Synthesis of a Central Intermediate in the Biosynthesis of Di- and Trideoxysugars☆

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The synthesis of disodium (6-deoxy-α-D-*ribo*-hexopyran-3-ulosyl) (2′-deoxythymidin-5′-yl) diphosphate (**1**) is described. To this end, D-glucose is transformed into known furanose derivative **2** possessing a 3-*C*-methylene group as latent functionality for 3-ulose generation. From **2**, 3,6-dideoxy derivative **6** was synthesized; ensuing acid catalyzed cleavage of the 1,2-*O*-isopropylidene group and then *O*-acetylation furnished the required pyranose **8α,β**, which could be selectively deacetylated at the anomeric oxygen to afford **9α,β**. Treatment with phosphitylating agent **13e** and then oxidation led to dibenzylphosphate derivative **15e** which could be chemoselectively debenzylated by hydrogenolysis without affecting the olefinic double bond (→ **17**); de-*O*-acetylation and then ozonolysis afforded the unprotected phosphate intermediates **18** and **19**, respectively. Both compounds could be successfully used for the synthesis of **1** by employing the nucleoside phosphate morpholidate procedure for the generation of nucleoside diphosphate sugars. Ozone cleavage of the olefinic double bond in **20** could be successfully performed even in the presence of the thymine moiety.

Many antibiotics contain deoxy-, aminodeoxy, and *C*-branched deoxysugar units; elucidation of their biosynthesis is still under investigation[1][2]. An important first intermediate in the biosynthetic pathway is dTDP-6-deoxy-D-*xylo*-4-hexulose (Scheme 1, **B**; instead of dTDP also the corresponding CDP intermediate is found), which is generated from dTDP-glucose (**A**, dTDP-Glc) with the help of an NAD-dependent dTDP-glucose-4,6-dehydratase (e.g. from *E. coli*); **B** is a direct precursor of the commonly occurring 6-deoxysugars[1][2][3][4]. From **B** in a pyridoxamine/pyridoxal phosphate mediated enzymatic reaction also 3,6-dideoxysugars and derivatives are accessible. For the biosynthesis of 2,6- and 4,6-dideoxysugars an isomerase apparently converts **B** into the corresponding dTDP-6-deoxy-D-*ribo*-3-hexulose **C**, which serves as the next key intermediate for the preparation of the important dideoxy-, trideoxy, aminodeoxy, and *C*-branched sugars[2][3][4][5]; the presence of **C** in equilibrium with **B** has been recently claimed[4]. For the establishment of the biosynthesis of di- and trideoxy sugars (e.g. with 4,6-dehydratase- or isomerase-deficient mutants)[2] the availability of **C** is very important. Yet, the synthesis of **C** is particularly difficult due to the hydrolytic instability of nucleoside diphosphates of deoxysugars[6] and the tendency of 3-ulosides to undergo β-elimination of the nucleoside diphosphate group[7]. We report here the details of the synthesis of **C** as disodium salt (= compound **1**)[8][9]; the synthesis is based on removal of all protecting groups (in the penultimate or last reaction step) and introduction of the 3-oxo function by ozonolysis of the corresponding methylene group, in order to avoid β-elimination during the various chemical transformation.

For the introduction of a methylene group at C-3 and deoxygenation at C-6, D-glucose was converted into 1,2:5,6-di-*O*-isopropylidene-3-methylene derivative **2** (Scheme 2) employing published procedures[10]; selective cleavage of the 5,6-*O*-isopropylidene group with 50% acetic acid (→ **3**) and subsequent regioselective 6-*O*-tosylation with one equivalent of tosyl chloride in pyridine afforded mainly desired **4** together with some di-*O*-tosyl derivative **5** (**4**/**5** ≈ 9:1) which could be readily separated. The structures of compounds **3** and **4** could be confirmed based on the NMR data of the corresponding 5,6-di-*O*-trichloroacetylcarbamoyl **3a** and 5-*O*-trichloroacetyl carbamoyl derivative **4a**, respectively. The 6-deoxy compound **6** was obtained from **4** in 83% yield by reaction with $LiAlH_4$ in ether at room temperature. Treatment of **6** with 80% acetic acid at 60 °C resulted in cleavage of the isopropylidene group (→ **7α,β**); Subsequent acetylation with acetic anhydride in pyridine afforded the anomeric tri-*O*-acetyl derivatives **8α** and **8β** which were separated in order to get unequivocal structural assignments. Treatment of **8α,β** with hydrazinium acetate[11] in DMF at 40 °C resulted in 1-*O*-unprotected pyranose derivatives **9α,β** in high overall yield.

For exploratory studies on the stability of the desired intermediates, ozonolysis[12] of **8β** in dichloromethane/methanol at −78 °C was performed furnishing 3-uloside **10β** in practically quantitative yield. Surprisingly, also regioselective removal of the anomeric *O*-acetyl group was possible by treatment with hydrazinium acetate in DMF at 40 °C affording 1-*O*-unprotected-3-ulose **11α,β** (α,β-mixture) in good yield; the same compound was accessible from **9α,β** by the standard ozonolysis procedure. Yet, the attempts to

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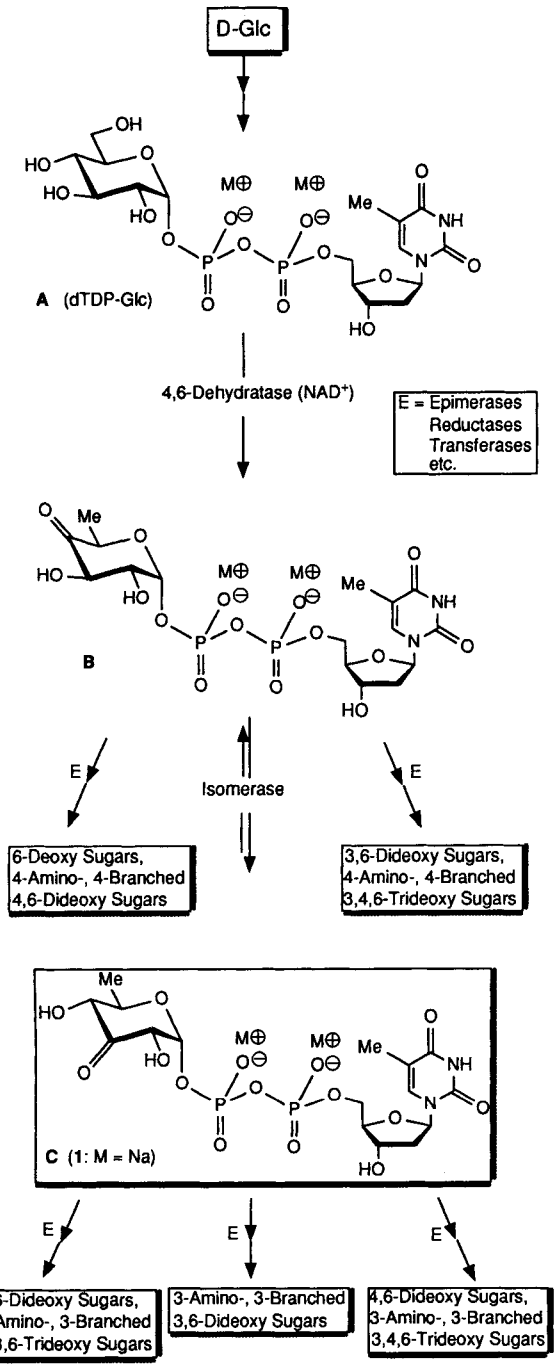
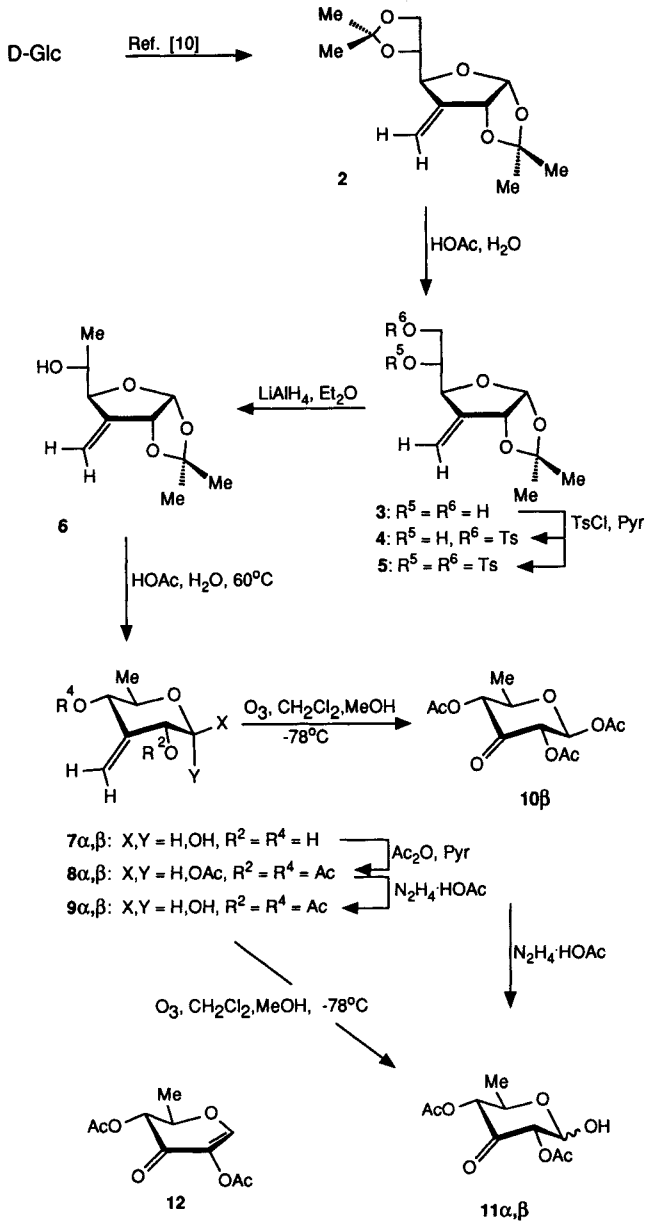
Scheme 1



Scheme 2



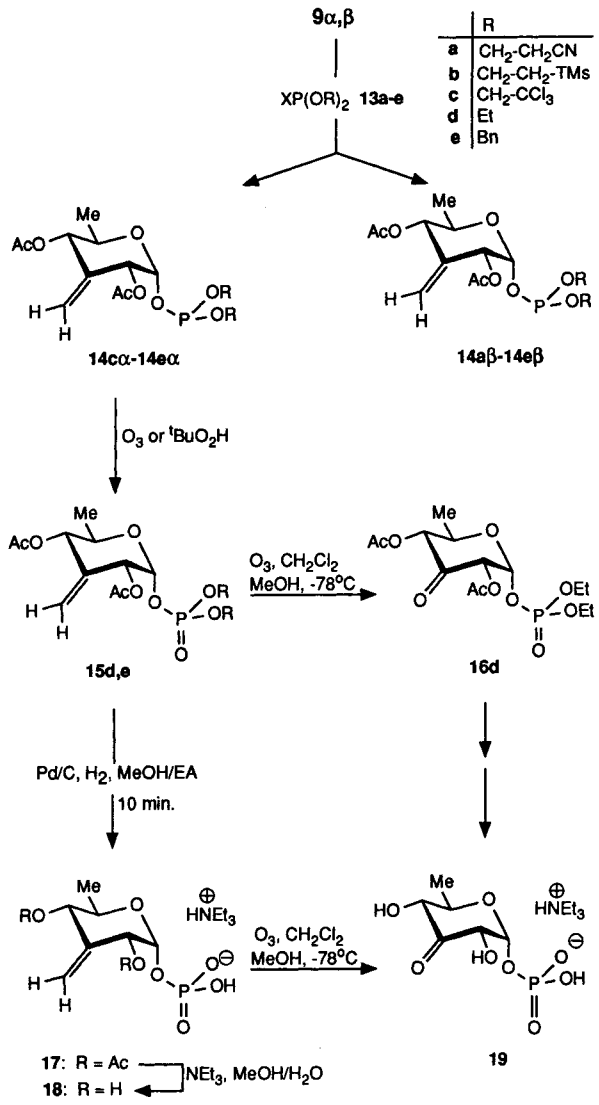
phosphitylate **11**, in order to synthesize finally phosphate derivatives, were not successful; application of typical phosphitylation procedures[13] did either not lead to any reaction or – not unexpectedly – elimination product **12** was formed. Therefore, as outlined above, 3-methylene intermediate **9** was employed for the excecution of the synthesis of target molecule **1**.

Phosphitylation of **9** was investigated with various reagents (Scheme 3, **13a–e**; X = Cl or iPr_2N) because, after oxidation to the corresponding phosphates, mild hydrolysis to the desired *O*-unprotected phosphates was desirable. Reaction of **9** with the phosphitylation reagents **13a**[14] and **13b**[15] (X = diisopropylamino) in dichloromethane/acetonitrile in the presence of tetrazole as catalyst afforded exclusively the undesired β-phosphites **14aβ** and **14bβ**, repsectively; the structures were assigned with the help of their NMR data[16]. With **9** and bis(trichloroethoxy)phosphorochloridite **13c** as phosphitylating agent[17] in the presence of Hünig's base a separable 1:1 mixture of the anomers **14cα** and **14cβ** was obtained. Yet, oxidation of **14c** with ozone, in order to get the corresponding phosphate, led partly to ozonolysis of the methylene group and partly to cleavage of the glycosidic bond; the latter reaction was also observed for attempts to oxidize the phosphite moiety with either *tert*-butyl hydroperoxide or with *m*-chloroperbenzoic acid (MCPBA). Obviously, less electron-withdrawing substituents at the phosphite moiety were required: in order to increase the nucleophilicity of the phosphorous atom.

Therefore, from **9** and diethylphosphorochloridite **13d**[18] in the presence of Hünig's base diethyl phosphite **14d** was prepared, furnishing a 1:1 mixture of the anomers **14dα** and **14dβ** which was separated by flash chromatography. As expected, ozone oxidation of **14dα** under controlled conditions afforded cleanly the diethyl phosphate **15d**; however, continuation of the ozonisation led also to quantitative cleavage of the methylene group, thus providing 3-ulose phosphate **16d**; this compound could be also directly obtained from **14dα** without the isolation of **15d**. Yet, attempts to cleave the *O*-ethyl and *O*-acetyl groups in **16d** led again to elimination (→ **12**) and/or cleavage of the glycosidic bond (→ **9**). However, these reactions exhibited that benzyl phosphates would be appropriate intermediates for obtaining the target molecule if hydrogenolytic *O*-debenzylation is fast compared to hydrogenation of the olefin moiety. Therefore, from **9** and di-*O*-benzyldiisopropylaminophosphitamide[14] (**13e**) in the presence of tetrazole dibenzylphosphite **14e** was synthesized, furnishing again a 1:1 mixture of the anomers **14eα** and **14eβ** (total yield 80%) which could be separated by flash chromatography. Oxidation of **14eα** with *tert*-butyl hydroperoxide in dichloromethane furnished the dibenzyl phosphate **15e** in 94% yield. Controlled hydrogenolysis of **15e** in the presence of palladium on carbon as catalyst in methanol/ethyl acetate (EA) as solvents for 10 minutes led to chemoselective *O*-debenzylation affording the desired unprotected phosphate **17** in 88% yield. Due to the presence of the negative charge at the phosphate moiety, **17** could be readily *O*-deacetylated by treatment with methanol/water in the presence of triethylamine as base, thus providing the desired unprotected 3,6-dideoxy-3-*C*-methylene-D-*ribo*-hexopyranosyl phosphate (**18**) as triethylammonium salt in high overall yield. The 3-ulose phosphate **19** was obtained from **18** in almost quantitative yield by direct ozonolysis under standard conditions. The structural assignments of compounds **17**–**19** was based on their NMR and FAB-MS data (1-H; **17**: δ = 5.38, dd, $J_{1,2}$ = 3.6, $J_{1,P}$ = 7.3 Hz; **18**: δ = 5.24, dd, $J_{1,2}$ = 3.7, $J_{1,P}$ = 6.5 Hz; **19**: δ = 5.58, dd, $J_{1,2}$ = 4.3, $J_{1,P}$ = 6.7 Hz).

Two routes were used for the synthesis of target molecule **1** (Scheme 4). First the thymidine diphosphate derivative **20** was prepared from **18** using thymidine phosphomorpholidate[19] in pyridine and 4-Å molecular sieves; **20** was obtained in 51% yield by preparative HPLC (5% CH_3CN in 0.5 M $HNEt_3^+$ HCO_3^-) as the bis(triethylammonium) salt; as expected, it was stable at pH = 8. This compound is of interest for biological studies as the methylene analogue of **1**. In order to obtain target molecule **1**, a methanolic solution of **20** at −78 °C was mixed with a dichloromethane solution saturated with ozone at −78 °C, and the reaction mixture was separated by subsequent reversed-phase HPLC on RP-18 (3% CH_3CN in 0.5 M $HNEt_3^+$ HCO_3^-); ensuing lyophilization gave **1** in 22% yield as the bistriethylammonium salt along with recovered starting material. Due to low hydrolytic stability of this salt (half-life ca. 1 h at pH = 7), the disodium salt of **1** was obtained by ion exchange (Amberlite IR-120, Na^+ form), which, as expected[20], was much more stable. Surprisingly, a higher overall yield was obtained for the synthesis of **1** from **18** by changing the sequence of the reaction steps. Transformation of **18** into 3-ulose **19** (Scheme 3) led, in spite of the greater instability of **19** compared with **18**, with thymidine phosphomorpholidate and ensuing purification as described above, to **1** in 30% yield. Target molecule **1** was thus obtained in pure form (40 mg) and its structure was confirmed by NMR (^1H, ^{13}C, ^{31}P) and FAB-MS data.

Scheme 3



In conclusion, the synthetic strategy presented here is apparently variable and suitable for the generation of various interesting nucleosidediphosphate derivatives of deoxysugars[21], which occur as intermediates in their biosynthesis. Therefore, this methodology should make an important contribution to the elucidation of the various biosynthetic pathways employed by nature for deoxysugar production.

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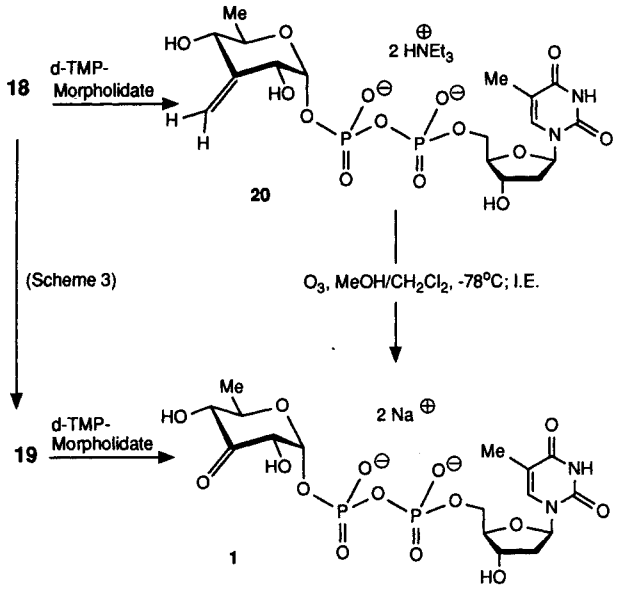
Scheme 4



Experimental Section

Solvents were purified in the usual way. – ^{1}H NMR spectra: Bruker AC-250 (250 MHz); internal standard tetramethylsilane (TMS). – Flash chromatography: Silica gel 60 (Baker: 0.04–0.063 mm). – Thin-layer chromatography (TLC): Foil plates, silica gel 60 F_{254} (Merck: layer thickness 0.2 mm). Preparative HPLC: RP 18, 250 × 16 mm (Knauer, Eurospher 100 C 18.7 mm). – Optical roations: Perkin-Elmer polarimeter 241 MC; 1-dm cell, temp. 20 °C. – Elemental analyses: Heraeus CHN-O-Rapid.

3-Deoxy-1,2-O-isopropylidene-3-C-methylene-α-D-ribo-hexofuranose (**3**): Compound **2**[10] (10 g, 39 mmol) was dissolved in acetic acid (50%, 100 ml) and stirred at room temperature for 2 d. The clear solution was neutralized with satd. sodium hydrogen carbonate solution, extracted with dichloromethane (4 × 400 ml) and the combined organic extracts were dried with magnesium sulfate. Concentration in vacuo yielded a yellowish residue, which was purified by flash chromatography (petroleum ether/ethyl acetate, 1:5) to yield 6.23 g (74%) of **3** as a colorless syrup. – TLC (petroleum ether/ethyl acetate, 1:5): R_f = 0.30, – $[\alpha]_D^{20}$ = +118.5 (*c* = 1, chloroform, ref.[22] $[\alpha]_D$ = +122). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35, 1.47 [2 s, 6 H, $C(CH_3)_2$], 2.62 (m, 1 H, OH), 3.00 (m, 1 H, OH), 3.68–3.70 (m, 3 H, 5-, 6A-, 6B-H), 4.73 (m, 1 H, 4-H), 4.88 (dd, $J_{1,2}$ = 4.1 Hz, 1 H, 2-H), 5.39–5.46 (m, 2 H, $=CH_2$), 5.79 (d, $J_{1,2}$ = 4.1 Hz, 1 H, 1-H). – $C_{10}H_{16}O_5$ 0.125 H_2O (218.48): calcd. C 54.97, H 7.50; found C 55.08, H 7.52.

3-Deoxy-1,2-O-isopropylidene-3-C-methylene-5,6-di-O-trichloroacetylcarbamoyl-α-D-ribo-hexofuranose (**3a**): To a solution of compound **3** (20 mg, 0.09 mmol) in deuteriochloroform (0.5 ml) was added trichloroacetyl isocyanate (1 drop). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35, 1.47 [2 s, 6 H, $C(CH_3)_2$], 4.40 (dd, $J_{5,6A}$ = 7.7, $J_{6A,6B}$ = 12.3 Hz, 1 H, 6A-H), 4.52 (dd, $J_{5,6B}$ = 2.7, $J_{6A,6B}$ = 12.3 Hz, 1 H, 6B-H), 4.93 (dd, $J_{1,2}$ = 4.0, *J* = 0.8 Hz, 1 H, 2-H), 4.99–5.01 (m, 1 H, 4-H), 5.32 (ddd, $J_{4,5}$ = 3.2, $J_{5,6A}$ = 7.7, $J_{5,6B}$ = 2.7 Hz, 1 H, 5-H), 5.38–5.59 (m, 2 H, $=CH_2$), 5.82 (d, $J_{1,2}$ = 4.0 Hz, 1 H, 1-H), 8.46, 8.58 (2 s, 2 H, 2 CON*H*).

3-Deoxy-1,2-isopropylidene-3-C-methylene-6-O-tolylsulfonyl-α-D-ribo-hexofuranose (**4**) *and 3-Deoxy-1,2-O-isopropylidene-3-C-methylene-5,6-di-O-tolylsulfonyl-α-D-ribo-hexofuranose* (**5**): To a solution of **3** (2 g, 9.25 mmol) in dry dichloromethane (60 ml) and dry pyridine (12 ml) was added *p*-toluenesulfonyl chloride (1.94 g, 10.02 mmol) at –10 °C over a period of 30 min. The reaction mixture was allowed to stand at 0 °C for 2 d. After addition of dichloromethane (100 ml), the mixture was extracted with satd. sodium hydrogen carbonate solution (4 × 50 ml) and the organic layer was dried with magnesium sulfate and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) yielded **4** (2.85 g, 83%) as a colorless syrup and **5** (0.44 g, 9%) as a colorless solid. **4**: TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.23. – $[\alpha]_D^{20}$ = +100.5 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32, 1.43 [2 s, 6 H, $C(CH_3)_2$], 2.41 (s, 3 H, $PhCH_3$), 2.73 (d, $J_{5,OH}$ = 5.7 Hz, 1 H, 5-OH), 3.83–3.92 (m, 1 H, 5-H), 4.00 (dd, $J_{5,6A}$ = 7.3, $J_{6A,6B}$ = 10.3 Hz, 1 H, 6A-H), 4.18 (dd, $J_{5,6A}$ = 3.0, $J_{6,6B}$ = 10.3 Hz, 1 H, 6B-H), 4.62–4.64 (m, 1 H, 2-H), 4.84 (d, *J* = 3.0 Hz, 1 H, 4-H), 5.38–5.43 (m, 2 H, $=CH_2$), 5.73 (d, $J_{1,2}$ = 4.0 Hz, 1 H, 1-H), 7.30–7.77 (m, 4 H, Ph). – $C_{17}H_{22}O_7S$ (370.42): calcd. C 55.12, H 5.99; found C 55.11, H 6.33. **5**: TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.32. – $[\alpha]_D^{20}$ = +70.4 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31, 1.36 [2 s, 6 H, $C(CH_3)_2$], 2.42 (s, 6 H, 2 $PhCH_3$), 4.05–4.08 (m, 2 H, 6A-H, 6B-H), 4.74 (ddd, *J* = 1.0, *J* = 3.2, *J* = 7.8 Hz, 1 H, 5-H), 4.80 (dd, $J_{1,2}$ = 4.1, *J* = 1.3 Hz, 1 H, 2-H), 4.87-4.88 (m, 1 H, 4-H), 5.22–5.49 (m, 2 H, $=CH_2$), 5.59 (d, $J_{1,2}$ = 4.1 Hz, 1 H, 1-H), 7.28-7.75 (m, 8 H, 2 Ph). – $C_{24}H_{28}O_9S_2$ (524.60): calcd. C 54.95, H 5.38; found C 54.62, H 5.76.

3-Deoxy-1,2-O-isopropylidene-3-C-methylene-6-O-tolylsulfonyl-5-O-trichloroacetylcarbamoyl-α-D-ribo-hexofuranose (**4a**): To a solution of compound **4** (20 mg, 0.05 mmol) in deuteriochloroform (0.5 ml) was added trichloroacetyl isocyanate (1 drop). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33, 1.43 [2 s, 6 H, $C(CH_3)_2$], 2.42 (s, 3 H, $PhCH_3$), 4.18 (dd, $J_{5,6A}$ = 3.4, $J_{6A,6B}$ = 11.6 Hz, 1 H, 6A-H), 4.26 (dd, $J_{5,6B}$ = 6.7, $J_{6A,6B}$ = 11.6 Hz, 1 H, 6B-H), 4.88 (dd, $J_{1,2}$ = 4.0, *J* = 0.8 Hz, 1 H, 2-H), 4.92–4.94 (m, 1 H, 4-H), 5.09-5.15 (m, 1 H, 5-H), 5.07–5.23 (m, 2 H, $=CH_2$), 5.74 (d, $J_{1,2}$ = 4.0 Hz, 1 H, 1-H), 7.31–7.76 (m, 4 H, *Ph*), 8.48 (s, 1 H, CON*H*).

3,6-Dideoxy-1,2-O-isopropylidene-3-C-methylene-α-D-ribo-hexofuranose (**6**): Under nitrogen, a solution of the tosylate **4** (2 g, 5.4 mmol) in dry diethyl ether (10 ml) was added slowly to a suspension of $LiAlH_4$ (410 mg, 10.8 mmol) in dry diethyl ether (10 ml). After 1 h, the reaction mixture was cooled to 0 °C , carefully quenched with satd. sodium sulfate solution (5 ml) and extracted with diethyl ether (4 × 50 ml). The combined extracts were washed with water (50 ml), dried with magnesium sulfate and concentrated under reduced pressure. Flash chromatography (toluene/acetone, 10:1) gave 895 mg (83%) of **6** as a colorless oil. – TLC (toluene/acetone, 5:1): R_f = 0.31. – $[\alpha]_D^{20}$ = +170.5 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08 (d, $J_{5,6}$ = 6.5 Hz, 3 H, 6-H), 1.30, 1.40 [2 s, 6 H, $C(CH_3)_2$], 2.51 (br.s, 1 H, 5-OH), 3.79 (m, 1 H, 5-H), 4.64 (ddd, $J_{4,5}$ = 4.8, *J* = 2.0, *J* = 1.4 Hz, 1 H, 4-H), 4.83 (ddd, $J_{1,2}$ = 4.2, *J* = 1.5, *J* = 1.3 Hz, 1 H, 2-H), 5.18–5.41 (m, 2 H, $=CH_2$), 5.78 (d, $J_{1,2}$ = 4.2 Hz, 2 H, 1-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.66 (s, 1 C, 6-C), 27.34, 27.46 [2 s, 2 C, $C(CH_3)_2$], 69.95 (s, 1 C, 5-C), 81.98, 83.94 (2 s, 2 C, 2-C, 4-C), 104.69, (s, 1 C, 1-C), 112.54 (s, 1 C, $=CH_2$). – $C_{10}H_{16}O_4$ (200.23): calcd. C 59.99, H 8.05; found C 60.00, H 7.98.

Acetyl O-(2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranoside) (**8α**) *and Acetyl O-(2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranoside)* (**8β**): A solution of compound **6** (2 g, 10 mmol) in acetic acid (80%, 20 ml) was heated to 60 °C for 3 h. The reaction mixture was concentrated in vacuo, codestillated with toluene and chloroform to yield crude **7** (1.6 g) as a colorless foam. The obtained solid was dissolved in acetic an-

hydride/pyridine (1:2, 6 ml) and stirred overnight. After evaporation in vacuo and codestillation with toluene, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to yield 1.69 g (59%) of **8α** as a colorless syrup and 570 mg (20%) of **8β** as colorless crystals. **8α**: TLC (toluene-acetone, 20:1): R_f = 0.35. – $[\alpha]_D^{20}$ = +112.7 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17, 1.20 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 2.07, 2.08 (2 s, 9 H, 3 $COCH_3$), 3.85 (dq, $J_{4,5}$ = 9.7, $J_{5,6}$ = 6.2 Hz, 1 H, 5-H), 4.97–5.08 (m, 3 H, 4-H, $=CH_2$), 5.44–5.47 (m, 1 H, 2-H), 6.20 (d, $J_{1,2}$ = 3.7 Hz, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.74 (s, 1 C, 6-C), 20.51, 20.64, 20.84 (3 s, 3 C, 3 $COCH_3$), 69.51, 70.45, 72.95 (3 s, 3 C, 2-C, 4-C, 5-C), 89.56, (s, 1 C, 1-C), 106.07 (s, 1 C, 3-C), 136.87 (s, 1 C, $=CH_2$), 169.20, 169.26, 169.30 (3 s, 3 C, 3 $COCH_3$). – $C_{13}H_{18}O_7$ (286.28): calcd. C 54.54, H 6.34; found C 54.19, H 6.36. **8β**: TLC (toluene/acetone, 20:1): R_f = 0.26. – $[\alpha]_D^{20}$ = +20.6 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 2.08, 2.11, 2.14 (3 s, 9 H, 3 $COCH_3$), 3.58 (dq, $J_{4,5}$ = 9.0, $J_{5,6}$ = 6.2 Hz, 1 H, 5-H), 4.99–5.02 (m, 2 H, $=CH_2$), 5.04–5.08 (m, $J_{4,5}$ = 9.0 Hz, 1 H, 4-H), 5.33 (ddd, $J_{1,2}$ = 7.9, *J* = 1.9 Hz, 1 H, 2-H), 5.53 (d, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.83 (s, 1 C, 6-C), 20.51, 20.62, 20.83 (3 s, 3 C, 3 $COCH_3$), 70.86, 72.95, 74.38 (3 s, 3 C, 2-C, 4-C, 5-C), 93.46 (s, 1 C, 1-C), 107.83 (s 1 C, 3-C), 138.39 (s, 1 C, $=CH_2$), 168.84, 169.10, 169.14 (3 s, 3 C, 3 $COCH_3$). – $C_{13}H_{18}O_7$ (286.28): calcd. C 54.54, H 6.34; C 54.52, H 6.26.

2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α/β-D-ribo-hexopyranose (**9α,β**): Compound **8** (1 g, 3.5 mmol) and hydrazinium acetate (430 mg, 1.1 eq) in dry *N,N*-dimethylformamide (25 ml) were stirred at 40 °C for 30 min, until the reaction mixture became a clear solution. After addition of ethyl acetate (100 ml), the mixture was extracted with water (3 × 50 ml) and the organic layer was dried with magnesium sulfate. Evaporation of the solvents and purification by flash chromatography (petroleum ether/ethyl acetate, 3:2) yielded **9α,β** (1:1, 794 mg, 93%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 3:2): R_f = 0.30. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (d, $J_{5,6}$ = 6.2 Hz, 1.5 H, 6α-H), 1.22 (d, $J_{5,6}$ = 6.1 Hz, 1.5 H, 6β-H), 2.12, 2.14, (2 s, 6 H, 2α-COCH_3, 2β-COCH_3), 3.45 (dq, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.1 Hz, 0.5 H, 5β-H), 3.94 (dq, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.2 Hz, 0.5 H, 5α-H), 4.48 (d, $J_{1,2}$ = 7.8 Hz, 0.5 H, 1β-H), 4.89-5.09 (m, 3 H, 4-H, $=CH_2$), 5.15 (dd, $J_{1,2}$ = 7.8 Hz, 0.5 H, 2β-H), 5.26 (d, $J_{1,2}$ = 3.7 Hz, 0.5 H, 1α-H), 5.33 (b, 0.5 H, 2α-H). – $C_{11}H_{16}O_6$ 0.5H_2O (253.25): calcd. C 52.17, H 6.76; found C 52.48, H 6.75.

Acetyl 2,4-Di-O-acetyl-6-deoxy-β-D-ribo-hexopyran-3-uloside (**10β**): Into a solution of **8β** (1.00 g, 3.49 mmol) in methanol/dichloromethane (1:1, 100 ml) at −78 °C was bubbled ozone until the solution was blue colored. Then, the excess ozone was removed by passing argon through the solution. After evaporation of the solvents pure **10β** (1.00, 99%) was obtained as a colorless solid. – TLC (petroleum ether/ethyl acetate, 5:2): R_f = 0.13. – $[\alpha]_D^{20}$ = +58 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.37 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.12, 2.13 (2 s, 9 H, 3 $COCH_3$) 3.81 (dq, $J_{4,5}$ = 10.3, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 4.99 (dd, $J_{2,4}$ = 1.1, $J_{4,5}$ = 10.3 Hz, 1 H, 4-H), 5.29 (dd, $J_{1,2}$ = 8.5, $J_{2,4}$ = 1.1 Hz, 1 H, 2-H), 5.78 (d, $J_{1,2}$ = 8.5 Hz, 1 H, 1-H). – $C_{12}H_{16}O_8$ (288.25): calcd. C 50.00, H 5.59; found C 50.00, H 5.59.

2,4-Di-O-acetyl-6-deoxy-α/β-D-ribo-hexopyran-3-ulose (**11α,β**). – *From* **9α,β**: Into a solution of compound **9α,β** (100 mg, 0.409 mmol) in methanol/dichloromethane (1:1, 5 ml) at −78 °C was bubbled ozone until the solution was blue colored. Then, the excess ozone was removed by passing argon through the solution. After evaporation of the solvents pure **11α,β** (101 mg, 99%) was obtained as a colorless foam.

From **10α,β**: A mixture of **10β** (0.29 g, 1.0 mmol) and hydrazinium acetate (0.10 g, 1.1 mmol) in dry dimethylformamide (1.5 ml) was heated to 40 °C until the solution was clear. After addition of ethyl acetate (40 ml) the solution was extracted with water (3 × 20 ml) and the organic solution was dried ($MgSO_4$) and concentrated. Flash chromatography (petroleum ether/ethyl acetate, 3:2) of the residue yielded **11α,β** (0.61 g, 71%) as a colorless solid. – TLC (petroleum ether/ethyl acetate, 3:2): R_f = 0.22. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (d, $J_{5,6}$ = 6.0 Hz, 3 H, 6-H), 2.16, 2.17 (2 s, 6 H, 2 $COCH_3$), 3.54 (s, 1 H, 1-OH), 3.77 (dq, $J_{4,5}$ = 10.1, $J_{5,6}$ = 6.0 Hz, 1 H, 5-H), 4.31 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1-H), 4.98 (d, $J_{4,5}$ = 10.1 Hz, 1 H, 4-H), 5.48 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 2-H). – $C_{10}H_{14}O_7$ 0.125 H_2O (248.47): calcd. C 48.34, H 5.78; found C 48.36, H 5.70.

2,4-Di-O-acetyl-1,5-anhydro-6-deoxy-hex-1-en-3-ulose (**12**): Compound **12** was obtained as elimination product in several reactions, i.e. in attempts to phosphitylate **11**. – TLC (toluene/acetone, 20:1): R_f = 0.36. – $[\alpha]_D^{20}$ = +159.8 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43 (d, $J_{5,6}$ = 6.4 Hz, 3 H, 6-H), 2.15, 2.18 (2 s, 6 H, 2 $COCH_3$), 4.56 (dq, $J_{4,5}$ = 12.2, $J_{5,6}$ = 6.4 Hz, 1 H, 5-H), 5.32 (d, $J_{4,5}$ = 12.2 Hz, 1 H, 4-H), 7.38 (s, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.21 (s, 1 C, 6-C), 20.06, 20.39 (2 s, 2 C, 2 $COCH_3$), 72.67, 78.06 (2 s, 2 C, 4-C, 5-C), 130.47 (s, 1 C, 2-C), 155.80 (s, 1 C, 1-C), 168.52, 169.26 (2 s, 2 C, 2 $COCH_3$), 182.17 (s, 1 C, 3-C). – $C_{10}H_{12}O_6$ (228.20): calcd. C 52.63, H 5.30; found C 52.82, H 5.46.

Bis(2-cyanoethyl)2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl Phosphite (**14aβ**): A solution of bis(2-cyanethyl) *N,N*-diisopropylphosphoramidite (167 mg, 0.61 mmol) in dry dichloromethane (1 ml) was added dropwise to a solution of **9α,β** (100 mg, 0.409 mmol) in dichloromethane/acetonitrile (1:1, 3 ml) under nitrogen at room temp. After addition of 1*H*-tetrazole (57 mg, 0.82 mmol) the mixture was stirred for 20 min. Concentration under reduced pressure and purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 1:1) yielded **14a,β** (146 mg, 86%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.40. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.15, 2.16 (2 s, 6 H, 2 $COCH_3$), 2.61-2.69 [m, 4 H, $P(OCH_2CH_2CN)_2$], 3.53 (dq, $J_{4,5}$ = 9.3, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 3.96-4.16 [m, 4 H, $P(OCH_2CH_2CN)_2$], 4.86 (dd, $J_{1,P}$ = 7.7, $J_{1,2}$ = 7.6 Hz, 1 H, 1-H), 4.96-5.07 (m, 3 H, 4-H, $=CH_2$), 5.32 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 2-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 137.92 (s, P_β). No further purification was performed because of the sensitivity of **14aβ** to moisture.

Bis(2-trimethylsilylethyl) 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl Phosphite (**14bβ**): A solution of bis(2-trimethylsilylethyl) *N,N*-diisopropylphosphoramidite (223 mg, 0.61 mmol) in dry dichloromethane (1 ml) was added dropwise to a solution of **9α,β** (100 mg, 0.409 mmol) in dichloromethane/acetonitrile (1:1, 3 ml) under nitrogen at room temp. After addition of 1H-tetrazole (57 mg, 0.82 mmol) the mixture was stirred for 20 min. Concentration under reduced pressure and purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 6:1 + 1% triethylamine) yielded **14bβ** (195 mg, 94%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.47. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.01-0.02 [m, 18 H, 2 $Si(CH_3)_3$], 0.84-1.20 [m, 4 H, $P(OCH_2CH_2TMS)_2$], 1.23 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.12, 2.14 (2 s, 6 H, 2 $COCH_3$), 3.49 (dq, $J_{4,5}$ = 9.3, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 3.88-4.22 [m, 4 H, $P(OCH_2CH_2TMS)_2$], 4.83 (dd, $J_{1,P}$ = 8.3, $J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 4.92-4.96 (m, 2 H, $=CH_2$), 5.06 (d, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 5.30 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 2-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 139.08 (s, P_b). – No further purification was performed because of the sensitivity of **14b,β** to moisture.

Bis(2,2,2-trichloroethyl) 2,4-Di-D-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl Phosphite (**14cα**) *and Bis(2,2,2-trichloroethyl) 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl Phosphite* (**14cβ**): To a solution of **9α,β** (500 mg, 2.05 mmol) and ethyldiisopropylamine (0.62 ml, 3.58 mmol) in dry acetonitrile (10 ml) was added bis(2,2,2-trichloroethyl)chlorophosphite (1.75 g, 3.07 mmol) at room temp. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1 + 1% triethylamine) to yield the anomeric mixture (1:1) **14cα,β** (1.13 g, 97%) as a colorless oil. **14cα**: TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.67. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.20 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 2.16 (s, 6 H, 2 COCH_3), 4.04 (dq, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.2 Hz, 1 H, 5-H), 4.37-4.53 [m, 4 H, P(OCH_2CCl$_3$)$_2$], 4.97-5.02 (m, 3 H, 4-H, =CH_2), 5.40 (br.s, 1 H, 2-H), 5.68 (dd, $J_{1,P}$ = 7.9, $J_{1,2}$ = 3.4 Hz, 1 H, 1-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 135.41 (s, $P_α$). **14cβ**: TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.60. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.15 (s, 6 H, 2 COCH_3), 3.52 (dq, $J_{4,5}$ = 9.3, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 4.37-4.53 [m, 4 H, P(OCH_2CCl$_3$)$_2$], 4.95 (dd, $J_{1,P}$ = 7.5, $J_{1,2}$ = 7.6, 1 H, 1-H), 4.97-5.02 (m, 2 H, =CH_2), 5.08 (d, $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 5.35 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 2-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 136.82 (s, $P_β$). – No further purification was performed because of the sensitivity of **14cα** and **14cβ** to moisture.

Diethyl 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl Phosphite (**14dα**) *and Diethyl 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl Phosphite* (**14dβ**): To a solution of **9α,β** (3.0 g, 12.3 mmol) and ethyldiisopropylamine (3.72 ml, 21.5 mmol) in dry acetonitrile (60 ml) was added diethyl chlorophosphite (6.7 g, 18.4 mmol) at room temp. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to yield **14dα** (1.65 g, 37%) and **14dβ** (1.65 g, 37%) as colorless oils. **14dα**: TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.32. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 1.23 [2 t, 6 H, P(OCH$_2$CH_3)$_2$], 2.12, 2.15 (2 s, 6 H, 2 COCH_3), 3.80-4.02 [m, 5 H, 5-H, P(OCH_2CH$_3$)$_2$], 4.96-5.06 (m, 3 H, 4-H, =CH_2), 5.34-5.36 (m, 1 H, 2-H), 5.56 (dd, $J_{1,P}$ = 8.4, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 139.51 (s, $P_α$). **14dβ**: TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.29. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18-1.26 [m, 9 H, 6-H, P(OCH$_2$CH_3)$_2$], 2.12, 2.13 (2 s, 6 H, 2 COCH_3), 3.50 (dq, $J_{4,5}$ = 9.4, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 3.79–3.96 [m, 4 H, P(OCH_2CH$_3$)$_2$], 4.83 (dd, $J_{1,P}$ = 8.5, $J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 4.91–4.95 (m, 2 H, =CH_2), 5.05 (d, $J_{4,5}$ = 9.4 Hz, 1 H, 4-H), 5.29 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 2-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 138.95 (s, $P_β$). – Because of the sensitivity to moisture, **14dα** and **14dβ** were used for the next step without further purification.

Dibenzyl (2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl) Phosphite (**14eα**) *and Dibenzyl (2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl) Phosphite* (**14eβ**): A solution of dibenzyl *N,N*-diisopropylphosphoramidite[14] (2.83 g, 8.2 mmol) in dry dichloromethane (20 ml) was added dropwise to a solution of **9α,β** (1 g, 4.09 mmol) in acetonitrile/dichloromethane (1:1, 20 ml) under nitrogen at room temp. After addition of 1 M tetrazole (717 mg, 10.2 mmol) the reaction mixture was stirred for 20 min. Concentration under reduced pressure and purfication of the residue by flash chromatography (petroleum ether/ethyl acetate, 10:1 + 1% triethylamine) yielded **14eα** (800 mg, 40%) and **14eβ** as colorless oils. **14eα**: TLC (petroleum ether/ethyl acetate, 8:1): R_f 0.24. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 1.97, 2.17 (2 s, 6 H, 2 COCH_3), 3.99 (dq, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.2 Hz, 1 H, 5-H), 4.86–4.94 (m, 4 H, 2 CH_2Ph), 4.95–5.11 (m, 3 H, 4-H, =CH_2), 5.41 (dd, $J_{1,2}$ = 3.5, $J_{2,4}$ = 1.1 Hz, 1 H, 2-H), 5.68 (dd, $J_{1,P}$ = 8.3, $J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 7.24–7.38 (m, 10 H, 2 CH$_2$*Ph*). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 138.85 (s, $P_α$). **14eβ**: TLC (petroleum ether/ethyl acetate, 8:1): R_f = 0.20. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.00, 2.16 (2 s, 6 H, 2 COCH_3), 3.53 (dq, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 4.66–5.18 (m, 8 H, 1-H, 4-H, 2 CH_2Ph, = CH$_2$), 5.41 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 2-H), 7.19–7.36 (m, 10 H, 2 CH$_2$*Ph*). – ^{31}P-NMR (161.7 MHz, $CDCl_3$): δ = 138.37 (s, $P_β$). Because of the sensitivity to moisture, **14eα** and **14eβ** were used for the next step without further purification.

Diethyl 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl Phosphate (**15dα**) *and Diethyl 2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-β-D-ribo-hexopyranosyl Phosphate* (**15dβ**): Into a solution of **14dα** and **14dβ** (1:1, 0.72 g, 1.98 mmol) in methanol/dichloromethane (1:1, 40 ml) was bubbled ozone, until the starting material was disappeared (TLC control). Then, the excess ozone was removed by passing argon through the solution. Concentration under reduced pressure and flash chromatography (petroleum ether/ethyl acetate, 1:1) yielded **15dα** and **15dβ** (1:1, 655 mg, 87%) as a colorless solid. – TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.29. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (d, $J_{5,6}$ = 6.2 Hz, 1.5 H, 6α-H), 1.22 (d, $J_{5,6}$ = 6.1 Hz, 1.5 H, 6β-H), 1.25–1.32 [m, 6 H, α-P(OCH$_2$CH_3)$_2$, β-P(OCH$_2$CH_3)$_2$], 2.12–2.13 (m, 6 H, 2α-COCH_3, 2 β-COCH_3), 3.55 (dq, $J_{4,5}$ = 9.2, $J_{5,6}$ = 6.1, 0.5 H, 5β-H), 3.93 (dq, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2 Hz, 0.5 H, 5α-H), 4.00–4.16 [m, 4 H, α- Symbol 'P(OCH_2CH$_3$)$_2$, β-P(OCH_2CH$_3$)$_2$], 4.965.06 (m, 3 H, 4-H, =CH_2), 5.09 (dd, $J_{1,P}$ = 7.5, $J_{1,2}$ = 7.6 Hz, 0.5 H, 1β-H), 5.30 (d, $J_{1,2}$ = 7.6 Hz, 0.5 H, 2β-H), 5.36 (β, 0.5 H, 2α-H), 5.70 (dd, $J_{1,P}$ = 6.5, $J_{1,2}$ = 3.5 Hz, 0.5 H, 1α-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = –2.55 (s, $P_α$), –2.08 (s, $P_β$). – $C_{15}H_{25}O_9P$ (380.33): calcd. C 47.37, H 6.63; found C 47.56, H 6.80.

Dibenzyl (2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl) Phosphate (**15e**): Under nitrogen, the phosphite **14eα** (530 mg, 1.08 mmol) was dissolved in dry dichloromethane (10 ml) and a solution of *tert*-butyl hydroperoxide (910 ml, 3 M in toluene) was injected slowly while stirring. After addition of triethylamine (5 drops) the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1 + 1% triethylamine) to give **15e** (517 mg, 94%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.26. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.12, 1.14 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 1.97, 2.15 (2 s, 6 H, 2 COCH_3), 3.91 (dq, $J_{4,5}$ = 9.7 Hz, 1 H, 5-H), 5.01-5.10 (m, 7 H, 4-H, 2 CH_2Ph, =CH_2), 5.39–5.41 (m, 1 H, 2-H), 5.83 (dd, $J_{1,P}$ 6.4, $J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 7.25–7.38 (m, 10 H, 2 CH$_2$*Ph*). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = –2.07 (s, $P_α$). – Because of the sensitivity to moisture, **15e** was used for the next step without further purification.

Diethyl 2,4-Di-O-acetyl-6-deoxy-α-D-ribo-hexopyran-3-ulosyl Phosphate (**16d**): Into a solution of compound **14dα** (1.0 g, 2.74 mmol) or **15d** (1.04 g, 2.74 mmol) in methanol/dichloromethane (1:1, 50 ml) at –78 °C was bubbled ozone until the solution was blue colored. Then, the excess ozone was removed by passing argon through the solution. After evaporation of the solvents pure **16d** (1.0 g, 95%) was obtained as a colorless solid. – TLC (petroleum ether/ethyl acetate, 1:1): R_f = 0.12. – $[α]_D^{20}$ = +84.5 (*c* = 1, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 [t, 6 H, P(O)(OCH$_2$CH_3)$_2$], 1.37 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H), 2.15, 2.19 (2 s, 6 H, 2 COCH_3), 4.05–4.18 [m, 4 H, P(O)(OCH_2CH$_3$)$_2$], 4.31 (dq, $J_{4,5}$ = 10.1, $J_{5,6}$ = 6.1 Hz, 1 H, 5-H), 5.04 (dd, $J_{2,4}$ = 0.7, $J_{4,5}$ =

10.1 Hz, 1 H, 4-H), 5.44–5.47 (m, 1 H, 2-H), 6.04 (dd, $J_{1,P}$ = 6.7, $J_{1,2}$ = 4.2 Hz, 1 H, 1-H). – ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 2.61 (s, P_α). – $C_{14}H_{23}O_{10}P$ (382.30): calcd. C 43.98, H 6.06; found C 43.91, H 6.06.

Bis(triethylammonium) (2,4-Di-O-acetyl-3,6-dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl) Phosphate (**17**): A mixture of **15e** (125 mg, 248 mmmol) and palladium on charcoal (10%, 10 mg) in methanol/ethyl acetate (1:1, 6 ml) was shaken under hydrogen. After 10 min the reaction mixture was passed immediately through a pad of Celite and after addition of triethylamine (3 drops) the filtrate was concentrated in vacuo. Flash chromatography over a short silica gel column (chloroform/methanol, 2:1→1:1), followed by filtration through RP 18-material yielded **17** (91 mg, 88%) as a white powder. – TLC (chloroform/methanol, 1:1): R_f = 0.23. – ^{1}H NMR (250 MHz, D_2O): δ = 1.03 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H), 1.07 [t, J = 7.3 Hz, 9 H, $N(CH_2CH_3)_3$], 2.10, 2.04 (2 s, 6 H, 2 $COCH_3$), 3.00 [q, J = 7.3 Hz, 6 H, $N(CH_2CH_3)_3$], 3.88 (dq, $J_{4,5}$ = 9.6, $J_{5,6}$ = 6.2 Hz, 1 H, 5-H), 4.85–4.94 (m, 3 H, 4-H, $=CH_2$), 5.21 (br.s, 1 H, 2-H), 5.38 (dd, $J_{1,P}$ = 7.3, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, D_2O): δ = 9.17 [s, 3 C, $N(CH_2CH_3)_3$], 17.63 (s, 1 C, 6-C), 21.11 (s, 2 C, 2 $COCH_3$), 47.60 [s, 3 C, $N(CH_2CH_3)_3$], 70.07-74.64 (2 s, 2 C, 4-C, 5-C), 71.95 (d, $J_{2,P}$ = 8.3 Hz, 1 C, 2-C), 92.78 (d, $J_{1,P}$ = 5.0 Hz, 1 C, 1-C), 107.98 (s, 1 C, 3-C), 137.26 (s, 1 C, $=CH_2$), 173.67, 173.76 (2 s, 2 C, 2 $COCH_3$). – ^{31}P NMR (161.7 MHz, D_2O): δ = −1.25 (s, P_α). – FAB-MS (negative mode, matrix: 3-nitrobenzyl alcohol): *m/z* (%): 263 (9) $[M - HOAc - H^+]^-$, 281 (27) $[M - C_2H_2O - H^+]^-$, 323 (100) $[M - H^+]^-$, 605 (7) $[2 M - C_2H_2O - H^+]^-$, 647 (22) $[2 M - H^+]^-$. – $C_{11}H_{17}O_9P$ 0.90 triethylamine (415.29).

Bis(triethylammonium) (3,6-Dideoxy-3-C-methylene-α-D-ribo-hexopyranosyl) Phopshate (**18**): Compound **17** (400 mg, 963 mmol) was dissolved in a mixture of methanol/water/triethylamine (95:5:5, 15 ml) and stirred at room temp. for 1 d. After a second addition of methanol/water/triethylamine (10:5:2, 15 ml) the solution was further stirred for 4 d, until deacetylation was complete. The reaction mixture was concentrated in vacuo, codestillated with toluene/chloroform and finally purified by flash chromatography (chloroform/methanol/water, 3:2:0.25). Filtration through a pad of RP 18-material gave after lyophilization in water **18** (281 mg, 91%) as a white powder. – TLC (chloroform/methanol/water, 1:1:0.1): R_f = 0.11. – ^{1}H NMR (250 MHz, D_2O): δ = 1.05 [t, J = 7.3 Hz, 9 H, $N(CH_2CH_3)_3$], 1.07 (d, $J_{5,6}$ = 5.4 Hz, 3 H, 6-H), 2.97 [q, J = 7.3 Hz, 6 H, $N(CH_2CH_3)_3$], 3.52–3.62 (m, 2 H, 4-H, 5-H), 4.08 (m, 1 H, 2-H), 4.93–5.08 (m, 2 H, $=CH_2$), 5.24 (dd, $J_{1,P}$ = 6.5, $J_{1,2}$ = 3.7 Hz, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, D_2O): δ = 9.16 [s, 3 C, $N(CH_2CH_3)_3$], 18.11 (s, 1 C, 6-C), 47.61 [s, 3 C, $N(CH_2CH_3)_3$], 70.89 (d, $J_{2,P}$ = 8.9 Hz, 1 C, 2-C), 71.80-73.40 (2 s, 2 C, 4-C, 5-C), 95.48 (d, $J_{1,P}$ = 6.3 Hz, 1 C, 1-C), 105.58 (s, 1 C, 3-C), 146.30 (s, 1 C, $=CH_2$). – ^{31}P NMR (161.70 MHz, D_2O): δ = 3.97 (s, P_α). – FAB-MS (negative mode, matrix: 3-nitrobenzyl alcohol): *m/z* (%): 239 (100) $[M - H^+]^-$, 281 (20) $[M + C_2H_2O - H^+]^-$, 479 (12) $[2 M - H^+]^-$. – $C_7H_{13}O_7P$ 0.80 triethylamine (321.10).

Bis(triethylammonium) (6-Deoxy-α-D-ribo-hexopyran-3-ulosyl) Phosphate (**19**): The phosphate **18** (40 mg, 125 mmol) was dissolved in dry methanol/dichloromethane (1:1, 4 ml) and cooled to −78 °C. Oxidation occurr by passing in an oxygen-ozone stream for 70 sec. Excess ozone was removed by bubbling a stream of argon through the reaction mixture. Finally the solution was allowed to warm up to room temp., concentrated under reduced pressure and codestillated with chloroform/dichloromethane to yield **19** (40 mg, quant.) as an amorphous powder. – TLC (chloroform/methanol/water, 3:2:0.25): R_f = 0.10. – ^{1}H NMR (250 MHz, D_2O): δ = 1.09 [t, J = 7.3 Hz, 9 H, $N(CH_2CH_3)_3$], 1.23 (d, $J_{5,6}$ = 5.8 Hz, 3 H, 6-H), 3.00 [q, J = 7.3 Hz, 6 H, $N(CH_2CH_3)_3$], 3.86–3.99 (m, 2 H, 4-H, 5-H), 4.44 (m, 1 H, 2-H), 5.58 (dd, $J_{1,P}$ = 6.7, $J_{1,2}$ = 4.3 Hz, 1 H, 1-H). – ^{13}C NMR (62.9 MHz, [D$_7$]-DMF): δ = 13.82 [s, 3 C, $N(CH_2CH_3)_3$], 23.98 (s, 1 C, 6-C), 51.16 [s, 3 C, $N(CH_2CH_3)_3$], 77.70-83.52 (2 s, 2 C, 4-C, 5-C), 81.71 (d, $J_{2,P}$ = 5.2 Hz, 1 C, 2-C), 103.06 (d, $J_{1,P}$ = 4.3 Hz, 1 C, 1-C), 199.54 (s, 1 C, 3-C). – ^{31}P NMR (161.7 MHz, D_2O): δ = −1.44 (s, P_α). – FAB-MS [negative mode, matrix: methanol/glycerin (1:1)]: *m/z* (%): 97 (49) $[H_2PO_4]^-$, 241 (100) $[M - H^+]^-$, 333 (16) $[M + Gly - H^+]^-$, 483 (12) $[2 M - H^+]^-$. – $C_6H_{11}O_8P$ 0.80 triethylamine (323.07).

Bis(triethylammonium) (3″,6″-Dideoxy-3″-C-methylene-α-D-ribo-hexopyranosyl) (2′-Deoxythymidine-5′-yl) Diphosphate (**20**): To a solution of **18** (50 mg, 156 mmol) in dry pyridine (2 ml) was added 4 Å molecular sieves, which was dried by heating at 250°C/10^{-3} Torr. The solution was stirred at room temp. for 2 h under argon. The dTMP morpholidate (126 mg, 193 mmol), previously dried by repeated evaporation with dry pyridine (5 × 10 ml), was dissolved in dry pyridine (2 ml) and added dropwise over a period of 10 min to the stirred solution. The reaction was monitored by analytical HPLC (5% acetonitrile in 0.5 M triethylammonium hydrogen carbonate solution) and after standing for 5 d, the reaction mixture was evaporated to dryness. Purification of the residue by preparation HPLC (5% acetonitrile in 0.5 M triethylammonium hydrogen carbonate solution, t_R = 22 min) gave after lyophilization in water **20** (56 mg, 51%) as a white solid. – TLC (chloroform/methanol/water, 3:4:0.25): R_f = 0.30. – ^{1}H NMR (250 MHz, D_2O): δ = 1.05 (d, $J_{5'',6''}$ = 5.8 Hz, 3 H, 6″-H), 1.07 [t, J = 7.3 Hz, 18 H, 2 $N(CH_2CH_3)_3$], 1.73 (s, 3 H, CH_3), 2.13–2.18 (m, 2 H, 2′A-H, 2′B-H), 2.97 [q, J = 7.3 Hz, 12 H, 2 $N(CH_2CH_3)_3$], 3.61–3.63 (m, 2 H, 4″-H, 5″-H), 3.95-3.97 (m, 3 H, 4′-H, 5′A-H, 5′B-H), 4.08 (m, 1 H, 2″-H), 4.42 (m, 1 H, 3′-H), 4.97-5.04 (m, 2 H, $=CH_2$), 5.37 (dd, $J_{1'',P}$ = 7.0, $J_{1'',2''}$ = 3.7 Hz, 1 H, 1″-H), 6.16 (dd, $J_{1',2'A}$ = 6.8, $J_{1',2'B}$ = 7.1 Hz, 1 H, 1′-H), 7.52 (d, J = 0.9 Hz, 1 H, 6-H). – ^{13}C NMR (62.9 MHz, D_2O): δ = 9.17 [s, 3 C, $N(CH_2CH_3)_3$], 12.59 (s, 1 C, CH_3), 18.20 (s, 1 C, 6″-C), 39.56 (s, 1 C 2′-C), 47.63 [s, 3 C, $N(CH_2CH_3)_3$], 66.32 (d, $J_{5',P}$ = 5.2 Hz, 1 C, 5′-C), 71.07 (d, $J_{2'',P}$ = 9.1 Hz, 1 C, 2″-C), 71.82-73.44 (m, 3 C, 3′-C, 4″-C, 5″-C), 85.92 (s, 1 C, 1′-C), 86.35 (d, $J_{4',P}$ = 9.1 Hz, 1 C, 4′-C), 96.25 (d, $J_{1'',P}$ = 6.4 Hz, 1 C, 1″-C), 105.62 (s, 1 C, 3″-C), 112.62 (s, 1 C, 5-C), 138.33 (s, 1 C, 6-C), 146.54 (s, 1 C, $=CH_2$), 152.60 (s, 1 C, 2-C), 167.40 (s, 1 C, 4-C). – ^{31}P NMR (161.7 MHz, D_2O): δ = −12.35 (d, $J_{P,P'}$ = 22.5 Hz, 1 P), −10.81 (d, $J_{P,P'}$ = 22.5 Hz, 1 P). – FAB-MAS (negative mode, matrix: methanol/glycerin, 1:1): *m/z* (%): 321 (9) [dTMP − H$^+$]$^-$, 401 (12) [dTDP − H$^+$]$^-$, 543 (30) $[M - H^+]^-$, 635 (4) $[M - Gly\text{-}H^+]^-$. $-C_{17}H_{26}N_2O_{14}P_2$ 1.5 triethylamine (696.13).

Disodium (6″-Deoxy-α-D-ribo-hexopyran-3″-ulosyl) (2′-Deoxythymidine-5′-yl) Diphosphate (**1**). – *Via Ozonolyis:* Compound **20** (40 mg, 57.5 mmol) was dissolved in dry methanol (6 ml) and cooled to −78 °C and satd. with ozone, until the characteristical blue color persisted. The ozone satd. dichloromethane (5 ml) was added dropwise to the solution, until TLC shows a slower moving non ultraviolett absorbing byproduct. Excess ozone was removed by bubbling a stream of argon through the reaction mixture. Concentration in vacuo yielded a yellowish residue, which was purified by preparative HPLC (3% acetonitrile in 0.01 M triethylammonium hydrogen carbonate solution, t_R = 12 min). Lyophilization of the resulting solutions gave **1** (9 mg, 22%) along with recovered **20** (28 mg, 70%), all as amorphous solids. The triethylammonium salt of compound **1** was dissolved in water and treated with ion exchanger (Amberlite IR 120, Na^+ form). After filtration, the solution was

concentrated under reduced pressure and finally lyophilized to give the much more stable disodium salt of compound **1**.

By the Morpholidate Procedure: The dTMP morpholidate (187 mg, 288 mmol), previously dried by repeated evaporation with dry dimethylformamide (5 × 10 ml) at 10^{-3} Torr, was dissolved in dry dimethylformamide (2 ml) and stirred with freshly activated 4-Å molecular sieves at room temp. for 2 h under argon. A solution of the phosphate **19** (60 mg, 186 mmol) in dry dimethylformamide (2 ml) was added dropwise while stirring. The reaction was monitored by analytical HPLC. After standing for 5 d, the reaction mixture was concentrated under reduced pressure at 10^{-3} Torr. Purification of the residue by preparative HPLC (3% acetonitrile in 0.05 M triethylammonium hydrogen carbonate solution, t_R = 15 min) and following lyophilization gave the triethylammonium salt of compound **54** (40 mg, 30%) as an amorphous solid. The diphosphate **1** was converted in his disodium salt as described before. – TLC (chloroform/methanol/water, 3:4:0.25): R_f = 0.28. – ^{1}H NMR (250 MHz, D_2O): δ = 1.05 (d, $J_{5'',6''}$ = 5.8 Hz, 3 H, 6''-H), 1.73 (s, 3 H, CH_3), 2.14–2.18 (m, 2 H, 2'A-H, 2'B-H), 3.93–4.07 (m, 5 H, 4'-H, 5'A-H, 5'B-H, 4''-H, 5''-H), 4.41–4.56 (m, 2 H, 3'-H, 2''-H), 5.67 (dd, $J_{1'',P}$ = 7.1, $J_{1'',2''}$ = 4.3 Hz, 1 H, 1''-H), 6.13 (dd, $J_{1',2'A}$ = 6.6, $J_{1',2'B}$ = 6.9 Hz, 1 H, 1'-H), 7.55 (s, 1 H, 6-H). – ^{31}P NMR (161.7 MHz, D_2O): δ = –10.64 (d, $J_{P,P'}$ = 22.5 Hz, 1 P), –6.02 (d, $J_{P,P'}$ = 22.5 Hz, 1 P). – FAB-MS [negative mode, matrix: methanol/glycerin (1:1)]: *m/z* (%): 4.01 (78) [dTDP – H^+]$^-$, 493 (12) [dTDP + Gly – H^+]$^-$, 545 (100) [M – H^+]$^-$, 637 (12) [M + Gly – H^+]$^-$, 1091 (8) [2 M – H^+]$^-$. – $C_{16}H_{22}N_2O_{15}P_2$ 2 Na (590.30).

☆ Dedicated to Professor *Gottfried Huttner* on the occasion of his 60th birthday.

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