl_3$, 250 MHz): δ 1.06 (9H, s, $C(CH_3)_3$), 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 ($\mathit{C}(CH_3)_3$), 24.82 (cyclopentyl), 26.69 ($C(\mathit{C}H_3)_3$), 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)thymine[13] (610 mg, 2.50 mmol) in CH_3CN (5 ml) and the mixture was cooled to -30 °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).

REFERENCES

1. The naturally occurring nucleoside oxetanocin A exhibits promising anti-HIV activity. Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077.
2. 2',3'-Dideoxy-3'-*C*-hydroxymethyl nucleosides have shown anti-HIV activity. See *e.g.*: Svansson, L.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993 (cytosine derivative); Tseng, C. K.-H.; Marquez, V. E.; Milne, G. W. A.; Wysocki, Jr., R. J.; Mitsuya, H.; Shirasaki, T.; Driscoll, J. S. *J. Med. Chem.* **1991**, *34*, 343 (adenine derivative).
3. For a report describing oligonucleotide analogues containing dephospho inter-nucleoside linkages: De Mesmaeker, A.; Häner, R.; Martin, P.; Moser, H. E. *Acc. Chem. Res.* **1995**, *28*, 366.
4. Mann, J.; Weymouth-Wilson, A. C. *Carbohydr. Res.* **1991**, *216*, 511.
5. Mann, J.; Weymouth-Wilson, A. C. *Synlett* **1992**, 67.
6. Mann, J.; Weymouth-Wilson, A. C. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3141.

7. Brown, D.; Cardin, C. J.; Mann, J. *J. Chem. Soc. Chem. Commun.* **1995**, 825.
8. Only a few β-D-*threo*-configurated 2',3'-dideoxynucleosides have been reported to exhibit anti-HIV activity: Tronchet, J. M. J.; Zsély, M.; Capek, K.; Komaromi, I.; Geoffroy, M.; De Clercq, E.; Balzarini, J. *Nucleosides Nucleotides* **1994**, *13*, 1871.
9. Addition of 2-propanol and isolation of the intermediate photoadduct without immediate silylation has been reported earlier.[6]
10. This deoxygenation method has been reported earlier. Dolan, S. C.; MacMillan, J. *J. Chem. Soc. Chem. Commun.* **1985**, 1588; Kakefuda, A.; Yoshimura, Y.; Sasaki, T.; Matsuda, A. *Tetrahedron* **1993**, *49*, 8513.
11. Silylation was performed by a method described earlier. Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 805.
12. These reactions were performed by methods described earlier. Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780.
13. Wittenburg, E. *Z. Chem.* **1964**, *1*, 303.
14. Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654.
15. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.
16. When the main purpose is biological testing, evaluation of novel nucleosides as anomeric mixtures is a rational approach.

Received January 12, 1996
Accepted April 10, 1996