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Synthesis of Cyclopropyl Carbocyclic Nucleosides

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Abstract: As representatives of a novel class of carbocyclic nucleoside analogues (±)-*cis*-, (-)-*cis* and (±)-*trans* 9-(2-hydroxymethylcyclopropyl)-adenine (= [2-(6-amino-purin-9-yl)-cyclopropyl]-methanol) were synthesized from the corresponding dialkyl 1,2-cyclopropane dicarboxylates.

INTRODUCTION

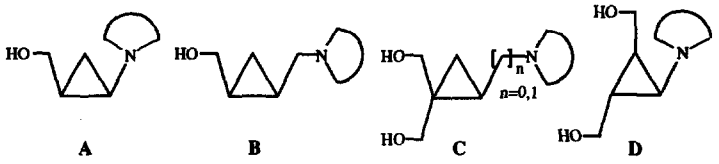
More than 60% of all diseases in Europe, North America and Japan are caused by the action of viruses, amongst them bronchitis, hepatitis, influenza, infections by several strains of herpes as well as by human immunodeficiency virus (HIV). [1] In the chemotherapy of these infections analogues of nucleosides have been used, and thus throughover decades [2] many modified nucleosides have been discovered that inhibit the replication of these viruses to a more or less pronounced extent. The vast majority of these analogues act through a similar mechanism in which they are first metabolized to the 5′-triphosphate derivative which inhibits the viral reverse transcriptase or they serve as a substrate for incorporation into the viral DNA; in consequence, this results in a chain termination. [3]

Nucleoside analogues prepared so far can be divided into three categories: 1) phosphate modified, 2) base modified, and 3) sugar modified; most of the commonly known active compounds belong to the two latter groups. Modifications of the sugar moiety include chain extensions at the anomeric centre and at the C(5′) position, (hetero)substitutions, deoxygenations or eliminations leaving the ring size of the ribose skeleton the same.[4] Of pronounced interest are compounds, however, whose ribose unit has been subject to major changes either by its replacement by a cyclopentane[5] or cyclopentene[6] (carbasugars), oxetane[7] or cyclobutane[8] ring ((carba)oxetanocins) or by an acyclic chain; the latter "acyclo concept" finally led to highly active compounds such as (carba)acyclovir[9] or (carba)ganciclovir.[10]

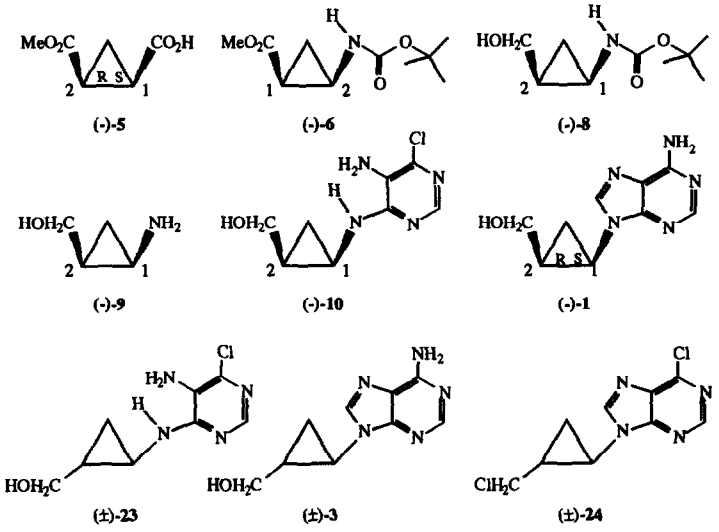
RESULTS AND DISCUSSION

Molecular modelling studies indicated that cyclopropane analogues of type **A** can be regarded as potential candidates for biological evaluation for antiviral activity.[11] Results from these calculations, conformational analyses and molecular modelling are indirectly supported, inasmuch as compounds of type **B** possessing an additional methylene spacer between the cyclopropane unit and the heterocycle[12] as well as compounds with a (in)direct attachment of the heterocycle but with two geminal or vicinal [12,13] hydroxymethyl units at the

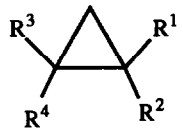
cyclopropane skeleton (type **C** and type **D**) have shown significant antiviral activity;[14] to the best of our knowledge, however, hitherto no syntheses of compounds of type **A** or their *trans* epimers have been reported.



(-)-*Cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**1**), (±)-*cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**2**) and (±)-*trans*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**3**) were chosen as primary synthetic target molecules. Thus, treatment of (±)-dimethyl 1,2-cyclopropane dicarboxylate (**4**) which was easily obtained in 39% yield from the reaction of methyl acrylate with methyl chloroacetate [15-17] in the presence of sodium hydride, with *pig liver esterase* (PLE)[18-22] at pH=7.2 afforded 90% of (1 *S*, 2 *R*)-**5**; **5** showed an optical rotation $[\alpha]_D^{20}$ -17.5° indicating an enantiomeric excess ee≥99.5%. *Curtius* degradation of the carboxylate moiety with diphenyl-phosphorylazide in the presence of *tert.*-butanol and triethylamine[23-25] at 50-55°C resulted in the formation of the *N*-BOC protected methyl 2-amino-1-cyclopropane carboxylate **6**. When this reaction was performed at reflux temperature a significant amount (18.7%) of the corresponding *trans* epimer **7** (*vide infra*) was formed. Compound **6** gave upon treatment with diisobutylaluminium hydride (DIBAH)[26] at -78°C, 54% of (-)-*cis*-[2-(*tert.*-butoxycarbonylamino)-cyclopropyl]-methanol (**8**).



The hydrolytic stability of this *N*-BOC group is remarkably high but could finally be cleaved off upon treatment with 6 N hydrochloric acid at 40-45°C for 3h; the crude 2-hydroxymethyl-cyclopropylamine **9** was treated without further purification with 5-amino-4,6-dichloro-pyrimidine in the presence of triethylamine to yield 57% of **10**. The sequence to the target compound was completed by an acid-catalyzed reaction of **10** with an excess of triethylorthoformate followed by treatment of the crude reaction mixture with ammonia (75°C, 14 bar, 18 h) in an autoclave. Thus, (-)-*cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**1**) was obtained from **10** in 45% yield.



No	R^1	R^2	R^3	R^4
2	9-Adenyl	H	CH_2OH	H
4	CO_2Me	H	CO_2Me	H
7	$NHCO_2{}^tBu$	H	H	CO_2Me
11	COOH	H	CO_2Me	H
12	CO_2H	H	CO_2H	H
13	$NHCO_2{}^tBu$	H	CO_2Me	H
14	$NHCO_2Me$	H	CON_3	H
15	$NHCO_2{}^tBu$	H	CH_2OH	H
16	NH-4-(5-amino-6-chloro-pyrimidine)	H	CH_2OH	H
17	CO_2Me	H	H	CO_2Me
18	CO_2Me	H	H	CO_2H
19	CO_2Et	H	H	CO_2Et
20	CO_2Et	H	H	CO_2H
21	CO_2Et	H	H	$NHCO_2{}^tBu$
22	CH_2OH	H	H	$NHCO_2{}^tBu$
25	CO_2Et	H	CO_2Et	H
26	CH_2OH	H	H	NH_2

The synthesis of (±)-*cis*-9-(2-hydroxymethyl-cyclopropyl)-adenine (**2**) started from the racemic diester **4** whose treatment with sodium hydroxide [27] afforded a mixture of (±) monomethyl ester **11** and of the (±) diacid **12** (**11**:**12** = 79:21 by ^{1}H-NMR). *Curtius* degradation of this mixture afforded **13** as well as considerable amounts of labile **14**. The formation of the latter product can be explained by the cleavage of the methyl ester **11** resulting in the formation of methanol which also competes with *tert.*-butanol. The presence of the carbonyl azide moiety in **14** is indicated by the presence of an adsorption at $\nu = 2148\ cm^{-1}$ in the IR spectrum. Reduction

of **13** with DIBAH gave a 57% yield of (±)-**15**. Subsequent reaction of **15** with 6 N hydrochloric acid and 5-amino-4,6-dichloro-pyrimidine afforded **16** whose treatment with triethyl orthoformate/ hydrochloric acid followed by ammonolysis resulted in the formation of (±)-**2** in 51% yield. The *cis* configuration of **13** was unambiguously confirmed by an independent synthesis of the corresponding trans isomer **7** starting from (±)-**17**. Thus, **17** was treated with PLE to afford 83% of the racemic monoester **18** whose *Curtius* degradation in the presence of *tert.*-butanol gave the *trans*-ester **7**.

The synthesis of (±)-**3** was performed in a similar way starting from (±)-*trans* -diethyl 1,2-cyclopropane dicarboxylate (**19**) (obtained in 43% yield from the reaction of ethyl acrylate and ethyl chloroacetate/sodium hydride).[12, 15, 16] Reactions of **19** with aqueous solutions of metal hydroxides [27] proceeded sluggish under a variety of conditions and gave only low yields of **20** whereas treatment of **19** with PLE at pH=7.2 in a pH-stat equipment afforded the racemic cyclopropane-1,2-dicarboxylic acid monoethylester (**20**) in 95% yield. *Curtius* degradation of **20** in the presence of *tert.*-butanol gave 54% of (±) **21**. Reduction of **21** with DIBAH at -78°C for 3 h afforded **22** in 68% yield whereas reduction of **21** with calcium borohydride[28] gave **22** in only 49% yield after a reaction time of several days. Cleavage of the *N*-protecting group followed in succession by reaction with 5-amino-4,6-dichloro-pyrimidine (→ 68% of **23**), triethyl orthoformate/hydrochloric acid (→ **24**)[29] and ammonia resulted in the formation of 37% of (±)-*trans*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**3**). Preliminary testing of **1**, **2** and **3** and their respective triphosphates indicated significant antiviral activity justifying a more extensive screening which is presently in progress.

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), 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 ninhydrine (1%) solution followed by gentle heating, or by treatment with iodine).

(-)-*Cis*-9-(2-hydroxymethyl-cyclopropyl) adenine = (-)-*cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (1).- A suspension of **10** (0.49 g, 2.28 mmol), freshly distilled triethyl orthoformate (5.41 g, 36.5 mmol) and hydrochloric acid (36%, 0.26 g, corresponding to 1.2 equivalents) was stirred at 25°C for 3.5 h. Then the pH of the reaction mixture was adjusted by the careful addition of sodium bicarbonate and water (10 *ml*) to 7-8. This aqueous solution was extracted with EtOAc (5 x 50 *ml*), the combined organic phases were dried ($MgSO_4$) and the solvent was removed. The remaining residue was dissolved in liquid ammonia (15 *ml*) in an autoclave. After heating to 75°C (bath) for 18 h (internal pressure 14 bar) the ammonia was evaporated and the residue was dissolved in methanol. The solvent was removed and the residue subjected to chromatography (silica gel, EtOAc, then EtOAc/methanol 5:1 → 3:1) to afford **1** (0.21 g, 45%) as a white solid; mp 166-168°C, $[\alpha]_D^{20}$ -17.0° (*c*, 0.7 MeOH); R_F (EtOAc/MeOH 3:1) 0.30; IR (KBr): 3296*br s*, 3124*br s*, 2365*m*, 2345*m*, 1734*w*, 1676*s*, 1604*s*, 1570*s*, 1507*m*, 1477*s*, 1420*s*, 1388*m*, 1334*s*,

1300*s*, 1258*m*, 1196*m*, 1105*m*, 1055*s*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.18 (*s*, 1 H, H-C(2')), 8.13 (*s*, 1 H, H-C(8')), 7.28 (*s*, 2 H, NH_2, exchangeable with D_2O), 4.74 (*br*, 1 H, OH, exchangeable with D_2O), 3.49 (*ddd*, *J* = 7.2, 7.2, 4.3, 1 H, H-C(1)), 3.38-3.31 (*m*, 1 H, CH_2O), 3.06-2.98 (*m*, 1 H, CH_2O), 1.59-1.50 (*m*, 1 H, H-C(2)), 1.34-1.25 (*m*, 1 H, C(3)), 1.23-1.16 (*m*, 1 H, C(3)); ^{1}H-NMR (250 MHz, DMSO-d_6, D_2O): 8.16 (*s*, 1 H, H-C(2')), 8.12 (*s*, 1 H, H-C(8')), 3.49 (*ddd*, *J* = 7.2, 7.2, 4.3, 1 H, H-C(1)), 3.24 (*dd*, *J* = 11.7, 6.0, 1 H, CH_2O), 3.05 (*dd*, *J* = 11.7, 7.9, 1 H, CH_2O), 1.59-1.50 (*m*, 1 H, H-C(2)), 1.35-1.26 (*m*, 1 H, C(3)), 1.20-1.13 (*m*, 1 H, C(3)); ^{1}H-NMR (250 MHz, MeOH-d_4): 1.21 (*ddd*, *J* = 6.8, 6.3, 4.3, 1 H, H-C(3)), 1.44 (*ddd*, *J* = 9.2, 7.2, 6.3, 1 H, H-C(3)); ^{13}C-NMR (62 MHz, DMSO-d_6): 155.97 (*s*, C(6)), 152.42 (*d*, C(2')), 150.73 (*s*, C(4')), 142.11 (*d*, C(8')), 118.84 (*s*, C(5')), 59.30 (*t*, OCH_2), 28.78 (*d*, C(1)), 19.56 (*d*, C(2)), 8.33 (*t*, C(3)); UV(methanol): λ_{max} 260 nm, ε 14750; MS (ei, 80 eV, 131°C): 205 (14.4%), 188 (13.6%), 174 (23.2%), 164 (26.7%), 149 (17.4%), 148 (15.1%), 136 (100.0%), 135 (52.5%), 108 (22.8%); Anal. calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13; found: C, 52.50; H, 5.22; N, 34.42.

(±)-*Cis*-9-(2-hydroxymethyl cyclopropyl)adenine = (±)-*cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (2).- According to the preparation of **1** from **16** (0.42 g, 1.96 mmol) triethyl orthoformate (4.68 g, 31.6 mmol) and 36% hydrochloric acid (0.23 g, 1.2 equivalents) and ammonolysis (15 *ml* liq. ammonia, 76°C, 11-12 bar, 18 h) **2** (0.20 g, 51%) was obtained as a white solid; mp 168-171°C , R_F (EtOAc/MeOH 3:1) 0.30; showed the same IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra as **1**; Anal. calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13; found: C, 52.52; H, 5.19; N, 34.37.

(±)-*Trans*-9-(2-hydroxymethyl-cyclopropyl) adenine = (±)-*trans*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (3) .- According to the preparation of **1** from **23** (0.79 g, 3.68 mmol) triethyl orthoformate (8.77 g, 59.2 mmol) and 36% hydrochloric acid (0.44 g, 1.2 equivalents) and ammonolysis (15 *ml* liq. ammonia, 76°C, 14 bar, 18 h) **3** (0.28 g, 37%) was obtained; mp 172-173°C; R_F (EtOAc/MeOH 3:1) 0.21; IR (KBr): 3280*br s*, 3120*br s*, 2890*m*, 2720*w*, 2660*w*, 1885*w*, 1660*s*, 1600*s*, 1565*s*, 1505*w*, 1470*s*, 1450*m*, 1410*s*, 1390*w*, 1370*m*, 1330*s*, 1300*s* 1250*m*, 1220*m*, 1190*w*, 1175*w*, 1120*m*, 1100*w*, 1080*w*, 1070*m*, 1040*w*, 1020*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.15 (*s*, 1 H, H-C(2')), 8.08 (*s*, 1 H, H-C(8')), 7.17 (*s*, 2 H, NH_2, D_2O exchangeable), 4.74 (*t*, *J* = 5.5, 1 H, OH, exchangeable with D_2O), 3.55 (*virt. t*, *J* = 5.5, 2 H, OCH_2), H-C(1) hidden by solvent, 1.76-1.68 (*m*, 1 H, H-C(2)), 1.30-1.23 (*m*, 1 H, C(3)), 1.10-1.02 (*m*, 1 H, C(3)); ^{1}H-NMR (250 MHz, DMSO-d_6, D_2O): 8.19 (*s*, 1 H, H-C(2')), 8.13 (*s*, 1 H, H-C(8')), 3.57 (*virt. d*, *J* = 6.5, 2 H, OCH_2), 3.38 (*ddd*, *J* = 7.0, 4.0, 3.4, 1 H, H-C(1)), 1.71 (*ddd*, *J* = 9.5, 6.5, 3.4, 1 H, H-C(2)), 1.28 (*ddd*, *J* = 9.5, 6.0, 4.0, 1 H, H-C(3)), 1.12 (*ddd*, *J* = 7.0, 6.5, 6.0, 1 H, H-C(3)); ^{13}C-NMR (62 MHz, DMSO-d_6): 155.86 (*s*, C(6)), 152.39 (*d*, C(2')), 150.43 (*s*, C(4')), 140.58 (*d*, C(8')), 118.86 (*s*, C(5')), 61.14 (*t*, OCH_2), 29.09 (*d*, C(1)), 21.16 (*d*, C(')), 9.99 (*t*, C(3)); UV(methanol): λ_{max} 258 nm, ε 16667; MS (ei, 80 eV, 141°C): 205 (18.2%), 188 (19.9%), 174 (35.3%), 164 (37.2%), 149 (19.8%), 148 (19.5%), 136 (100.0%), 108 (32.3%); Anal. calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13; found: C, 52.44; H, 5.35; N, 34.28.

(±)-*Cis*-dimethyl 1,2-cyclopropane dicarboxylate (4) and (±)-*trans*-dimethyl 1,2-cyclopropane dicarboxylate (17).- According to the procedure given for the synthesis of **25** from methyl acrylate (34.4 g, 400 mmol), methyl chloroacetate (43.4 g, 400 mmol) and sodium hydride (12.5 g, corresponds to 417 mmol) (40-50°C, then 25° for 12 h) a mixture of **4/17** (42 g) was obtained after distillation (35-84°C, 0.1

mbar) which was subjected to column chromatography (silica gel, EtOAc/hexanes 1:20 → 1:10) to afford **4** (24.6 g, 39%) and **17** (11.9 g, 19%).

Data of **4**.- n_D = 1.4445, R_F (EtOAc/Hex 1:4) 0.39; IR (film): 3000*w*, 2950*m*, 2845*w*, 1730*s*, 1435*s*, 1385*s*, 1370*s*, 1360*s*, 1285*m*, 1260*m*, 1200*s*, 1165*s*, 1105*s*, 1065*m*, 1045*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 3.70 (*s*, 6 H, 2 x OCH_3), 2.05-2.11 (*m*, 2 H, H-C(1), H-C(2)), 1.63-1.70 (*m*, 1 H, H_A-C(3)), 1.22-1.30 (*m*, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 170.12 (*s*, 2 x CO), 52.05 (*q*, 2 x OCH_3), 21.37 (*d*, C(1), C(2)), 11.79 (*t*, C(3)); MS (ei, 80 eV, 30°C): 158 (2.2%), 127 (100.0%), 99 (29.7%), 98 (24.8%), 85 (2.8%), 83 (3.4%), 71 (12.7%), 59 (21.7%), 55 (9.9%), 41 (13.1%).

Data of **17**.- n_D = 1.4415, R_F (EtOAc/Hex 1:4) 0.66; IR (film): 3100*w*, 3060*w*, 3000*w*, 2960*m*, 2900*w*, 2840*m*, 1740*s*, 1720*s*, 1440*s*, 1400*m*, 1335*s*, 1310*s*, 1270*s*, 1200*s*, 1170*s*, 1120*m*, 1090*w*, 1055*m*, 1020*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 3.70 (*s*, 6 H, 2 x OCH_3), 2.17 (*dd*, *J* = 8.7, 5.9, 2 H, H-C(1), H-C(2)), 1.46-1.40 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.91 (*s*, 2 x CO), 52.08(*q*, 2 x OCH_3), 22.17 (*d*, C(1), C(2)), 15.33 (*t*, C(3)); MS (ei, 80 eV, 30°C): 158 (1.2%), 127 (100.0%), 126 (54.6%), 99 (43.1%), 98 (66.5%), 71 (16.0%), 59 (39.6%).

(-)-*Cis*-cyclopropane-1,2-dicarboxylic acid monomethylester (5).- A suspension of **4** (10.0 g, 63.2 mmol) in water (50 *ml*) was adjusted to pH 7 with 1 N NaOH and at 26°C PLE (0.5 *ml* of a suspension containing 30 mg/3 *ml* of enzyme, Boehringer-Mannheim Ltd.) was added. The pH was maintained at pH 7.2 by addition of 1 N NaOH using a pH-stat equipment; after 7 days more PLE (1 *ml*) was added. The reaction came to completion after an additional 14 days and the reaction mixture was concentrated at reduced pressure, then acidified (pH 1-2) by addition of 10% HCl and extracted with diethyl ether (5 x 100 *ml*). The combined organic phases were dried ($MgSO_4$) and the solvent removed. The remaining oil crystallized upon standing at -26°C to afford **5** (8.2 g, 90%) as a white solid; mp 77-79°C (lit.:[18] 81-83°C), $[\alpha]_D^{20}$ -17.5° (*c* 0.97 $CHCl_3$) (lit.:[20] -15.3° (*c*, 1 $CHCl_3$)); IR (KBr): 3041*m*, 2959*m*, 2365*w*, 1725*s*, 1546*m*, 1452*s*, 1388*s*, 1220*s*, 1181*s*, 1122*m*, 1100*m*, 1067*m*, 1033*s*, 1007*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 8.87 (*br s*, 1 H, OH, exchangeable with D_2O), 3.71 (*s*, 3 H, CH_3), 2.16-2.07 (*m*, 2 H, H-C(1), H-C(2)), 1.69 (*ddd*, *J* = 7.0, 6.5, 5.1, 1 H, H_A-C(3)), 1.32 (*ddd*, *J* = 8.5, 8.0, 5.1, 1 H, H_B-C(3)); ^{13}C-NMR (62 MHz, $CDCl_3$): 175.63 (*s*, COOH), 170.53 (*s*, COOMe), 52.41 (*q*, OCH_3), 22.35 and 21.24 (each *d*, C(1) and C(2)), 12.41 (*t*, C(3)); MS (ei, 80 eV, 93°C): 144 (1.0%), 127 (2.7%), 113 (100.0%), 99 (25.3%), 84 (37.9%), 68 (39.6%), 59 (37.6%), 45 (36.7%), 41 (7.9%).

(-)-*Cis*-methyl 2-(*tert.*-butoxycarbonylamino)-1-cyclopropane carboxylate (6).- To a stirred solution of **5** (7.17 g, 49.7 mmol) in dry *tert.*-butanol (20 *ml*) dry triethylamine (5.06 g, 50 mmol) and diphenyl-phosphorylazide (16.51 g, 60 mmol) were added. The solution was warmed to 50-55°C under argon and stirred for 16 h (higher temperatures caused significant *cis* → *trans* isomerization). After cooling to 25°C the excess of *tert.*-butanol was removed under reduced pressure and the residual oil was subjected to column chromatography (silica gel, EtOAc/hexanes 1:10) to afford **6** (5.0 g, 47%) as a white solid; mp 63-65°C, $[\alpha]_D^{20}$ -65.34° (*c*, 1.23 $CHCl_3$); R_F (EtOAc/Hex 1:3) 0.50; IR (KBr): 3380*s*, 3105*w*, 2982*m*, 1727*s*, 1695*s*, 1560*m*, 1507*s*, 1444*s*, 1383*s*, 1368*s*, 1272*s*, 1240*s*, 1198*s*, 1175*s*, 1155*s*, 1093*m*, 1075*m*, 1053*m*, 1014*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 5.28 (*br s*, 1 H, NH, exchangeable with D_2O), 3.71 (*s*, 3 H, OCH_3), 3.37-3.33 (*m*, 1 H, H-C(2)), 1.90 (*ddd*, *J* = 7.5, 7.0, 6.5, 1 H, H-C(1)), 1.44 (*s*, 9 H, 3 x CH_3 of *t.*-Bu), 1.30-1.15 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 172.26 (*s*, COOR), 155.90 (*s*, CO of *t.*-Bu), 79.61 (*s*, C_q of *t.*-Bu),

51.83 (*q*, OCH_3), 31.44 (*d*, C(2)), 28.29 (*q*, 3 x CH_3 of *t*.-Bu), 18.98 (*d*, C(1)), 14.09 (*t*, C(3)); MS (ei, 80 eV, 40°C): 215 (0.8%), 159 (3.3%), 142 (3.2%), 128 (2.1%), 115 (8.7%), 83 (15.0%), 57 (100.0%); Anal. calcd. for $C_{10}H_{17}NO_4$ (215.25): C, 55.80; H, 7.96; N, 6.51; found: C, 55.94; H, 7.83; N, 6.48.

(±)-*Trans*-methyl-2-[*tert*-butoxycarbonyl)amino]-1-cyclopropane-carboxylate (7).- From **5** upon treatment with triethylamine, diphenyl-phosphorylazide in *tert.*-butanol under reflux in 18.7% yield; alternatively according to the preparation of **20** from **17** (2.0 g, 12.7 mmol) **18** (1.51 g, 83%) was obtained. *Curtius* degradation of **18** (0.5 g, 3.47 mmol) in the presence of *tert.*-butanol afforded **7** (0.138 g, 18.5%) as a white solid, mp 93.5-94.5°C, R_F (EtOAc/Hex 1:3) 0.41; IR (KBr): 3365*s*, 3210*w*, 3101*m*, 3072*w*, 3004*m*, 2988*s*, 2957*m*, 2780*w*, 1729*s*, 1689*s*, 1654*m*, 1617*m*, 1660*m*, 1515*s*, 1449*s*, 1435*s*, 1397*s*, 1374*s*, 1368*s*, 1333*s*, 1279*s*, 1256*s*, 1233*s*, 1195*s*, 1172*s*, 1114*m*, 1074*s*, 1054*s*, 1037*m*, 1017*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 5.10 (*br s*, 1 H, NH, exchangeable with D_2O), 3.68 (*s*, 3 H, OCH_3), 3.03-3.02 (*br m*, 1 H, H-C(2)), 1.77-1.72 (*m*, 1 H, H-C(1)), 1.44 (*s*, 9 H, 3 x CH_3 of *t*.-Bu), 1.44-1.35 (*m*, 1 H, H_A-C(3)), 1.12 (*m*, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 172.52 (*s*, COOR), 155.74 (*s*, CO of *t*.-Bu), 79.90 (*s*, C_q of *t*.-Bu), 51.77 (*q*, OCH_3), 32.14 (*d*, C(2)), 28.28 (*q*, 3 x CH_3 of *t*.-Bu), 22.45 (*d*, C(1)), 15.58 (*t*, C(3)); MS (ei, 80 eV, 50°C): 215 (0.23%), 200 (0.16%), 159 (2.7%), 142 (2.7%), 128 (2.3%), 115 (9.0%), 110 (2.5%), 83 (14.7%), 57 (100.0%); Anal. calcd. for $C_{10}H_{17}NO_4$ (215.25): C, 55.80; H, 7.96; N, 6.51; found: C, 55.83; H, 7.84; N, 6.26.

(-)-*Cis*-[2-(*tert.*-butoxycarbonylamino)-cyclopropyl]-methanol (8).- DIBAH (70 *ml*, 1 M in toluene, Fluka, used as received) was cooled to -78°C under argon. A solution of **6** (4.22 g, 19.6 mmol) in dry toluene (45 *ml*) was slowly added at that temperature over a period of 60 min. Stirring at -78°C was continued for 3 h and then the reaction was quenched by successive addition of methanol (10 *ml* of a 10% solution in toluene), methanol (1 *ml*) and water (20 *ml*). The mixture was allowed to warm to 25°C, the white precipitate was filtered off and washed with EtOAc (100 *ml*). The washings and the filtrate were combined, dried ($MgSO_4$) and the solvent was removed in vacuo to afford a colourless oil which was subjected to column chromatography (silica gel, EtOAc/hexanes 1:5 → 1:3) to afford **8** (1.98 g, 54%) as a white solid; mp 60.5-61.5°C; R_F (EtOAc/Hex 1:1) 0.39, $[\alpha]_D^{20}$ -45.1° (*c*, 1.1 $CHCl_3$); IR (KBr): 3483*m*, 3378*s*, 3078*w*, 2983*m*, 2945*m*, 2879*m*, 2362*w*, 2344*w*, 1689*s*, 1645*s*, 1560*m*, 1508*s*, 1461*m*, 1447*m*, 1420*m*, 1391*m*, 1368*s*, 1279*s*, 1258*s*, 1239*s*, 1163*s*, 1083*m*, 1030*s*, 1019*s*; ^{1}H-NMR (300 MHz, $CDCl_3$): 5.34 (*s*, 1 H, NH, exchangeable with D_2O), 3.91 (*dd*, *J* = 11.5, 3.6, 1 H, CH_2O), 3.63-3.53 (*br*, 1 H, OH, exchangeable with D_2O), 3.15 (*dd*, *J* = 11.5, 8.5, 1 H, CH_2O), 2.60 (*ddd*, *J* = 6.8, 6.1, 5.1, 1 H, H-C(1)), 1.45 (*s*, 9H, 3 x CH_3 of *t*.-Bu), 1.42-1.34 (*m*, 1 H, H-C(2)), 0.91 (*ddd*, *J* = 8.8, 6.1, 5.2, 1 H, H_A-C(3)), 0.28 (*ddd*, *J* = 5.8, 5.2, 5.1, 1 H, H_B-C(3)); ^{13}C-NMR (62 MHz, $CDCl_3$): 158.46 (*s*, CO of *t*.-Bu), 80.39 (*s*, C_q of *t*-Bu), 61.48 (*t*, OCH_2), 28.31 (*q*, 3 x CH_3 of *t*-Bu), 26.67 (*d*, C(1)), 20.81 (*d*, C(2)), 9.16 (*t*, C(3)); MS (ei, 80 eV, 40°C): 131 (13.7%), 114 (2.2%), 100 (5.9%), 83 (11.0%), 57 (100.0%); Anal. calcd. for $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15; N, 7.48; found: C, 57.82; H, 8.99; N, 7.32.

(-)-*Cis*-[2-(5-amino-6-chloro-pyrimidin-4-yl-amino)-cyclopropyl]-methanol (10).- To a solution of **8** (0.95 g, 5.07 mmol) in tetrahydrofuran (10 *ml*) aqueous hydrochloric acid (6 N, 2 *ml*) was added and the mixture was warmed to 40-45°C for 3 h. The solvent was removed and the remaining brown oil was suspended in triethylamine (16 g, 158 mmol). A suspension of 5-amino-4,6-dichloro-pyrimidine (1.0 g, 6.1 mmol) in *n*-butanol (45 *ml*) was added and the mixture was heated under reflux for 23 h. After cooling to 25°C

the solvent was evaporated in vacuo and the remaining oil subjected to chromatography (silica gel, EtOAc/methanol 10:1) to afford **10** (0.62 g, 57%) as a slightly yellow solid; mp 180-182°C; R_F (EtOAc/MeOH 7:1) 0.43, $[\alpha]_D^{20}$ -94.7° (*c*, 0.95 MeOH); IR (KBr): 3343*s*, 3244*s*, 3009*m*, 2925*m*, 2871*m*, 1733*w*, 1700*m*, 1652*s*, 1581*s*, 1486*m*, 1464*s*, 1412*s*, 1357*m*, 1339*m*, 1244*m*, 1203*m*, 1152*m*, 1101*m*, 1029*m*; ^{1}H-NMR (300 MHz, DMSO-d_6): 7.80 (*s*, 1 H, H-C(2')), 6.82 (*d*, *J* = 2.4, 1 H, HN-C(1), D_2O exchangeable), 5.08 (*s*, 2 H, NH_2, exchangeable with D_2O), 4.17 (*dd*, *J* = 6.3, 4.7, 1 H, OH, exchangeable with D_2O), 2 H CH_2O hidden by solvent, 2.90 (*dddd*, *J* = 10.4, 7.1, 4.0, 2.4, 1 H, H-C(1)), 1.26-1.18 (*m*, 1 H, H-C(2)), 0.97 (*ddd*, *J* = 8.5, 8.0, 5.4, 1 H, H_A-C(3)), 0.50 (*ddd*, *J* = 10.4, 5.4, 4.0, 1 H, H_B-C(3)); ^{1}H-NMR (300 MHz, DMSO-d_6, D_2O): 3.44 (*dd*, *J* = 11.4, 7.1, 1 H, CH_2O), 3.30 (*dd*, *J* = 11.4, 7.1, 1 H, CH_2O); ^{13}C-NMR (75 MHz, DMSO-d_6): 152.69 (*s*, C(6')), 145.34 (*d*, C(2')), 136.60 (*s*, C(4')), 123.45 (*s*, C(5')), 59.60 (*t*, OCH_2), 28.30 (*d*, C(1)), 19.88 (*d*, C(2)), 9.23 (*t*, C(3)); MS (ei, 80 eV, 139°C): 216 (2.0%), 214 (9.0%), 199 (3.0%), 197 (12.5%), 185 (33.0%), 183 (100.0%), 171 (9.7%), 169 (29.5%), 157 (31.6%), 155 (31.6%), 146 (10.1%), 144 (32.3%), 119 (20.1%), 101 (31.6%); Anal. calcd. for $C_8H_{11}ClN_4O$ (214.66): C, 44.76; H, 5.17; N, 26.10; Cl, 16.52; found: C, 45.01; H, 5.25; N, 25.80.

(±)-*Cis*-methyl-2-[(*tert*-butoxycarbonyl)amino]-1-cyclopropane-carboxylate (13).- The diester **4** (10.0 g, 63.2 mmol) was refluxed in methanol (60 *ml*) whilst an aqueous solution of sodium hydroxide (2.52g, 63 mmol in 4 *ml* water) was added over a period of 2 h.[27] The mixture was cooled to 25°C and the methanol was evaporated. Water (10 *ml*) was added and the solution was again concentrated. The resulting aqueous solution was extracted with diethyl ether (3 x 50 *ml*) to remove any residual diester. The aqueous layer was acidified to pH 1-2 by adding conc. HCl, and extracted with diethyl ether (4 x 50 *ml*). The combined organic phases were dried ($MgSO_4$) and the solvent was removed to afford a mixture (6.78 g) of *cis*-(1 *RS*, 2 *RS*)-cyclopropane-1,2-dicarboxylic acid monomethylester **11** (79% by ^{1}H-NMR) and *cis*-(1 RS, 2 RS)-cyclopropane-1,2-dicarboxylicacid **12** (21 % by ^{1}H-NMR). To a stirred solution of this mixture (5.99 g) in tert-butanol (20 *ml*) triethylamine (4.21 g, 42 mmol) and diphenyl-phosphorylazide (13.74 g, 50 mmol) were added. The solution was warmed to 50-55 °C under Ar and stirred for 16 h. After cooling to 25°C the solvent was removed under reduced pressure and the residual oil was purified by column chromatography (EtOAc/hexanes=1/10) yielding **13** (1.014 g, 14 %) as a white solid, mp 65-67°, R_F (EtOAc/Hex 1:5) 0.24; **13** showed the same IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra as **6**.

As a byproduct **(±)-*cis*-2-[(methoxycarbonyl)amino]-1-cyclopropane-carbonyl azide (14)** (2.04 g, 33%) was obtained as a white solid; mp 70-78°C (under decomposition), R_F (EtOAc/Hex 1:3) 0.30; IR (KBr): 3311*s*, 3102*w*, 3086*w*, 3029*w*, 2987*w*, 2944*m*, 2853*w*, 2787*w*, 2445*w*, 2362*w*, 2220*m*, 2148*s*, 1844*w*, 1722*s*, 1684*s*, 1653*m*, 1617*w*, 1576*w*, 1559*m*, 1526*s*, 1457*m*, 1440*s*, 1389*s*, 1368*m*, 1269*s*, 1253*s*, 1199*s*, 1164*s*, 1090*m*, 1054*m*, 1035*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.07 (*br s*, 1 H, NH), 3.73 (*s*, 3 H, OCH_3), 3.57-3.47 (*m*, 1 H, H-C(2)), 1.98-1.93 (*m*, 1 H, H-C(1)), 1.40-1.33 (*m*, 1 H, H_A-C(3)), 1.25-1.19 (*m*, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 172.05 (*s*, CON_3), 156.53 (*s*, NCO), 51.92 (*q*, OCH_3), 31.12 (*d*, C(2)), 18.40 (*d*, C(1)), 13.94 (*t*, C(3)); MS (ei, 80 eV, 40°C): 125 (2%), 124 (13%), 98 (13%), 82 (19%); too unstable to obtain a correct elemental analysis.

(±)-*Cis*-[2-(*tert*.-butoxycarbonylamino)-cyclopropyl]-methanol (15).-According to the preparation of **8** from **13** (1.014 g, 4.71 mmol) and DIBAH (25 *ml*, 1 M in toluene) **15** (0.503 g, 57%) was obtained as a white solid; mp: 62-64°, R_F (EtOAc/Hex 1:3) 0.14; **15** showed the same IR, ^{1}H-NMR, ^{13}C-

NMR and MS spectra as **8**; Anal. calcd. for $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15; N, 7.48; found: C, 57.92; H, 9.04; N, 7.25.

(±)-*Cis*-[2-(5-amino-6-chloro-pyrimidin-4-ylamino)-cyclopropyl]-methanol (16).- According to the preparation of **10** from **15** (0.496g, 2.65 mmol) **16** (0.415 g, 73%) was obtained as a white solid; mp 205-209°C, R_F (EtOAc/MeOH 7:1) 0.43; **15** showed the same IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra as **10**; Anal. calcd. for $C_8H_{11}ClN_4O$ (214.66): C, 44.76; H, 5.17; N, 26.10; found: C, 44.93; H, 5.27; N, 26.37.

(±)-*Trans*-diethyl 1,2-cyclopropane dicarboxylate (19) and (±)-*cis*-diethyl 1,2-cyclopropane dicarboxylate (25).-[15-17, 30, 31] To a suspension of sodium hydride (6.25 g of a 80% dispersion in mineral oil, 208.4 mmol) in dry toluene (25 *ml*) 5 *ml* of a mixture of ethyl chloroacetate (24.5 g, 200 mmol) and ethyl acrylate (20.0 g, 200 mmol) was added dropwise. To initiate the reaction methanol (2 *ml*) was added and the temperature gradually raised to 50-60°C. Within a few minutes the reaction became self-sustaining and the remaining mixture was added so that the temperature did not exceed 60°C. After completion of addition, stirring at 60° was continued for an additional 60 min. After cooling to 25°C the excess of sodium hydride was destroyed by the careful addition of methanol, then water (50 *ml*) and brine (75 *ml*) were added, the organic layer was separated and the aqueous phase extracted with EtOAc (5 x 100 *ml*), the organic layers were combined, dried ($MgSO_4$) and the solvents were removed. The residual brown oil was distilled (40-83°, 0.2 mbar) to afford a mixture of **19/25** (19.9 g). The two isomers were separated by column chromatography (silica gel, EtOAc/hexanes 1:20 → 1:10) yielding **19** (16.1 g, 43%) and **25** (1.7 g, 5%).

Data for **19**.- n_D = 1.440, R_F (EtOAc/Hex 1:4) 0.63; IR (film): 3110*w*, 3060*w*, 2980*s*, 2930*m*, 2900*w*, 1735*s*, 1720*s*, 1465*m*, 1445*m*, 1410*s*, 1385*s*, 1370*s*, 1325*s*, 1305*s*, 1265*s*, 1210*s*, 1180*s*, 1160*m*, 1090*m*, 1045*s*, 1035*s*; ^{1}H-NMR (250 MHz, $CDCl_3$): 4.15 (*q*, *J* = 7.1, 4 H, 2 x OCH_2), 2.18-2.12 (*m*, 2 H, H-C(1), H-C(2)), 1.45-1.39 (*m*, 2 H, $H_{A,B}$-C(3)), 1.27 (*t*, *J* = 7.1, 6 H, 2 x CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 171.50 (*s*, 2 x CO), 60.97 (*t*, 2 x OCH_2), 22.33 (*d*, C(1), C(2)), 15.27 (*t*, C(3)), 14.18 (*q*, 2 x CH_3); MS (ei, 80 eV, 30°C): 186 (11.9%), 159 (8.7%), 141 (100%), 114 (23.5%), 113 (28.1%), 112 (36.5%), 86 (19.8%), 85 (41.3%), 84 (26.1%).

Data for **25**.- n_D= 1.440 (lit.: 1.4420 [30] or 1.4404 [31]), R_F (EtOAc/Hex 1:4) 0.32; IR (film): 2980*s*, 2930*m*, 2900*m*, 1745*s*, 1725*s*, 1470*m*, 1445*m*, 1400*s*, 1380*s*, 1345*s*, 1280*m*, 1185*s*, 1100*s*, 1060*m*, 1020*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 4.22 (*q*, *J* = 7.2, 2 H, OCH_2), 4.21 (*q*, *J* = 7.2, 2 H, OCH_2), 2.14-2.08 (*m*, 2 H, H-C(1), H-C(2)), 1.77-1.69 (*m*, 1 H, H_A-C(3)), 1.31 (*t*, *J* = 7.2, 6 H, 2 x CH_3) 1.37-1.24 (*m*, 1 H, H_B-C(3)); ^{13}C-NMR (75 MHz, $CDCl_3$): 169.61 (*s*, 2 x CO), 60.84 (*t*, 2 x OCH_2), 21.59 (*d*, C(1), C(2)), 14.17 (*t*, 2 x CH_3), 11.55 (*t*, C(3)); MS (ei, 80 eV, 42°C): 186 (6.5%), 159 (5.1%), 141 (62.6%), 113 (100.0%).

(±)-*Trans*-cyclopropane-1,2-dicarboxylic acid monoethylester (20).- A suspension of **19** (10.0 g, 53.7 mmol) in water (45 *ml*) was adjusted to pH 7 with 1 N NaOH and at 26°C PLE (0.5 *ml*) was added. The pH was maintained constant at 7.2 by addition of 1 N NaOH using a pH-stat equipment. The reaction terminated after 5-6 days (all of **19** had been consumed as determined by TLC). The mixture was concentrated, acidified to pH 2 by addition of 10% HCl and extracted with diethyl ether (5 x 100 *ml*). The combined organic phases were dried ($MgSO_4$) and the solvent removed to afford **20** (8.1 g, 95%) as a white solid; mp 52-54°C (lit.: 56-57°C[32], 58-60°C[27]); IR (KBr): 2994*m*, 1734*s*, 1468*m*, 1428*m*, 1381*s*, 1324*s*,

1241*s*, 1185*s*, 1113*m*, 1090*m*, 1061*m*, 1032*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 11.36 (*br s*, 1 H, OH, exchangeable with D_2O), 4.16 (*q*, *J* = 7.1, 2 H, OCH_2), 1.27 (*t*, *J* = 7.1, 3 H, CH_3), 2.26-2.13 (*m*, 2 H, H-C(1), H-C(2)), 1.56-1.37 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C-NMR (62 MHz, $CDCl_3$): 177.93 (*s*, COOH), 171.45 (*s*, COOEt), 61.28 (*t*, OCH_2), 23.01 and 22.02 (each *d*, C(1) and C(2)), 15.80 (*t*, C(3)), 14.14 (*q*, CH_3); MS (ei, 80 eV, 40°C): 158 (7.8%), 141 (1.7%), 131 (19.4%), 86 (38.7%), 85 (16.5%).

(±)-*Trans*-ethyl 2-(*tert.*-butoxycarbonylamino)-1-cyclopropane carboxylate (21).- According to the preparation of **6** from **20** (9.36 g, 59.2 mmol), *tert.*-butanol (30 *ml*), triethylamine (6.0 g, 59.3 mmol) and diphenylphosphorylazide (16.31 g, 59.3 mmol) **21** (7.3 g, 54%, white solid) was obtained after a reaction time of 6 h under reflux; mp 83-86°; R_F (EtOAc/Hex 1:3) 0.42; IR (KBr): 3365*s*, 2991*m*, 2942*m*, 1721*s*, 1688*s*, 1560*m*, 1516*s*, 1465*m*, 1448*m*, 1407*m*, 1373*m*, 1367*m*, 1328*s*, 1277*s*, 1259*m*, 1229*s*, 1188*s*, 1162*s*, 1114*m*, 1097*m*, 1075*m*, 1053*m*, 1042*m*, 1028*m*; ^{1}H-NMR (300 MHz, $CDCl_3$): 4.7 (*br s*, 1 H, NH), 4.14 (*q*, *J* = 7.1, 1 H, OCH_2), 4.13 (*q*, *J* = 7.1, 2 H, OCH_2), 3.02-3.01 (*m*, 1 H, H-C(2)), 1.72 (*ddd*, *J* = 9.0, 5.5, 3.0, 1 H, H-C(1)), 1.45 (*s*, 9 H, 3 x CH_3 of *t*-Bu), 1.39 (*ddd*, *J* = 12.0, 5.5, 3.0, 1 H, H_A-C(3)), 1.26 (t, *J* = 7.1, 3 H, CH_3), 1.09 (*ddd*, *J* = 9.0, 5.5, 4.0, 1 H, H_B-C(3)); ^{13}C-NMR (62 MHz, $CDCl_3$): 172.33 (*s*, COOR), 155.91 (*s*, CO of *t*-Bu), 80.06 (*s*, C_q of *t*-Bu), 60.72 (*t*, OCH_2), 32.00 (*d*, C(2)), 28.31 (*q*, 3 x CH_3 of *t*-Bu), 22.57 (*d*, C(1)), 15.69 (*t*, C(3)), 14.23 (*q*, CH_3); MS (ei, 80 eV, 55°C): 229 (0.3%), 214 (0.3%), 173 (3.5%), 156 (3.4%), 129 (9.7%), 113 (6.8%), 100 (15.1%); Anal. calcd. for $C_{11}H_{19}NO_4$ (229.28): C, 57.63; H, 8.35; N, 6.11; found: C, 57.42; H, 8.43; N, 6.11.

(±)-*Trans*-[2-(*tert.*-butoxycarbonylamino)-cyclopropyl]-methanol (22).- According to the preparation of **8** from **21** (5.0 g, 21.8 mmol) and DIBAH (100 *ml*, 1 M in toluene) **22** (2.78 g, 68%) was obtained as an oil; R_F (EtOAc/Hex 1:1) 0.25; IR (film): 3330*br s*, 3065*w*, 3000*m*, 2970*s*, 2930*s*, 2870*m*, 1685*s*, 1515*s*, 1450*s*, 1390*s*, 1365*s*, 1275*s*, 1250*s*, 1170*s*, 1090*s*, 1040*s*, 1030*s*; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.25 (*br s*, 1 H, NH, exchangeable with D_2O), 3.59-3.49 (m, 2 H, OCH_2 and OH, exchangeable with D_2O), 3.32-3.30 (*m*, 1 H, OCH_2), 2.34 (*ddd*, *J* = 7.5, 6.5, 3.0, 1 H, H-C(1)), 1.40 (*s*, 9 H, 3 x CH_3 of *t*-Bu), 1.11 (*ddd*, *J* = 6.5, 6.3, 3.0, 1 H, H-C(2)), 0.72-0.61 (*m*, 2 H, $H_{A,B}$-C(3)) ;^{13}C-NMR (75 MHz, acetone-d_6): 157.51 (*s*, CO of *t*-Bu), 78.87 (*s*, C_q of *t*-Bu), 64.32 (*t*, OCH_2), 28.77 (*d*, C(1)), 28.59 (*q*, 3 x CH_3 of *t*-Bu), 23.61 (*d*, C(2)), 11.43 (*t*, C(3)); MS (ei, 80 eV, 80°C): 172 (0.04%), 156 (0.01%), 131 (9.0%), 100 (4.6%), 90 (4.1%), 70 (5.9%), 57 (100.0%), 47 (57.0%); Anal. calcd. for $C_9H_{17}NO_3$ (187.24): C, 57.73; H, 9.15; N, 7.48; found: C, 57.60; H, 9.16; N, 7.37.

(±)-*Trans*-[2-(5-amino-6-chloro-pyrimidin-4-ylamino)-cyclopropyl]-methanol (23).- According to the preparation of **10** from **22** (2.0 g, 10.7 mmol) **23** (1.56 g, 68%) was obtained as a slightly yellow solid; mp 171-176 °C; R_F (EtOAc/MeOH 5:1) 0.53; IR (KBr): 3370*s*, 3220*s*, 3000*m*, 2900*w*, 2820*m*, 1660*s*, 1570*s*, 1490*s*, 1450*s*, 1420*s*, 1390*m*, 1330*s*, 1290*w*, 1205*w*, 1190*w*, 1165*w*, 1150*w*, 1115*w*, 1075*m*, 1040*s*, 1000*s*; ^{1}H-NMR (300 MHz, DMSO-d_6): 7.77 (*s*, 1 H, H-C(2')), 7.03 (*d*, *J* = 2.4, 1 H, HN-C(1), exchangeable with D_2O), 5.01 and 5.00 (each *s*, 2 H, NH_2, exchangeable with D_2O), 4.61 (*br*, 1 H, OH, exchangeable with D_2O), 2 H CH_2O hidden by solvent, 2.71-2.65 (*m*, 1 H, H-C(1)), 1.18-1.11 (*m*, 1 H, H-C(2)), 0.75-0.71 (*m*, 1 H, H_A-C(3)), 0.68-0.61 (*m*, 1 H, H_B-C(3)); ^{1}H-NMR (300 MHz, DMSO-d_6, D_2O): 3.42 (*d*, *J* = 6.8, 2 H, CH_2O); ^{13}C-NMR (62 MHz, DMSO-d_6): 152.61 (*s*, C(6')), 145.55 (*d*, C(2')), 136.60 (*s*, C(4')), 123.53 (*s*, C(5')), 62.50 (*t*, OCH_2), 28.76 (*d*, C(1)), 22.06 (*d*, C(2)), 11.31 (*t*, C(3)); MS (ei, 80 eV, 128°C): 216 (1.9%), 214 (7.9%), 199 (3.1%), 197 (31.7%), 185 (12.9%), 183 (100.0%), 171 (8.3%),

169 (25.3%), 157 (28.6%), 155 (22.5%), 144 (28.2%), 119 (13.1%), 101 (21.3%); Anal. calcd. for $C_8H_{11}ClN_4O$ (214.66): C, 44.76; H, 5.17; N, 26.10; Cl, 16.52; found: C, 44.80; H, 5.19; N, 26.22.

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