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Synthesis of Racemic Carbocyclic Cyclopropanoid Nucleoside Analogues

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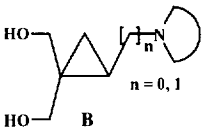
Abstract: As further representatives of a novel class of carbocyclic nucleoside analogues (±)-*cis*- and (±)-*trans*-(2-hydroxymethylcyclopropyl)-uracil, -thymine, and -inosine were synthesized from the corresponding dialkyl 1,2-cyclopropane dicarboxylates.

INTRODUCTION

Nucleoside analogues have been used quite successfully for the chemotherapy of viral infections. In order to obtain biological activity as well as molecules resisting biodegradation suitable modifications have to be made. Thus, among others, alterations of the sugar moiety have been performed including deoxygenations, eliminations, chain extensions at C(5') and at the anomeric centre, (hetero)substitutions as well as modifications with replacement of the ribose ring by a cyclopentane[1], cyclopentene[2], oxetane[3], cyclobutane ring [4] or even by an acyclic chain.[5, 6]

A



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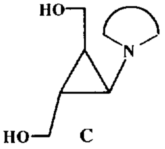

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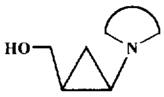
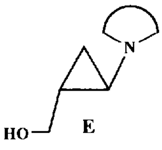
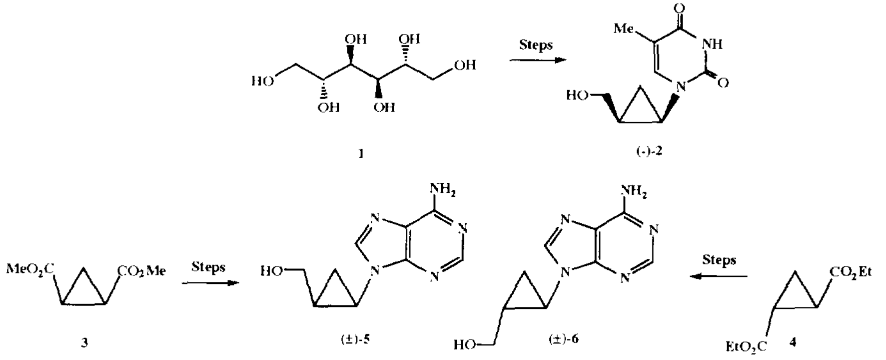


D



E

Syntheses of cyclopropanoid derivatives of types **A**[7], **B** and **C**[7, 8] have been accomplished several years ago and promising antiviral and/or antitumor activity has been found for these compounds. Most recently first syntheses of compounds of type **D** [9, 10] and type **E** [9] have been reported. Thus, syntheses of compounds of type **D** have been performed either by a chiral pool approach starting from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**1**) leading to the thymine analogue **(-)-2** or starting from dialkyl cyclopropane dicarboxylates **3** and **4** leading to the (±) adenosine analogues **5** and **6**, possessing *cis* or *trans* configuration at the cyclopropane ring.[9,11]



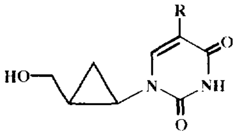
1
(-)-2
3
(±)-5
(±)-6
4

RESULTS AND DISCUSSION

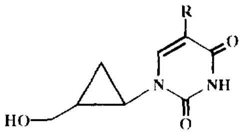
The compounds *cis* **(±)-5** and especially *trans* **(±)-6** showed weak antitumor activity against the ovarian cancer cell line OVCAR-3 [12] but no activity in an *in-vitro* anti-HIV assay.[12] For a more systematic evaluation of the antitumor and antiviral activity of this novel class of compounds and in order to obtain leading structures possessing a higher activity the synthesis of the uracil analogues **(±)-7** (*cis*) and **(±)-8** (*trans*), the thymine analogues **(±)-2** (*cis*) and **(±)-9** (*trans*) as well as the inosine analogues **(±)-10** (*cis*) and **(±)-11** (*trans*) was undertaken.

The synthesis of the thymine analogue *cis*-**(±)-2** started from well accessible *cis*-(±) cyclopropane-1,2-dicarboxylic acid monomethyl ester (**12**).[9] Reaction of **(±)-12** with ethyl chloroformate / triethylamine [13] in acetone resulted in the formation of the corresponding mixed anhydride **13** which – without isolation – was treated with sodium azide to afford a 79% yield of the corresponding carbonyl azide **14**. Treatment of **(±)-14** with tert.-butanol at 50-55°C gave 2-tert.-butoxycarbonylamino-cyclopropane carboxylic acid methyl ester [**(±)-15**] in 63% yield. Reduction of **15** with diisobutyl aluminium hydride in toluene at -78°C for 3 h gave a 59% yield of the primary alcohol **16**. The cleavage of the BOC-protecting group was performed with 6 N hydrochloric acid in tetrahydrofuran at 40-45°C during 3 h to afford the aminoalcohol **(±)-17**. **(±)-17** was silylated with tert.-butyldimethylchlorosilane in dichloromethane / pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine to give **18** in an overall yield of 89%. Treatment of **(±)-18** with 3-methoxy-2-methyl-acryloyl isocyanate (**19**) [14-16] (which was prepared *in situ* from 3-methoxy-2-methyl-acryloyl chloride and silver cyanate)[15, 17] gave a 40% yield of **(±)-20**. The cyclisation reaction of **(±)-20** with 2 N sulfuric acid [18] at 70°C gave the *cis*-configurated thymine analogue **(±)-2** in 67% yield.

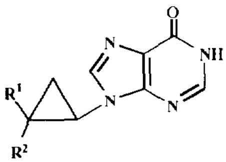
The synthesis of the racemic *trans* analogue **(±)-9** followed this synthetic route. Thus, 2-(hydroxymethyl-cyclopropyl)-carbamic acid tert.-butyl ester [**(±)-21**][9] was deprotected with 6 N hydrochloric acid followed by a silylation with tert.-butyldimethylchlorosilane in dichloromethane / pyridine in the presence of catalytic amounts of 4-dimethylaminopyridine to afford **(±)-22** in an overall yield of 98%.



(±)-2 R = Me
(±)-7 R = H

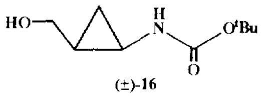


(±)-8 R = H
(±)-9 R = Me



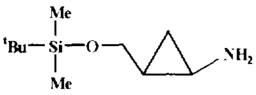
(±)-10 $R^1 = CH_2OH$, $R^2 = H$
(±)-11 $R^1 = H$, $R^2 = CH_2OH$

(±)-12 R = COOH
(±)-13 R = C(=O)-O-C(=O)-OEt
(±)-14 R = C(=O)-N_3
(±)-15 R = NH-C(=O)-O-ᵗBu

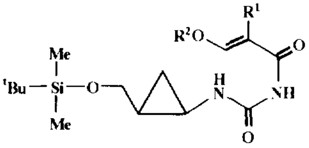


(±)-16

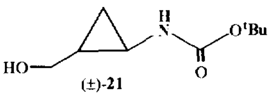
(±)-17



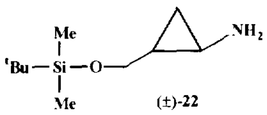
(±)-18



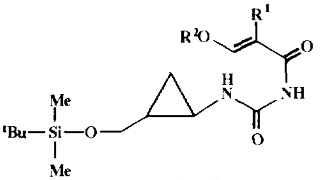
(±)-20 $R^1 = R^2 = Me$
(±)-28 $R^1 = H$, $R^2 = Et$



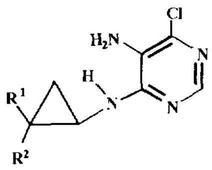
(±)-21



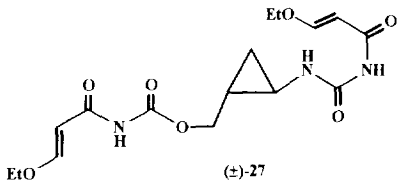
(±)-22



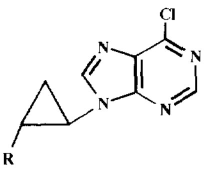
(±)-23 $R^1 = R^2 = Me$
(±)-26 $R^1 = H$, $R^2 = Et$



(±)-30 $R^1 = CH_2OH$, $R^2 = H$
(±)-31 $R^1 = H$, $R^2 = CH_2OH$



(±)-27



(±)-32 $R = CH_2OH$
(±)-35 $R = CH_2Cl$

Treatment of **(±)-22** with 3-methoxy-2-methyl-acryloyl isocyanate **(19)**[16] gave 31% of the desired **23** besides 29% of the amide **24**.

The synthesis of the *trans* uracil analogue **(±)-8** was performed by a similar strategic plan. Starting from **(±)-22** and **25**[19] the intermediate **26** was obtained in 23% yield besides 20% of the bis-addition product 27. Acid treatment of **(±)-26** resulted in deprotection of the primary alcohol function as well as ring closure to give 75% of the *trans* uracil analogue **(±)-8**.

For the synthesis of the racemic *cis* uracil analogue **(±)-7** again **(±)-18** was used as a convenient starting material. Treatment of **(±)-18** with 3-ethoxy-acryloyl isocyanate **25**[19] gave 35% of **(±)-28** besides 16% of the amide **29**. Treatment of **(±)-28** with 2 N sulfuric acid at 70°C afforded the desired *cis* **(±)-7** in 84% yield.

The synthesis of the *cis* configurated inosine derivative **(±)-10** started from the well accessible[9] **(±)-30** which was allowed to react in succession with triethyl orthoformate / conc. hydrochloric acid and 0.5 N aqueous sodium hydroxide solution. Thus **(±)-10** was obtained in an overall yield of 41%. The racemic *trans* analogue **(±)-11** was prepared by a similar route starting from known **(±)-31**.[9] The reaction of **(±)-32** with 0.5 N aqueous sodium hydroxide solution gave **(±)-11** in 64% yield.

EXPERIMENTAL

Melting points are uncorrected (*Reichert* hot stage microscope), optical rotations were obtained using a Perkin-Elmer 243B polarimeter (1 cm micro-cell), NMR spectra (internal Me_4Si) were recorded using either a Bruker AM250 or a Varian XL300 instrument (δ given in ppm, *J* in Hz, internal Me_4Si, C' and H' correspond to the atoms of the heterocycle or its synthetic precursor), IR spectra (film or KBr pellet) on a Perkin-Elmer 298 instrument or on a Perkin-Elmer 1605 FT-IR, MS spectra were taken either on a MAT311A or a Varian-112S instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by dipping in an ethanolic ninhydrin (1%) solution followed by gentle heating, or by treatment with iodine).

(±)-cis-1-(2-Hydroxymethyl-cyclopropyl)-5-methyl-1H-pyrimidine-2,4-dione (2).- According to the preparation of **9** from **20** (0.50 g, 1.46 mmol) and sulfuric acid (2 N, 4 *ml*) **2** (0.19 g, 67%) was obtained as a white solid; mp 199-202 °C; R_F (EtOAc) 0.20; IR (KBr): 3460*m*, 3155*m*, 3078*m*, 3022*m*, 2924*m*, 2833*m*, 1678*s*, 1559*m*, 1534*w*, 1507*w*, 1476*m*, 1448*m*, 1419*m*, 1387*m*, 1361*m*, 1330*m*, 1302*s*, 1235*m*, 1181*w*, 1149*m*, 1075*m*, 1048*m*, 1039*m*, 1021*m*, 1003*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 11.24 (*s*, 1 H, NH, exchangeable with D_2O), 7.47 (*d*, *J* = 1.2, 1 H, H-C(6')), 4.36 (*t*, *J* = 5.4, 1 H, OH, exchangeable with D_2O), 3.29-3.25 (*m*, 2 H, OCH_2), 3.06 (*ddd*, *J* = 7.4, 7.3, 4.5, 1 H, H-C(1)), 1.75 (*d*, *J* = 1.2, 3 H, CH_3), 1.38-1.33 (*m*, 1 H, H-C(2)), 1.07 (*ddd*, *J* = 9.0, 7.4, 6.3, 1 H, H_A-C(3)), 0.85 (*ddd*, *J* = 6.4, 6.3, 4.5, 1 H, H_B-C(3)); ^{1}H-NMR (300 MHz, DMSO-d_6/D_2O): 3.35 (*dd*, *J* = 11.7, 7.2, 2 H, OCH_2), 3.22 (*dd*, *J* = 11.7, 6.6, 1 H, OCH_2); ^{13}C-NMR (75 MHz, DMSO-d_6): 163.91 (*s*, C(4')), 152.11 (*s*, C(2')), 141.87 (*d*, C(6')), 108.14 (*s*, C(5')), 59.16 (*t*, OCH_2), 34.70 (*d*, C(1)), 20.39 (*d*, C(2)), 11.93 (*q*, CH_3), 8.79 (*t*, C(3)); UV (methanol): λ_{max} 267 nm, ε 20023; MS (ei, 80 eV, 132 °C): 197 (1.2%), 196 (8.8%), 179 (1.3%), 166 (5.3%), 165 (16.9%), 128 (6.5%), 127 (100.0%), 126 (18.9%), 123 (12.5%), 122 (80.8%), 109 (8.4%), 107 (13.8%), 106 (12.3%); Anal. calcd. for $C_9H_{12}N_2O_3$ (196.21): C, 55.10; H, 6.16; found: C, 55.25; H, 5.92.

(±)-cis-1-(2-Hydroxymethyl-cyclopropyl)-1H-pyrimidine-2,4-dione (7).- According to the preparation of **8** from **28** (1.67 g, 4.88 mmol) and sulfuric acid (2 N, 12 *ml*) **7** (0.75 g, 84%) was obtained as a white solid; mp 170-173 °C; R_F (EtOAc/MeOH 3:1) 0.54; IR (KBr): 3447*s*, 3128*m*, 3018*m*, 2871*m*, 2819*m*, 1684*s*, 1559*m*, 1534*m*, 1507*m*, 1470*m*, 1457*m*, 1437*m*, 1424*s*, 1390*m*, 1358*m*, 1323*m*, 1285*s*, 1248*m*, 1172*m*, 1152*m*, 1115*w*, 1075*m*, 1956*m*, 1031*m*, 1012*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 11.22 (*br s*, 1 H, NH, exchangeable with D_2O); 7.59 (*d*, *J* = 8.0, 1 H, NCH=), 5.50 (*d*, *J* = 8.0, 1 H, COCH=), 4.42-4.41 (*br*, 1 H, OH, exchangeable with D_2O), 3.31-3.28 (*m*, 2 H, OCH_2), 3.09 (*ddd*, *J* = 7.4, 7.0, 4.5, 1 H, H-C(1)), 1.37 (*ddd*, *J* = 9.0, 7.0, 6.6, 1 H, H-C(2)), 1.07 (*ddd*, *J* = 9.0, 7.4, 6.3, 1 H, H_A-C(3)), 0.84 (*ddd*, *J* = 6.6, 6.3, 4.5, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 163.45 (*s*, C(4')), 152.12 (*s*, C(2')), 146.22 (*d*, C(6')), 100.54 (*d*, C(5')), 58.95 (*t*, OCH_2), 34.78 (*d*, C(1)), 20.13 (*d*, C(2)), 8.58 (*t*, C(3)); UV (methanol): λ_{max} 262 nm, ε 7944; MS (ei, 80 eV, 156 °C): 183 (1.0%), 182 (6.2%), 152 (3.4%), 151 (10.3%), 113 (100.0%), 108 (60.6%), 96 (8.5%), 95 (14.5%), 93 (22.9%), 80 (22.6%); Anal. calcd. for $C_8H_{10}N_2O_3$ (182.18): C, 52.74; H, 5.53; found: C, 52.69; H, 5.32.

(±)-trans-1-(2-Hydroxymethyl-cyclopropyl)-1H-pyrimidine-2,4-dione (8).- **26** (14.5 mg, 4.23 mmol) was dissolved in sulfuric acid (2 N, 1.5 *ml*) and stirred for 1 h at 72 °C. After cooling to 25 °C the mixture was neutralised with NaOH (2 N) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/MeOH 1:1) to yield **8** (58 mg, 75%) as a white solid; mp 168-171 °C; R_F (EtOAc/MeOH 3:1) 0.54; IR (KBr): 3438*s*, 3135*m*, 3089*m*, 3005*m*, 2931*m*, 2871*m*, 2811*m*, 1683*s*, 1469*s*, 1428*s*, 1391*s*, 1302*s*, 1242*m*, 1195*w*, 1107*w*, 1067*w*, 1016*s*; ^{1}H-NMR (300 MHz, DMSO-d_6): 11.22 (*br s*, 1 H, NH, exchangeable with D_2O); 7.51 (*d*, *J* = 8.0, 1 H, NCH=), 5.49 (*d*, *J* = 8.0, 1 H, COCH=), 3.48-3.37 (*m*, 2 H, OCH_2), 2.86 (*ddd*, *J* = 7.4, 3.7, 3.7, 1 H, H-C(1)), 1.40-1.34 (*m*, 1 H, H-C(2)), 1.00-0.87 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 163.21 (*s*, C(4')), 151.28 (*s*, C(2')), 145.07 (*d*, C(6')), 100.36 (*d*, C(5')), 61.07 (*t*, OCH_2), 34.25 (*d*, C(1)), 21.89 (*d*, C(2)), 10.75 (*t*, C(3)); UV (methanol): λ_{max} 262 nm, ε 8564; MS (ei, 80 eV, 134 °C): 182 (5.9%), 165 (0.1%), 152 (3.5%), 151 (9.5%), 113 (100.0%), 108 (69.2%), 96 (7.7%), 95 (13.6%), 93 (30.0%), 80 (22.3%); HRMS: calcd for $C_8H_{10}N_2O_3$: 182.06914, found: 182.06916.

(±)-trans-1-(2-Hydroxymethyl-cyclopropyl)-5-methyl-1H-pyrimidine-2,4-dione (9).- A solution of **23** (0.65 g, 1.90 mmol) in sulfuric acid (2 N, 5.0 *ml*) was stirred for 1 h at 72 °C then cooled to 25 °C, neutralised with NaOH (2 N), and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc) to yield **9** (0.21 g, 57%) as a white solid; mp 159-163°C; R_F (EtOAc) 0.14; IR (KBr): 3394*m*, 3148*m*, 3062*m*, 3014*m*, 2926*m*, 2837*m*, 1773*m*, 1734*s*, 1718*s*, 1700*s*, 1696*s*, 1685*s*, 1653*s*, 1647*s*, 1570*m*, 1560*m*, 1545*m*, 1534*m*, 1522*m*, 1507*m*, 1477*m*, 1457*m*, 1437*m*, 1430*s*, 1384*m*, 1302*s*, 1156*m*, 1102*m*, 1014*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 11.16 (*s*, 1 H, NH, exchangeable with D_2O), 7.39 (*d*, *J* = 1.2, 1 H, H-C(6')), 4.59 (*t*, *J* = 5.5, 1 H, OH, exchangeable with D_2O), 3.43 (*dd*, *J* = 5.9, 5.5, 2 H, OCH_2), 2.84 (*ddd*, *J* = 7.2, 3.7, 3.7, 1 H, H-C(1)), 1.75 (*d*, *J* = 1.2, 3 H, CH_3), 1.38 (*dddd*, *J* = 6.2, 5.9, 3.2, 3.2, 1 H, H-C(2)), 1.00-0.87 (*m*, 2 H, $H_{A,B}$-C(3)); ^{1}H-NMR (300 MHz, DMSO-d_6/D_2O): 3.44 (*d*, *J* = 5.9, 2 H, OCH_2); ^{13}C-NMR (75 MHz, DMSO-d_6): 163.79 (*s*, C(4')), 151.27 (*s*, C(2')), 140.78 (*d*, C(6')), 107.89 (*s*, C(5')), 61.16 (*t*, OCH_2), 34.02 (*d*, C(1)), 21.90 (*d*, C(2)), 11.79 (*q*, CH_3), 10.86 (*t*, C(3)); UV (methanol): λ_{max} 268 nm, ε 18988; MS (ei, 80 eV, 110 °C): 197 (1.3%), 196 (9.9%), 179 (1.5%), 166 (5.2%), 165 (19.3%), 128 (5.7%), 127 (96.8%), 126 (19.9%), 123 (15.2%), 122 (100.0%), 109 (9.5%), 107 (19.3%), 106 (16.3%), 94 (20.1%), 82 (25.2%), 80 (29.8%); Anal. calcd. for $C_9H_{12}N_2O_3$ (196.21): C, 55.10; H, 6.16; found: C, 55.24; H, 6.23.

***(±)-cis-9-(2-Hydroxymethyl-cyclopropyl)-1,9-dihydro-purin-6-one (10).*-** A suspension of **30** (0.43 g, 2.00 mmol),[9] triethyl orthoformate (4.76 g, 32.12 mmol) and hydrochloric acid (36%, 0.24 g, corresponding to 1.2 equivalents) was stirred at 25 °C overnight. Then the pH of the mixture was adjusted to 7-8 by addition of sodium bicarbonate and water (10 *ml*). The resulting aqueous solution was extracted with EtOAc (5 x 50 *ml*), the organic phase was dried ($MgSO_4$) and the solvent removed. Without further purification the crude product was dissolved in NaOH (0.5 N, 50 *ml*) and refluxed for 2 h. The mixture was allowed to cool to 25°C, then neutralised with diluted aqueous hydrochloric acid and the resulting aqueous solution was evaporated under reduced pressure. Column chromatography (EtOAc → EtOAc/MeOH 5:1 → EtOAc/MeOH 3:1) of the residue yielded unchanged **30** (76 mg, 18%) and **10** (0.17 g, 41%) as a white solid; mp 235-240°C; R_F (EtOAc/MeOH 3:1) 0.17; IR (KBr): 3394*s*, 3127*m*, 3052*m*, 2846*m*, 1844*w*, 1830*w*, 1792*w*, 1772*w*, 1734*m*, 1700*s*, 1696*s*, 1684*s*, 1675*s*, 1653*s*, 1647*m*, 1636*m*, 1617*m*, 1592*s*, 1570*m*, 1559*m*, 1550*m*, 1534*m*, 1521*m*, 1517*m*, 1507*m*, 1496*w*, 1473*m*, 1457*m*, 1437*w*, 1413*m*, 1395*m*, 1340*m*, 1225*w*, 1185*w*, 1130*w*; ^{1}H-NMR (300 MHz, DMSO-d_6): 8.06 and 8.05 (each *s*, 1 H, H-C(2') and H-C(8')), 3.52 (*ddd*, *J* = 7.3, 7.3, 4.4, 1 H, H-C(1)), 3.22 (*dd*, *J* = 11.6, 6.0, 1 H, CH_2O), 3.11 (*dd*, *J* = 11.6, 7.5, 1 H, CH_2O), 1.55-1.47 (*m*, 1 H, H-C(2)), 1.27 (*ddd*, *J* = 8.8, 7.5, 6.0, 1 H, H_A-C(3)), 1.20 (*ddd*, *J* = 6.5, 6.5, 4.5, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 156.42 (*s*, C(6')), 149.71 (*s*, C(4')), 145.32 (*d*, C(2')), 141.04 (*d*, C(8')), 124.02 (*s*, C(5')), 59.09 (*t*, OCH_2), 29.30 (*d*, C(1)), 19.43 (*d*, C(2)), 8.51 (*t*, C(3)); UV (methanol): λ_{max} 248 nm, ε 7993; MS (ei, 80 eV, 202 °C): 207 (2.1%), 206 (15.7%), 187 (15.9%), 176 (5.9%), 175 (23.1%), 165 (33.9%), 150 (11.0%), 149 (11.3%), 148 (19.4%), 137 (94.9%), 136 (27.3%), 120 (10.7%), 109 (17.9%), 83 (8.6%), 71 (23.3%), 44 (100.0%); HRMS: calcd. for $C_9H_{10}N_4O_2$: 206.08036, found: 206.08038.

***(±)-trans-9-(2-Hydroxymethyl-cyclopropyl)-1,9-dihydro-purin-6-one (11).*-** A solution of **32** (180 mg, 0.80 mmol) in NaOH (0.5 N, 30 *ml*) was heated under reflux for 2 h then cooled to 25°C and the mixture was neutralised with diluted aqueous hydrochloric acid; the solvent was evaporated and the residue subjected to column chromatography (EtOAc → EtOAc/MeOH 3:1) to afford **11** (106 mg, 64%) as a white solid; mp 228-231°C; R_F (EtOAc/MeOH 3:1) 0.20; IR (KBr): 3396*s*, 3114*m*, 3084*m*, 3039*m*, 2844*m*, 2801*m*, 1869*w*, 1844*w*, 1830*w*, 1792*w*, 1772*w*, 1734*m*, 1700*s*, 1696*s*, 1684*s*, 1653*s*, 1647*m*, 1635*m*, 1617*m*, 1589*s*, 1559*m*, 1550*m*, 1534*m*, 1521*m*, 1517*m*, 1507*m*, 1496*m*, 1473*m*, 1457*m*, 1437*m*, 1419*s*, 1352*m*, 1327*m*, 1307*m*, 1225*m*, 1197*w*, 1163*m*, 1131*m*, 1048*m*, 1031*m*; ^{1}H-NMR (300 MHz, MeOH-d_4): 8.06 and 8.05 (each *s*, 1 H, H-C(2') and H-C(8')), 3.74 (*dd*, *J* = 12.3, 5.8, 1 H, CH_2O), 3.62 (*dd*, *J* = 12.3, 6.7, 1 H, CH_2O), 3.43 (*ddd*, *J* = 7.5, 3.8, 3.8, 1 H, H-C(1)), 1.82-1.76 (*m*, 1 H, H-C(2)), 1.38 (*ddd*, *J* = 9.8, 6.2, 3.8, 1 H, H_A-C(3)), 1.20 (*ddd*, *J* = 7.5, 6.3, 6.2, 1 H, H_B-C(3)); ^{1}H-NMR (300 MHz, DMSO-d_6): 8.05 (*s*, 2 H, H-C(2') and H-C(8')), 3.54 (*d*, *J* = 5.6, 2 H, CH_2O), 3.40 (*ddd*, *J* = 7.5, 3.9, 3.8, 1 H, H-C(1)), 1.75-1.68 (*m*, 1 H, H-C(2)), 1.25 (*ddd*, *J* = 9.6, 5.8, 3.9, 1 H, H_A-C(3)), 1.07 (*ddd*, *J* = 7.5, 6.0, 5.8, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 156.57 (*s*, C(6')), 149.36 (*s*, C(4')), 145.41 (*d*, C(2')), 139.94 (*d*, C(8')), 124.10 (*s*, C(5')), 60.86 (*t*, OCH_2), 29.33 (*d*, C(1)), 21.25 (*d*, C(2)), 10.07 (*t*, C(3)); UV (methanol): λ_{max} 250 nm, ε 12503; MS (ei, 80 eV, 168 °C): 208 (1.3%), 207 (1.3%), 206 (20.7%), 187 (14.4%), 176 (8.0%), 175 (24.7%), 165 (45.6%), 150 (10.9%), 149 (12.4%), 148 (27.8%), 137 (100.0%), 136 (42.2%), 121 (12.3%), 120 (11.2%), 109 (24.5%); HRMS calcd. for $C_9H_{10}N_4O_2$: 206.08036; found: 206.08039.

(±)-cis-2-Methoxycarbonyl-1-cyclopropane carbonyl azide (14).- A solution of (±)-cis dimethyl cyclopropane dicarboxylate (30.00 g, 0.19 mol)[9] in methanol (150 *ml*) was heated under reflux while an aqueous solution of sodium hydroxide [(7.60 g, 0.19) mol in water (15 *ml*)] was added over a period of 2 h.[24] The mixture was cooled to 25 °C and the methanol was evaporated. Water (30 *ml*) was added and the solution was concentrated again. The resulting aqueous solution was extracted with diethyl ether (4 x 50 *ml*) to remove any residual diester. The aqueous layer was acidified with conc. hydrochloric acid to pH 3, extracted with diethyl ether (5 x 50 *ml*), the combined organic phases were dried over $MgSO_4$, filtered and concentrated to yield a mixture (19.35 g) of (±)-cis-cyclopropane-1,2-dicarboxylic acid (14% by ^{1}H-NMR) and (±)-cis-cyclopropane-1,2-dicarboxylic acid monomethylester **(12)** (86% by ^{1}H-NMR). This mixture (10.00 g) was dissolved in acetone (30 *ml*) and cooled to 0°C as successively triethylamine (10.54 g, 0.10 mol) and a solution of ethyl chloroformate (11.30 g, 0.10 mol) in acetone (6 *ml*) was added dropwise. A white precipitate formed instantaneously. After stirring the mixture for 0.5 h at 0 °C a solution of sodium azide (9.03 g, 0.14 mol) in water (10 *ml*) was added dropwise and stirring was continued at 0 °C for an additional hour. Ice cold water (30 *ml*) was added followed by extraction with diethyl ether (4 x 40 *ml*). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford **14** (8.15 g, 79%) as a colourless oil; R_F (EtOAc/Hex 1:7) 0.35; IR (film): 3020*w*, 2957*w*, 2856*w*, 2359*m*, 2329*m*, 2278*m*, 2144*s*, 1742*s*, 1739*s*, 1733*s*, 1713*s*, 1704*s*, 1699*s*, 1135*s*, 1076*s*, 1038*s*, 1001*m*, 914*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.72 (*s*, 3 H, OCH_3), 2.21-2.03 (*m*, 2 H, H-C(1) and H-C(2)), 1.77 (*ddd*, *J* = 6.8, 6.8, 5.1, 1 H, H_A-C(3)), 1.34 (*ddd*, *J* = 8.3, 8.3, 5.1, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 176.51 (*s*, CON_3), 169.66 (*s*, $COOCH_3$), 52.34 (*q*, OCH_3), 23.45 and 23.20 (each *d*, C(1) and C(2)), 12.88 (*t*, C(3)); MS (ei, 80 eV, 30 °C): 169 (0.1%), 138 (5.8%), 128 (7.5%), 127 (100.0%), 110 (2.1%), 99 (4.0%), 98 (2.9%), 86 (5.0%), 82 (8.8%), 71 (12.3%), 68 (5.3%), 59 (17.4%); HRMS: calcd. for $C_6H_7N_3O_3$: 169.04873; found: 169.04871.

(±)-cis-2-(Tert.-butyldimethylsilyloxymethyl)-cyclopropylamine (18) .- **14** (7.79 g, 46.1 mmol) was dissolved in tert.-butanol (40 *ml*) and stirred at 50-55°C overnight. After cooling to 25°C the solvent was removed under reduced pressure and (±)-cis-methyl-2-(tert.-butoxycarbonylamino)-1-cyclopropane carboxylate **(15)** (6.25 g, 63%)[9] was obtained by column chromatography (EtOAc/Hex 1:10 → 1:5) as a white solid. According to the preparation previously reported[9] from **15** (3.17 g, 14.73 mmol) and DIBAH (75 *ml*, 1 M in toluene) (±)-cis-(2-hydroxymethylcyclopropyl) carbamic acid tert.-butyl ester **(16)** was obtained as a white solid (1.63 g, 59%). To a solution of **(±)-16** (1.10 g, 5.87 mmol) in tetrahydrofuran (12 *ml*) aqueous hydrochloric acid (6 N, 2.2 *ml*) was added. After stirring the mixture for 3 h at 40-45 °C the solvent was evaporated. Any remaining water was removed by azeotropic distillation with toluene (3 x 10 *ml*). Crude **17** was obtained as a brown oil. [^{1}H-NMR (300 MHz, DMSO-d_6): 3.78 (*dd*, *J* = 12.2, 5.2, 1 H, OCH_2), 3.66 (*dd*, *J* = 12.2, 8.6, 1 H, OCH_2), 2.70-2.60 (*m*, 1 H, H-C(1)), 1.35-1.25 (*m*, 1 H, H-C(2)), 0.95-0.80 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 58.35 (*t*, OCH_2), 26.09 (*d*, C(1)), 17.37 (*d*, C(2)), 6.99 (*t*, C(3))]. Without further purification **17** was dissolved in dry dichloromethane (5 *ml*) and dry pyridine (2 *ml*), tert.-butyldimethylsilylchlorosilane (2.66 g, 17.65 mmol), and catalytic amounts of 4-dimethylaminopyridine were added. The mixture was stirred for 40 h under argon at 25 °C. The solvents were evaporated and the residue subjected to column chromatography (EtOAc/MeOH 10:1→ 3:1) to afford **18** (1.06 g, 89%) as an oil; IR (film): 3446*s*, 2958*s*, 2928*s*, 2883*s*, 2856*s*, 1869*w*, 1844*w*, 1829*m*, 1792*w*, 1772*m*, 1762*w*, 17527*w*, 1751*m*, 1740*w*, 1734*m*, 1718*m*, 1706*m*, 1701*w*, 1696*m*, 1684*m*, 1675*m*, 1669*m*, 1663*m*, 1653*s*, 1647*m*, 1636*m*, 1623*m*, 1617*m*, 1576*m*, 1570*m*, 1559*m*, 1554*m*, 1550*m*, 1540*m*, 1534*m*, 1521*m*, 1517*m*, 1507*m*, 1496*m*, 1490*m*, 1472*m*, 1381*m*, 1362*m*, 1253*s*, 1172*m*, 1108*m*, 1071*s*, 1051*m*, 1002*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 8.55 (*br s*, 2 H, NH_2, exchangeable with D_2O), 4.22 (*dd*, *J* = 11.1, 2.9, 1 H, OCH_2), 4.04 (*dd*, *J* = 11.1, 4.5, 1 H, OCH_2), 2.85 (*ddd*, *J* = 5.5, 3.5, 3.5, 1 H, H-C(1)), 1.28-1.23 (*m*, 1 H, H-C(2)), 1.10-0.95 (*m*, 2 H, $H_{A,B}$-C(3)), 0.90 (*s*, 9 H, 3 x CH_3 of t.-Bu), 0.12 (*s*, 6 H, 2 x CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 60.24 (*t*, OCH_2), 26.92 (*d*, C(1)), 25.93 (*q*, 3 x CH_3 of t.-Bu), 18.19 (*s*, C_q of t.-Bu), 15.65 (*d*, C(2)), 6.41 (*t*, C(3)), -5.30 and -5.38 (each *q*, 2 x CH_3); MS (ei, 80 eV, 83 °C): 186 (2.1%), 184 (1.7%), 145 (7.2%), 144 (85.4%), 127 (3.2%), 126 (3.3%), 114 (8.2%), 99 (5.2%), 89 (7.6%) 75 (71.1%), 73 (37.9%), 69 (24.1%), 56 (100.0%); HRMS: calcd. for $C_{10}H_{23}NOSi$: 201.15489, found: 201.15493.

(±)-cis-1-[2-(Tert.-butyldimethylsilyloxymethyl)-cyclopropyl]-3-(3-methoxy-2-methylacryloyl) urea (20).- According to the preparation of **23** **18** (1.02 g, 5.07 mmol) was dissolved in dry dimethylformamide (10 *ml*) and a solution of 3-methoxy-2-methylacryloyl isocyanate (**19**) [prepared from silver cyanate (2.28 g, 15.21 mmol) in benzene (10 *ml*) and 3-methoxy-2-methyl-acryloyl chloride (**34**)[16] (1.02 g, 7.58 mmol) in benzene (4 *ml*)] was added. Work up as described for **23** afforded **24** (0.11 g, 13%; for its characterisation – *vide infra*) and **20** (0.69 g, 40%) as a white solid; mp 87-91°C; R_F (EtOAc/Hex 1/5) 0.18; IR (KBr): 3274*m*, 2954*m*, 2882*m*, 2855*m*, 1844*w*, 1793*w*, 1773*m*, 1734*m*, 1718*m*, 1695*s*, 1662*s*, 1617*m*, 1576*m*, 1559*s*, 1550*s*, 1517*m*, 1507*m*, 1490*m*, 1473*m*, 1465*m*, 1419*w*, 1409*m*, 1367*m*, 1340*w*, 1300*m*, 1257*s*, 1150*m*, 1100*m*, 1078*s*, 1045*m*; ^{1}H-NMR (250 MHz, DMSO-d_6): 10.2 (*s*, 1 H, OCNHCO), 8.70 (*s*, 1 H, NH), 7.43 (*s*, 1 H, CH), 3.78 (*s*, 2 H, OCH_2), 3.50-3.47 (*m*, 1 H, H-C(1)), 3.30 (*s*, 3 H, OCH_3), 2.76 (*m*, 1 H, H-C(2)), 1.59 (*s*, 3 H, CH_3), 1.20-1.10 (*m*, 1 H, H_A-C(3)), 0.85 (*s*, 9 H, 3 x CH_3 of t.-Bu), 0.41-0.32 (*m*, 1 H, H_B-C(3)), 0.02 and 0.01 (each *s*, 3 H, CH_3-Si); ^{13}C-NMR (62 MHz, DMSO-d_6): 169.36 (*s*, CO), 157.88 (*d*, CH), 154.85 (*s*, NHCONH), 106.90 (*s*, C_q), 61.87 (*t*, OCH_2), 61.00 (*q*, OCH_3), 26.28 (*d*, C(1)), 25.79 (*q*, 3 x CH_3 of t.-Bu), 18.32 (*d*, C (2)), 17.91 (*s*, C_q of t.-Bu), 10.10 (*t*, C(3)), 8.75 (*q*, CH_3), -2.31 (*q*, 2 x CH_3); MS (ei, 80 eV, 96 °C): 343 (0.4%), 342 (1.7%), 327 (1.3%), 287 (3.1%), 286 (9.6%), 285 (47.8%), 211 (1.6%), 210 (5.8%), 197 (16.6%), 170 (10.0%), 127 (4.4%), 101 (4.4%), 100 (16.29), 99 (100.0%); Anal. calcd. for $C_{16}H_{30}N_2O_4Si$ (342.51): C, 56.11; H, 8.83; found: C, 56.32; H, 8.71.

(±)-trans-2-(Tert.-butyldimethylsilyloxymethyl)-cyclopropylamine (22).- To a solution of (±)-**21** (0.82 g, 4.37 mmol)[9] in tetrahydrofuran (10 *ml*) aqueous hydrochloric acid (6 N, 1.65 *ml*) was added. After stirring the mixture for 3 h at 40-45 °C the solvent was evaporated. Residual water was removed by evaporation with toluene (3 x 10 *ml*); the remaining brown oil was dissolved in dry dichloromethane (5 *ml*), dry pyridine (2 *ml*), tert.-butyldimethylsilylchlorosilane (1.32 g, 8.76 mmol), and catalytic amounts of 4-dimethylaminopyridine were added. The mixture was stirred for 40 h under argon at 25 °C. The solvents were evaporated and the residue subjected to column chromatography (EtOAc/MeOH 3:1) to afford **22** (0.86 g, 98%) as an oil; IR (film): 3448*m*, 2955*s*, 2930*s*, 2898*s*, 2858*s*, 1845*w*, 1830*w*, 1793*w*, 1773*w*, 1762*w*, 1752*w*, 1740*w*, 1734*m*, 1718*m*, 1701*m*, 1696*m*, 1685*m*, 1676*m*, 1670*m*, 1663*m*, 1653*m*, 1647*m*, 1636*m*, 1624*m*, 1617*m*, 1576*m*, 1570*m*, 1559*m*, 1540*m*, 1534*m*, 1522*m*, 1517*m*, 1507*m*, 1497*m*, 1491*m*, 1473*m*, 1465*m*, 1437*m*, 1420*m*, 1388*m*, 1363*w*, 1252*m*, 1132*m*, 1097*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83 (*br s*, 2 H, NH_2, exchangeable with D_2O), 3.72 (*dd*, *J* = 10.6, 4.1, 1 H, OCH_2), 3.65 (*dd*, *J* = 10.6, 4.1, 1 H, OCH_2), 2.56 (*ddd*, *J* = 7.4, 3.7, 3.7, 1 H, H-C(1)), 1.66-1.60 (*m*, 1 H, H-C(2)), 1.13 (*ddd*, *J* = 10.0, 6.2, 3.7, 1 H, H_A-C(3)), 0.93-0.81 (*m*, 1 H, H_B-C(3)), 0.87 (*s*, 9 H, 3 x CH_3 of t.-Bu), 0.03 (*s*, 6 H, 2 x CH_3); ^{13}C-NMR (63 MHz, $CDCl_3$): 60.78 (*t*, OCH_2), 25.87 (*q*, 3 x CH_3 of t.-Bu and *d*, C(1)), 19.08 (*d*, C(2)), 18.27 (*s*, C_q of t.-Bu), 7.65 (*t*, C(3)), -4.56 and -4.63 (each *q*, 2 x CH_3); MS (ei, 80 eV, 92 °C): 201 (0.2%), 184 (10.7%), 144 (66.0%), 114 (9.8%), 96 (19.8%), 89 (11.3%) 75 (97.7%), 73 (68.0%), 69 (44.0%), 56 (100.0%); HRMS calcd. for $C_{10}H_{23}NOSi$: 201.15489; found: 201.15490.

3-Methoxy-2-methylacryloyl isocyanate (19).- The synthesis of the reagent **19** started from methyl 2-methyl-acrylate (**36**) which was brominated to yield 90% of 2,3-dibromo-2-methyl-propionic acid methyl ester (**37**).[16] Reaction of **37** with sodium methoxide followed by treatment with sodium hydrogen sulfate gave 62% of methyl 3-methoxy-2-methyl acrylate (**38**).[16] **38** was saponified with 2 N aqueous sodium hydroxide and the acrylic acid **39**[19] was obtained in 96% yield; **39** was treated with oxalylic chloride to afford 3-methoxy-2-methyl-acryloyl chloride (**34**) which – without isolation – was allowed to react with silver cyanate to give **19**. Selected analytical data: (**37**): n_D 1.5038; lit.: 1.505;[16] bp 102-104 °C (15 mm), lit.: bp 86 °C (15 mm);[16] IR (film): 3474*w*, 3005*w*, 2984*w*, 2954*m*, 2844*w*, 1745*s*, 1451*s*, 1381*m*, 1297*s*, 1236*s*, 1199*s*, 1172*s*, 1102*m*, 1079*s*, 1049*s*; ^{1}H-NMR (300 MHz, $CDCl_3$): 4.22 (*d*, *J* = 9.8, 1 H, CH_2), 3.83 (*s*, 3 H, OCH_3), 3.75 (*s*, *J* = 9.8, 1 H, CH_2), 2.03 (*s*, 3 H, CH_3); ^{13}C-NMR (63 MHz, $CDCl_3$): 168.94 (*s*, CO), 55.22 (*s*, C), 53.35 (*q*, OCH_3), 38.09 (*t*, CH_2), 26.35 (*q*, CH_3); MS (ei, 80 eV, 30 °C): 262 (0.2%), 260 (0.4%), 258 (0.2%), 231 (0.5%), 229 (1.1%), 227 (0.5%), 203 (3.8%), 201 (7.2%), 199 (4.1%), 181 (64.5%), 179 (63.5%), 153 (13.0%), 151 (14.2%), 122 (13.0%), 121 (15.1%), 120 (13.8%), 119 (15.6%); **38**: n_D 1.4540, lit.: 1.460,[16] 1.455[19]; bp 75-77 °C (15 mm), lit.: 175-176 °C (760 mm),[16] 66-67 °C (10 mm);[19] R_F (EtOAc/Hex 1:8) 0.55; IR (film): 2951*m*, 2850*w*, 1711*s*, 1651*s*, 1437*m*, 1389*w*, 1359*m*, 1298*s*, 1246*s*, 1190*s*, 1122*s*, 758*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.28 (*d*, *J* = 1.3, 1 H, CH), 3.81 (*s*, 3 H, OCH_3); 3.70 (*s*, 3 H, $COOCH_3$), 1.73 (*d*, *J* = 1.3, 3 H, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 169.02 (*s*, CO), 158.32 (*d*, CH), 106.02 (*s*, C), 61.07 (*q*, OCH_3), 51.13 (*q*, OCH_3 ester), 9.05 (*q*, CH_3); MS (ei, 80 eV, 30 °C): 132 (0.6%), 131 (5.3%), 130 (84.5%), 115 (37.0%), 99 (100.0%), 83 (59.8%), 75 (59.5%); **39**: mp 104-105 °C, lit.: 106°C;[19] IR (KBr): 3629*w*, 2954*s*, 2652*m*, 2585*m*, 1663*s*, 1646*s*, 1560*m*, 1534*w*, 1507*w*, 1448*m*, 1436*m*, 1388*m*, 1363*m*, 1325*s*, 1259*s*, 1163*s*, 1140*s*; ^{1}H-NMR (300 MHz, DMSO-d_6): 11.82 (*br s*, 1 H, OH), 7.31 (*d*, *J* = 1.3, 1 H, CH), 3.80 (*s*, 3 H, OCH_3), 1.59 (*d*, *J* = 1.3, 3 H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): 169.26 (*s*, CO), 158.69 (*d*, CH), 104.87 (*s*, C), 60.96 (*q*, OCH_3), 9.13 (*q*, CH_3); MS (ei, 80 eV, 30 °C): 118 (0.8%), 117 (5.6%), 116 (100.0%), 102 (1.6%), 101 (31.0%), 99 (41.9%), 98 (10.9%), 87 (12.9%), 84 (30.0%), 83 (89.8%), 71 (20.7%), 70 (22.2%), 69 (13.5%).

(±)-trans-1-(3-Methoxy-2-methyl-acryloyl)-3-(2-tert.-butyldimethylsilyloxymethyl-cyclopropyl)-urea (23) and 3-methoxy-2-methyl-acrylamide (24).- A solution of **19** [from of 3-methoxy-2-methyl-acryloyl chloride (1.57 g, 11.67 mmol) and silver cyanate (3.51 g, 23.42 mmol) in dry benzene (20 *ml*)] was prepared and added dropwise over 0.5 h under argon to a -40°C cold solution of **22** (1.57 g, 7.80 mmol) in dry dimethylformamide (16 *ml*). Stirring was continued for 1 h at -35 °C. The mixture was allowed to warm to

25°C and stirred for an additional hour. Then a saturated, ice cold solution of NaHCO$_3$ (20 *ml*) was added and the reaction mixture was extracted with EtOAc (4 x 30 *ml*), the combined organic phases were dried over MgSO$_4$ and concentrated. Column chromatography (EtOAc/Hex 1:5 → 1:1 → EtOAc) yielded **23** (0.83 g, 31%) and **24** (0.39 g, 29%).

Data for **23**: White solid; mp 87-90 °C; R$_F$ (EtOAc/Hex 1:5) 0.20; IR (KBr): 3263*m*, 2959*m*, 2929*m*, 2894*m*, 2856*m*, 1684*s*, 1658*s*, 1647*s*, 1617*m*, 1576*m*, 1559*s*, 1550*s*, 1522*m*, 1473*m*, 1457*m*, 1437*w*, 1298*s*, 1252*s*, 1190*m*, 1151*s*, 1127*s*, 1102*m*, 1075*m*, 1041*m*, 1019*w*; ^{1}H-NMR (300 MHz, DMSO-d$_6$): 9.67 (*s*, 1 H, OC-NH-CO), 8.57 (*d*, *J* = 3.5 1 H, NH), 7.41 (*d*, *J* = 1.2, 1 H, CH), 3.78 (*s*, 3 H, OCH$_3$), 2 H, OCH$_2$ partially hidden by solvent, 2.55-2.47 (*m*, 1 H, H-C(1)), partially hidden by solvent), 1.59 (*d*, *J* = 1.2, 3 H, CH$_3$), 1.15-1.05 (*m*, 1 H, H-C(2)), 0.84 (*s*, 9 H, 3 x CH$_3$ of t.-Bu), 0.66-0.61 (*m*, 2 H, H$_{A,B}$-C(3)), 0.02 (*s*, 6 H, 2 x CH$_3$-Si); ^{13}C-NMR (75 MHz, DMSO-d$_6$): 169.63 (*s*, CO), 158.16 (*d*, CH), 154.47 (*s*, NHCONH), 106.94 (*s*, C$_q$), 63.68 (*t*, OCH$_2$), 61.15 (*q*, OCH$_3$), 26.67 (*d*, C(1)), 25.90 (*q*, 3 x CH$_3$ of t.-Bu), 21.56 (*d*, C (2)), 18.02 (*s*, C$_q$ of t.-Bu), 10.93 (*t*, C(3)), 8.87 (*q*, CH$_3$), -5.15 (*q*, 2 x CH$_3$); MS (ei, 80 eV, 85 °C): 344 (0.2%), 343 (0.9%), 342 (3.2%), 329 (0.2%), 328 (0.6%), 327 (2.4%), 287 (4.5%), 286 (13.5%), 285 (91.9%), 211 (3.7%), 210 (10.6%), 197 (25.6%), 170 (9.5%), 101 (7.4%), 100 (28.2%), 99 (100.0%); Anal. calcd. for $C_{16}H_{30}N_2O_4Si$ (342.51): C, 56.11; H, 8.83; found: C, 56.41; H, 8.79.

Data for **24:** White solid; mp 104-106°C, lit.: 109-111°C;[23] R$_F$ (EtOAc) 0.15; IR (KBr): 3346*s*, 3171*s*, 2941*m*, 2847*m*, 2779*w*, 2368*w*, 2344*w*, 1734*m*, 1700*s*, 1653*s*, 1595*s*, 1560*m*, 1521*m*, 1507*m*, 1457*m*, 1424*s*, 1385*m*, 1361*m*, 1241*s*, 1179*m*, 1146*s*, 1005*w*, 972*m*, 885*m*; ^{1}H-NMR (300 MHz, MeOH-d$_4$): 7.17 (*d*, *J* = 1.3, 1 H, CH), 4.85 (*s*, 2 H, NH$_2$), 3.79 (*s*, 3 H, OCH$_3$), 1.72 (*d*, *J* = 1.3, 3 H, CH$_3$); ^{13}C-NMR (75 MHz, MeOH-d$_4$): 173.92 (*s*, CO), 157.15 (*d*, CH), 108.42 (*s*, =C$_q$), 61.32 (*q*, OCH$_3$), 9.37 (*q*, CH$_3$); MS (ei, 80 eV, 49 °C): 116 (5.9%), 115 (100.0%), 100 (71.6%), 99 (72.1%), 86 (26.2%), 83 (86.4%), 69 (10.5%), 60 (27.3%), 56 (47.1%), 55 (35.2%), 44 (61.5%), 41 (79.4%).

3-Ethoxy-acryloyl isocyanate (25).- The reagent **25** was easily accessible starting from commercially available ethyl 3-ethoxy-acrylate (**40**) which upon treatment with 2 N NaOH [19,25] gave 68 % of 3-ethoxy-acrylic acid (**41**). **41** was reacted in succession with oxalylic chloride to afford 3-ethoxy-acryloyl chloride (**33**)[14, 19] in almost quantitative yield which was treated with silver cyanate (*vide supra*) to yield 3-ethoxy-acryloyl isocyanate (**25**). Selected analytical data: (**41**): mp 108-109 °C; lit. 110.5 °C,[25] 109 °C,[19] 107-109 °C;[14] IR (KBr): 3091*m*, 2994*m*, 2897*m*, 2590*m*, 1772*w*, 1734*m*, 1684*s*, 1602*s*, 1560*m*, 1534*m*, 1507*w*, 1496*w*, 1474*m*, 1457*w*, 1430*s*, 1394*w*, 1341*m*, 1307*s*, 1271*m*, 1258*m*, 1261*s*, 1177*s*, 1114*m*, 1014*m*; ^{1}H-NMR (300 MHz, DMSO-d$_6$): 11.60 (*br*, 1 H, OH), 7.51 (*d*, *J* = 12.6, 1 H, OCH=), 5.14 (*d*, *J* = 12.6, 1 H, OCH=), 3.95 (*q*, *J* = 7.0, 2 H, OCH$_2$), 1.25 (*t*, *J* = 7.0, 3 H, CH$_3$); ^{13}C-NMR (75 MHz, DMSO-d$_6$): 168.05 (*s*, CO), 162.09 (*d*, OCH=), 96.56 (*d*, =CHCO), 66.59 (*t*, OCH$_2$), 14.39 (*q*, CH$_3$); MS (ei, 80 eV, 30 °C): 117 (2.2%), 116 (37.3%), 101 (19.4%), 99 (14.4%), 98 (7.8%), 73 (28.7%), 71 (60.2%), 70 (100.0%), 69 (65.1%).

(±)-trans-[2-(Tert.-butyldimethylsilyloxymethyl)-cyclopropyl]-3-(3-ethoxy-acryloyl)-urea (26) and (3-ethoxy-acryloyl) carbamic acid 2-[3-(3-ethoxy-acryloyl)-ureido]-cyclopropylmethyl ester (27).- A suspension of silver cyanate (1.12 g, 7.47 mmol) (dried over phosphorus pentoxide for 3 h under reduced pressure) in dry benzene (7 *ml*) was heated under reflux under argon for 0.5 h. **33** (0.50 g, 3.71 mmol)[19] in dry benzene (1.5 *ml*) was added to the refluxing mixture and stirring was continued for 0.5 h. After cooling to 25 °C the suspension was stirred for one more hour. In a separate round bottom flask **22** (0.50 g, 2.48 mmol) was dissolved in dry dimethylformamide (10 *ml*) and cooled to -40°C. The solution of the acylisocyanate in benzene was added dropwise over 0.5 h under argon at -35 °C to the solution of the amine. Stirring was continued for 1 h at -35 °C. The mixture was allowed to warm to 25 °C and stirred for one more hour. A saturated ice-cold solution of $NaHCO_3$ (20 *ml*) was added and the reaction mixture was extracted with EtOAc (4 x 30 *ml*); the combined organic phases were dried over $MgSO_4$ and concentrated. Column chromatography (EtOAc/Hex 1:1 → 3:1 → 5:1) of the residue yielded **26** (0.20 g, 23%) and **27** (0.18 g, 20%).

Data for **26**.- Yellowish solid; mp 106-109 °C; R_F (EtOAc/Hex 1:3) 0.24; IR (KBr): 3271*m*, 3102*m*, 2956*m*, 2931*m*, 2897*m*, 2857*m*, 1734*m*, 1701*s*, 1648*s*, 1608*s*, 1559*m*, 1534*s*, 1496*m*, 1473*m*, 1395*w*, 1383*m*, 1346*m*, 1313*m*, 1246*s*, 1191*m*, 1151*s*, 1128*m*, 1109*m*, 1095*s*, 1074*m*, 1055*m*, 1043*m*, 1019*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 10.00 (*s*, 1 H, OCNHCO), 8.45 (*d*, *J* = 3.2, 1 H, NH), 7.50 (*d*, *J* = 12.3, 1 H, OCH=), 5.46 (*d*, *J* = 12.3, 1 H, CH=), 3.90 (*q*, *J* = 7.0, 2 H, OCH_2), 3.51 and 3.52 (each *d*, *J* = 5.7 and *J* = 5.1, 2 H, $SiOCH_2$), 2.51-2.46 (*m*, 1 H, H-C(1), partially hidden by solvent), 1.21 (*t*, *J* = 7.0, 3 H, CH_3), 1.12-1.07 (*m*, 1 H, H-C(2)), 0.82 (*s*, 9 H, 3 x CH_3 of t.-Bu), 0.64-0.59 (*m*, 2 H, $H_{A,B}$-C(3)), -0.04 (*s*, 6 H, 2 x CH_3-Si); ^{13}C-NMR (63 MHz, DMSO-d_6): 167.66 (*s*, CO), 162.00 (*d*, OCH=), 154.32 (*s*, NHCONH), 98.28 (*d*, OC-CH=), 67.22 (*t*, OCH_2), 63.50 (*t*, $SiOCH_2$), 26.44 (*d*, C(1)), 25.80 (*q*, 3 x CH_3 of t.-Bu), 21.48 (*d*, C(2)), 17.93 (*s*, C_q of t.-Bu), 14.35 (*q*, CH_3), 10.83 (*t*, C(3)), -5.25 (*q*, 2 x CH_3-Si); MS (ei, 80 eV, 121 °C): 342 (1.5%), 327 (1.3%), 287 (3.3%), 286 (11.1%), 285 (53.2%), 210 (8.0%), 197 (22.7%), 189 (2.4%), 188 (7.8%), 187 (50.1%), 170 (1.5%), 100 (13.4%), 99 (100%); HRMS: calcd. for $C_{16}H_{30}N_2O_4Si$: 342.19749, found: 342.19748.

Data for **27**.- Yellowish solid; mp 169-170 °C; R_F (EtOAc) 0.38; IR (KBr): 3268*s*, 3142*m*, 3097*m*, 2984*m*, 2940*m*, 2887*w*, 1772*s*, 1734*m*, 1705*s*, 1680*s*, 1609*s*, 1550*s*, 1521*s*, 1499*s*, 1467*s*, 1412*m*, 1396*m*, 1350*m*, 1333*m*, 1312*m*, 1287*m*, 1250*s*, 1220*s*, 1183*s*, 1154*s*, 1086*m*, 1056*s*, 1019*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 10.32 and 10.08 (each *s*, 1 H, CONHCO), 8.51 (*d*, *J* = 3.2, 1 H, NH), 7.57 (*d*, *J* = 12.3, 1 H, OCH=), 7.54 (*d*, *J* = 12.4, 1 H, OCH=), 5.85 (*d*, *J* = 12.4, 1 H, =HC-CO), 5.50 (*d*, *J* = 12.3, 1 H, =HC-CO), 4.05-3.87 (*m*, 6 H, 3 x OCH_2), 2.68-2.63 (*m*, 1 H, H-C(1)), 1.32-1.14 (*m*, 1 H, H-C(2)), 1.25 and 1.24 (each *t*, *J* = 7.0, 6 H, 2 x CH_3), 0.86-0.76 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (75 MHz, DMSO-d_6): 167.60 and 165.26 (each *s*, 2 x CO), 162.39 and 161.97 (each *d*, 2 x OCH), 154.24 and 151.64 (each *s*, NHCONH and NH-COO), 98.52 and 98.21 (each *d*, 2 x HC-CO), 67.17 and 67.12 (each *t*, 3 x OCH_2), 27.20 (*d*, C(2)), 18.31 (*d*, C(1)), 14.31 (*q*, 2 x CH_3), 11.42 (*t*, C(3)); MS (ei, 80 eV, 179 °C): 369 (0.02%), 256 (0.04%), 239 (0.03%), 211 (3.3%), 210 (14.8%), 197 (5.5%), 159 (20.5%), 141 (3.2%), 100 (9.3%), 99 (100.0%), 71 (82.9%); Anal. calcd. for $C_{16}H_{23}N_3O_7$ (369.37): C, 52.03; H, 6.28; found: C, 52.30; H, 6.29.

(±)-cis-1-[2-(Tert.-butyldimethylsilyloxymethyl)-cyclopropyl]-3-(ethoxyacryloyl)-urea (28) and 3-ethoxyacrylamide (29).- According to the preparation of **26** **18** (3.18 g, 15.79 mmol) was dissolved in dry dimethylformamide (15 *ml*). 3-Ethoxyacryloyl isocyanate [prepared from silver cyanate (7.11 g, 47.43 mmol) in benzene (20 *ml*) and **33** (3.19 g, 23.71 mmol) in benzene (10 *ml*)][19] was added to the solution of the amine. Work up as described for **26** afforded **28** (1.85 g, 34%) and **29** (0.43 g, 16%).

Data for **28**: White solid; mp 71-73 °C, R_F (EtOAc/Hex 1:3) 0.16; IR (KBr): 3239*m*, 3107*m*, 2956*m*, 2899*m*, 2857*m*, 1845*w*, 1793*w*, 1773*m*, 1734*m*, 1707*s*, 1685*s*, 1654*m*, 1647*m*, 1636*m*, 1617*s*, 1577*m*, 1560*m*, 1534*s*, 1507*m*, 1497*m*, 1473*m*, 1448*m*, 1420*w*, 1395*m*, 1378*m*, 1362*w*, 1340*m*, 1314*m*, 1243*s*, 1165*s*, 1143*s*, 1108*m*, 1078*s*, 1015*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 9.60 (*s*, 1 H, OCNHCO), 8.77 (*d*, *J* = 3.0, 1 H, NH), 7.59 (*d*, *J* = 12.3, 1 H, OCH=), 5.35 (*d*, *J* = 12.3, 1 H, CH=), 3.93 (*q*, *J* = 7.1, 2 H, OCH_2), 3.74 (*dd*, *J* = 11.1, 6.4, 1 H, $SiOCH_2$), 3.61 (*dd*, *J* = 11.1, 7.7, 1 H, $SiOCH_2$), 2.86-2.82 (*m*, 1 H, H-C(1)), 1.32 (*t*, *J* = 7.1, 3 H, CH_3), 1.28-1.20 (*m*, 1 H, H-C(2)), 0.99-0.88 (*m*, 1 H, H_A-C(3)), 0.87 (*s*, 9 H, 3 x CH_3 of t.-Bu), 0.49 (*ddd*, *J* = 6.0, 6.0, 4.4, 1 H, H_B-C(3)), 0.04 (*s*, 6 H, 2 x CH_3-Si); ^{13}C-NMR (63 MHz, DMSO-d_6): 167.86 (*s*, CO), 162.46 (*d*, OCH=), 156.65 (*s*, NHCONH), 98.11 (*d*, OC-CH=), 67.17 (*t*, OCH_2), 62.37 (*t*, $SiOCH_2$), 26.55 (*d*, C(1)), 25.91 (*q*, 3 x CH_3 of t.-Bu), 18.99 (*d*, C(2)), 18.29 (*s*, C_q of t.-Bu), 14.45 (*q*, CH_3), 10.67 (*t*, C(3)), -5.33 (*q*, 2 x CH_3-Si); MS (ei, 80 eV, 121 °C): 343 (0.5%), 342 (1.8%), 327 (1.6%), 287 (3.6%), 286 (12.2%), 285 (63.6%), 229 (1.5%), 211 (2.4%), 210 (7.8%), 197 (24.0%), 187 (46.9%), 170 (8.5%), 99 (100.0%), 75 (20.4%), 73 (23.1%), 71 (65.1%); Anal. calcd. for $C_{16}H_{30}N_2O_4Si$ (342.51): C, 56.11; H, 8.83; found: C, 56.21; H, 8.68.

Data for **29**: White solid; mp 146-152 °C; lit.: 147 °C,[20] 151-152 °C,[21] 152 °C;[22] R_F (EtOAc) 0.31; IR (KBr): 3317*m*, 3159*m*, 2984*m*, 2942*w*, 1844*w*, 1830*w*, 1793*w*, 1773*w*, 1762*w*, 1734*m*, 1718*m*, 1700*m*, 1696*m*, 1684*s*, 1675*s*, 1653*s*, 1636*m*, 1617*m*, 1590*s*, 1560*m*, 1554*m*, 1534*m*, 1522*m*, 1517*w*, 1507*m*, 1499*w*, 1491*w*, 1476*m*, 1465*m*, 1457*m*, 1437*m*, 1420*m*, 1323*m*, 1265*m*, 1209*s*, 1137*m*, 1110*m*, 1019*m*; ^{1}H-NMR (300 MHz, MeOH-d_4): 7.49 (*d*, *J* = 12.4, 1 H, OCH=), 5.39 (*d*, *J* = 12.4, 1 H, =CH), 3.94 (*q*, *J* = 7.0, 2 H, OCH_2), 1.33 (*t*, *J* = 7.0, 3 H, CH_3); ^{13}C-NMR (75 MHz, MeOH-d_4): 172.18 (*s*, CO), 161.32 (*d*, OCH), 98.85 (*d*, =CH), 67.72 (*t*, OCH_2), 14.83 (*q*, CH_3); MS (ei, 80 eV, 60°C): 116 (1.0%), 115 (13.4%), 100 (42.3%), 99 (13.6%), 86 (18.8%), 72 (25.0%), 71 (100.0%), 69 (16.7%), 44 (38.8%), 43 (29.8%), 42 (12.2%); HRMS : calcd for $C_5H_9NO_2$: 115.0633; found: 115.0633.

(±)-trans-[2-(9H-6-Chloro-purin-9-yl)-cyclopropyl]-methanol (32).- A suspension of **31** (0.61 g, 2.84 mmol),[9] triethyl orthoformate (6.78 g, 45.76 mmol) and hydrochloric acid (36%, 0.34 g, corresponding to 1.2 equivalents) was stirred at 25 °C for 3 h. Then the pH of the mixture was adjusted to 7-8 by addition of solid sodium bicarbonate and water (10 *ml*). The resulting aqueous solution was extracted with EtOAc (5 x 50 *ml*), the combined organic phases were dried ($MgSO_4$) and the solvent was removed. Column chromatography of the residue (EtOAc/Hex 1:1 → EtOAc → EtOAc/MeOH 10:1) afforded (±)-trans-6-chloro-9-(2-chloromethyl-cyclopropyl)-9H-purine (**35**) (0.14 g, 21%)[9] and **32** (0.24 g, 37%) as a white solid; mp 86-90 °C; R_F (EtOAc/MeOH 8:1) 0.49; IR (KBr): 3331*s*, 3060*s*, 2983*m*, 2867*m*, 2480*w*, 1844*w*, 1830*w*, 1772*w*, 1762*w*, 1751*w*, 1734*w*, 1718*m*, 1700*w*, 1594*s*, 1559*s*, 1521*w*, 1499*m*, 1449*s*, 1406*s*, 1340*s*, 1227*s*, 1148*m*, 1098*m*, 1047*s*; ^{1}H-NMR (300 MHz, MeOH-d_4): 8.73 (*s*, 1 H, H-C(2')), 8.56 (*s*, 1 H, H-C(8')), 4.63 (*br*, 1 H, OH), 3.78 (*dd*, J = 11.5, 5.8, 1 H, OCH_2), 3.68 (*dd*, J = 11.5, 6.6, 1 H, OCH_2), 3.54 (*ddd*, J = 6.9, 2.6, 3.1, 1 H, H-C(1)), 1.91-1.86 (*m*, 1 H, H-C(2)), 1.47 (*ddd*, J = 11.5, 6.1, 3.6, 1 H, H_A-C(3)), 1.27 (*ddd*, J = 6.9, 6.3, 6.1, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, MeOH-d_4): 153.97 (*s*, C(6')), 152.71 (*d*, C(2')), 150.94 (*s*, C(4')), 148.53 (*d*, C(8')), 132.28 (*s*, C(5')), 63.26 (*t*, OCH_2), 31.25 (*d*, C(1)), 22.58 (*d*, C(2)), 11.02 (*t*, C(3)); MS (ei, 80 eV, 91 °C): 226 (0.3%), 225 (0.5%), 224 (0.3%), 223 (0.7%); 209 (1.3%), 207 (7.5%), 205 (9.0%), 195 (11.0%), 193 (27.9%), 185 (3.3%), 183 (12.5%), 157 (51.5%), 155 (100.0%); 154 (13.4%), 119 (11.9%); Anal. calcd. for $C_9H_9ClN_4O$ (224.65): C, 48.12; H, 4.04; found: C, 48.30; H, 4.12.

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REFERENCES AND NOTES

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