Pergamon

Tetrahedron, Vol. 52, No. 18, pp. 6383-6396, 1996
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/96 $15.00 + 0.00

S0040-4020(96)00272-4

Enantiomerically Pure Cyclopropanoid Nucleoside Analogues: Synthesis and Analysis

René Csuk * [a] and Yvonne von Scholz [b]

[a] Institut für Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Straße 2, D-06120 Halle (Saale), Germany;

[b] Pharm.-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 364, D-69120 Heidelberg, Germany.

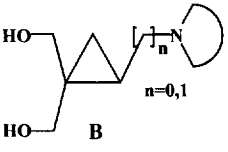
Abstract: Enantiomerically pure cyclopropanoid nucleoside analogues were synthesized by a chemoenzymatic approach starting from racemic dialkyl 1,2-cyclopropane dicarboxylates. Their enantiomeric purity can be easily verified by HPLC analysis using Chiralcel OD or Chiralcel OD-R columns.

INTRODUCTION

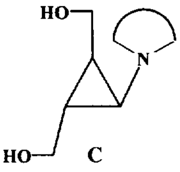
Cyclopropanoid nucleoside analogues of the type **A** possessing an additional methylene spacer between the cyclopropane unit and the heterocycle [1] as well as compounds with a (in)direct attachment of the heterocycle but with two geminal or vicinal hydroxymethyl units [1, 2] at the cyclopropane skeleton (type **B** or type **C**) have shown significant antiviral activity.

Recently, first syntheses of racemic compounds of type **D** or **E** starting from dialkyl cyclopropane dicarboxylates **1** or **2** leading to racemic adenosine [3], uridine [4], thymidine [4] or inosine [4] analogues possessing *cis* or *trans* configuration at the cyclopropane ring have been reported.[5] Enantiomerically pure compounds, however, have only been obtained up to now in a few instances by using a rather lengthy chiral pool approach starting from D-mannitol. [6]

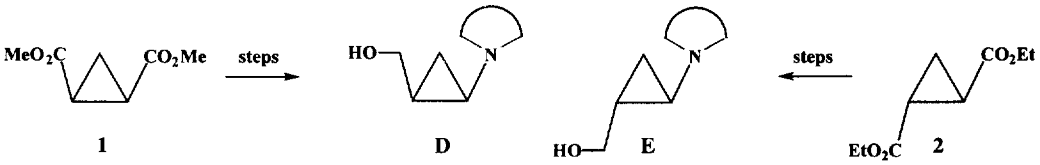
A



B



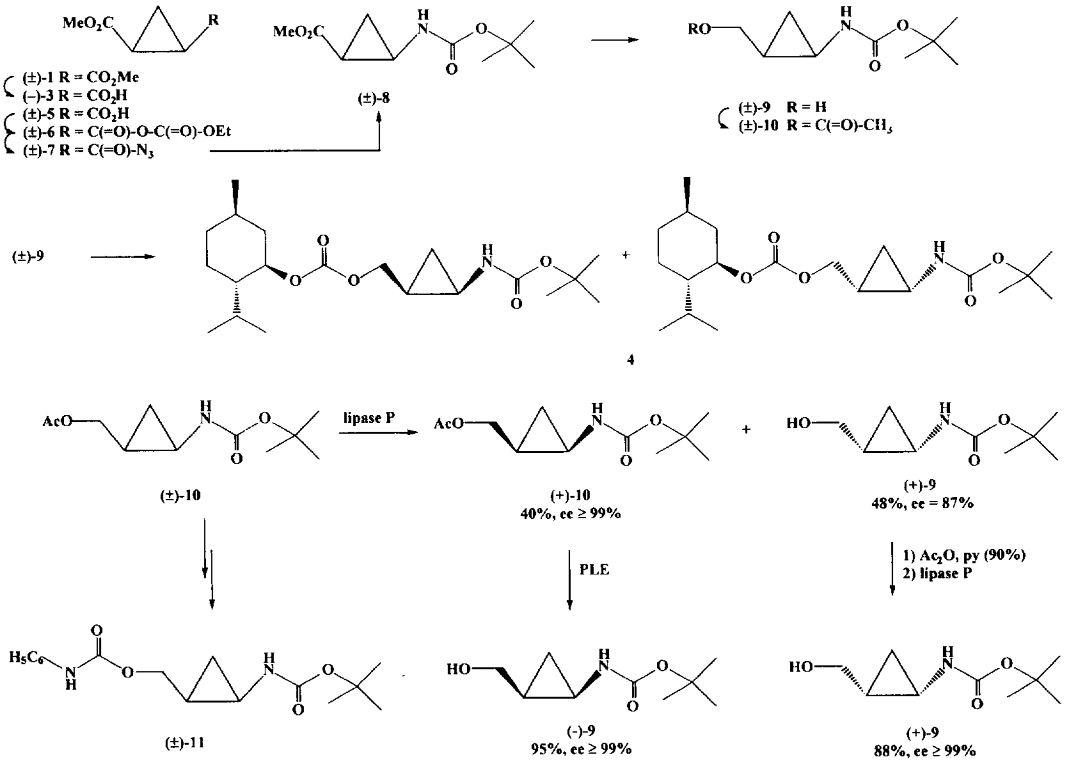
C



RESULTS AND DISCUSSION

Inasmuch as the extrapolation of the structural features of active compounds for the design of new inhibitors can only be done with caution due to the complexicity of the nucleoside metabolism and the relatively small number of active analogues conspire to limit structure-activity relationships to only broad generalizations [7] it seemed of interest to establish a convenient route to enantiomerically pure cyclopropanoid nucleoside analogues; it is well established that enantiomeric nucleoside analogues exhibit different biological activities.[8]

In a first approach (±)-*cis* dimethyl 1,2-cyclopropane dicarboxylate **(±)-1** was used as an educt. Treatment of **(±)-1** with pig liver esterase (PLE) [3, 9-13] at pH=7.2 afforded 90% of **(1 *S*, 2 *R*)-3**; **(-)-3** showed an optical rotation of $[\alpha]_D^{25}$ -17.5° indicating an enantiomeric excess of ≥ 99.5%. *Curtius* degradation of this enantiomerically pure material under a variety of conditions, however, led to partial racemization, the extend of which depending on the reaction time and temperature. Since the separation of the diastereomeric menthyl carbamates **4** also failed, a different approach had to be envisaged; the racemic *cis*-(±) methyl cyclopropane-1,2-dicarboxylate **(±)-5** [3] was allowed to react with ethyl chloroformate/triethylamine [14] in acetone resulting in the formation of the corresponding mixed anhydride **6** [14] which – without isolation – was treated with sodium azide to afford a 79% yield of the corresponding carbonyl azide **7**. [4]



Treatment of **(±)-7** with *tert.*-butanol at 50-55°C gave methyl 2-*tert.*-butoxycarbonylamino-cyclopropane carboxylate [**(±)-8**] in 63% yield. Reduction of **(±)-8** with diisobutyl aluminium hydride in toluene at -78°C for 3 hours gave a 59% yield of the primary alcohol **(±)-9**.[15] Acetylation of **(±)-9** with acetanhydride/pyridine yielded 94% of the racemic acetate **(±)-10** that was subjected to enzymatic hydrolysis with a broad variety of hydrolytic enzymes including esterases, lipases, acylases and proteases. For most of these enzymes **(±)-10** was either a non-substrate or the enzyme showed inspecific hydrolysis of the ester moiety. The lipase P from *Pseudomonas fluorescens*, however, gave a clean enantioselective hydrolysis.

Table 1: Enzymatic Hydrolyses of **(±)-10** (pH = 7, 27-30°C, pH-stat conditions)

Enzyme	Conversion [%]	ee of **(+)-10** [%]	ee of **(+)-9** [%]
lipase PS	41	20	56
lipase F	41	60	55
lipolase L100	56	71	53
lipase M	61	96	53
lipase P2	81	99	15
lipase P	51	99	87

This hydrolysis was performed in a pH-stat equipment maintaining the pH = 7 constant throughout the reaction by titrating the liberated acetic acid by the addition of 0.1 N sodium hydroxide; this led to 40% of enantiomerically pure **(+)-10** and 48% of **(+)-9** (possessing an ee of 87%) were obtained after extractive work up and chromatography. Therefore, this enantiomerically enriched **(+)-9** was re-esterified with acetic anhydride/pyridine and this acetate was subjected to a second enzymatic hydrolysis with the lipase P thus resulting in the formation of 88% of **(+)-9** the enantiomeric purity of which was determined by HPLC ≥99%. Treatment of **(+)-10** with PLE or subjecting it to a *Zemplen* saponification (NaOMe in MeOH) afforded 95% of **(-)-9**. Thus, both enantiomers of **9** are conveniently obtained each in an enantiomeric pure form.

The enantiomeric purity of **(+)**- or **(-)-9** was determined after derivatization with phenyl isocyanate to the corresponding phenyl-carbamic acid derivative **11** by HPLC using a Chiralcel OD-R column (Fig. 1).

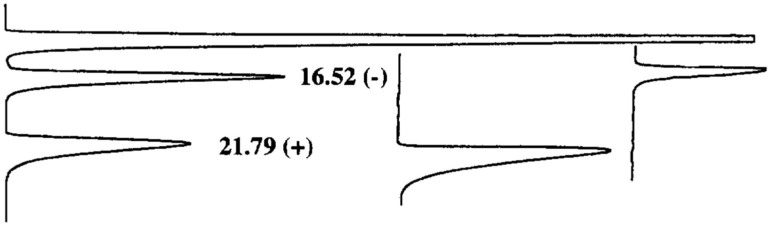
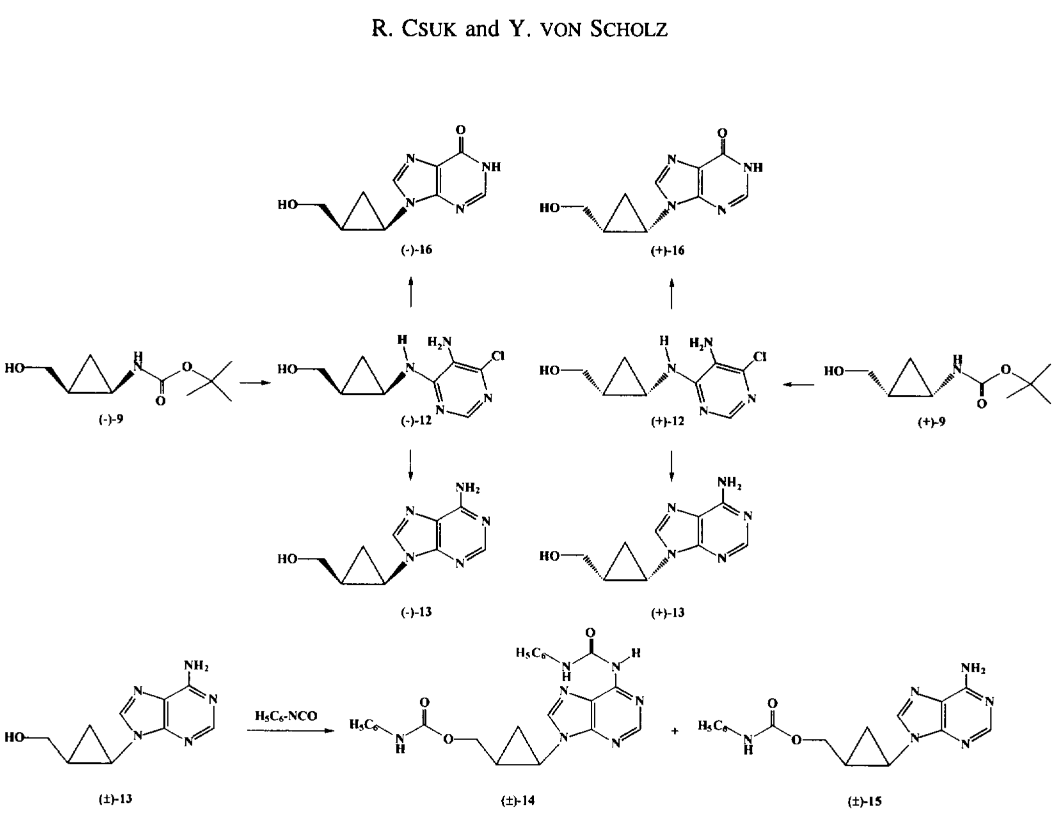


Fig. 1: HPLC of (±)-, (+)- and (-)-**9** on a Daicel Chiralcel OD-R column [MeOH/H_2O (pH = 4) 85:15, 0.4 *ml*/min; 23 kg/cm^2, UV at 280 nm]

Cleavage of the *N*-BOC protecting group in **9** was performed with 6 N hydrochloric acid at 40-45 °C for 3 hours; the crude 2-hydroxymethyl-cyclopropylamines were treated without further purification with 5-amino-4,6-dichloro-pyrimidine in the presence of triethylamine to yield **(+)-12** (74%) and **(-)-12** (75% yield), respectively. An acid-catalyzed reaction of **12** with an excess of triethyl orthoformate followed by treatment of the crude reaction mixture with ammonia in an autoclave finally resulted in the formation of (+)- or (-) *cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol (**13**).



The enantiomeric purity of **(+)-13** and **(-)-13** was determined by HPLC directly on a Daicel Chiralcel OD column using 2-propanol/hexane 5:95 + 0.1 % diethylamine as the solvent (Fig. 2); although a clean baseline separation was obtained, the retention times were rather long (t_R **(+)-13**: 101 min, t_R **(-)-13**: 120 min). But also, as for the determination of the enantiomeric purity of **9**, a derivatization *in-situ* with phenyl isocyanate was successful and these derivatives **14** could be separated cleanly on a Daicel Chiralcel OD-R column using acetonitrile/water (70:30, pH = 4.0 by addition of perchloric acid) as the solvent; again the signals were baseline separated and the retention times were significantly reduced (t_R **(-)-14** 18.9 min, t_R **(+)-14** 26.3 min). The enantiomeric derivatives **15** showed no separation under these conditions (t_R = 8.80 min).

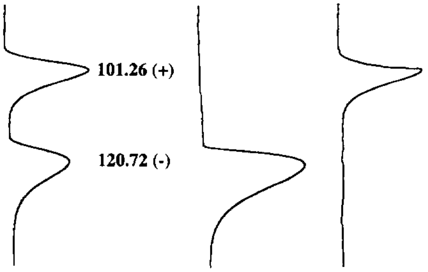
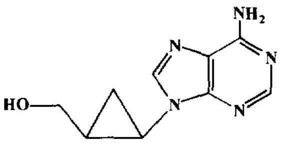
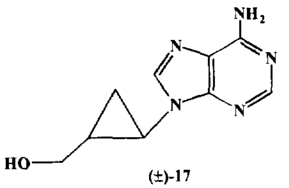


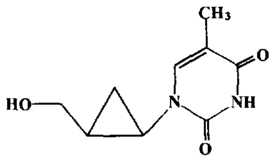
Fig. 2: HPLC of (±)-, (+)- and (-)-**13** on a Daicel Chiralcel OD-column (2-propanol/hexane 5:95 + 0.1% DEA, 0.8 *ml*/min, 16 kg/cm^2, UV at 280 nm).

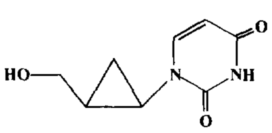
The reaction of **(+)-** or **(-)-12** with triethyl orthoformate in the presence of aqueous hydrochloric acid followed by treatment with sodium hydroxide gave the inosine analogues **(-)-** and **(+)-16**, respectively. Their enantiomeric purity was again checked by HPLC after derivatization with phenyl isocyanate.

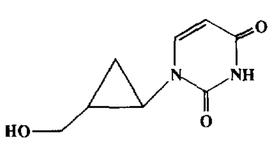
The determination of the enantiomeric purity of the corresponding *trans*-analogues can be performed in an analogous manner although with some limitations. Whereas a clean separation of the two enantiomers by HPLC on Chiralcel OD is achieved for the (±)-*trans* adenosine derivative **(±)-17** and the (±)-*trans*-thymidine analogue **(±)-18**, no separation was obtained for the racemic *trans* uridine derivative **(±)-19**. Interestingly enough, a clean base-line separation was achieved for the two enantiomers of the (±)-*cis* uridine analogue **(±)-20**. The retention times for the *trans*-configurated derivatives are significantly shorter than those of their corresponding *cis*-analogues clearly indicating a smaller affinity of the former to the chiral selector; this explains the decreased ability of this HPLC column for resolving the *trans*-configurated cyclopropanoid nucleoside analogues.


(±)-13


(±)-17


(±)-21


(±)-20


(±)-19

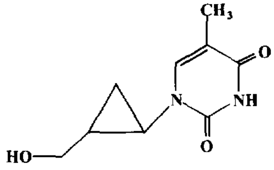
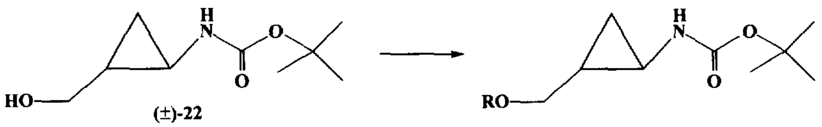

(±)-18

Table 2: Dependence of HPLC retention times (t_R in min) on a Chiralcel OD-column using 2-propanol/ hexane mixtures as eluents (additional containing 0.1% of diethylamine; 0.8 *ml*/min, UV at 280 nm)

ratio 2-propanol : hexane	**(±)-13** (*cis* A)	**(±)-17** (*trans* A)	**(±)-21** (*cis* T)	**(±)-18** (*trans* T)	**(±)-20** (*cis* U)	**(±)-19** (*trans* U)
05 : 95	101.26 (-)	102.16 (-)				
	120.72 (+)	110.59 (+)				
10 : 90	33.76 (-)	30.62 (-)	79.18 (-)			
	39.52 (+)	32.83 (+)	92.88 (+)			
13 : 87			58.70 (-)	52.22 (-)		
			70.80 (+)	58.32 (+)		
20 : 80			26.90 (-)	23.94 (-)	47.02 (-)	44.43
			31.18 (+)	27.54 (+)	58.56 (+)	

In order to obtain enantiomerically pure *trans*-analogues the enzymatic hydrolysis of suitable derivatives of racemic (±)-*trans*-**22** was investigated in more detail.[16]


(±)-22

(±)-23 R = $C(=O)-CH_3$
(±)-24 R = $C(=O)-C_5H_{11}$
(±)-25 R = $C(=O)-C_6H_5$

Thus, the acetate (±)-**23**, the hexanoate (±)-**24** and the benzoate (±)-**25** were prepared by acylation of (±)-**22** and subjected to enzymatic hydrolysis. Whereas the benzoate **25** proofed unsuitable due to its slow solubility in the aqueous buffer solution, the hexanoate (±)-**24** was an excellent substrate for many enzymes (for all the lipases, for PLE but also for pronase, acylase I and chymotrypsin) but unfortunately all of these hydrolyses were unspecific. With the acylase from *Aspergillus sp.*, however, remaining (-)-**24** was obtained with an ee of 32% and (-)-**22** showed an ee of 15% (conversion rate 64%). Performing the hydrolyses with acetylcholine esterase (conversion rate 78%) gave (-)-**24** with an ee of 17% but (-)-**22** was obtained with a rather low ee of 6%. The acetate (±)-**23** was inselectively hydrolyzed in the presence of PLE, Novoenzyme 435 or the lipase from *Rhizopus arrhizus*. Several of the enzyme employed showed some selectivity (*cf.* Table 3); the best results were obtained with the lipase PS, lipolase 100L), pancreatin and chymotrypsin .

Table 3: Enzymatic hydrolyses of (±)-**23** (pH=7, 27-30 °C, pH-stat conditions)

Enzyme	Conversion [%]	ee of **23** [%][a]	ee of **22** [%][a]
lipase P	78	27 (+)	13 (+)
lipolase 100L	62	49 (-)	32 (-)
lipase PS	71	64 (+)	7 (+)
lipase M	82	18 (+)	2 (+)
lipase AY	45	22 (+)	14 (+)
lipase F	53	3 (-)	3 (-)
lipase A_6	43	26 (+)	16 (+)
lipolase powder	22	21 (-)	17 (-)
ACE	24	13 (-)	27 (-)
lipase W	22	<1	6 (+)
protease	31	3 (-)	4 (-)
lipase CC	32	20 (+)	16 (+)
PPL	20	40 (-)	40 (-)
pancreatin	26	6 (-)	47 (-)
chymotrypsin A_4	3	11 (+)	28 (+)
acylase I	40	14 (+)	14 (+)
lipase MM	57	30 (-)	13 (-)
lipase CL	29	14 (-)	12 (-)

[a] (predominant enantiomer)

Due to this rather low enantioselectivity the acetylation of (±)-**22** by irreversible enzymatic acyl transfer using vinyl acetate as the acyl donor, lipase PS as the enzyme and *tert.*-butyl methyl ether as the solvent was investigated as an alternative. The rate of conversion for this reaction was determined by HPLC using a reverse phase RP18 column and the enantiomeric purity of **22** was determined as its phenyl carbamate **26** using HPLC and the Chiralcel OD-R column and was shown to be 49%. Since these chemoenzymatic routes to enantiomerically pure *trans*-configurated derivatives failed, a chiral pool approach is now under investigation in our labs.

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). HPLC was performed on a Merck-Hitachi L6200A/L4000/D2500 instrument (UV detection at 280 nm) using a either a Chiralcel OD (4.6 x 250 mm, 10μm, Daicel Chemical Industries, 2-propanol/hexane 5:95 + 0.1 % diethylamine, flow 0.8 *ml*/min, 16 kg/cm^2) or a Chiralcel OD-R (4.6 x 250 mm, 10 μm, Daicel Chemical Industries, methanol/water [(pH = 4 (by addition of perchloric acid) 85:15, 0.4 *ml*/min, 23 kg/cm^2] column; the pH-stat equipment was obtained from Metrohm.

The enzymes were used as obtained: acetylcholine esterase ACE (*bovine brain*, Sigma, 25°C, pH 7), acetylcholine esterase ACE (*Electrophorus electricus*, Boehringer-Mannheim, Ltd, 37°C, pH 7), acylase I (*Aspergillus melleus*, Fluka, 25°C, pH 7), acylase I (*Aspergillus sp.*, Fluka, 25°C, pH 7), AMG 200 L™ (Novo, 25°C, pH 7), Aquazym ultra™ (Novo, 25°C, pH 7), chymotrypsin A_4 (*bovine pancreas*, Boehringer-Mannheim Ltd, 25°C, pH 7) esterase R (*rabbit liver*, Sigma, 30°C, pH 7), Fungamyl 800 L™ (Novo, 25°C, pH 7), leucine aminopeptidase (*hog kidney*, Boehringer-Mannheim Ltd, 25°C, pH 7), lipase A_6 (*Aspergillus niger*, Amano Ltd, 25°C, pH 7), lipase AY (*Candida rugosa*, Amano, 25°C, pH 7), lipase B (*Candida antarctica* recombinant with *Aspergillus oryzae* immobilized on a macroporous acrylic resin, Novo, 37°C, pH 8), lipase CR (*Candida rugosa*, Boehringer-Mannheim, Ltd, 25°C, pH 7), lipase M (*Mucor javanicus*, Amano, 25°C, pH 7), lipase N (*Rhizopus niveus*, Amano, 25°C, pH 7), lipase P (*Pseudomonas fluorescens*, Amano, 37°C, pH 7), lipase P2 (*Pseudomonas fluorescens*, Fluka, 25 °C, pH 7), lipase W (*wheat germ*, Amano, 37°C, pH 7), Lipolase™ (Novo, 25°C, pH 7), pancreatin (*porcine pancreas*, Sigma, 37°C, pH 7.5), papain (*Carica papaya*, Fluka, 25°C, pH 7), penicillinase type I (*Bacillus cereus*, Sigma, 25°C, pH 7), PLE (*porcine liver esterase*, Boehringer-Mannheim Ltd, 25°C, 37°C, pH 7), pronase (*Streptomyces griseus*, Fluka, 25°C, pH 7.5, 8.0, 8.5, 9.0, respectively), subtilisin (*Bacillus licheniformis*, Fluka, 25°C, pH 8), lipase F (*Rhizopus javanicus*, Amano, 25°C, pH 7), lipase PS (*Pseudomonas sp.*, Amano, 25°C, pH 7), lipase MM (*Mucor miehei*, Fluka, pH 7.0, 37°C), lipase CL (*Candida lipolytica*, Fluka, 37°C, pH 7), protease (*Aspergillus oryzae*, Sigma, 37°C, pH 7), PPL (*porcine pancreatic lipase*, Sigma, 37°C, pH 7), Termamyl 60 L™ (Novo, 25°C, pH 7), thermolysin (*Bacillus thermoproteolyticus*, Fluka, 37°C, pH 7).

General procedure for the derivatization with phenylisocyanate for investigations by HPLC. – To a solution of the corresponding educt (1 mg) in dry diethyl ether (2 *ml*) abs. triethylamine (0.25 *ml*) and phenylisocyanate (10 *μl*) were added and the mixture was warmed to 50-55°C for 30 min. The solvent was removed under reduced pressure and the residue was suspended in methanol (5 *ml*, HPLC quality) and filtered (membrane filter, 45 μm). A volume of 10 *μl* of this filtrate was usually used for the HPLC investigation.

***(3* R*)-Menthyl-[(1* RS*, 2* RS*)-*cis*-2-(*N*-tert.-butoxycarbonylamino)-cyclopropyl]-methyl-carbamate* (4).** – To a solution of (±)-**9** (0.20 g, 10.7 mmol) in dry pyridine (1.0 *ml*) (-)-(1 *R*)-menthyl-chloroformate (0.47 g, 2.14 mmol) was added and stirred for 1 h at 25 °C. Then the solvent was evaporated and the residue subjected to chromatography (ethyl acetate/hexane 1:10) and **4** (0.29 g, 73%) was obtained as an inseparable 1:1 mixture of diastereomers; mp 84-95 °C; R_F (ethyl acetate/hexane 1:10) 0.17; $[\alpha]_D^{25}$ -54.3° (*c* 0.92, $CHCl_3$); IR (KBr): ν 3367*m*, 3081*w*, 2958*s*, 2871*s*, 1742*s*, 1738*s*, 1733*s*, 1716*s*, 1703*s*, 1699*s*, 1694*s*, 1683*s*, 1520*s*, 1516*s*, 1505*s*, 1495*s*, 1489*s*, 1456*s*, 1392*s*, 1367*s*, 1271*s*, 1173*s*, 1079*s*, 1040*m*, 1008*m*, 981*m*, 958*s*;

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (br *s*, 1 H, NH), 4.53 (*ddd*, *J* = 10.9, 10.8, 4.4, 1 H, H-C(3) (menthyl)), 4.34-4.25 (*m*, 1 H, OCH_2), 4.14-4.05 (*m*, 1 H, OCH_2), 2.71-2.65 (*m*, 1 H, H-C(2) (cyclopropyl)), 2.11-2.04 and 1.99-1.94 (each *m*, 1 H, H-C(1) (menthyl) and H-C(4) (menthyl)), 1.73-1.63 (*m*, 2 H, CH_2 (menthyl)), 1.45 (*s*, 9 H, 3 x CH_3 (*tert*.-butyl)), 1.58-1.14 (*m*, 2 H, CH_2 (menthyl) and *m*, 1 H, H-C(1) (cyclopropyl)), 1.12-0.79 (*m*, 2 H, CH_2 (menthyl); *m*, 1 H, CH (isopropyl) and *m*, 1 H, H_A-C(3) (cyclopropyl)), 0.93 and 0.91 (each d, *J* = 6.9 and *J* = 5.9, 3 H, CH_3 (isopropyl)), 0.80 (*d*, *J* = 6.9, 3 H, CH_3 (menthyl)), 0.56-0.49 (*m*, 1 H, H_B-C(3) (cyclopropyl)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.59 (*s*, NCO), 154.89 (*s*, CO), 79.49 (*s*, C_q (*tert*.-butyl)), 78.40 (*d*, C(3)), 66.87 and 66.79 (each *t*, OCH_2), 47.01 (*d*, C(4)), 40.74, 34.07 and 23.32 (each *t*, C(2), C(5) and C(6)), 31.38 (*d*, CH (isopropyl)), 28.31 (*q*, 3 x CH_3 (*tert*.-butyl)), 27.34 (*d*, C(2) (cyclopropyl)), 26.09 (*d*, C(1)), 21.95 and 20.70 (each *q*, CH_3 (isopropyl) and d, C(1) (cyclopropyl)), 16.27 and 16.13 (each *q*, CH_3 (menthyl)), 11.30 and 11.10 (each *t*, C(3) (cyclopropyl)); MS (e.i., 80 eV, 85 °C): 297 (0.1%), 296 (0.8%), 232 (0.2%), 231 (1.3%), 230 (0.5%), 176 (5.2%), 175 (12.1%), 169 (8.7%), 139 (13.8%), 138 (5.9%), 130 (7.8%), 114 (12.5%), 113 (54.4%), 95 (8.0%), 83 (28.6%), 69 (96.4%), 57 (100.0%); Anal. calcd. for $C_{20}H_{35}NO_5$ (369.50): C, 65.01; H, 9.55; N, 3.79; found: C, 65.25; H, 9.41; N, 3.67.

(±)-(1 **RS**, *2* **RS***)*-**cis** ***Methyl 2-(tert.-butoxycarbonylamino)-cyclopropane carboxylate*** **[(±)-8]**. – A solution of **(±)-7** (7.27 g, 42.97 mmol) in *tert*.-butanol (35 *ml*) was stirred at 50-55 °C overnight. After cooling to 25 °C the solvent was removed under reduced pressure and the residue subjected to column chromatography (silica gel, ethyl acetate/hexane 1:10 → 1:5) and **(±)-8** (5.84 g, 63%) was obtained as a white solid; mp 65-67 °C; R_F (ethyl acetate/hexane 1:5) 0.24; IR (KBr): ν 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, $CDCl_3$): δ 5.28 (*br s*, 1 H, NH, exch. 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 (*tert*.-butyl)), 1.30-1.15 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.26 (*s*, COOR), 155.90 (*s*, CO (*tert*.-butyl)), 79.61 (*s*, C_q(*tert*.-butyl)), 51.83 (*q*, OCH_3), 31.44 (*d*, C(2)), 28.29 (*q*, 3 x CH_3 (*tert*.-butyl)), 18.98 (*d*, C(1)), 14.09 (*t*, C(3)); MS (e.i., 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.

(±)-(1 **RS**, *2* **RS***)*-**cis**-***[2-(tert.-Butoxycarbonylamino)-cyclopropyl]-methanol*** **[(±)-9]**. – DIBAH (70 *ml*, 1 M in toluene, Fluka, used as received) was cooled to -78 °C under argon. A solution of **(±)-8** (3.17 g, 14.37 mmol) in dry toluene (20 *ml*) was slowly added at this 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 ethyl acetate (100 *ml*). The washings and the filtrate were combined, dried ($MgSO_4$) and the solvent was removed *in vacuo* to afford **(±)-9** (1.77 g, 64%) as a white solid; mp 62-64 °C; R_F (ethyl acetate/hexane 1:3) 0.14; IR (KBr): ν 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, $CDCl_3$): δ 5.34 (*s*, 1 H, NH, exch. with D_2O), 3.91 (*dd*, *J* = 11.5, 3.6, 1 H, CH_2O), 3.63-3.53 (*br s*, 1 H, OH, exch. 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(2)), 1.45 (*s*, 9H, 3 x CH_3 (*tert*.-butyl)), 1.42-1.34 (*m*, 1 H, H-C(1)), 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, $CDCl_3$): δ 158.46 (*s*, CO (*tert*.-butyl)), 80.39 (*s*, C_q (*tert*.-butyl)), 61.48 (*t*, OCH_2), 28.31 (*q*, 3 x CH_3(*tert*.-butyl)), 26.67 (d, C(2)), 20.81 (*d*, C(1)), 9.16 (*t*, C(3)); MS (e.i., 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.

(-)-(1 **R**, *2* **S***)*-**cis**-***[2-(tert.-Butoxycarbonylamino)-cyclopropyl]-methanol*** **[(-)-9]**. – To a solution of **(+)-10** (1.215 g, 5.3 mmol) in water (30 *ml*) PLE (0.1 *ml* of a suspension containing 10 mg/*ml* of enzyme, Boehringer-Mannheim Ltd.) was added. The pH of the reaction mixture was maintained at 7 by addition of 0.5 N sodium hydroxide using a pH-stat equipment. The reaction came to completion after addition of 10.33 *ml* of

NaOH. The reaction mixture was extracted with ethyl acetate (4 x 30 *ml*) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated under reduced pressure and **(-)-9** (0.99 g, 95%) was obtained as a white solid; mp 75-77 °C; R_F (ethyl acetate/hexane 1:3) 0.14; $[\alpha]_D^{25}$ -114.2 (*c* 0.74, $CHCl_3$); ee ≥ 99%; Anal. calcd. for $C_9H_{17}NO_3$ (187.24): C, 57.73, H, 9.15; N, 7.48; found: C, 57.65; H, 9.01, N, 7.32.

***(+)-(1* S, *2* R*)*-cis-*[2-(tert.-Butoxycarbonylamino)-cyclopropyl]-methanol* [(+)-9] *and (+)-(1 R, 2 S)*-cis-*methyl [2-(tert.-butoxycarbonylamino)-cyclopropyl] acetate* [(+)-10].** – A solution of **(±)-10** (3.06 g, 13.33 mmol) in water (40 *ml*) was adjusted to pH=7.0 and lipase P (5 mg) was added. The pH of the reaction mixture was maintained at pH=7 by addition of 0.5 N sodium hydroxide solution using the pH-stat equipment; the reaction was stopped after consumption of 13.656 *ml* of NaOH (corresponding to a conversion of 51%) and the reaction mixture was extracted with ethyl acetate (4 x 30 *ml*). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue subjected to column chromatography (ethyl acetate/hexane 1:10 → 1:5 → ethyl acetate) to afford **(+)-10** (1.23 g, 40%) and the alcohol **9** (1.21 g, 48%, enantiomerically enriched, mp 73-75°C, R_F (ethyl acetate/hexane 1:3) 0.14, $[\alpha]_D^{25}$ +101.0 (*c* 0.97, $CHCl_3$), ee = 87% by HPLC).

Data for **(+)-10**: white solid, mp 49-51 °C, R_F (ethyl acetate/hexane 1:3) 0.36, $[\alpha]_D^{25}$ +44.1 (*c* 1.07, $CHCl_3$), ee ≥ 99%; spectroscopic data correspond to those of **(±)-10**; Anal. calcd. for $C_{11}H_{19}NO_4$ (229.28): C, 57.63, H, 8.35, N, 6.11; found: C, 57.92, H, 8.17, N, 5.99.

This enantiomerically enriched **9** (1.12 g, 5.95 mmol) was dissolved in pyridine (1 *ml*) and acetylated with acetanhydride (0.73 g, 7.15 mmol) to afford the ester **10** (1.225 g, 90%, *vide supra*; mp 48-49 °C, $[\alpha]_D^{25}$-38.0 (*c* 0.79, $CHCl_3$, ee = 87% by HPLC). Enzymatic hydrolysis was performed with lipase P as described above (consumption of 0.2 N NaOH 21.624 *ml* corresponding to a conversion rate of 91%). After usual work up **(+)-9** (0.79 g, 88%) and **(+)-10** (0.07 g, 7%, ee ≥ 99%) were obtained.

Data for **(+)-9**: white solid, mp 76-78 °C, $[\alpha]_D^{25}$+113.5 (*c* 0.89, $CHCl_3$), ee ≥ 99% by HPLC; Anal. calcd. for $C_9H_{17}NO_3$ (187.24): C, 57.73, H, 9.15, N, 7.48; found: C, 57.89, H, 9.11, N, 7.63.

***(±)-(1* RS, *2* RS*)*-cis *Methyl [2-(tert.-butoxycarbonylamino)-cyclopropyl] acetate* [(±)-10].** – To a solution of **(±)-9** (0.3 g, 1.6 mmol) in dry pyridine (1 *ml*) acetic anhydride (0.2 g, 1.92 mmol) was slowly added at 0 °C. The reaction was allowed to warm to 25 °C and stirred for 4 h. Then methanol (3 *ml*) was slowly added, the solvents were removed under diminished pressure and the residue was suspended in water (5 *ml*). This suspension was extracted with dichloromethane (3 x 30 *ml*), the combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The residue was subjected to column chromatography (silica gel, ethyl acetate/hexane 1:10 → 1:5) to afford **(±)-10** (0.35 g, 94%) as a white solid; mp 28-30 °C; R_F (ethyl acetate/hexane 1:3) 0.36; IR (film): ν 3354*m*, 2979*m*, 1738*s*, 1717*s*, 1699*s*, 1695*s*, 1505*s*, 1456*m*, 1393*m*, 1367*s*, 1239*s*, 1169*s*, 1080*m*, 1028*m*, 823*w*, 820*w*; ^1H NMR (300 MHz, $CDCl_3$): δ 5.24-5.14 (*br s*, 1 H, NH), 4.25 (*dd*, *J* = 11.8, 5.6, 1 H, OCH_2), 4.01 (*dd*, *J* = 11.8, 9.0, 1 H, OCH_2), 2.68 (*ddd*, *J* = 10.2, 5.7, 2.1, 1 H, H-C(2)), 2.08 (*s*, 3 H, CH_3), 1.45 (*s*, 9 H, 3 x CH_3 (*tert*.-butyl)), 1.40-1.17 (*m*, 1 H, H-C(1)), 1.06-0.99 (*m*, 1 H, H_A-C(3)), 0.45 (*ddd*, *J* = 5.7, 5.2, 5.2, 1 H, H_B-C(3)); ^{13}C NMR (63 MHz, $CDCl_3$): δ 171.42 (*s*, CO), 156.86 (*s*, CO (*tert*.-butyl)), 79.55 (*s*, C_q(*tert*.-butyl)), 63.64 (*t*, OCH_2), 28.35 (*q*, 3 x CH_3 (*tert*.-butyl)), 27.31 (*d*, C(2)), 21.08 (*d*, C(1)), 16.26 (*q*, CH_3), 10.88 (*t*, C(3)); MS (e.i., 80 eV, 30 °C): 174 (0.1%), 173 (1.0%), 170 (0.6%), 169 (3.8%), 157 (0.2%), 156 (2.3%), 127 (0.3%), 126 (2.8%), 125 (0.3%), 113 (32.2%), 100 (1.6%), 96 (9.6%), 70 (38.2%), 69 (68%), 57 (100.0%), 43 (40.6%), 41 (58.4%); Anal. calcd. for $C_{11}H_{19}NO_4$ (229.28): C, 57.63, H, 8.35, N, 6.11; found: C, 57.90; H, 8.06; N, 5.92.

***(±)-(1* RS, *2* R S*)*-cis-N-*Phenyl-[2-(*N-*tert.-butoxycarbonylamino)-cyclopropyl]-methyl carbamate* [(±)-11] *and methyl phenyl-carbamate* (27).** – To a solution of **(±)-9** (0.11 g, 0.58 mmol) in dry diethyl ether (2 *ml*) phenylisocyanate (0.14 g, 1.18 mmol) was added and the mixture was stirred at 50 °C for 4 h. After cooling to 25 °C methanol (2 *ml*) was added, the mixture was stirred for an additional 10 min and then the solvents were removed under reduced pressure. The residue was subjected to column chromatography (silica gel, ethyl acate/hexane 1:10 → 1:5) and **(±)-11** (0.12 g, 68%) and **27** (0.054 g, 30%) were obtained.

Data for **(±)-11**: white solid; mp 136-138 °C; R_F (ethyl acetate/hexane 1:2) 0.35; UV (methanol): λ_{max} 230 nm, ε = 14800; IR (KBr): ν 3365*m*, 2986*w*, 1844*w*, 1792*w*, 1772*w*, 1734*m*, 1704*s*, 1685*s*, 1653*m*, 1647*m*, 1636*m*, 1617*m*, 1604*m*, 1576*w*, 1559*m*, 1533*s*, 1512*s*, 1473*w*, 1457*m*, 1447*m*, 1419*w*, 1391*w*, 1372*w*, 1362*m*, 1317*m*, 1275*m*, 1229*s*, 1160*m*, 1089*m*, 1066*w*, 1017*m*; ^{1}H NMR (250 MHz, d_4-methanol): δ 7.42-7.39, 7.31-7.22, 7.03-6.97 (*m*, 5 H, H-C_{phenyl}), 4.14-4.08 (*m*, 2 H, OCH_2), 2.72-2.65 (*m*, 1 H, H-C(2)), 1.42 (*s*, 9 H, 3 x CH_3(*tert*.-butyl)), 1.42-1.26 (*m*, 1 H, H-C(1)), 1.02-0.93 (*m*, 1 H, H_A-C(3)), 0.54-0.47 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (63 MHz, d_4-methanol): δ 157.03 (*s*, COO of *tert*.-butyl), 153.85 (*s*, $COOCH_2$), 137.93 (*s*, C_q, phenyl), 129.07, 123.52, 118.85 (each *d*, C_{phenyl}), 79.65 (*s*, C_q(*tert*.-butyl)), 64.34 (*t*, OCH_2), 28.39 (*d*, C(2)), 27.43 (*q*, 3 x CH_3(*tert*.-butyl)), 16.50 (*d*, C(1)), 10.85 (*t*, C(3)); MS (e.i., 80 eV, 94 °C): 306 (0.1%), 250 (0.2%), 233 (0.8%), 213 (0.5%), 212 (3.6%), 170 (0.8%), 169 (7.3%), 138 (10.0%), 137 (7.8%), 114 (7.2%), 113 (27.1%), 93 (33.5%), 69 (44.4%), 57 (100.0%); Anal. calcd. for $C_{16}H_{22}N_2O_4$ (306.36): C, 62.73; H, 7.24; N, 9.14; found: C 62.96; H, 6.98; N, 9.15.

Data for **27**:[17] white solid; mp 40-41 °C; R_F (ethyl acetate/hexane 1:6) 0.32; IR (KBr): ν 3301*s*, 3139*m*, 3082*m*, 3020*m*, 2955*m*, 2845*w*, 2780*w*, 1946*w*, 1705*s*, 1654*m*, 1616*s*, 1604*s*, 1549*s*, 1502*s*, 1490*s*, 1448*s*, 1329*s*, 1318*s*, 1238*s*, 1192*s*, 1179*m*, 1086*s*, 846*m*, 770*m*, 753*s*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39-7.25 (*m*, 4 H, H-C_{phenyl}), 7.09-7.02 (*m*, 1 H, H-C_{phenyl}), 6.76 (br *s*, 1 H, NH), 3.76 (*s*, 3 H, OCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 154.21 (*s*, CO), 137.96 (*s*, C_q, phenyl), 129.05, 123.49, 118.85 (each *d*, C_{phenyl}), 52.31 (*q*, OCH_3); MS (e.i., 80 eV, 30 °C): 152 (10.0%), 151 (100.0%), 150 (1.0%), 135 (3.1%), 120 (10.9), 119 (44.7%), 107 (6.8%), 106 (80.8%), 93 (8.6%), 92 (40.1%), 91 (11.2%), 79 (10.7%), 77 (25.0%).

(-)-(1* R*, 2* S*)-*cis*-[2-(5-Amino-6-chloro-pyrimidin-4-yl-amino)-cyclopropyl]-methanol **[(-)-12]**. – A solution of **(-)-9** (0.89 g, 4.74 mmol) in THF (6 *ml*) and 6 N aqueous hydrochloric acid (2 *ml*) was stirred for 3 h at 40-45 °C. Then the solvents were removed under reduced pressure and the remaining dark oil was suspended in triethylamine (15 *ml*) and *n*-butanol (30 *ml*). After addition of 5-amino-4,6-dichloro-pyrimidine (1.167 g, 7.11 mmol) the reaction mixture was heated under reflux for 24 h, then the solvents were evaporated and the residue subjected to column chromatography (ethyl acetate → ethyl acetate/methanol 10:1) to afford **(-)-12** (0.76 g, 75%) as a white solid; mp 180-183 °C; R_F (ethyl acetate/methanol 7:1) 0.43; $[\alpha]_D^{25}$ -142.1 (*c* 0.76, methanol); ee ≥ 99%; IR (KBr): ν 3345*s*, 3245*s*, 3010*m*, 2925*m*, 2870*m*, 1735*w*, 1700*m*, 1655*s*, 1580*s*, 1487*m*, 1465*s*, 1410*s*, 1355*m*, 1340*m*, 1245*m*, 1205*m*, 1155*m*, 1101*m*, 1030*m*; ^{1}H NMR (300 MHz, d_6-DMSO): δ 7.80 (*s*, 1 H, H-C(2')), 6.83 (*d*, *J* = 2.4, 1 H, HN-C(1), exch. with D_2O), 5.10 (*s*, 2 H, NH_2, exch. with D_2O), 4.15 (*dd*, *J* = 6.3, 4.7, 1 H, OH, exch. with D_2O), 2.90 (*dddd*, *J* = 10.4, 7.1, 4.0, 2.4, 1 H, H-C(2)), 1.26-1.18 (*m*, 1 H, H-C(1)), 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, d_6-DMSO + D_2O): δ 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, d_6-DMSO): δ 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(2)), 19.88 (*d*, C(1)), 9.23 (*t*, C(3)); MS (e.i., 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 $C_8H_{11}ClN_4O$ (214.65): C, 44.76; H, 5.17; N, 26.10; Cl, 16.52; found: C, 45.01; H, 5.25; N, 25.80.

(+)-(1* S*, 2* R*)-*cis*-[2-(5-Amino-6-chloro-pyrimidin-4-yl-amino)-cyclopropyl]-methanol **[(+)-12]**. – According to the preparation of **(-)-12** from **(+)-9** (0.89 g, 4.74 mmol) **(+)-12** (0.76 g, 74%) was obtained as a white solid; mp 178-180 °C, $[\alpha]_D^{25}$ +140.8 (*c* 0.71, methanol), ee ≥ 99%; Anal. calcd. for $C_8H_{11}ClN_4O$ (214.65): C, 44.76; H, 5.17; N, 26.10; found: C, 44.99; H, 5.27; N, 25.93.

(-)-(1* S*, 2* R*)-*cis*-9-(2-Hydroxymethyl-cyclopropyl)-adenine (= (-)-(1* R*, 2* S*)-*cis*-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol) **[(-)-13]**. – A suspension of **(-)-12** (0.25 g, 1.17 mmol) in triethyl orthoformate

(2.77 g, 18.7 mmol) and hydrochloric acid (36%, 0.14 g, 1.4 mmol) was stirred for 4 h at 25 °C. By addition of sodium hydrogen carbonate (0.2 g) and water (10 *ml*) the pH of the reaction mixture was adjusted to 7-8 and the aqueous solution was extracted with ethyl acetate (5 x 50 *ml*); the combined organic phases were dried ($MgSO_4$) and the solvent was removed. Ammonolysis of the residue (15 *ml* anhydrous ammonia, 14 bar, 78 °C bad temperature, 18 h, steel autoclave) followed by column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 10:1 → 5:1 → 3:1) gave **(-)-13** (0.14 g, 59%) as a white solid; mp 168-171 °C, R_F (ethyl acetate/methanol 3:1) 0.30; $[\alpha]_D^{25}$ -50.0 (*c* 0.84, methanol); UV (methanol) $\lambda_{max} = 260$ nm, $\varepsilon = 14750$; ee ≥ 99%; IR (KBr): ν 3297*br s*, 3125*br s*, 2367*m*, 2344*m*, 1735*w*, 1678*s*, 1605*s*, 1570*s*, 1510*m*, 1475*s*, 1420*s*, 1390*m*, 1335*s*, 1302*s*, 1260*m*, 1195*m*, 1105*m*, 1055s; ^{1}H NMR (250 MHz, d$_6$-DMSO): δ 8.17 (*s*, 1 H, H-C(2')), 8.15 (*s*, 1 H, H-C(8')), 7.30 (*s*, 2 H, NH_2, exch. with D_2O), 4.75 (*br*, 1 H, OH, exch. with D_2O), 3.50 (*ddd*, *J* = 7.2, 7.2, 4.3, 1 H, H-C(1)), 3.39-3.30 (*m*, 1 H, CH_2O), 3.07-2.99 (*m*, 1 H, CH_2O), 1.60-1.50 (*m*, 1 H, H-C(2)), 1.35-1.25 (*m*, 1 H, H_A-C(3)), 1.25-1.15 (*m*, 1 H, H_B-C(3)); ^{1}H NMR (250 MHz, d$_6$-DMSO + D_2O): δ 8.15 (*s*, 1 H, H-C(2')), 8.11 (*s*, 1 H, H-C(8')), 3.49 (*ddd*, *J* = 7.2, 7.2, 4.3, 1 H, H-C(1)), 3.25 (*dd*, *J* = 11.7, 6.0, 1 H, CH_2O), 3.06 (*dd*, *J* = 11.7, 7.9, 1 H, CH_2O), 1.60-1.50 (*m*, 1 H, H-C(2)), 1.35-1.25 (*m*, 1 H, C(3)), 1.20-1.15 (*m*, 1 H, C(3)); ^{1}H NMR (250 MHz, d$_4$-methanol): δ 1.20 (*ddd*, *J* = 6.8, 6.3, 4.3, 1 H, H_A-C(3)), 1.45 (*ddd*, *J* = 9.2, 7.2, 6.3, 1 H, H_B-C(3)); ^{13}C NMR (62 MHz, d$_6$-DMSO): δ 155.98 (*s*, C(6')), 152.45 (*d*, C(2')), 150.75 (*s*, C(4')), 142.09 (*d*, C(8')), 118.82 (*s*, C(5')), 59.35 (*t*, OCH_2), 28.77 (*d*, C(1)), 19.54 (*d*, C(2)), 8.32 (*t*, C(3)); MS (e.i., 80 eV, 131 °C): 205 (14.0%), 188 (12.1%), 174 (20.0%), 164 (27.4%), 149 (14.7%), 148 (12.5%), 136 (100.0%), 135 (55.4%), 108 (23.9%); Anal. calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13; found: C, 52.55; H, 5.28; N, 34.47.

(+)-(1 R, 2 S)-cis-9-(2-Hydroxymethyl-cyclopropyl)-adenine (= (+)-(1 S, 2 R)-cis-[2-(6-amino-purin-9-yl)-cyclopropyl]-methanol) **[(+)-13]**. – According to the preparation of **(-)-13** from **(+)-12** (0.3 g, 1.40 mmol) **(+)-13** (0.19 g, 65%) was obtained as a white solid; mp 168-170 °C, $[\alpha]_D^{25}$ +50.6 (*c* 0.87, methanol); Anal. calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13; found: C, 52.65; H, 5.31; N, 34.38.

(±)-(1 RS, 2 RS)-cis-N-Phenyl-2-[6-(3-phenyl-ureido)-purin-9-yl]-cyclopropyl methyl carbamate **[(±)-14]** ***and (±)-(1 RS, 2 RS)-cis-N-phenyl-[2-(6-amino-purin-9-yl)-cyclopropyl]-methyl carbamate*** **[(±)-15]**. – To a solution of **(±)-13** (0.08 g, 0.37 mmol) in dry diethyl ether (2 *ml*) triethylamine (100 *ml*) and phenylisocyanate (150 *ml*, 1.33 mmol) were added and the mixture was stirred for 12 h at 50-55 °C under argon. The solvents were removed under reduced pressure and the residue was subjected to chromatography (silica gel, ethyl acetate/hexane 1:1 → ethyl acetate → ethyl acetate/methanol 10:1) to afford **(±)-14** (0.08 g, 46%) and **(±)-15** (0.053 g, 45%).

Data for **(±)-14**: white solid, mp: 197-210 °C; R_F (ethyl acetate/methanol 20:1) 0.50; UV (methanol): λ_{max1} 280 nm ($\varepsilon = 20795$), $\lambda_{max2} = 234$ ($\varepsilon = 20386$); IR (KBr): ν 3341*m*, 3203*m*, 3117*m*, 3027*m*, 2964*m*, 1899*w*, 1725*s*, 1705*s*, 1653*m*, 1598*s*, 1581*s*, 1564*s*, 1534*s*, 1501*s*, 1468*m*, 1445*s*, 1403*m*, 1375*m*, 1341*m*, 1313*s*, 1267*m*, 1233*s*, 1203*s*, 1154*m*, 1084*m*, 1062*s*, 1029*m*; ^{1}H NMR (300 MHz, d$_6$-DMSO): δ 11.85 (*s*, 1 H, NH), 10.07 and 9.56 (each *s*, 1 H, NH), 8.63 (*s*, 1 H, H-C(2')), 8.50 (*s*, 1 H, H-C(8')), 7.63-7.60, 7.39-7.33, 7.24-7.19, 7.11-7.06, 6.94-6.89 (*m*, 10 H, H-C_{Phenyl}), 3.89-3.76 (*m*, 2 H, OCH_2 and *m*, 1 H, H-C(1)), 1.84-1.81 (*m*, 1 H, H-C(2)), 1.65-1.59 (*m*, 1 H, H_A-C(3)), 1.50-1.45 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (75 MHz, d$_6$-DMSO): δ 152.74 and 152.03 (*s*, C(6') and HNCONH), 150.68 and 149.36 (*s*, C(4') and HNCOO), 150.30 (*d*, C(2')), 144.22 (*d*, C(8')), 138.65 and 138.19 (each *s*, $C_{q,\ Phenyl}$), 128.63, 128.31, 122.89, 122.01, 119.15, 117.86 (each *d*, C_{Phenyl}), 120.09 (*s*, C(5')), 62.41 (*t*, OCH_2), 29.39 (*d*, C(1)), 16.33 (*d*, C(2)), 8.46 (*t*, C(3)); MS (e.i., 80 eV, 197 °C): 444 (0.8%), 443 (3.0%), 351 (1.2%), 350 (3.7%), 325 (7.5%), 324 (32.7%), 214 (8.1%), 205 (4.7%), 188 (58.9%), 187 (10.2%), 186 (11.2%), 174 (9.1%), 162 (17.6%), 161 (10.8%), 136 (39.9%), 135 (16.8%), 119 (100.0%); HRMS calcd. for $C_{23}H_{21}N_7O_3$: 443.1705; found: 443.1704.

Data for **(±)-15**: white solid; mp: 100-102 °C; R_F (ethyl acetate/methanol 7:1) 0.13; UV (methanol) λ_{max1} 261 nm ($\varepsilon = 9691$), $\lambda_{max2} = 237$ ($\varepsilon = 16853$); IR (KBr): ν 3324*s*, 3188*s*, 1718*s*, 1647*s*, 1599*s*, 1545*s*, 1500*m*, 1476*m*, 1445*s*, 1419*m*, 1383*m*, 1314*s*, 1224*s*, 1107*w*, 1083*m*, 1061*m*, 1027*m*; ^{1}H NMR (300 MHz, d$_6$-DMSO): δ 9.63 (*s*, 1 H, NH), 8.16 and 8.15 (each *s*, 1 H, H-C(2') and H-C(8')), 7.41-7.39, 7.27-7.21, 7.00-6.95

(*m*, 5 H, H-C_{Phenyl} and 2 H, NH_2), 3.89 (*dd*, *J* = 11.8, 7.6, 1 H, OCH_2), 3.71 (*dd*, *J* = 11.8, 7.6, 1 H, OCH_2), 3.66 (*ddd*, *J* = 7.4, 7.4, 4.4, 1 H, H-C(2)), 1.82-1.71 (*m*, 1 H, H-C(1)), 1.56-1.51 (*m*, 1 H, H_A-C(3)), 1.44-1.37 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (75 MHz, d_6-DMSO): δ 155.62 (*s*, C(6')), 152.93 (*s*, CO), 152.27 (*d*, C(2')), 150.66 (*s*, C(4')), 141.25 (*d*, C(8')), 138.71 (*s*, $C_{q,\ Phenyl}$), 128.37, 122.04, 117.90 (each *d*, C_{Phenyl}), 118.67 (*s*, C(5i)), 62.80 (*t*, OCH_2), 29.02 (*d*, C(2)), 16.06 (*d*, C(1)), 8.70 (*t*, C(3)); MS (e.i., 80 eV, 183 °C): 326 (1.2%), 325 811.6%), 324 (59.5%), 205 (5.9%), 204 (14.4%), 188 (100.0%), 187 (15.1%), 186 (20.4%), 174 (17.7%), 173 (10.3%), 162 (24.4%), 161 (12.3%), 149 (13.6%), 136 (68.2%), 135 (24.3%), 119 (31.9%); HRMS calcd. for $C_{16}H_{16}N_6O_2$: 324.1333; found: 324.1331.

(-)-(1 S, *2* R*)-*cis*-9-(2-Hydroxymethyl-cyclopropyl)-1,9-dihydro-purin-6-one* **[(-)-16]**. – A suspension of **(-)-12** in triethyl orthoformate (2.65 g, 17.89 mmol), aqueous hydrochloric acid (36%, 0.13 g, 1.3 mmol) was stirred at 25 °C for 3h. By addition of sodium hydrogencarbonate (0.2 g) and water (10 *ml*) the pH of the reaction mixture was adjusted to pH 7-8 and the aqueous phase was extracted with ethyl acetate (5 x 50 *ml*). The combined organic phases were dried ($MgSO_4$), the solvents were removed and the residue was suspended in an aqueous sodium hydroxide solution (0.5 N, 28 *ml*) and heated under reflux for 1h. After cooling to 25 °C the pH of the reaction mixture was adjusted to 7 by the careful addition of aqueous hydrochloric acid (18%), then the solvents were removed, the residue was subjected to column chromatography (ethyl acetate → ethyl acetate/methanol 5:1 → 3:1) and **(-)-16** (0.09 g, 38%) and unchanged **(-)-12** (0.03 g, 14%) were obtained; mp 235-240 °C, R_F (ethyl acetate/methanol 3:1) 0.17; UV λ_{max} 248 nm, ε = 7990; $[\alpha]_D^{25}$ -40.0 (*c* 0.75, DMSO); ee ≥ 99%; IR (KBr): ν 3395*s*, 3130*m*, 3050*m*, 2845*m*, 1845*w*, 1830*w*, 1790*w*, 1770*w*, 1735*m*, 1700*s*, 1695*s*, 1685*s*, 1675*s*, 1655*s*, 1650*m*, 1635*m*, 1620*m*, 1590*s*, 1570*m*, 1560*m*, 1550*m*, 1535*m*, 1520*m*, 1520*m*, 1510*m*, 1495*w*, 1475*m*, 1460*m*, 1440*w*, 1410*m*, 1395*m*, 1340*m*, 1225*w*, 1185*w*, 1130*w*; ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.06 and 8.05 (each *s*, 1 H, H-C(2') and H-C(8')), 3.54 (*ddd*, *J* = 7.3, 7.3, 4.4, 1 H, H-C(1)), 3.20 (*dd*, *J* = 11.6, 6.0, 1 H, CH_2O), 3.10 (*dd*, *J* = 11.6, 7.5, 1 H, CH_2O), 1.55-1.45 (*m*, 1 H, H-C(2)), 1.29 (*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, d_6-DMSO): δ 156.50 (*s*, C(6')), 149.70 (*s*, C(4')), 145.30 (*d*, C(2')), 141.14 (*d*, C(8')), 124.11 (*s*, C(5')), 59.11 (*t*, OCH_2), 29.30 (*d*, C(1)), 19.44 (*d*, C(2)), 8.49 (*t*, C(3)); MS (e.i., 80 eV, 202 °C): 207 (2.5%), 206 (17.5%), 187 (16.2%), 176 (5.0%), 175 (24.8%), 165 (31.0%), 150 (12.0%), 149 (10.9%), 148 (18.3%), 137 (93.1%), 136 (26.4%), 120 (11.9%), 109 (18.4%), 83 (9.1%), 71 (24.3%), 44 (100.0%); HRMS calcd. for $C_9H_{10}N_4O_2$: 206.08036, found: 206.08038.

(+)-(1 R, *2* S*)-*cis*-9-(2-Hydroxymethyl-cyclopropyl)-1,9-dihydro-purin-6-one* **[(+)-16]**. – According to the preparation of **(-)-16** from **(+)-12** (0.31 g, 1.46 mmol) **(+)-16** (0.14 g, 45%) and unchanged starting material (0.04 g, 12%) were obtained; mp 234-239 °C; $[\alpha]_D^{25}$ +40.3 (*c* 0.77, DMSO); ee ≥ 99%; HRMS calcd. for $C_9H_{10}N_4O_2$: 206.08036, found: 206.08038.

(±)-(1 **RS**, *2* **RS***)-***trans** *Methyl [2-(tert.-butoxycarbonylamino)-cyclopropyl] acetate* **(±)-(23)**. – According to the preparation of **(±)-10** from **(±)-22** (1.54 g, 8.24 mmol) and acetic anhydride (1.0 g, 9.89 mmol) and pyridine (2.0 *ml*) **(±)-23** (1.57 g, 83%) was obtained as a white solid; mp 30-32 °C; R_F (ethyl acetate/hexane 1:3) 0.39; IR (film): ν 3348*s*, 2978*s*, 1739*s*, 1733*s*, 1717*s*, 1699*s*, 1695*s*, 1683*s*, 1652*m*, 1538*s*, 1520*m*, 1505*s*, 1456*s*, 1367*s*, 1317*m*, 1239*s*, 1167*s*, 1097*m*, 1032*s*, 972*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (*d*, *J* = 2.5, 1 H, NH), 4.00 (*dd*, *J* = 11.3, 7.3, 1 H, OCH_2), 3.92 (*dd*, *J* = 11.3, 7.7, 1 H, OCH_2), 2.48-2.45 (*m*, 1 H, H-C(2)), 2.07 (*s*, 3 H, CH_3), 1.44 (*s*, 9 H, 3 x CH_3 (*tert.*-butyl)), 1.33-1.21 (*m*, 1 H, H-C(1)), 0.83-0.72 (*m*, 1 H, $H_{A,B}$-C(3)); ^{13}C NMR (63 MHz, $CDCl_3$): δ 170.68 (*s*, CO), 155.96 (*s*, CO (*tert.*-butyl)), 79.37 (*s*, C_q (*tert.*-butyl)), 65.83 (*t*, OCH_2), 28.15 (*q*, 3 x CH_3 (*tert.*-butyl)), 27.87 (*d*, C(2)), 20.77 (*d*, C(1)), 19.12 (*q*, CH_3), 12.01 (*t*, C(3)); MS (e.i., 80 eV, 30 °C): 214 (0.1%), 173 (0.6%), 170 (0.2%), 169 (1.3%), 156 (0.2%), 126 (1.4%), 125 (0.1%), 113 (16.8%), 100 (0.8%), 96 (3.9%). 70 (18.2%), 69 (25.1%), 57 (100.0%), 43 (13.6%), 41 (19.5%); Anal. calcd. for $C_{11}H_{19}NO_4$ (229.28): C, 57.63, H, 8.35, N, 6.11; found: C, 57.77; H, 8.27; N, 5.99.

(±)-(1* RS, *2* RS*)*-trans *Methyl [2-(tert.-butoxycarbonylamino)-cyclopropyl] hexanoate **[(±)-24].** – To a solution of (±)-**22** (2.5 g, 13.35 mmol) in dry pyridine (2.0 *ml*) caproic acid anhydride (3.43 g, 16.02 mmol) was added and the reaction was stirred for 6 h at 25 °C. Usual work up (addition of methanol, extraction with dichloromethane, chromatography on silica gel, ethyl acetate/hexane 1:10) gave (±)-**24** (3.62 g, 95%) as a colourless oil; R_F (ethyl acetate/hexane 1:5) 0.35; IR (film): ν 3358*s*, 2959*s*, 2873*s*, 1719*s*, 1697*s*, 1508*s*, 1458*s*, 1366*s*, 1316*m*, 1248*s*, 1167*s*, 1097*s*, 1025*m*, 993*m*, 867*w*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (br *s*, 1 H, NH), 4.03 (*dd*, *J* = 11.6, 7.0, 1 H, OCH_2), 3.95-3.90 (*m*, 1 H, OCH_2), 2.48-2.47 (*m*, 1 H, H-C(2)), 2.31 (*t*, *J* = 7.5, 2 H, $COCH_2$), 1.68-1.58 (*m*, 2 H, CH_2), 1.44 (*s*, 9 H, 3 x CH_3 (*tert*.-butyl)), 1.36-1.24 (*m*, 4 H, 2 x CH_2 and *m*, 1 H, H-C(1)), 0.90 (*t*, *J* = 6.9, 3 H, CH_3), 0.80-0.74 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.65 (*s*, CO), 155.96 (*s*, CONH), 79.54 (*s*, C_q (*tert*.-butyl)), 65.71 (*t*, OCH_2), 34.22 and 31.28 (each *t*, CH_2), 28.33 (*q*, 3 x CH_3 (*tert*.-butyl) and *d*, C(2)), 24.61 and 22.29 (each *t*, CH_2), 19.35 (*d*, C(1)), 13.90 (*q*, CH_3), 12.22 (*t*, C(3)); MS (e.i., 80 eV, 96 °C): 270 (0.1%), 230 (0.06%), 229 (0.4%), 173 (0.2%), 170 (0.5%), 169 (2.3%), 117 (7.5%), 113 (29.4%), 99 (3.7%), 69 (38.8%), 57 (100.0%); Anal. calcd. for $C_{15}H_{27}NO_4$ (285.38): C, 63.13; H, 9.54; N, 4.91; found: C, 62.91, H, 9.44, N, 4.71.

(±)-(1* RS, *2* RS*)*-trans *Methyl [2-(tert.-butoxycarbonylamino)-cyclopropyl] benzoate **[(±)-25].** – Acylation of (±)-**22** (1.0 g, 5.34 mmol) at 0 °C with benzoyl chloride (0.9 g, 6.41 mmol) in the presence of pyridine (3 *ml*) followed by usual work up and chromatography (silica gel, ethyl acetate/hexane 1:10) afforded (±)-**25** (1.43 g, 92%) as a white solid; mp 94-97 °C; R_F (ethyl acetate/hexane 1:5) 0.32; IR (KBr): ν 3369*s*, 3016*w*, 2981*m*, 2931*w*, 2896*w*, 1909*w*, 1713*s*, 1683*s*, 1648*m*, 1617*w*, 1601*m*, 1586*m*, 1559*m*, 1530*s*, 1491*m*, 1469*m*, 1453*m*, 1445*m*, 1393*m*, 1368*s*, 1318*s*, 1284*s*, 1251*s*, 1178*s*, 1161*s*, 1119*s*, 1081*m*, 1068*m*, 1044*w*, 1029*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08-8.04 and 7.59-7.41 (*m*, 5 H, H-C_{phenyl}), 4.84 (*br s*, 1 H, NH), 4.30 (*dd*, *J* = 11.5, 6.8, 1 H, OCH_2), 4.20-4.17 (*m*, 1 H, OCH_2), 2.59-2.57 (*m*, 1 H, H-C(2)), 1.44 (*s*, 9 H, 3 x CH_3(*tert*.-butyl)), 1.44-1.38 (*m*, 1 H, H-C(1)), 0.88-0.84 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.50 (*s*, CO), 156.24 (*s*, NHCO), 132.85 (*d*, C_{phenyl}), 130.21 (*s*, $C_{q,\ phenyl}$), 129.58 und 128.27 (each *d*, C_{phenyl}), 79.55 (*s*, C_q (*tert*.-butyl)), 66.42 (*t*, OCH_2), 28.30 (*d*, C(2) and *q*, 3 x CH_3 (*tert*.-butyl)), 19.31 (*d*, C(1)), 12.27 (*t*, C(3)); MS (e.i., 80 eV, 85 °C): 276 (0.1%), 236 (0.3%), 235 (1.3%), 218 (0.5%), 175 (0.4%), 170 (1.0%), 169 (6.4%), 162 (0.3%), 123 (18.2%), 113 (54.5%), 105 (31.9%), 77 (17.6%), 70 (36.0%), 69 (74.9%), 57 (100.0%); Anal. calcd. for $C_{16}H_{21}NO_4$ (291.35): C, 65.96; H, 7.26; N, 4.81; found: C, 65.81; H, 7.24; N, 4.60.

(±)-(1* RS, *2* RS*)*-trans-N*-Phenyl-[2-(*N*-tert.-butoxycarbonylamino)-cyclopropyl]-methyl-carbamate **[(±)-26].** – According to the preparation of (±)-**11** from (±)-**22** (0.15 g, 0.79 mmol) (±)-**26** (0.22 g, 91%) was obtained as a white solid; mp 134-136 °C; R_F (ethyl acetate/hexane 1:3) 0.37; UV (methanol): λ_{max} 236 nm, ε = 14758; IR (KBr): ν 3340*s*, 2982*m*, 1704*s*, 1684*s*, 1653*m*, 1647*m*, 1597*s*, 1526*s*, 1500*m*, 1466*m*, 1445*s*, 1391*m*, 1369*m*, 1315*s*, 1278*s*, 1236*s*, 1162*s*, 1108*m*, 1059*m*, 1021*m*; ^{1}H NMR (250 MHz, d_4-methanol): δ 7.44-7.40, 7.30-7.22, 7.06-6.97 (*m*, 5 H, H-C_{phenyl}), 4.02-3.99 (*m*, 2 H, OCH_2), 2.47 (*ddd*, *J* = 8.5, 3.1, 3.1, 1 H, H-C(2)), 1.44 (*s*, 9 H, 3 x CH_3 (*tert*.-butyl)), 1.27 (*ddd*, *J* = 7.7, 7.7, 3.1, 1 H, H-C(1)), 0.78-0.72 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (63 MHz, d_4-methanol): δ 159.02 (*s*, COO of *tert*.-butyl), 156.03 (*s*, $COOCH_2$), 140.23 (*s*, $C_{q,\ phenyl}$), 129.77, 123.95, 119.86 (each *d*, C_{phenyl}), 80.27 (*s*, C_q (*tert*.-butyl)), 67.66 (*t*, OCH_2), 29.10 (*d*, C(2)), 28.76 (*q*, 3 x CH_3 (*tert*.-butyl)), 20.16 (*d*, C(1)), 11.96 (*t*, C(3)); MS (e.i., 80 eV, 94 °C): 306 (0.3%), 250 (0.2%), 233 (0.3%), 213 (0.8%), 212 (5.1%), 170 (0.9%), 169 (6.8%), 138 (9.6%), 137 (6.2%), 114 (6.8%), 113 (26.8%), 93 (39.7%), 69 (39.1%), 57 (100.0%); Anal. calcd. for $C_{16}H_{22}N_2O_4$ (306.36): C, 62.73; H, 7.24; N, 9.14; found: C, 62.94; H, 7.06; N, 8.91.

Enzymatic acetylation of (±)-(1* R S, *2* RS*)*-trans*-[2-(tert.-butoxycarbonylamino)-cyclopropyl]-methanol **[(±)-22]** ***with lipase PS.*** To a solution of (±)-**22** (0.07 g, 0.35 mmol) in *tert*.-butyl-methyl ether (2 *ml*) and vinyl acetate (0.3 g, 3.47 mmol) lipase PS (25 mg) was added. After 6h two samples were taken and investigated by HPLC: determination of the rate of conversion [57% **23** + 43% **22** (possessing an ee of 49%; determined on a Chiralcel OD-R column after derivatization with phenylisocyanate)]: RP18 (Merck), MeHO/H_2O 40:60; 0.5 *ml*/min, 53 kg/cm^2, UV at 230 nm, t_R **22**: 14 min, t_R **23**: 26.4 min; rate of conversion determined from the areas under curve corrected for the different absorption coefficients for **23** and **22** at λ = 230 nm.

ACKNOWLEDGMENT

Financial support by the European Communities (SC1*-CT92-0780) and the Fonds der Chemischen Industrie is gratefully acknowledged; we are indebted to *Prof. Dr. R. Neidlein*, Pharmazeutisch-Chemisches Institut, Universität Heidelberg, for his encouragement, to *Dr. P. Rosyk* for his help with the manuscript and to Perkin-Elmer for support. Thanks are also due to Amano Ltd. and Novo Nordisk Ltd. for the generous donation of enzymes.

REFERENCES AND NOTES

Dedicated to Prof. Dr. Gunther Seitz on the occasion of his 60th birthday

1 Ashton, W. T.; Canning Meurer, L.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L., *J. Med. Chem.* **1988**, *31*, 2304-2315.

2 Norbeck, D. W.; Sham, H. L.; Herrin, T.; Rosenbrook, W.; Plattner, J. J., *J. Chem. Soc., Chem. Commun.* **1992**, 128-129; Katagiri, N.; Sato, H.; Kaneko, C., *Chem. Pharm. Bull.* **1990**, *38*, 3184-3186; Kaneko, S.; Katagiri, S., *Jpn. Kokai Tokkyo Koho* 04074169 (9.3.1992), *C.A.* **1992**, *117*, 70271x; Nishiyama, S.; Ueki, S.; Watanabe, T.; Yamamura, S.; Kato, K.; Takita, T., *Tetrahedron Lett.* **1991**, *32*, 2141-2; Katagiri, N.; Sato, H.; Kaneko, C., *Nucleosides Nucleotides* **1992**, *11*, 707-711; *cf.* also: Izawa, T.; Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T., *J. Chem. Soc. Perkin Trans I* **1992**, 2519-2525.

3 Csuk, R.; von Scholz, Y. *Tetrahedron* **1994**, *50*, 10431-10442.

4 Csuk, R.; von Scholz, Y. *Tetrahedron* **1995**, *51*, 7193-7206.

5 Some of these compounds showed weak antitumor activity against several tumor cell lines but no activity in an *in-vitro* anti-HIV assay. Thanks are due to the NIH for providing *in vitro* testing results by the NIH National Cancer Institute Developmental Therapeutics Program.

6 Zhao, Y.; Yang, T.-F.; Lee, M.; Chun, B. K.; Du, J.; Schinazi, R. F.; Lee, D.; Newton, M. G.; Chu, C. K., *Tetrahedron Lett.* **1994**, *35*, 5405-5408.

7 For a recent conformational study: Maag, H.; Nelson, J. T.; Steiner, J. L. R.; Prisbe, E. J., *J. Med. Chem.* **1994**, *37*, 431- 435 and refs. cited therein.

8 Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H., *J. Med. Chem.* **1985**, *28*, 1385-1386.

9 Sabbioni, G.; Jones, J. B., *J. Org. Chem.* **1987**, *52*, 4565-4570.

10 Sabbioni, G.; Shea, M. L.; Jones, J. B., *J. Chem. Soc., Chem. Commun.* **1984**, 236-238.

11 Laumen, K.; Schneider, M., *Tetrahedron Lett.* **1985**, *26*, 2073-2076.

12 Walser, P.; Renold, P.; N'Goka, V.; Hosseinzadeh, F.; Tamm, C., *Helv. Chim. Acta* **1991**, *74*, 1941-1952.

13 Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J. K. *Helv. Chim. Acta* **1983**, *66*, 2501-2511.

14 Cannon, J. G.; Garst, J. E., *J. Org. Chem.* **1975**, *40*, 182-184.

15 Norbeck, D. W.; Rosen, T. J.; Sham, H. L., *US Pat.* 4988703 (29.01.1991), *C.A.* **1991**, *115*, 50218r.

16 In addition, derivatization of **(±)-22** using (1 *R*)-menthyl chloroformate, (1 *R*)-menthyloxy acetyl chloride, (1 *S*) camphanic acid chloride or (+)-di-*O*-acetyl- L-tartaric anhydride to afford diastereomers differing sufficiently in their properties to allow a separation failed. The corresponding mixtures of diastereomers were obtained in fair to excellent yields but they could not be separated by chromatography, nor by distillation nor by fractional crystallization.

17 Thomson, J. B.; Brown, P.; Djerassi, C., *J. Am. Chem. Soc.* **1966**, *88*, 4049-4051; Rao, C. N. R.; Rao, K. G.; Goel, A.; Balasubramanian, D., *J. Chem. Soc., Sect. A* **1971**, *19*, 3077-3086.

(*Received in Germany* 12 *January* 1996; *revised* 23 *February* 1996; *accepted* 29 *February* 1996)