Chiral Pool Synthesis of 4a-Substituted Carbocyclic Cyclopentanoid Nucleoside Precursors, I

René Csuk\textsuperscript{a,*}, Petra Dörr\textsuperscript{b}, Martin Kühn\textsuperscript{b}, Claus Krieger\textsuperscript{c}, and Mikhail Y. Antipin\textsuperscript{d}

\textsuperscript{a} Institut für Organ. Chemie, Martin-Luther-Universität Halle-Wittenberg.
Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany
\textsuperscript{b} Pharmazeutisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 364, D-69120 Heidelberg, Germany
\textsuperscript{c} Max-Planck-Institut für Medizinische Forschung, Jahn-Straße 29, D-69120 Heidelberg, Germany
\textsuperscript{d} Institute of Organoelement Compounds, Russian Academy of Science, Vavilow St. 28 B-334, Moscow 117813, Russia

* Reprint requests to Prof. Dr. R. Csuk. E-mail: csuk@chemie.uni-halle.de

Z. Naturforsch. 54b, 1068–1078 (1999); received May 21, 1999

Nucleosides, Carbohydrates, X-Ray Data

Introduction

Natural nucleosides and their analogues have been widely studied as potential fungicidal, antitumor and antiviral agents. However, since these nucleosides are substrates for enzymatic degradations a number of modifications have been carried out on both, the hetero-cycle and the sugar portion to avoid or at least to slow down these deactivating processes. Thus, the replacement of the oxygen of the furan ring by a methylene group leads to the synthesis of carbocyclic analogues of nucleosides. Since then, carbocyclic analogues of sugars have attracted considerable attention as potential inhibitors of carbohydrate metabolism. A number of carbocyclic nucleosides \cite{1,2,3} have been reported as potential anti-HIV \cite{4,5} and anti-HBV \cite{6} agents. Among them, the cyclopentanoid derivative carbovir \cite{4,7}, is one of the most interesting compounds. In the course of our ongoing efforts toward the synthesis of carbocyclic nucleoside analogues we set out to develop an approach to five-membered sugars possessing a suitable functional group at the C(4a')-position. To obtain enantiomerically pure materials a chiral pool approach starting from D-ribono-1,4-lactone was chosen.

Results and Discussion

Thus, the cyclopentene derivative (3a\textsuperscript{R}, 6a\textsuperscript{R})-6-benzoyloxymethyl-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-one \cite{8} has been used quite successfully as a valuable starting material for the synthesis of various nucleoside analogues \cite{9,10}. During the course of developing new cyclopentanoid antitumor agents we became interested in the synthesis of derivatives carrying additional substituents at the positions 4 and/or 4a (carbohydrate numbering has been used throughout this work for convenience) and 1 seemed to be an ideal starting material since it can be synthesized in large amounts by a chiral pool approach starting from 5-O-benzyl-2,3-O-isopropylidene-D-ribono-1,4-lactone \textsuperscript{(2)} \cite{11,12}. Chain elongation at the anomeric centre with dimethyl lithiomethyl-phosphonate \cite{8,13} gave in 84% yield the corresponding phosphonate \textsuperscript{3} that was treated with sodium methoxide to afford the acyclic phosphonate \textsuperscript{4}. Whereas oxidations with CrO\textsubscript{3} \cite{13}, DMSO/ \((CF_3CO)_2O \) \cite{14}, Swern oxidation \cite{15} as well as oxidations using PDC or PDC failed to give good yields on a larger preparative scale, oxidation of \textsuperscript{4} with Dess-Martin’s periodinane \cite{16–19} gave access to \textsuperscript{5} as well as a byproduct that was shown to be an inseparable 1:1 mixture of the anomeric

---

Introduction

Natural nucleosides and their analogues have been widely studied as potential fungicidal, antitumor and antiviral agents. However, since these nucleosides are substrates for enzymatic degradations a number of modifications have been carried out on both, the hetero-cycle and the sugar portion to avoid or at least to slow down these deactivating processes. Thus, the replacement of the oxygen of the furan ring by a methylene group leads to the synthesis of carbocyclic analogues of nucleosides. Since then, carbocyclic analogues of sugars have attracted considerable attention as potential inhibitors of carbohydrate metabolism. A number of carbocyclic nucleosides \cite{1,2,3} have been reported as potential anti-HIV \cite{4,5} and anti-HBV \cite{6} agents. Among them, the cyclopentanoid derivative carbovir \cite{4,7}, is one of the most interesting compounds. In the course of our ongoing efforts toward the synthesis of carbocyclic nucleoside analogues we set out to develop an approach to five-membered sugars possessing a suitable functional group at the C(4a')-position. To obtain enantiomerically pure materials a chiral pool approach starting from D-ribono-1,4-lactone was chosen.

Results and Discussion

Thus, the cyclopentene derivative (3a\textsuperscript{R}, 6a\textsuperscript{R})-6-benzoyloxymethyl-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-one \cite{8} has been used quite successfully as a valuable starting material for the synthesis of various nucleoside analogues \cite{9,10}. During the course of developing new cyclopentanoid antitumor agents we became interested in the synthesis of derivatives carrying additional substituents at the positions 4 and/or 4a (carbohydrate numbering has been used throughout this work for convenience) and 1 seemed to be an ideal starting material since it can be synthesized in large amounts by a chiral pool approach starting from 5-O-benzyl-2,3-O-isopropylidene-D-ribono-1,4-lactone \textsuperscript{(2)} \cite{11,12}. Chain elongation at the anomeric centre with dimethyl lithiomethyl-phosphonate \cite{8,13} gave in 84% yield the corresponding phosphonate \textsuperscript{3} that was treated with sodium methoxide to afford the acyclic phosphonate \textsuperscript{4}. Whereas oxidations with CrO\textsubscript{3} \cite{13}, DMSO/ \((CF_3CO)_2O \) \cite{14}, Swern oxidation \cite{15} as well as oxidations using PDC or PDC failed to give good yields on a larger preparative scale, oxidation of \textsuperscript{4} with Dess-Martin’s periodinane \cite{16–19} gave access to \textsuperscript{5} as well as a byproduct that was shown to be an inseparable 1:1 mixture of the anomeric
phosphonates 6 and 7. The compounds 6/7 are characterized by the presence of a tert-butyl group in the $^1$H NMR spectrum at $\delta = 1.48/1.49$ ppm, respectively. The anomic carbon shows $\delta = 48.46/50.60$ ppm with $^{3}J_{CP} = 128$ Hz whereas for the acetalic C(5) a $^{3}J_{CP} \approx 5$ Hz was measured. Inspection of Dreiding models revealed that a re-face attack of tert-butanol onto C(5) in 5 should dominate over a si-face attack due to the presence of the isopropylidene acetal, therefore 6/7 should possess a (S)-configuration at the acetalic centre. Chromatographic fractions that contained an excess of either 6 or 7 showed fast equilibrium in solution to afford again a 1:1 mixture of these compounds.

Cyclization [13] of 5 afforded a mixture of (+)- and (−)-1 that was easily separated to yield the pure enantiomer (−)-1 and racemic (±)-1. 1 is characterized by its IR spectrum by a carbonyl signal at $\nu = 1722$ cm$^{-1}$; the olefinic H-C(4a) is found at $\delta = 6.22$ ppm showing an allylic coupling to H$_{A,B}$-C(5) of 1.5 Hz. Reduction of 1 at 0 °C with sodium borohydride in the presence of cerium(III) chloride [13] gave after a re-face attack 8 in a stereospecific manner with a newly created stereogenic centre possessing (S)-configuration. Protection of the hydroxy function in 8 with chlorotrisopropylsilane/pyridine in the presence of catalytical amounts of DMAP afforded the [1,3]dioxol 9 in 90% yield. Under similar conditions 10 was obtained.

The epoxidation of 8 with $m$-CPBA [20–23] at room temperature led to a 1:2 mixture of the two epoxides 11 and 12.

To establish the absolute configuration at the newly created stereogenic centres, 9 was epoxidized under the same conditions to afford the epoxide 13. Although the similarity in the spectral data between 13 and 11 indicated that both compounds possess the same absolute configuration at the stereogenic centres, these spectral data allowed no unambiguous assignment. Therefore, both, 12 and 11 were silylated and gave 14 and 13, the latter of which has been identical in every respect with that material obtained from the epoxidation reaction of 9. Treatment of the epoxides 11 and 12 with 2,4-dinitrobenzoyl chloride afforded the nitrobenzoates 15 and 16, and the absolute
configuration of the latter was determined by a X-ray analysis; the atomic coordinates, bond lengths and angles, torsion angles and thermal parameters are available on request from the Director of the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB21EW. The main results of this X-ray analysis are depicted in Fig. 1. Therefore, the assignment of the absolute configuration of all stereogenic centres was possible for compounds 11-16, respectively.

Interestingly enough, treatment of (+)-1 with m-CPBA gave rise in 70% yield to a product 17 whose elemental analysis corresponded well with an expected epoxide 18 but the $^1$H NMR spectrum showed a triplet at $\delta = 6.24$ with $J = 1.9$ Hz, and in the $^{13}$C NMR spectrum two signals at $\delta = 117.7$ and $\delta = 149.9$ ppm indicated the presence of an olefinic double bond. The oxidation of $\alpha,\beta$-unsaturated ketones to $\alpha$-epoxy-ketones and their rearrangement to enol lactones is well documented; nevertheless no products corresponding to this reaction were found in our experiments. To gain an unambiguous structural assignment, however, suitable crystals of 17 were grown and subjected to a X-ray analysis whose results are depicted in Fig. 2. Therefore, 17 results from a Baeyer-Villiger-oxidation of 1.
Compound 12 itself seems to be a valuable intermediate for the synthesis of C(4a') substituted nucleoside analogues and it could be subjected to a nucleophilic displacement reaction at the hydroxy group using Mitsunobu conditions [24, 25] without affecting the epoxide moiety. Thus, reaction of 12 with triphenylphosphine, diethyl azodicarboxylate and 6-chloropurine gave 19 in 62% yield after chromatographic purification [26–31].

The $^1$H NMR spectrum of 19 showed – as compared to the spectrum of 12 – two additional signals at $\delta = 8.19$ and 8.62 ppm resulting from the presence of the purine moiety and in the IR spectrum the signal of the hydroxy group was missing. The synthetic potential of these novel synthetic precursors for the synthesis of cyclopentanoid nucleoside analogues is currently under investigation in our laboratories.

**Experimental**

*General methods:* [32]

*Dimethyl(6-O-benzyl-1-deoxy-3,4-O-isopropylidene-β-D-ribo-hex-2-ulofuranosyl)-phosphonate (3)*

To a solution of freshly distilled dimethyl methylphosphonate (24.0 g, 193.5 mmol) in dry THF (200 ml) at $-78^\circ$C n-butyllithium (120 ml, 1.6 M in hexane) was added within 40 min. After stirring for an additional 30 min at $-78^\circ$C a solution of 2 (21.4 g, 77 mmol) in dry THF (200 ml) was slowly added. Stirring was continued for an
additional 15 min, then a saturated aqueous solution of ammonium chloride (25 ml) was added, the reaction mixture was diluted with diethyl ether (500 ml), the organic layer was separated, and the aqueous phase was extracted with ether (10 × 100 ml). The combined organic phases were washed with brine (100 ml), dried (MgSO₄), and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:1) to afford 3 (25.9 g, 84%) as a colorless oil that crystallized upon refrigeration; m.p. 56 °C; [α]D²⁰ = −13.7° (c, 1.1 CHCl₃); Rf = 0.18 (hexane/ethyl acetate 1:1); (Lit.: [α]D²⁰ = −8.2° (c, 1.0 CHCl₃) [13]; ¹H NMR (300 MHz, CDCl₃): δ = 7.39–7.25 (m, 5 H, H-C(ar)); 4.61 (d, 1 H, J = 6.2 Hz, H-C(3)), 4.55 (s, 2 H, CH₂(ar)), 4.22 (dd, 1 H, J = 3.2, 6.0 Hz, H-C(4)), 3.92 (ddd, 1 H, J = 3.2, 6.0, 6.5 Hz, H-C(5)), 3.81 (d, 3 H, J = 2.7 Hz, POCH₃), 3.78 (d, 3 H, J = 2.7 Hz, POCH₃), 3.72 (dd, 1 H, J = 3.2, 9.9 Hz, H₆B-C(6)), 3.58 (dd, 1 H, J = 6.0, 9.9 Hz, H₆A-C(6)), 3.45 (ddd, 1 H, J = 14.3, 22.4 Hz, H₆B-C(1)), 3.35 (dd, 1 H, J = 14.3, 22.4 Hz, H₆A-C(1)), 2.70 (bs, 1 H, exchangeable with D₂O, HO-C(5)), 1.43 (s, 3 H, CH₃(isopropyl)), 1.34 (s, 3 H, CH₃(isopropyl)); ¹³C NMR (75 MHz, CDCl₃): δ = 201.33 (d, JCP = 6.7 Hz, C(2)), 137.69 (s, C₆(α)), 128.25, 127.63 125.79 (d, C₆(α)), 111.21 (s, C₆(β)), 82.64 (d, JCP = 2.3 Hz, C(4)), 77.36 (d, C(5)), 73.43 (t, CH₃(ar)), 71.55 (d, C(3)), 70.82 (t, C(6)), 53.13 (dq, JCP = 5.4 Hz, POCH₃), 53.03 (dq, JCP = 6.7 Hz, POCH₃), 37.20 (dt, JCP = 131.0 Hz, C(1)), 26.95 (q, CH₃(isopropyl)); MS (FAB, glycerol): 403; MS (FAB, glycerol + LiCl): 409.

Analysis for C₁₃H₂₇O₈P (402.38)
  Calcd C 53.73 H 6.76%.
  Found C 53.90 H 6.89%.

Dimethyl(6-O-benzyl-1-deoxy-3,4-O-isopropylidene-D-erythro-2,5-hexodiulosyl)-phosphonate (5)

To a solution of 4 (10.1 g, 25 mmol) in abs. dichloromethane (100 ml) a solution of Dess-Martin’s periodinane (10.7 g, 26 mmol) in abs. dichloromethane (100 ml) was added in several portions. Dry tert-butanol (2.0 g, 27 mmol) was added and stirring was continued at 25 °C until tlc indicated the absence of any starting material. After dilution with diethyl ether (500 ml), a saturated aqueous solution of sodium hydrogencarbonate (500 ml) was added, the phases were separated, the organic layer was extracted with diethyl ether (4 × 200 ml) and the combined organic phases were dried (MgSO₄); the solvent was removed under reduced pressure and the residue subjected to column chromatography (silica gel, hexane/ethyl acetate 5:1 → 3:1 → 1:1) to afford 5 (7.6 g, 76%) as an oil; [α]D²⁰ = −17.5° (c, 1.5 CHCl₃); Rf = 0.42 (ethyl acetate); (Lit.: [α]D²⁰ = −14.1° (c, 1.0 CHCl₃) [13]); ¹H NMR (250 MHz, CDCl₃): δ = 7.38–7.25 (m, 5 H, H-C(ar)), 4.84 (t, 1 H, J = 5.7 Hz, H-C(4)), 4.75 (t, 1 H, J = 5.7 Hz, H-C(3)), 4.63 (s, 2 H, CH₂(ar)), 4.48 (d, 1 H, J = 18.4 Hz, H₆B-C(6)), 4.40 (d, 1 H, J = 18.3 Hz, H₆A-C(6)), 3.83 (d, 3 H, J = 1.9 Hz, POCH₃), 3.79 (d, 3 H, J = 1.9 Hz, POCH₃), 3.54
To a solution of periodinane (745 mg, 1.76 mmol) in abs. dichloromethane (7 ml) a solution of 
4 (180 mg, 0.45 mmol) in abs. dichloromethane (5 ml) was added in one portion. After the 
addition of dry tert-butanol (200 mg, 2.7 mmol) stirring at 25 °C was continued for 7 h, then the 
reaction was diluted with diethyl ether (200 ml) and a saturated aqueous solution of sodium 
hydrogen carbonate (150 ml) was added. Work up as above and chromatography (silica gel, hexane/ 
ethyl acetate 5:1 → 3:1 → 2:1) gave a 1:1 mixture of 6/7 (151 mg, 71 %) as a semicrystalline oil; m.p.: 
35 °C; MS (ei, 80 eV, 105 °C): 472 (M, 0.6%), 457 (M-CH₃, 0.7%), 416 (1.4%), 399 (2.7%), 366 
(2.3%), 341 (6.1%), 310 (10.1%), 267 (86.8%), 223 (15.9%), 209 (95.1%), 191 (66.5%), 165 (15.2%), 
151 (21.8%), 127 (14.4%), 91 (100%); By repeated chromatography a temporarily separation of 6 and 7 
could be achieved.

Data for 6. – \( R_F = 0.76 \) (ethyl acetate), \( R_F = 0.70 \) (ethyl acetate). Data for 6. – ¹H NMR (300 MHz, CDCl₃): \( \delta = 7.29-7.40 \) (m, 5 H, H-C(ar)), 4.99 (dd, 1 H, J = 5.6, 6.9, 9.0 Hz, H-C(7a)), 4.68 
(\( d, 1 H, J = 5.6, H-C(3a) \)), 4.63 (d, 2 H, J = 2.2 Hz, CH₂(ar)), 4.51 (d, 1 H, J = 18.2 Hz, H₂A \( \beta \) 
CH₂(OBn)), 4.40 (d, 1 H, J = 18.2 Hz, H₂B \( \beta \) CH₂(OBn)), 3.81, 3.77 (d, 3 H, J = 2.6 Hz, POCH₃), 3.25 
(dd, 1 H, J = 9.0, 21.1 Hz, H-C(6)), 1.49 (s, 9 H, CH₃(tert-butyl)), 1.44, 1.32 (s, 3 H, 2 x 
CH₃-CH₂(2)), ¹³C NMR (75 MHz, CDCl₃): \( \delta = 203.90 \) (s, C(7)), 164.97 (ds, J_CP = 5.8 Hz, C(4)), 
137.09 (s, C(4)), 128.26, 127.83, 127.75 (d, C(2)), 111.07 (s, C(2)), 82.50 (s, C₆(tert-butyl)), 
80.02 (d, C(7a)), 73.99 (d, C(3a)), 73.20 (t, CH₂(ar)), 73.02 (t, CH₂(OBn)), 53.58 (dq, J_CP = 
6.7 Hz, POCH₃), 53.30 (dq, J_CP = 6.4 Hz, POCH₃), 50.60 (dd, J_CP = 128.8 Hz, C(6)), 27.88 (q, 
CH₂(tert-butyl)), 27.22, 26.26 (q, 2 x CH₃).

Data for 7. – ¹H NMR (300 MHz, CDCl₃): \( \delta = 7.30-7.40 \) (m, 5 H, H-C(ar)), 4.68 (\( d, 1 H, J = 6.8 \) 
Hz, H-C(3a)), 4.77 (dd, 1 H, J = 5.3, 6.8, 11.1 Hz, H-C(7a)), 4.63 (s, 2 H, CH₂(ar)), 4.53 (d, 1 H, J = 
18.5 Hz, H₂A-CH₂(OBn)), 4.42 (d, 1 H, J = 18.5 Hz, H₂B-CH₂(OBn)), 3.81, 3.77 (d, 3 H, J = 2.6 Hz, 
POCH₃), 3.45 (dd, 1 H, J = 5.3, 22.9 Hz, H-C(6)), 1.48 (s, 9 H, CH₃(tert-butyl)), 1.46, 1.34 (s, 3 H, 2 x 
CH₃), ¹³C NMR (75 MHz, CDCl₃): \( \delta = 204.58 \) (s, C(7)), 165.26 (ds, J_CP = 5.1 Hz, C(4)), 137.02 
(s, C(3a)), 128.25, 127.82, 127.74 (d, C(ar)), 111.14 (s, C(2)), 82.83 (s, C₆(tert-butyl)), 79.87 (d, C(7a)), 
74.03 (d, C(3a)), 73.15 (t, CH₂(ar)), 72.65 (t, CH₂(OBn)), 53.34 (dq, J_CP = 6.7 Hz, POCH₃), 
53.24 (dq, J_CP = 6.4 Hz, POCH₃), 48.46 (dd, J_CP = 128.8 Hz, C(6)), 27.81 (q, CH₃(tert-butyl)), 26.64, 
26.05 (q, 2 x CH₃).

(3aS,4S,6aR)-6-(Benzyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (8)

To a -20 °C cold solution of (-)-1 (1.0 g, 3.65 mmol) and CeCl₃ • 7 H₂O (1.12 g, 3.01 mmol) 
in methanol (7 ml) sodium borohydride (0.15 g, 3.94 mmol) was added in several portions and the 
mixture was allowed to warm to 25 °C. The pH was adjusted to 5 by the addition of acetic acid, 
water (15 ml) was added and the mixture was extracted with diethyl ether (3 × 30 ml). The 
combined organic layers were washed with brine, dried (MgSO₄), and the solvent was removed under reduced 
pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 10:1) to afford 8 (0.95 g, 94%); \([\alpha]_D^0 +20.4^0 \) (c, 1.6 CHCl₃); \( R_F = 0.64 \) (hexane/ethyl acetate 1:1); 
¹H NMR (300 MHz, CDCl₃): \( \delta = 7.33-7.24 \) (m, 5 H, H-C(ar)), 5.82 (d, 1 H, J = 1.5 Hz, H-C(5)), 
4.97 (d, 1 H, J = 5.4 Hz, H-C(6a)), 4.77 (t, 1 H, J = 5.5 Hz, H-C(3a)), 4.58 (s, 3 H, CH₃(2)), H-C(4)), 
4.16 (s, 2 H, CH₂(OBn)), 2.76 (d, 1 H, J = 9.2 Hz, OH)), 1.43, 1.40 (s, 3 H, 2 x CH₃); ¹³C NMR (62.89 
MHz, CDCl₃): \( \delta = 142.34 \) (s, C(6)), 137.84 (s, C(9a)), 131.24 (d, C(5)), 128.30, 127.50 (d, C(ar)), 
112.40 (s, C(2)), 82.92, 77.69, 73.21 (d, C(4), C(3a), C(6a)), 72.81 (t, CH₂(ar)), 66.16 (t, CH₂(OBn)), 
27.58, 26.56 (q, 2 x CH₃); MS (ei, 80 eV, 150 °C): 278 (1.4%), 263 (4.3%), 220 (5.7%), 168 (5.2%), 
110 (6.1%), 107 (10.4%), 92 (15.8%), 91 (100%).
(3aS,4S,6aR)-6-(Benzyloxy-methyl)-4-(triisopropylsilyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]-dioxol (9)

To a solution of 8 (500 mg, 1.81 mmol) in dry pyridine (4 ml) containing 4-dimethylaminopyridine (250 mg, 2.0 mmol) triisopropyletherosilane (420 mg, 2.2 mmol) was added and the mixture stirred at 25°C for 24 h. After dilution of this suspension with dichloromethane (15 ml) and ice water (5 ml) the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 25 ml); the combined organic layers were washed with brine, dried (MgSO4), the solvent was removed and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 50:1) to afford 9 (778 mg, 99.0%) as an oil; [α]D20 +6.3 (c, 1.0, CHC13), Rf = 0.43 (hexane/ethyl acetate 10:1); 1H NMR (300 MHz, CDCl3): δ = 7.17-7.27 (m, 5 H, H-C(ar)), 5.68 (s, 1 H, H-C(5)), 4.81 (1, 1 H, J = 5.6 Hz, H-C(6a)), 4.64 (m, 1 H, H-C(4)), 4.61 (1, 1 H, J = 5.6 Hz, H-C(3a)), 4.48 (s, 2 H, CH2(ar)), 4.09 (s, 2 H, CH2(OBn)), 1.31, 1.30 (s, 3 H, 2 × CH3), 1.03 (s, 18 H, CH2-TIPS), 0.98 (s, 3 H, CH-TIPS); 13C NMR (62 MHz, CDCl3): Δd = 141.98 (s, C(6)), 138.36 (s, C(9)), 132.26 (d, C(5)), 128.34, 127.94 (d, C(6)), 112.44 (s, C(2)), 83.28, 79.49, 74.81 (d, C(4), C(3a), C(6a)), 73.30 (t, CH2(ar)), 66.94 (t, CH2(OBn)), 27.99, 26.49 (q, 2 × CH3); 18.42 (q, CH3(TIPS)), 12.84 (d, CH(TIPS)); MS (ei, 80 eV, 120°C): 417 (M-CH3, 0.4%), 332 (M-2CH3, 10%), 240 (M-CH3-(2 × isopropyl)-Bn, 2.0%), 225 (20%), 201 (1.9%), 183 (4.4%), 155 (5.5%), 131 (3.3%), 103 (3.5%), 91 (100%).

Analysis for C25H40O4Si (432.68)
Calcd C 69.40 H 9.32%.
Found C 69.54 H 9.21%.

(1S,2R,3R)-4-(Benzyloxy-methyl)-1-O-(tert-butyl-dimethylsilyl)-2,3-O-(isopropylidene-cyclopent-4-ene = (3aR,4S,6aR)-6-(benzyloxy-methyl)-4-(tert-butyl-dimethylsilyloxy)-2,2-dimethyl-3a,6a-dihydro-cyclopenta[d][1,3]-dioxol (10)

To a solution of 8 (0.829 g, 3.00 mmol) in abs. dichloromethane (25 ml) dry pyridine (1.5 ml, 18.6 mmol), DMAP (100 mg, 0.8 mmol) and tert-butylidimethylchlorosilane (0.60 g, 4.0 mmol) were added and the mixture was stirred for 15 h. Then the suspension was diluted with dichloromethane (25 ml) and ice water (10 ml). The layers were separated, the aqueous phase was extracted with dichloromethane (3 × 50 ml), the combined organic phases washed with brine, dried (MgSO4), and the solvents were removed under reduced pressure to yield a residue, subjected to column chromatography (silica gel, hexane/ethyl acetate 20:1) to afford 10 (1.05 g, 90%); +18.6° (c, 1.6 CHCl3), Rf = 0.71 (hexane/ethyl acetate 3:1); 1H NMR (300 MHz, CDCl3): δ = 7.35-7.22 (m, 5 H, H-C(ar)), 5.72 (s, 1 H, H-C(4a)), 4.87 (m, 1 H), 4.64 (m, 2 H), 4.45 (s, 2 H, CH2(ar)), 4.16 (s, 2 H, H2(C5)), 1.41 (s, 3 H, CH3(isopropyl)), 1.37 (s, 3 H, CH3(isopropyl)), 0.93 (s, 9 H, CH3(tert-buty1)), 0.13 (s, 6 H, 2 × CH3-Si); 13C NMR (62 MHz, CDCl3): δ = 141.82 (s, C(4)), 138.18 (s, C(9)), 131.72, 128.40, 127.70, 127.65 (d, C(4)), 112.22 (s, C(6a)), 82.93, 79.00, 74.61 (d, C(1), C(2), C(3)), 72.91 (t, CH2(ar)), 6.66 (s, C(4)), 27.47 (q, CH3(isopropyl)), 26.88 (q, CH3(isopropyl)), 25.88 (q, CH3(tert-buty1)), 18.41 (s, C(9)), -4.47 (q, CH3-Si), -4.85 (q, CH3-Si); MS (80 eV, 115°C): 376 (M+1, 0.3%), 375 (M-15, 1%), 332 (M-tert-buty1, 9.7%).

Analysis for C29H44O4Si (390.59)
Calcd C 67.65 H 8.77%.
Found C 67.27 H 8.64%.

(4aS,4a,Anhydro-5-O-benzyl-4a-carba-2,3-O-isopropylidene-β-L-lyxofuranose = (1S,2S,3S,4R,5S)-2-benzyloxymethyl-7,7-dimethyl-6,8,9-trioxo-tricyclo [3.3.1.2 3]nonan-4-ol (11) and (4a R)-4,4a-anhydro-5-O-benzyl-4a-carba-2,3-O-isopropylidene-β-D-ribofuranose = (1S,2R,3R,4R,5S)-2-Benzoxymethyl-7,7-dimethyl-6,8,9-trioxo-tricyclo [3.3.1.2 3]nonan-4-ol (12)

To a solution of 8 (1.10 g, 3.98 mmol) in dichloromethane (25 ml) m-CPBA (70%, 1.88 g, 7.61 mmol) was added and the mixture stirred for 12 h. Work up was performed as described for 13, followed by chromatography (silica gel, hexane/ethyl acetate 10:1 → 6:1 → 2:1) to give 11 (0.35 g, 30%) and 12 (0.76 g, 65%). Data for 11. – [α]D20 +11.8° (c, 1.4 CHCl3); Rf = 0.46 (hexane/ethyl acetate 4:1); 1H NMR (300 MHz, CDCl3): δ = 7.36-7.25 (m, 5 H, H-C(ar)), 4.78 (dd, 1 H, J = 1.1, 5.7 Hz, H-C(3)), 4.62 (s, 2 H, CH2(ar)), 4.53 (vrt, 1 H, J = 5.7 Hz, H-C(2)), 4.17 (1d, 1 H, J = 11.9 Hz, Hα-C(5)), 4.11 (d, 1 H, J = 5.9 Hz, H-C(1)), 3.57 (s, 1 H, H-C(4a)), 3.53 (d, 1 H, J = 11.9 Hz, Hβ-C(5)), 2.9 (bs, 1 H, OH), 1.52, 1.40 (s, 3 H, 2 × CH3(isopropyl)); 13C NMR (75 MHz, CDCl3): δ = 137.63 (s, C(9)), 128.15, 127.48 (d, C(4)), 117.21 (s, C(6a)), 79.80, 79.16 (d, C(1), C(2)), 73.25 (t, CH2(ar)), 66.17 (t, C(3)), 67.60 (s, C(4)), 66.37 (t, C(5)), 63.40 (d, C(4a)), 26.13, 24.49 (q, 2 × CH3(isopropyl)); MS (ei, 80 eV, 110°C): 293 (M+1, 0.6%), 292 (M, 3.5%), 277 (M-CH3, 13.3%).
15.8%), 171 (8.3%), 110 (20.6%), 107 (21.6%), 101 (35.2%), 91 (100%).

Analysis for C_{16}H_{20}O_{5} (292.33)
Calcd C 65.74 H 6.89%.
Found C 65.58 H 6.81%.

Data for 12. [α]_{D}^{20} +46.9° (c, 1.1 CHCl_{3}); R_{F} = 0.15 (hexane/ethyl acetate 4:1); \textsuperscript{1}H NMR (300 MHz, CDCl_{3}): δ = 7.42–7.27 (m, 5 H, H-C(ar)), 4.76 (d, 1 H, J = 11.8 Hz, H_{A}-CH_{3}(ar)), 4.52 (d, 1 H, J = 11.8 Hz, H_{B}-CH_{2}(ar)), 4.53–4.50 (m, 1 H, H-C(2)), 4.17 (dd, 1 H, J = 1.5, 6.1 Hz, H-C(l)), 3.81 (s, 1 H, H-C(4a)), 3.62 (s, 1 H, J = 11.4 Hz, H-A-C (5)), 3.61 (m, 5 H, H-C(ar)), 4.67 (d, 1 H, J = 6.6 Hz, H-C(3)), 4.65 (d, 1 H, J = 11.7 Hz, H_{A}-CH_{2}(ar)), 4.51 (d, 1 H, J = 11.7 Hz, H_{B}-CH_{2}(ar)), 4.44 (dt, 1 H, J = 1.1, 6.4 Hz, H-C(2)), 4.30 (d, 1 H, J = 11.4 Hz, H_{A}-C(5)), 3.61 (d, 1 H, J = 11.4 Hz, H_{B}-C(5)), 3.47 (d, 1 H, J = 1.3 Hz, H-C(4a)), 1.59, 1.30 (s, 3 H, 2 x CH_{3}(isopropyl)), 1.10 (s, 3 H, CH-TIPS), 1.05 (s, 18 H, CH_{2}-TIPS); \textsuperscript{13}C NMR (75 MHz, CDCl_{3}): δ = 137.79 (s, C_{α}(ar)), 128.13, 127.48 (d, C_{α}(ar)), 113.06 (s, C_{δ}(isopropyl)), 82.06, 79.23 (d, C(1), C(2)), 73.13 (t, C_{δ}(ar)), 70.38 (d, C(3)), 67.90 (s, C(4)), 64.44 (t, C(5)), 64.14 (d, C(4a)), 26.59, 25.78 (q, 2 x CH_{3}(isopropyl)), 17.88 (q, CH_{3}(TIPS)), 17.69 (q, CH_{3}(TIPS)), 12.16 (d, CH(TIPS)); MS (ei, 80 eV, 140 °C): 448 (M, 0.5%), 433 (M–CH_{3}, 6.9%), 405 (28.3%), 347 (41.1%), 185 (8.0%), 157 (5.9%), 103 (13.9%), 92 (23.3%), 91 (100%).

Analysis for C_{25}H_{40}O_{5}Si (448.26)
Calcd C 66.93 H 8.99%.
Found C 66.84 H 8.82%.

(4aR)4,4a-Anhydro-5-O-benzyl-4a-carba-1-O-(triisopropylsilyl)-2,3-O-isopropylidened-β-D-ribofuranose = (1S,2R,3S,4R,5S)-2-benzoxymethyl-7,7-dimethyl-4-triisopropylosilyloxy-6,8,9-trioxa-tricyclo[3.3.1.2^-]nonane (14)

To a solution of 9 (500 mg, 1.15 mmol) in dichloromethane (15 ml) m-CPBA (70%), 543 mg, 2.2 mmol) was added, and the mixture was stirred for 6 h. After addition of dichloromethane (15 ml) and ice water (5 ml), the aqueous phase was extracted with dichloromethane (3 x 25 ml), the combined organic layers were washed with brine (10 ml), dried (MgSO_{4}), the solvent was removed in vacuo and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 50:1 → 10:1) to afford 14 (733 mg, 88.3%) as a colorless oil; [α]_{D}^{20} +15.9° (c, 1.0 CHCl_{3}), R_{F} = 0.73 (hexane/ethyl acetate 2.5:1); \textsuperscript{1}H NMR (300 MHz, CDCl_{3}): δ = 7.25–7.35 (m, 5 H, H-C(ar)), 4.67 (d, 1 H, J = 6.6 Hz, H-C(3)), 4.65 (d, 1 H, J = 11.7 Hz, H_{A}-CH_{2}(ar)), 4.51 (d, 1 H, J = 11.7 Hz, H_{B}-CH_{2}(ar)), 4.44 (dt, 1 H, J = 1.1, 6.4 Hz, H-C(2)), 4.30 (d, 1 H, J = 11.4 Hz, H_{A}-C(5)), 3.61 (d, 1 H, J = 11.4 Hz, H_{B}-C(5)), 3.47 (d, 1 H, J = 1.3 Hz, H-C(4a)), 1.59, 1.30 (s, 3 H, 2 x CH_{3}(isopropyl)), 1.10 (s, 18 H, CH_{3}(TIPS)), 1.09 (s, 3 H, CH(TIPS)); \textsuperscript{13}C NMR (75 MHz, CDCl_{3}): δ = 137.71 (s, C_{α}(ar)), 128.31, 127.88, 127.72 (d, C_{α}(ar)), 113.74 (s, C_{δ}(isopropyl)), 78.02 (d, C(1)), 77.52 (d, C(2)), 73.58 (t, C_{δ}(ar)), 71.38 (d, C(3)), 68.20 (t, C(5)), 65.72 (d, C(4a)), 63.23 (s, C(4)), 26.26, 25.79 (q, 2 x CH_{3}(isopropyl)), 18.00 (q, CH_{3}(TIPS)), 12.38 (d, CH(TIPS)); MS (ei, 80 eV, 113 °C): 433 (M–CH_{3}, 2.5%), 405 (M–isopropyl, 9.1%), 347 (9.4%), 239 (6.3%), 227 (3.2%), 199 (4.5%), 159 (5.5%), 157 (2.5%), 131 (5.3%), 129 (3.8%), 91 (100%).
Analysis for C$_2$H$_4$O$_2$Si (448.26)
Calcd C 66.93 H 8.99%
Found C 66.86 H 8.97%

(4aS,4a)-Anhydro-5-O-benzyl-4a-carba-2,3-O-isopropylidene-1-O-(3,5-dinitrobenzoyl)-β-L-lyxofuranose = (1S,2S,3S,4R,5S)-2-benzyloxymethyl-7,7-dimethyl-6,8,9-trioxa-tricyclo[3.3.1.2']-non-4-yl-3,5-dienzoate (15)

To a solution of 11 (100 mg, 0.34 mmol) in dry pyridine (1 ml) 3,5-dinitrobenzoylchloride (158 mg, 0.68 mmol) was added, the mixture was stirred at 25 °C for 30 min, poured onto ice water (5 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic phases were dried (MgSO$_4$), the solvent removed under reduced pressure and residue subjected to chromatography (silica gel, hexane/ethyl acetate 10:1) to afford 15 (146 mg, 88% as white crystals; m.p. 128 °C; [α]$_D$ = -13.0° (c, 0.9 CHCl$_3$); $R_F$ = 0.52 (hexane/ethyl acetate 2:1); $^1$H NMR (300 MHz, CDCl$_3$): δ = 9.23 (t, 1 H, J = 2.1, H-C(4')), 9.18 (d, 2 H, J = 2.1, H-C(2'), H-C(6')), 7.26–7.39 (m, 5 H, H-C$_9$(Bn)), 5.32 (d, 1 H, J = 5.6, H-C(1)), 4.83 (dd, 1 H, J = 1.0, 5.6, H-C(3)), 4.76 (t, 1 H, J = 5.5, H-C(2)), 4.66 (s, 2 H, CH$_2$(Bn)), 4.26 (d, 1 H, J = 11.9, H$_2$-C(5)), 3.85 (s, 1 H, H-C(4a)), 3.73 (d, 1 H, J = 11.9, H$_2$-C(5)), 1.32, 1.27 (s, 3 H, 2 x CH$_3$(isopropyl)); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 161.21 (s, C=O), 148.56 (s, C$_3$(3'), C$_3$(5')), 137.52 (s, C$_9$(Bn), 133.12 (s, C(1')), 129.37 (d, C$_9$(2'), C$_9$(6')), 128.30, 127.69, 127.59 (d, C$_9$(Bn), 122.54 (d, C(4'))), 113.64 (s, C$_3$(isopropyl)), 79.80 (d, C(2)), 77.03 (d, C(3)), 73.55 (t, CH$_3$(Bn)), 72.38 (d, C(1)), 68.43 (t, C(5)), 65.83 (s, C(4)), 60.63 (d, C(4a)), 26.42, 24.81 (q, 2 x CH$_3$(isopropyl)); MS (ei, 80 eV, 178 °C): 487 (M+1, 12%), 486 (M, 5.0%), 471 (M–CH$_3$, 15.2%), 365 (8.0%), 265 (3.1%), 195 (59.1%), 149 (15.6%), 111 (16.8%), 110 (21.3%), 91 (100%).

Analysis for C$_2$H$_2$N$_2$O$_{10}$ (292.33)
Calcd C 56.79 H 4.56 N 5.76%
Found C 56.75 H 4.59 N 5.57%

(4aR,4a)-Anhydro-5-O-benzyl-4a-carba-2,3-O-isopropylidene-1-O-(3,5-dinitrobenzoyl)-δ-D-ribofuranose = (1S,2R,3S,4R,5S)-2-benzyloxymethyl-7,7-dimethyl-6,8,9-trioxa-tricyclo[3.3.1.2']-non-4-yl-3,5-dienzoate (16)

To a solution of 12 (200 mg, 0.68 mmol) in dry pyridine (1 ml) 3,5-dinitrobenzoylchloride (315 mg, 1.37 mmol) was added, the mixture was stirred at 25 °C for 30 min. Work up was performed as described for 15 and after chromatography (silica gel, hexane/ethyl acetate 2.5:1) 16 (297 mg, 90%) was obtained; m.p. 135–136 °C; [α]$_D$ = +23.0° (c, 1.2 CHCl$_3$); $R_F$ = 0.23 (hexane/ethyl acetate 2:1); $^1$H NMR (300 MHz, CDCl$_3$): δ = 9.20 (s, 3 H, H-C(2'), H-C(4'), H-C(6')), 7.27–7.33 (m, 5 H, H-C$_9$(Bn)), 5.24 (dd, 1 H, J = 1.7, 5.1, H-C(1)), 4.87–4.91 (m, 2 H, H-C(3), H-C(2)), 4.66 (d, 1 H, J = 11.8, H$_A$-CH$_2$(Bn)), 4.55 (d, 1 H, J = 11.8, H$_B$-CH$_2$(Bn)), 3.91 (d, 1 H, J = 11.5, H$_A$-C(5)), 3.83 (s, 1 H, H-C(4a)), 3.72 (d, 1 H, J = 11.5, H$_B$-C(5)), 1.56, 1.31 (s, 3 H, 2 x CH$_3$(isopropyl)); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 162.07 (s, C=O), 148.42 (s, C$_3$(3'), C$_3$(5')), 137.37 (s, C$_9$(Bn), 133.07 (s, C(1')), 129.58 (d, C$_9$(2'), C$_9$(6')), 128.31, 127.77, 127.71 (d, C$_9$(Bn)), 122.43 (d, C(4')), 114.96 (s, C$_3$(isopropyl)), 78.21 (d, C(2)), 75.98 (d, C(3)), 73.78 (d, C(1)), 73.58 (d, CH$_2$(Bn)), 67.40 (t, C(5)), 64.50 (s, C(4)), 62.51 (d, C(4a)), 26.34, 25.89 (q, 2 x CH$_3$(isopropyl)); MS (ei, 80 eV, 132 °C): 486 (M, 0.03%), 471 (M–CH$_3$, 16.7%), 365 (13.2%), 195 (14.5%), 149 (6.9%), 111 (9.7%), 91 (100%).

Analysis for C$_2$H$_2$N$_2$O$_{10}$ (292.33)
Calcd C 56.79 H 4.56 N 5.76%
Found C 56.68 H 4.59 N 5.49%

R. Csek et al. • 4a-Substituted Carbocyclic Cyclopentanoid Nucleoside Precursors, I
To a solution of triphenylphosphine (430 mg, 1.64 mmol) and 6-chloropurine (262 mg, 1.64 mmol) in abs. THF was slowly added, and the mixture was stirred for 1 h. Then a solution of diethyl azodicarboxylate (0.27 ml, 95%, 1.64 mmol) in abs. THF (5 ml) was added, stirred for 3 days, the solvents were removed under reduced pressure and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 3:1) to afford 19 (364 mg, 62%) as viscous oil; \([\alpha]_D^20 -4.2^\circ;\) RF = 0.25 (hexane/ethyl acetate 1:1); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.62\) (m, 1 H, H-C (2')), 8.19 (s, 1 H, H-C (8')), 7.28 - 7.33 (m, 5 H, H-Car(Bn)), 5.32 (d, 1 H, J = 7.0 Hz, H-C(1)), 5.09 (s, 1 H, H-C(4)), 4.80 (d, 1 H, J = 7.0 Hz, H-C(5)), 4.66 (d, 1 H, J = 11.8 Hz, H\(_A^-\)-CH\(_2\)(Bn)), 4.60 (d, 1 H, J = 11.8 Hz, H\(_B^-\)-CH\(_2\)(Bn)), 4.02 (d, 1 H, J = 11.8 Hz, H\(_A^-\)-CH\(_2\)(OBn)), 3.92 (d, 1 H, J = 11.8 Hz, H\(_B^-\)-CH\(_2\)(OBn)), 3.65 (d, 1 H, J = 1.4 Hz, H-C(3)), 1.61, 1.29 (s, 3 H, 2 x CH\(_3\)); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)): \(\delta = 151.83\) (d, C(2')), 151.33 (s, C(6')), 151.05 (s, C(4')), 144.35 (d, C(8')), 137.41 (s, C\(_6\)(Bn)), 131.78 (s, C(5')), 128.21, 127.66, 127.60, 127.59 (d, C\(_7\)(Bn)), 113.96 (s, C(7)), 86.81 (d, C(5)), 79.69 (d, C(1)), 73.30 (t, CH\(_2\)(Bn)), 69.57 (s, C(2)), 66.76 (t, CH\(_2\)(OBn)), 63.25 (d, C(3)), 59.30 (d, C(4)), 26.17, 25.36 (q, 2 x CH\(_3\)); MS (ei, 80 eV, 191 °C): 430 (M + 2, 0.5%), 429 (M + 1, 0.3%), 428 (M, 1.7%), 415 (7.2%), 414 (4.8%), 413 (M-CH\(_3\), 20.1%), 324 (2.5%) 322 (7.3%), 307 (3.6%), 264 (10.2%), 249 (3.3%), 237 (3.5%), 235 (4.9%), 209 (5.3%), 207 (13.5%), 199 (3.2%), 197 (10.3%), 157 (10.2%), 155 (30.2%), 153 (6.8%), 126 (17.9%), 110 (12.1%), 91 (100%); HRMS calcld. for: C\(_{21}\)H\(_{21}\)N\(_2\)O\(_3\)Cl: 428.1251; found: 428.1252.

**Acknowledgements**

Financial support by the European Communities (SC1*-CT92-0780) and the Fonds der Chemischen Industrie is gratefully acknowledged; we are indebted to Dr. P. Rosyk for his help with the manuscript and to Professor Dr. R. Neidlein, Pharmazeutisch-Chemisches Institut, Universität Heidelberg, for his encouragement.