Synthesis of Rigid Cyclopropanoid Nucleoside Analogues
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Dedicated to Prof. Dr. Wolfgang Wiegrebe, Regensburg, on the occasion of his 70th birthday
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A convenient synthesis has been developed for the synthesis of cyclopropanoid nucleoside analogues that possess no additional spacer groups between the heterocycle and the hydroxylated cyclopropane ring. For some of these compounds the respective enantiomers could be separated on an analytical scale by means of HPLC using chiral phases.

Introduction
Progress in the field of medicinal chemistry has been tremendous during the last decades. Thus, especially in the field of antitumor-active as well as antiviral-active compounds, quite a number of compounds have been devised, synthesized and applied to sick people for their benefit. Despite these improvements in medicinal care, however, bacterial as well as viral infectious diseases remain in the focus of interest due to the development and world-wide spreading of “new” diseases such as AIDS and hemorrhagic fevers caused by Ebola, Lassa or Dengue viruses as well as the returning of “old” diseases such as tuberculosis, malaria or cholera.

Cyclopropane derived drugs have gained considerable attraction due to their ability to show a variety of promising biological activities [1, 2]. More recently, cyclopropane derived nucleoside analogues have been in the focus of interest as potential chemotherapeutic agents [3–6]. Thus, a number of compounds possessing an additional spacer or an unsaturated group between the cyclopropane and the heterocycle as well as compounds with a (in)direct attachment of the heterocycle but with two vicinal or geminal hydroxymethyl units [7, 8] at the cyclopropane skeleton have been prepared. During our synthesis of antiviral-active compounds we became interested in cyclopropanoid nucleoside analogues, particularly in those target compounds where both the heterocycle and the hydroxyl group are directly attached to the cyclopropane ring.

Results and Discussion
Cyclopropanes with two vicinal functional groups directly attached to vicinal positions of the three-membered ring are scarcely found due to problems in their synthesis and due to pronounced instability under a number of quite different reaction conditions [9, 10]. Compound (±)-1, however, is easily available following well known procedures [11] and seemed to be a valuable starting material for our envisaged strategy.

Thus, compound (±)-1 was subjected to a modified Hofmann degradation [12] using (diacetoxyiodo)benzene/potassium hydroxide to obtain (±)-2. Treatment of 2 with potassium hydroxide in aqueous methanol gave the amine (±)-3.

In order to obtain analogues containing heterocycles of the purin type, the amine (±)-3 gave upon reaction with 3-methoxy-2-methylacryloyl-chloride in the presence of silver cyanate (±)-6 [14] whose treatment with 2 N sulphuric acid resulted in a cleavage of the THP-protecting group with simultaneous cyclization to afford the final compound (±)-7.
In a similar approach compound (±)-3 was allowed to react with 3-ethoxyacryloyl chloride/silver cyanate [15] to give (±)-8 that gave upon treatment with 2 N sulphuric acid target compound (±)-9.

Several of these compounds showed weak antitumor activity. Since it is well known that for many nucleoside analogues the biological activity of these compounds resides only in one enantiomer [16], a suitable chromatographic separation/analytical method had to be developed. As exemplified for cyclopropanes (±)-5 and (±)-9, a separation of the corresponding enantiomers can be achieved by HPLC using suitable chiral stationary phases. For these compounds the Daicel Chiralpak AD column gave a nice separation of the enantiomers of (±)-5 [(tR (−)-5 = 10.45 min and tR (+)-5 = 11.63 min; tR (−)-9 = 9.23 min and tR (+)-9 = 10.29 min with methanol as an eluent (0.5 ml/min) at 20 °C]; compound (±)-7, however, could be separated on this column but with a Chiralcel OD-column [1 ml/min hexane/2-propanol, tR (−)-7 = 148.77 min and tR (+)-7 = 157.28 min].

The stereoselective synthesis of these enantiomers and their incorporation in short artificial DNA and RNA fragments is presently under investigation in our labs.

Experimental Section

General methods: Melting Points are uncorrected (Leica hot stage microscope). NMR spectra (internal Me4Si) were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me4Si for 1H and 13C NMR spectra, internal CCl3F was used for 19F NMR spectra; C’ corresponds to the atoms of the heterocycle, C” to the atoms of the tetrahydropranlyoxy group). IR spectra (film or KBr pellet) were recorded on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. MS spectra were taken on an Integra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.5 kV, under nitrogen) instrument. TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium(IV) sulfate followed by gentle heating). Column chromatography was performed on silica gel 60 (FLUKA, 0.04–0.06 mm).

(±)-trans-2-Tetrahydro-2H-2-pyranlyoxy-1-cyclopropane carboxamide (±-1)

Preparation according to ref. [11]; Rf (ethyl acetate/methanol 10:1) 0.49; white solid; m.p. 87.1–88.0 °C. - IR (KBr): ν = 3377m, 3202w, 2947w, 2877w, 1662m, 1626m, 1457m, 1420w, 1376w, 1343w, 1276w, 1202w, 1162w, 1132m, 1112m, 1085w, 1038w, 1020m cm−1. - 1H NMR (400 MHz, CDCl3): δ = 5.94 (brs, 2 H, NH2), 4.70 (s, 1 H, 2°-H), 3.88–3.82 (m, 1 H, 6°-Hα), 3.72 (ddd, J = 6.45, 4.10, 2.25 Hz, 1 H, 2-H), 3.56–3.52 (m, 1 H, 6°-Hβ), 1.78–1.49 (m, 6 H, 3°-Hab, 4°-Hab, 5°-Hab), 1.33–1.17 (m, 2 H, 1-H, 3-Hab), 1.06 (ddd, J = 9.52, 5.42, 4.10 Hz, 1 H, 1-Hb), - 13C NMR (100 MHz, CDCl3): δ = 175.31 (s, CO), 99.85 (d, C-2°), 63.25 (t, C-6°), 58.06 (d, C-2), 31.20 (t, C-3°), 26.14 (d, C-1), 22.36 (t, C-5°), 19.99 (t, C-4), 15.87 (t, C-3). - MS (EI, 70 eV): m/z (%) = 186 (0.7), 168 (0.4), 140 (1.4), 124 (3.6), 113 (1.4), 101 (20), 85 (100). - HRMS calcld. for C9H15NO3: 185.10518; found: 185.10519.

(±)-Methyl N-TRANS-2-Tetrahydro-2H-2-pyranlyoxy-cyclopropylcarbamate (±-2)

To solution of (±)-1 (7.75 g, 41.84 mmol) containing KOH (6.03 g, 107.47 mmol) in methanol (100 ml) (diacetoxyiodo)benzene (13.42 g, 41.66 mmol) was added at 5 °C under stirring that was continued for an additional 2 h at r.t. The solvents were removed under reduced pressure, the residue dissolved in water (70 ml) and dichloromethane (30 ml) and the aqueous layer extracted with dichloromethane (4 × 30 ml). The combined organic layers were washed with water and brine (50 ml each), dried and evaporated. After column chro-
matography (hexane → ethyl acetate/hexane 1:2) (±)-2 (7.37 g, 82%) was obtained as a colourless oil: \( R_F \) (ethyl acetate/hexane 1:1) 0.5. – IR (film): \( \nu = 3327, 2947, 2871, 1736, 1525, 1454, 1358, 1303, 1259, 1202, 1160, 1131, 1111s, 1076s, 1039s \text{ cm}^{-1}. \) – 1H NMR (400 MHz, CDCl3): \( \delta = 4.82 \) (brs, 1 H, NH), 4.67 (s, 1 H, 2'-H), 3.90–3.84 (m, 1 H, 5'-H\(_{AB}\)), 3.62 (s, 3 H, CH\(_3\)), 3.57–3.51 (m, 1 H, 6'-H\(_B\)), 3.44 (ddd, \( J = 6.94, 4.00, 1.56 \text{ Hz} \), 1 H, 2-H), 2.78 (ddd, \( J = 4.64, 4.64, 2.78 \text{ Hz} \), 1 H, 1-H), 1.78–1.47 (m, 6 H, 3''-H\(_{AB}\), 5''-H\(_{AB}\), 4''-H\(_{AB}\), 0.98–0.97 (m, 1 H, 3-H\(_A\)). – 13C NMR (100 MHz, CDCl3): \( \delta = 157.50 \) (s, CO), 98.71 (d, C-2'), 62.33 (t, C-6'), 60.27 (q, CH\(_3\)), 56.10 (d, C-2), 30.30 (t, C-3'), 28.99 (d, C-1), 25.20 (t, C-5'), 19.14 (t, C-4'), 14.50 (t, C-3); MS (EI, 70 eV): \( m/z \) (%) = 216 (4.3), 204 (3.6), 156 (1.4), 131 (8.6), 114 (2.1), 102 (3.6), 85 (100). – HRMS calcld. for C\(_{10}H_{17}NO_4\): m/z 215.1157; found: 215.1157. – Analysis for C\(_{10}H_{17}NO_4\) (215.25): calcd. C 55.80, H 7.96, N 6.51; found C 55.61, H 8.15, N 6.79.

(±)-trans-Tetrahydro-2H-pyranoyloxy-cyclopropylamine (±)-3

A solution of (±)-2 (5.00 g, 23.23 mmol) containing KOH (24.50 g, 436.64 mmol), methanol (100 ml) and water (50 ml) was heated under reflux for 2 d, then the solvents were removed in vacuo and the residue dissolved in water (50 ml). After extraction with dichloromethane (5 × 50 ml) and evaporation (±)-3 (2.30 g, 63%) was obtained as a brown oil: \( R_F \) (ethyl acetate/hexane 1:1) 0.05. – IR (film): \( \nu = 3355, 3205, 2944, 2871, 1737, 1644, 1580, 1495, 1460, 1420, 1375, 1338, 1301, 1238, 1202, 1169, 1121, 1080, 1037 \text{ cm}^{-1}. \) – 1H NMR (200 MHz, CDCl3): \( \delta = 4.67–4.65 \) (m, 1 H, 2'-H), 3.86–3.76 (m, 1 H, 6'-H\(_A\)), 3.61–3.39 (m, 1 H, 6'-H\(_B\)), 3.30 (ddd, \( J = 14.95, 5.28, 2.25 \text{ Hz} \), 1 H, 1-H), 2.48 (ddd, \( J = 8.30, 4.59, 1.47 \text{ Hz} \), 1 H, 1-H), 1.83–1.41 (m, 6 H, 3''-H\(_{AB}\), 5''-H\(_{AB}\), 4''-H\(_{AB}\), 0.84 (ddd, \( J = 8.30, 6.15, 3.51 \text{ Hz} \), 1 H, 3-H\(_A\)), 0.69–0.44 (m, 1 H, 3-H\(_B\)). – 13C NMR (100 MHz, CDCl3): \( \delta = 99.74 \) (d, C-2'), 63.14 (t, C-6'), 58.90 (d, C-2), 31.34 (t, C-3'), 26.23 (d, C-1), 20.08 (t, C-5'), 17.14 (t, C-4'), 15.68 (t, C-3); – GC-MS: \( m/z \) (%) = 158 (0.02), 128 (0.4), 114 (0.1), 101 (0.2), 85 (100). – HRMS calcld. for C\(_{10}H_{17}ClNO_4\): 284.1039; found: 284.1040. – Analysis for C\(_{10}H_{17}ClNO_2\) (284.74): calcd. C 50.62, H 6.02, N 19.68; found C 50.69, H 6.29, N 19.81.

(±)-trans-2-(6-Chloro-9H-9-purinyl)cyclopropan-1-ol (±)-5

The reaction mixture consisting of (±)-4 (0.50 g, 1.76 mmol), triethyl orthoformate (4.17 g, 28.14 mmol) and aq. hydrochloric acid (36%, 0.30 g, 3.00 mmol) was stirred at r.t. for 4 h, then the pH was adjusted to 7 by the addition of an aqueous solution of NaHCO\(_3\), the aqueous layer was extracted with ethyl acetate (5 × 100 ml) and the combined organic phases were dried (MgSO\(_4\)) and evaporated. After column chromatography (ethyl acetate → ethyl acetate/methanol 10:1) (±)-5 (0.20 g, 54%) was obtained as a yellow solid; m.p. 145.9–146.3 °C. – \( R_F \) (ethyl acetate/methanol 10:1) 0.47. – UV (methanol) \( \lambda_{\text{max}} = 270 \text{ nm} \). log \( \varepsilon = 3.91. \) – IR (KBr): \( \nu = 3428, 3171, 3100, 3063, 1928, 1807, 1719, 1594, 1567, 1556, 1495, 1484, 1427, 1408, 1378, 1339, 1318, 1269, 1179, 1151, 1080, 778. – 1H NMR (400 MHz, CDCl3): \( \delta = 4.75, 4.69, 3.89, 0.85 \) (m, 1 H, 1-H), 2.42 (t, C-5'), 1.77 (t, C-4'), 1.27 (t, C-3'); – MS (EI, 70 eV): \( m/z \) (%) = 239 (100), 227 (11.3), 197 (9.4), 185 (3.8), 173 (7.3), 157 (8.4), 155 (6.4), 149 (5.9), 141 (4.3), 125 (12.2), 113 (13.7), 99 (23.0), 85 (100). – HRMS calcld. for C\(_{10}H_{17}ClNO_3\): 284.1039; found: 284.1040. – Analysis for C\(_{10}H_{17}ClNO_3\): 284.74: calcd. C 50.62, H 6.02, N 19.68; found C 50.69, H 6.29, N 19.81.
1302 m, 1220 s, 1199 s, 1166 m, 1151 m, 1100 m, 1076 m cm⁻¹. – ¹H NMR (400 MHz, CDCl₃): δ = 8.71 (s, 1 H, H-2′), 8.47 (s, 1 H, H-8′), 3.91 (ddd, J = 7.57, 4.35, 1.61 Hz, 1 H, H-1), 3.59 (ddd, J = 8.84, 4.74, 1.52 Hz, 1 H, H-2), 1.55 (ddd, J = 7.47, 7.47, 4.73 Hz, 1 H, 3-H₆A), 1.46 (ddd, J = 8.79, 7.33, 4.40 Hz, 1 H, -C₃-H₂B). – ¹³C NMR (100 MHz, CDCl₃): δ = 154.26 (s, C-6′), 153.12 (d, C-2′), 151.39 (s, C-4′), 148.61 (d, C-8′), 132.61 (s, C-5′), 51.60 (d, C-1), 33.23 (d, C-2), 15.72 (t, C-3). – MS (EI, 70 eV): m/z (%) = 212 (2.9), 210 (8.6), 183 (36.4), 181 (100.0), 169 (1.4), 167 (4.3), 156 (11.4), 154 (34.3), 145 (6.4), 129 (2.1), 127 (5.7), 119 (15.7), 104 (2.1). – HRMS Calcd. for C₅H₅ClN₄O: 210.03083; found: 210.03083.

(±)-1·trans-2-Hydroxycyclopentyl-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione ([±]-7)

A suspension of ([±]-6) (0.59 g, 1.98 mmol) in sulfuric acid (2 n, 20 ml) was stirred at 76 °C for 2 h, then cooled to r.t., neutralized by the addition of aqueous sodium hydroxide (8 N), and the solvents were removed under reduced pressure. The remaining residue was extracted with ethyl acetate (300 ml), the solvents were removed and the residue was subjected to chromatography ethyl acetate/methanol 10:1 to yield ([±]-7) (0.08 g, 22%) as a white solid; m.p. 208 °C. – Rₑ (ethyl acetate/methanol 10:1) 0.46. – UV (methanol): λmax = 275 nm, log ε = 3.78. – IR (KBr): ν = 3359 cm⁻¹, 3256 cm⁻¹, 3064 cm⁻¹, 2932 cm⁻¹, 2798 cm⁻¹, 2493 cm⁻¹, 2396 cm⁻¹, 1682 cm⁻¹, 1468 cm⁻¹, 1403 cm⁻¹, 1378 cm⁻¹, 1354 cm⁻¹, 1299 cm⁻¹, 1212 cm⁻¹, 1182 cm⁻¹, 1146 cm⁻¹, 1107 cm⁻¹, 1059 cm⁻¹, 1016 cm⁻¹ due was subjected to chromatography ethyl acetate/hexane 1:1 to yield ([±]-6) (0.59 g, 1.98 mmol) in sulfuric acid (2 n, 20 ml) 0.46.

(±)-[trans-2-(tetrahydro-2H-2-pyranyloxy)cyclopropyl]-urea ([±]-6)

From the reaction of ([±]-3) (1.50 g, 9.54 mmol) with silver cyanate (4.12 g, 27.49 mmol) and 3-methoxy-2-methylacryloyl-chloride (3.20 g, 23.79 mmol) in dry benzene (20 ml) ([±]-6) (0.76 g, 27%) was obtained after chromatography (ethyl acetate/hexane 1:1) as a yellow solid; m.p. 82.5–82.7 °C. – Rₑ (ethyl acetate/hexane 1:1) 0.55. – UV (methanol): λmax = 261 nm, log ε = 5.19. – IR (KBr): ν = 3435 cm⁻¹, 3255 cm⁻¹, 2946 cm⁻¹, 2857 cm⁻¹, 1697 cm⁻¹, 1615 cm⁻¹, 1512 cm⁻¹, 1468 cm⁻¹, 1450 cm⁻¹, 1403 cm⁻¹, 1378 cm⁻¹, 1354 cm⁻¹, 1299 cm⁻¹, 1212 cm⁻¹, 1182 cm⁻¹, 1146 cm⁻¹, 1107 cm⁻¹, 1059 cm⁻¹, 1016 cm⁻¹ due was subjected to chromatography ethyl acetate/hexane 1:1 to yield ([±]-6) (0.59 g, 1.98 mmol) in sulfuric acid (2 n, 20 ml) 0.46.

(±)-[trans-2-(tetrahydro-2H-2-pyranyloxy)cyclopropyl]-urea ([±]-8)

Starting from ([±]-3) (1.21 g, 770 mmol), silver cyanate (3.97 g, 26.49 mmol) and 3-ethoxycarbonyl chloride (1.97 g, 14.53 mmol) in dry benzene (20 ml) ([±]-8) (0.87 g, 38%) was obtained after chromatography (ethyl acetate/hexane 1:1) as a yellow solid; m.p. 94.7–94.9 °C. – Rₑ (ethyl acetate/hexane 1:1) 0.45. – UV (methanol): λmax = 252 nm, log ε = 4.29. – IR (KBr): ν = 3429 cm⁻¹, 3256 cm⁻¹, 3092 cm⁻¹, 2946 cm⁻¹, 1710 cm⁻¹, 1676 cm⁻¹, 1651 cm⁻¹, 1548 cm⁻¹, 1500 cm⁻¹, 1348 cm⁻¹, 1245 cm⁻¹, 1165 cm⁻¹, 1110 cm⁻¹, 1059 cm⁻¹, 1016 cm⁻¹ due was subjected to chromatography ethyl acetate/hexane 1:1 to yield ([±]-6) (0.59 g, 1.98 mmol) in sulfuric acid (2 n, 20 ml) 0.46.
J = 7.1 Hz, 3 H, CH₃), 1.03–0.74 (m, 2 H, 3-HA,B).  
- ¹³C NMR (50 MHz, CDCl₃): δ = 168.26 (s, CO), 162.62 (d, OCH=), 156.03 (s, NHCONH), 98.58 (d, OC-CH=), 98.09 (d, C-2'), 67.42 (t, OCH₂-ethyl), 62.12 (t, C-6'), 55.82 (d, C-2), 30.17 (t, C-3), 28.99 (d, C-1), 25.26 (t, C-5), 19.02 (t, C-4), 14.43 (q, CH₃), 14.30 (t, C-3).

- MS (EI, 70 eV): m/z (%) = 298 (1.8), 214 (30.7), 185 (44.3), 169 (2.9), 159 (0.7), 141 (1.4), 116 (4.3), 99 (82.1), 85 (100.0).

- HRMS calcd. for C₁₄H₂₂N₂O₅: 298.15286; found: 298.15287.


(±)-1-[trans-2-Hydroxyethylcyclopropyl]-1,2,3,4-tetrahydro-2,4-pyrimidinedione (±)-9

Treatment of (±)-8 (0.66 g, 2.21 mmol) with H₂SO₄ (2 n, 20 ml) (vide supra) afforded after chromatographic workup (ethyl acetate/methanol 10:1) (±)-9 (0.10 g, 27%) as a yellow solid; m.p. 198.4–198.7 °C. 
- RF (ethyl acetate/methanol 10:1) 0.32.
- UV (methanol): λ max = 271 nm, log ε = 3.8.
- IR (KBr): ν = 3378m, 3191m, 3058w, 1702s, 1458m, 1412w, 1387m, 1342w, 1299m, 1204w, 1153w, 1095w cm⁻¹. 
- ¹H NMR (500 MHz, CD₃OD): δ = 7.46 (d, J = 7.98 Hz, 1 H, 6'-H), 5.60 (d, J = 7.91 Hz, 1 H, 5'-H), 3.55 (dd, J = 7.64, 4.33, 1.63 Hz, 1 H, 2-H), 3.00 (dd, J = 8.67, 4.86, 1.67 Hz, 1 H, 1-H), 1.12 (dd, J = 8.65, 7.43, 4.31 Hz, 1 H, 3-H₃A), 1.14 (dd, J = 7.53, 7.53, 4.87 Hz, 1 H, 3-H₃B).

13C NMR (100 MHz, CD₃OD): δ 166.68 (s, C-4'), 153.68 (s, C-2'), 146.87 (d, C-6'), 102.37 (d, C-5'), 52.46 (d, C-2'), 38.76 (d, C-1), 16.12 (t, C-3). 
- MS (EI, 70 eV): m/z (%) = 168 (7.1), 149 (2.1), 139 (35.0), 125 (2.1), 112 (100.0), 108 (2.9), 96 (68.6). 
- HRMS calcd. for C₇H₈N₂O₃: 168.05349; found: 168.05349. 


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