

δ -Peptide Analogues of Pyranosyl-RNA

Part 1¹⁾

Nucleo- δ -peptides Derived from Conformationally Constrained Nucleo- δ -amino Acids: Preparation of Monomers ²⁾³⁾

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Cyclic nucleo- δ -amino acids that constitute monomers of a conformationally constrained nucleo- δ -peptide base-pairing system have been prepared. Their synthesis starts with an enantioselectively catalyzed chirogenic *Diels-Alder* reaction, proceeds *via* a regioselective ϵ -iodolactamization process, and ends with a regio- as well as diastereoselective introduction of nucleobases through S_N2 -type opening of a transiently formed *N*-acylaziridine ring. Extensive use of X-ray crystal-structure analysis has been made to support structure assignments.

1. Introduction. – 1.1. *General Introduction to a Series of Publications.* Pyranosyl-RNAs (p-RNAs; **B**) [9][10] are structurally close relatives of RNAs (**A**), with a ribopyranosyl moiety and with sugar centers C(2') and C(4') rather than C(3') and C(5') linked by phosphodiester groups. The nucleo- δ -peptides that we will describe in this series of papers (NDPs; see **C**) are conformational analogues of p-RNAs; they contain cyclohexane rings in place of pyranose rings, and carbamoylmethyl groups instead of phosphodiester bridges. In three parts, we will report on the synthesis of NDPs, their structure, and their base-pairing properties.

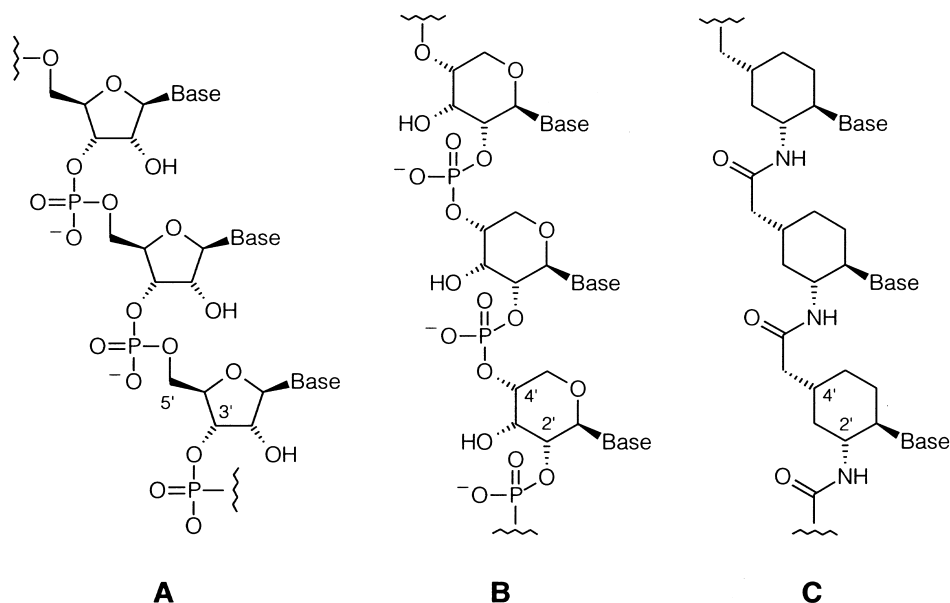
NDPs are new members of the growing class of nucleic-acid analogues that contain peptide-like backbones in place of the natural phosphodiesters and still have the capability of base-pairing [11].

The term peptides [12] covers polymers formed by condensation of the respective amino and carboxy groups of amino acids. *Emil Fischer* [13] has coined the term polypeptides which is now used in addition to oligopeptides and proteins to subclassify peptides. As amino acids, taking account of the growing separation of the two

¹⁾ Part 2: [1]; Part 3: [2].

²⁾ From diploma theses or postdoctoral reports of G.K. [3], A.F. [4], A.B. [5], T.B. [6], and S.S. [7].

³⁾ Abbreviations used in this paper: *ap*: anti-periplanar; Boc: *tert*-butoxycarbonyl; BOM: (benzyloxy)methyl; DMAP: 4-(dimethylamino)pyridine; DMF: dimethylformamide; DMSO: dimethyl sulfoxide; NOE: nuclear Overhauser enhancement; PMBz: 4-methoxybenzoyl; TADDOL: *α,α,α',α'*-tetraaryl-1,3-dioxolane-4,5-dimethanols; THF: tetrahydrofuran; TMS: tetramethylsilane. For acronyms of NMR techniques, see [8].

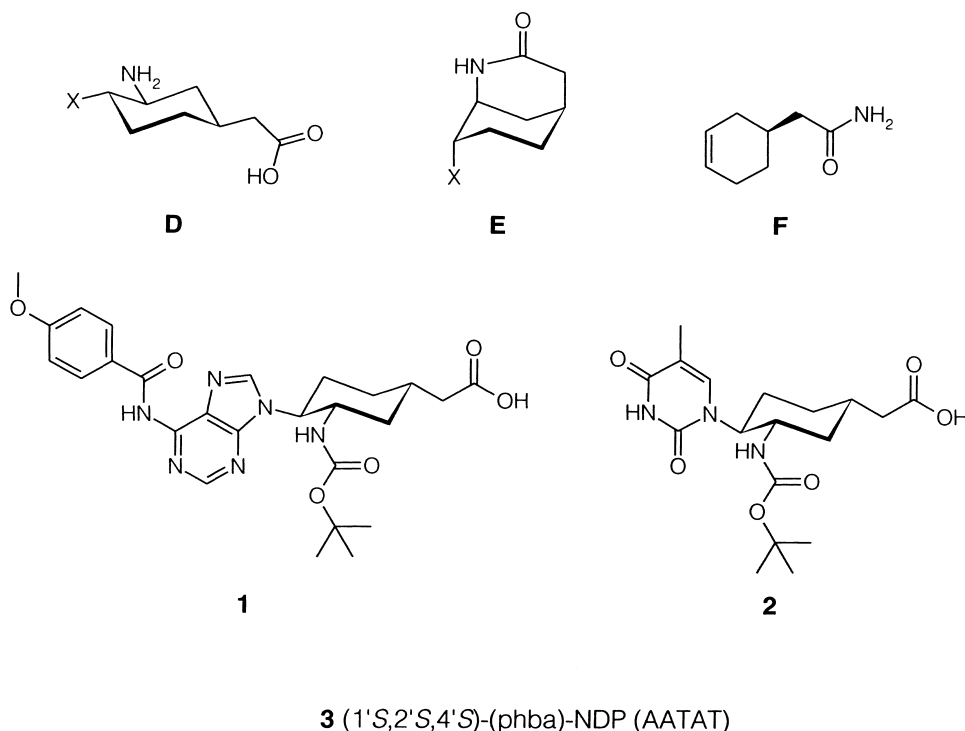


functional groups, are subdivided into α -, β -, γ -, δ -, ... amino acids, it is only consequent to follow Seebach [14] and Gellman [15] who subdivide peptides similarly into α -, β -, γ -, δ -, ... peptides. The β and δ centers of the δ -amino acids (and related δ -peptides) are connected by a trimethylene bridge to form a cyclohexane ring (see **D**) and to give rise to a conformationally constrained δ -amino acid (and the corresponding δ -peptide). The C-atoms of the cyclohexane ring are numbered in such a way that the (C(4'), C(3'), C(2')) segment corresponds to the (β , γ , δ) segment of the δ -peptide backbone. Substitution of the cyclohexane ring at C(1') by a nucleobase (Ade or Thy in this paper) leads to nucleo- δ -amino acids (NDAAs for short), which serve as the building blocks for conformationally constrained NDPs.

1.2. *Introduction to Part 1.* Oligomers **B** and **C** are configurationally and conformationally as close as possible. β -D-Ribopyranosyl-(2'–4')-oligonucleotides of type **B** are nearest to (1'*R*,2'*R*,4'*R*)-nucleo- δ -peptides of type **C**. Because of practical reasons, the oligomer types **C** and *ent*-**C** have been chosen as targets to be synthesized. In this paper, we describe the preparation of the NDAA-building blocks **1** and **2**. For preparation and pairing of oligomers of type *ent*-**C**⁴⁾, see Part 3 [2]. For NMR-spectroscopic analysis of the duplex formed by self-pairing of the chosen (1'*S*,2'*S*,4'*S*)-(phba)-NDP(AATAT) pentamer (**3**)⁵⁾, see Part 2 [1].

⁴⁾ Because of closer relationship between **B** and **C**, the latter has been chosen for figuration here in spite of the fact that examples of *ent*-**C** will be reported in Part 2 of this series.

⁵⁾ Ade and Thy, as usual, specify the residues of the nucleobases adenine and thymine. A and T refer to NDAA residues containing Ade and Thy; phba defines the [(HO)₂P(=O)–O–(CH₂)₃–C=O] radical fixed to the N-terminal radical of a NDP.



2. Stereoselective Synthesis of Nucleo- δ -amino Acids. – 2.1. *A Chirogenic Opening Move.* 1*r*,2*t*,4*t*-Trisubstituted cyclohexyl building blocks of type **D** (or *ent*-**D**) may be obtained straightforwardly from cyclohex-3-ene derivatives **F** (or *ent*-**F**), via type **E** (or *ent*-**E**) bicyclic lactams.

The two pathways⁶⁾ to enantiomeric lactams **12a** and *ent*-**12a** (see *Scheme 1*) both begin with a chirogenic *Diels-Alder* reaction between buta-1,3-diene (**4**) and 3-(propenoyl)-1,3-oxazolidin-2-one (**5**) (*Exper. 1.1.1*) [16], catalyzed by a *Seebach*'s TADDOL catalyst [17]. The absolute configuration of the *Diels-Alder* adduct obtained (in over 85% chemical yield) reflects the sense of chirality of the catalyst, which is, in this case, (4*R*,5*R*)- or (4*S*,5*S*)-2-methyl- $\alpha,\alpha,\alpha',\alpha'$ -2-pentaphenyl-1,3-dioxolane-4,5-dimethanol (**6**) [18][19] or (*ent*-**6**) [18][20], *in situ* complexed with (i-PrO)₂TiCl₂. The resulting complex *Lewis acid* [17] is essential for the reaction to take place under the mild conditions required for the preferential formation of **7** or *ent*-**7**). The enantioselection follows the pattern laid down by *Seebach et al.* [17][24]. By conventional techniques,

⁶⁾ Optimization was performed in the racemic series (see details in *Scheme 1*).

⁷⁾ Combination of α,β -unsaturated *N*-acryloyloxazolidinones and *Lewis acid* promoters was introduced by *Evans et al.* [21] into the *Diels-Alder* field. Use of chiral, non-racemic dienophiles leads to diastereoselection. According to observations of *Narasaka et al.* [22] on use of chiral, non-racemic promoters enantioselection takes place. Ti Complexes, especially, were most effective, if *Seebach*'s-TADDOLS [17][23] were used.

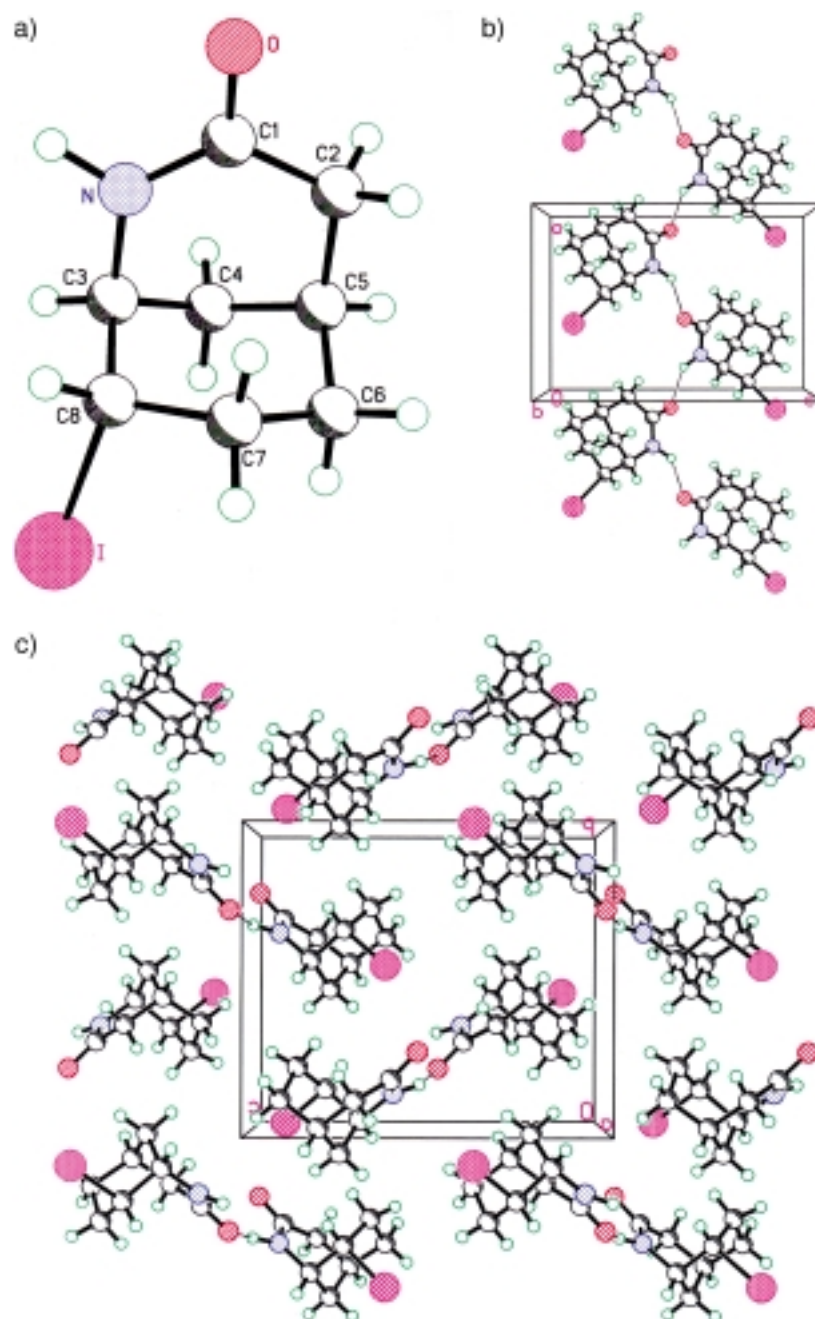


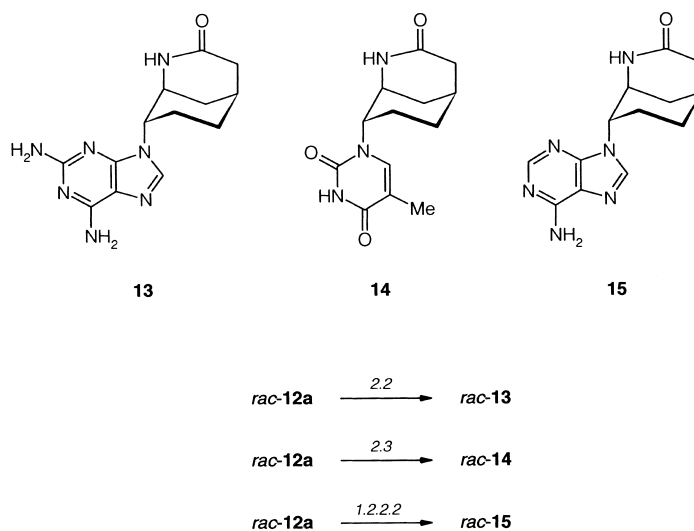
Fig. 1. Representation of the crystal structure of **12a** (Exper. 1.1.6). *a*) Molecular structure; *b*) H-bonded chains viewed down *b*; *c*) crystal packing viewed down *a*.

ibly that the constitution is that of a δ -lactam (and not a δ -lactone), as well as the relative (*1c,5r,8t*) and absolute (in this case (*1S,5S,8S*)) configurations of **12a**¹¹).

The six-membered heterocyclic ring containing the *ap*-oriented amide group has a conformation somewhere between a chair and a half-chair. The amide group is slightly non-planar with a torsion angle C(3)–N–C(1)–C(2) of 13(1)°. The six-membered carbocyclic ring has a chair conformation, with the I-atom in an axial position. This latter has an *ap*-orientation with respect to the amide group (*Fig. 1, a*). The amide group is involved in an intermolecular H-bonding with the amide groups of neighboring molecules (*Fig. 1, b*). The dimensions of the H-bonds are: N–H...O (symmetry code: $x - 0.5, 0.5 - y, 1 - z$) with N–H: 0.98 Å, H...O: 1.96 Å, N...O: 2.808(9) Å and angle N–H–O: 143°. The H-bonded molecules form a zigzag chain in the crystallographic *a*-direction, corresponding to the needle axis of the crystal (*Fig. 1, c*). The crystal packing shows no other intermolecular contacts shorter than the *van der Waals* distances.

2.3. From Iodolactams of Type 12a to Various NDAAs. With compounds of type **12a**, replacement of the I-atom by a nucleobase anion proceeded in two steps *via* a transitory *N*-acylaziridine [25] and with overall retention of configuration. Exploratory treatment of *rac*-**12a** with purine-2,6-diamine (see *Scheme 2*) led to *rac*-**13** in 80% yield.

Scheme 2



On recrystallization, spontaneous resolution takes place: the crystal used here contained the (*1R,5R,8R*)-enantiomer *ent*-**13** exclusively¹²). This – and the fact that all substituents present are axially oriented – is revealed by X-ray crystal-structure analysis (*Fig. 2*)¹³).

¹¹) (*S*)-Configuration, determined by anomalous scattering of (–)-**12a**, can be traced back to (–)-**7** (see *Scheme 1*). For the latter compound, erroneously, (*R*)-configuration has been reported [16].

¹²) (*1R,5R,8R*)-Configuration was determined by anomalous scattering.

¹³) For numbering of the atoms, see *Fig. 2, a*.

The six-membered heterocyclic ring shows a small deviation from a half-chair conformation. The amide group is slightly non-planar, with a torsion angle C(11)–N(12)–C(13)–C(14) of $-8.9(2)^\circ$. The six-membered carbocyclic ring has a slightly distorted chair conformation. The diaminopurine moiety is in an axial position with respect to this ring (*Fig. 2, a*). The purine system is approximately planar. The NH₂ group at C(2) shows a significant deviation from planarity, with the N-atom by 0.14 Å outside the plane through C(2), H_a–N(2), and H_b–N(2). The non-planarity of this NH₂ group may result from H-bonding forces. The NH₂ group at C(6), involved in only one H-bond, shows a much smaller deviation from planarity (the N-atom lies by 0.05 Å away from the plane through C(6), H_a–N(6), and H_b–N(6)). The shortest intramolecular contact distance is 2.51(1) Å between N(3) and H–C(11), and approaches the *van der Waals* contact distance.

The crystal packing shows a three-dimensional network of the H-bonds. Two parallel H-bonds interconnect the amide group and the diaminopurine group of neighboring molecules (*Fig. 2, b*). In addition, each H₂O molecule is connected by four H-bonds to the diaminopurine groups of three different molecules. The H-atom H_a–N(6) is not involved in H-bonding. The crystal packing (*Fig. 2, c*) shows one additional short intermolecular contact between O(13) and H–C(8) of a neighboring molecule (symmetry: $1.5 - x, 2 - y, 0.5 + z$). The observed distance of 2.29(1) Å between O(13) and H–C(8) is slightly shorter than the *van der Waals* distance of 2.4 Å between O- and H-atoms.

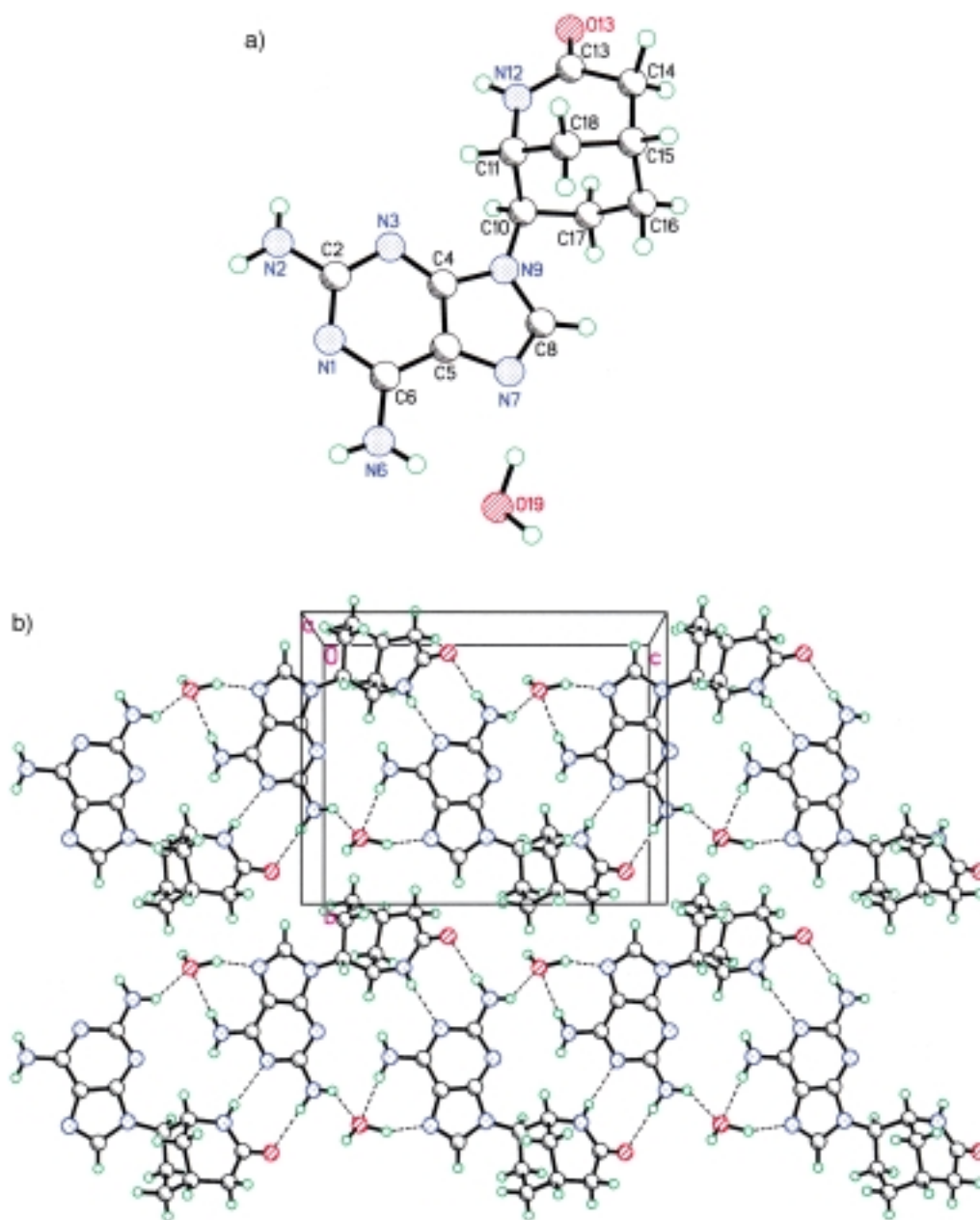
Reaction of *rac*-**12a** with thymine afforded the substitution product *rac*-**14** in 41% yield (*Scheme 2*). X-Ray crystal-structure analysis was also performed on this compound (*Fig. 3*)¹⁴.

The conformation of the lactam ring is close to a C(12)-envelope conformation (*Fig. 3, a*). The amide group is slightly non-planar with a ring torsion angle C(13)–N(14)–C(15)–C(16) of $5.7(3)^\circ$. The cyclohexane ring has a distorted chair conformation, with both the thymine and the amide groups in axial positions. The thymine group is approximately planar, and the largest torsion angle in the thymine ring is $1.8(3)^\circ$. The shortest intramolecular contact distance is 1.98(3) Å between H–C(6) and H_a–C(10), and is equal to the *van der Waals* distance between H-atoms. The crystal structure of *rac*-**14** shows zigzag chains of the H-bonded molecules running in the crystallographic [101] direction (*Fig. 3, b*). Each thymine moiety is connected by two H-bonds to the amide group of a neighboring molecule. H₂O Molecules form weak H-bonds between the amide O-atoms of different chains, giving rise to a three-dimensional network of H-bonds (*Fig. 3, c*).

Nucleobase-bearing lactams of types **13** and **14** (*Scheme 2*) can be prepared, without the need for protecting groups, from iodolactams of type **12a** and deprotonated purine-2,6-diamine or thymine. To convert these hydrolytically into the target NDAa, it is necessary to substitute the H-atom of the lactam group with, for example, a Boc group.

The advantages of the Boc group are not only that it prevents lactam proton abstraction, nor just that it facilitates the desired attack of a suitable nucleophile on the

¹⁴) For numbering of the atoms, see *Fig. 3, a*.



(Fig. 2)

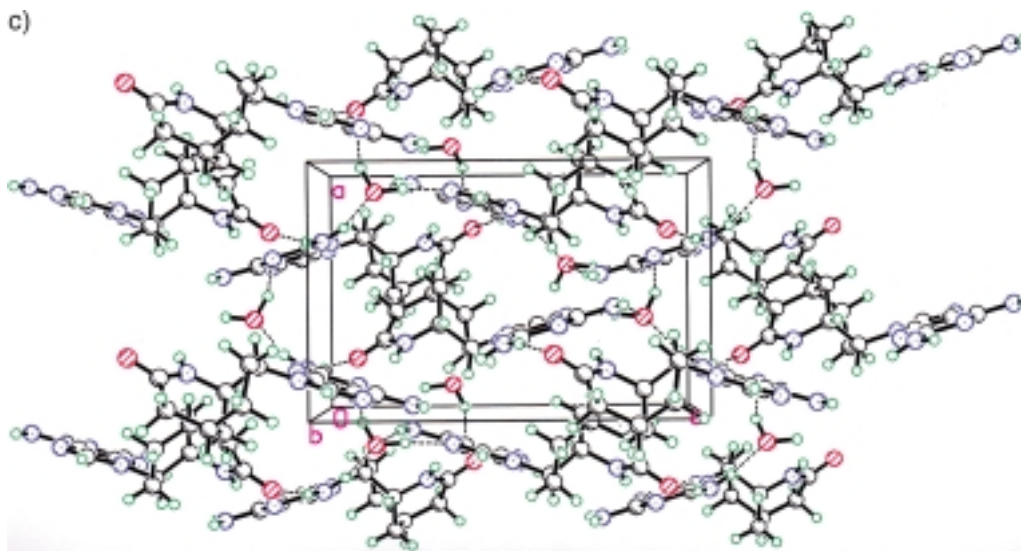


Fig. 2. Representation of the crystal structure of *ent*-**13** (Exper. 2.2). a) Molecular structure; b) H-bonding network in a layer parallel to the *bc* plane; c) crystal packing viewed down *b*.

lactam C=O group. As well as these, it also withstands the conditions required in the later oligomerization of the NDAAs.

Since we were unsuccessful in selectively protecting the amide N-atom of *rac*-**16a** (= **14**) with the Boc group, we next concentrated on the reaction of 3-(benzyloxymethyl)thymine [27] with lactams of type **12a**, obtaining substitution products of type **16b** in yields of >50%. These were then converted into the completely protected derivatives of type **16c** (see Scheme 3).

In a similar fashion, reaction of 6-(benzoylamino)purine [28] with **12a** (*rac*-**12a**) initially afforded **18a** (*rac*-**18a**) in 73% (70%) yield (see Scheme 4).

The structure of the deprotected adenylyl derivative *rac*-**18b** (= *rac*-**15**) was determined by X-ray crystal-structure analysis (Fig. 4)¹⁵.

The adenine group is approximately planar. The Atom C(10) deviates by 0.20 Å from the plane of the adenine group. The amide group shows a significant deviation from planarity with a ring torsion angle C(15)–N(16)–C(17)–C(18) of 9.2(2)°. The cyclohexane ring has a chair conformation and is slightly flattened at the C(10)–C(11) and C(11)–C(12) bonds. Both the adenine and the amide groups are in axial positions with respect to the carbocyclic ring (Fig. 4,a). The shortest intramolecular distance is 2.13(2) Å between H–C(8) and H_b–C(12) and is just outside the *van der Waals* distance between H-atoms. There is only one direct H-bond between molecules (Fig. 4,b). This connects the amide N-atom with N(7) of the adenine group of a neighboring molecule, resulting in H-bonded chains of molecules in the *b*-direction. All other H-bonds involve the H₂O molecule. This donates the H-bonds to atoms N(1) and

¹⁵) For numbering of the atoms, see Fig. 4,a.

O(17) of two different molecules and accepts a H-bond from the amino group (N(6)) of a third molecule, leading to a three-dimensional network of H-bonds (*Fig. 4,c*). The amino H-atom H(6_b) has an intermolecular contact distance of 2.63(2) Å with N(3) of a neighboring molecule. This distance is too long to be classified as a H-bond. The crystal structure shows parallel arrangements of neighboring adenine planes, which are related by a crystallographic inversion center (*Fig. 4,c*). The interplanar distance is 3.32 Å. The shortest interatomic distances within these adenine dimers are C(5)⋯C(5): 3.366(2) Å, C(6)⋯C(8): 3.390(2) Å, and N(9)⋯C(6): 3.402(2) Å.

The doubly protected lactams of the type **16c** may be converted into cyclohexane derivatives of the type **17a** by LiOOH-catalyzed¹⁶⁾ hydrolysis in yields >60% (*Scheme 3*). X-Ray crystal-structure analysis was performed on the completely deprotected racemic mixture *rac*-**17c** (*Fig. 5*)¹⁷⁾.

The cyclohexane ring has a chair conformation, with all three side-chains in equatorial positions (*Fig. 5,a*). The thymine group shows a small deviation from

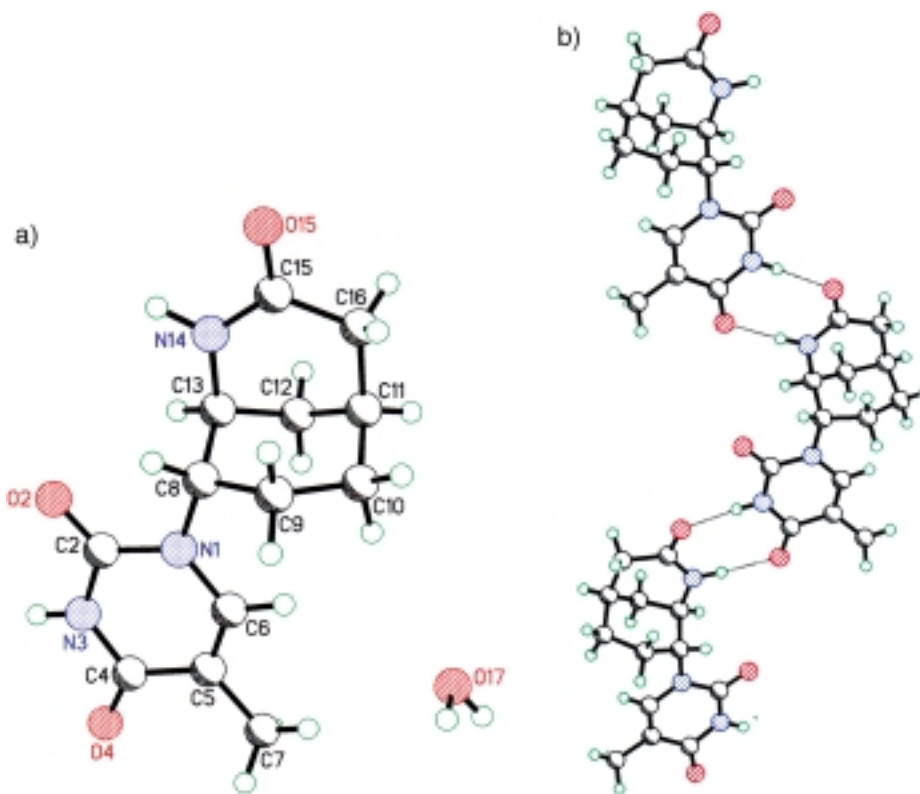


Fig. 3. Representation of the crystal structure of *rac*-**14** (*Exper. 2.3*). a) Molecular structure; b) H-bonded chains in the [101] direction; c) crystal packing viewed down *b*.

¹⁶⁾ LiOOH has been introduced as an exceptionally selective reagent for oxazolidone deacylation by *Evans et al.* [29] and was assumed to preferentially attack the ring C=O group in Boc-protected amides.

¹⁷⁾ For numbering of the atoms, see *Fig. 5,a*.

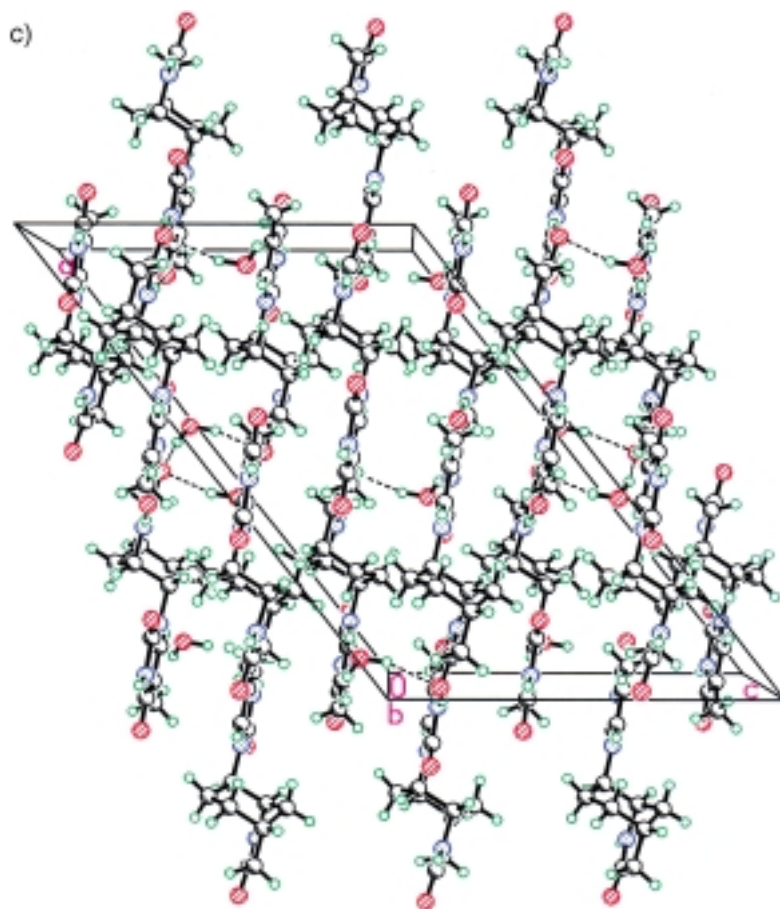


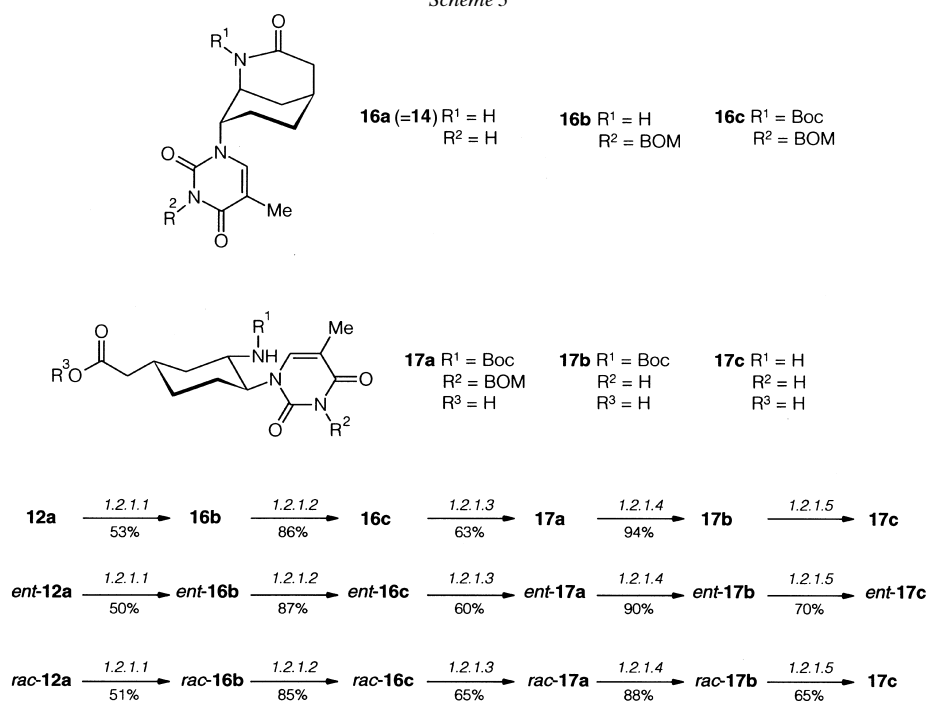
Fig. 3 (cont.)

planarity with C(2) by 0.09 Å out of the plane of the other five ring atoms. This deviation from planarity may result from crystal-packing forces. The shortest intramolecular distance is 2.28(2) Å between O(1) and H–C(6), and approaches the *van der Waals* contact distance of 2.4 Å between O and H. The crystal packing shows a three-dimensional network of intermolecular H-bonds (Fig. 5, *b* and *c*). All H-bonds except the N(3)–H_c⋯O(3) bond involve the H₂O molecules. Two additional intermolecular O⋯H distances approach the *van der Waals* contact distance: O(2)⋯H_b–C(7): 2.40(2) (–*x*, 2 – *y*, –*z*) and O(6)⋯H–C(4): 2.44(2) Å (*x*, 1.5 – *y*, 0.5 + *z*).

In the case of **18f** (Scheme 4), hydrolysis of the lactam to cyclohexane derivative **19** was carried out with the aid of LiOH¹⁸⁾. Cyclohexane derivatives **17b** (= **2**) and **19** (= **1**), activated in the form of *in situ* produced azabenzotriazyl esters, are promising candidates for NDAa solid-phase oligomerization, to be described in [1].

¹⁸⁾ Regioselective hydrolysis of *N*-Boc lactams with LiOH to the corresponding *ω*-amino acids was introduced by Grieco and co-workers [30], and applied by Weller and co-workers [31].

Scheme 3

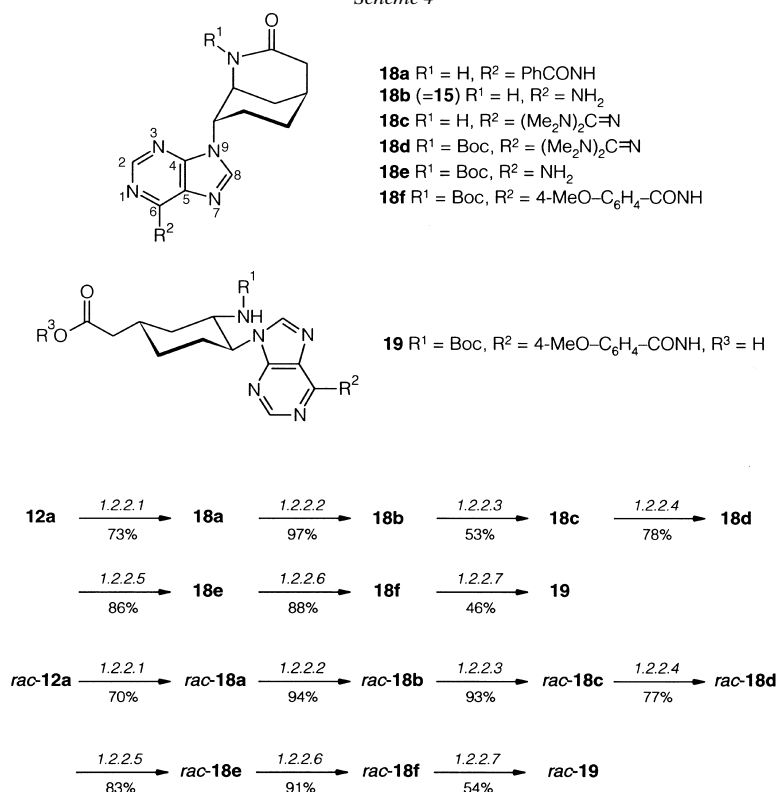


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Experimental Part

General. Solvents: THF and Et₂O were freshly distilled from sodium benzophenone ketyl, hexane, *p*-xylene, and pyridine from CaH₂ under Ar. TLC: glass plates 20 × 20 cm; silica gel *P/UV 254 + 366*, *Riedel de Haen*; preprepared *Kieselgel 60F/UV 254*, *Merck* or *Woelm*; layer thickness 0.25 mm. Glass plates 100 × 20 cm; silica gel *P/UV 254 + 366*; *Riedel de Haen*; layer thickness 1 mm; activated for 4 h at 140°. Chromatograms were made visible using *Fluotest (Quarzlampengesellschaft, Hanau)* or I₂. Column chromatography (CC): silica gel (63–200 m), *Macherey & Nagel, Merck* or *Woelm*. Flash chromatography (FC): silica gel (40–63 m), *Merck*. High-pressure liquid chromatography: anal. HPLC by *Waters 204* with *BBC Metrawatt Servogor 220* two-channel potentiometer recorder; prep. HPLC by *Waters Prep LC System 500*; bracketed information gives, in order, mobile phase, stationary phase, pump throughput, detector wavelength, and/or volume injected if appropriate. M.p (uncorrected): *Kofler* hot-plate microscope. UV: *Cary 15/Zeiss PMQ II/Perkin Elmer 552*. IR: *Beckmann 4230/Perkin Elmer 257*: in cm⁻¹; band positions standardized with a calibration film on polystyrene. NMR: *Varian T60* (¹H-NMR)/*Bruker HX90* with *Nicolet 1080* computer; *Bruker WH 270* with *BNC 28* and *Aspect 2000* computer; *Nicolet NT 300 WB* with *NIC 1280* data processor; *Bruker AM 300* with *Aspect 3000* computer (¹H- and ¹³C-NMR); δ values in ppm relative to TMS as internal standard (=0.00 ppm); *J* in Hz; usual abbreviations apply for signal fine structure; a ψ prefix denotes pseudomultiplicity; f.s. = fine structure. Probes for NOE measurements were degassed in high vacuum and sealed; positions of ¹³C-NMR signals were taken from the broad-band-decoupled spectra, fine structure (*s*, *d*, *t*, *q*) from the 'off-resonance' spectra. If not mentioned otherwise, CDCl₃ was used as solvent in NMR measurements. MS: *Varian CH 7/Varian MAT SM 1 B*. MS: Electrospray ionization (ES) mass spectra were measured on a *VG* single quadrupole mass spectrometer.

Scheme 4



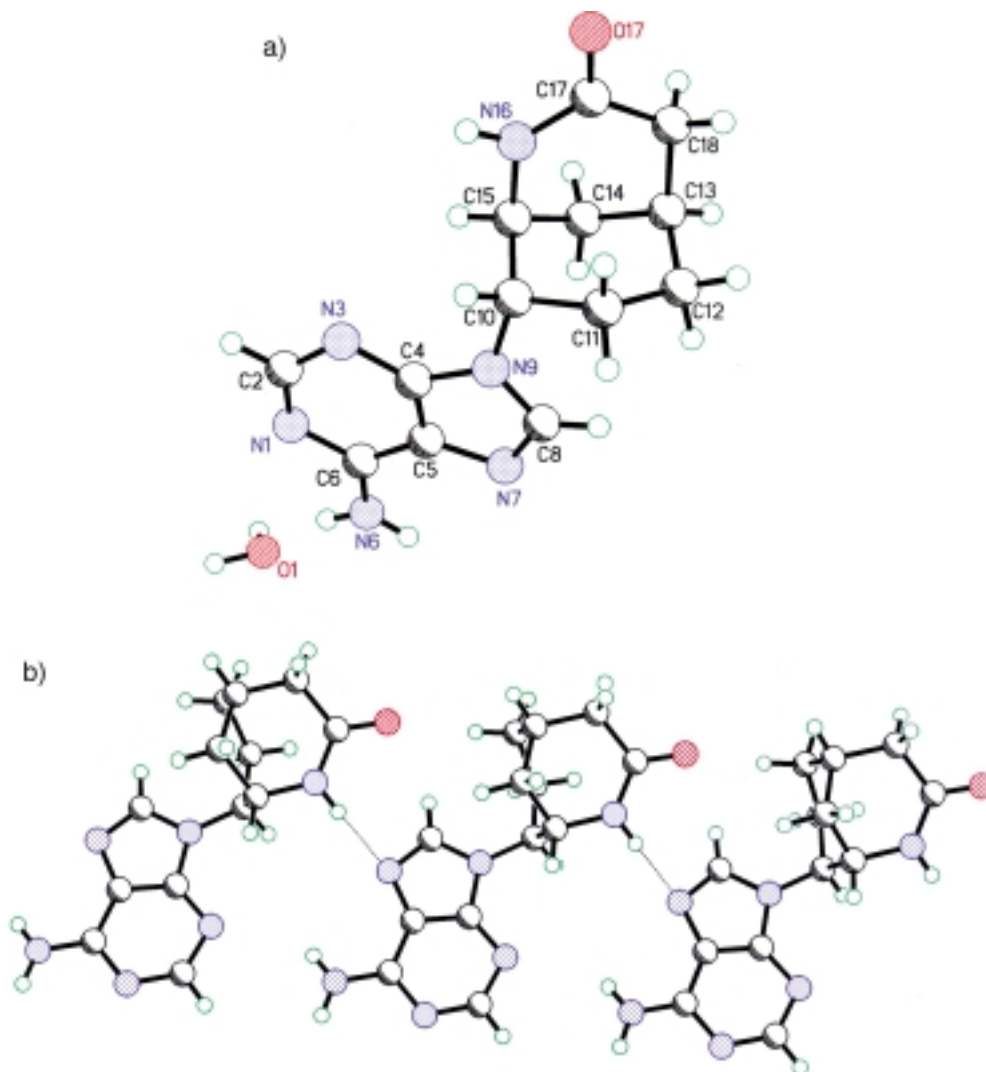
(Fisons, Manchester, UK). Elemental analyses were performed by the own laboratory (*M. Christof*). Crystallographic data (excluding structure factors) for **12a**, *rac*-**12b**, *ent*-**13**, *rac*-**14**, *rac*-**15**, and *rac*-**17c** have been deposited with the *Cambridge Crystallographic Data Centre* (CCDC) as deposition No. CCDC-111523 for **12a**, CCDC-111524 for *rac*-**12b**, CCDC-111525 for *ent*-**13**, CCDC-111526 for *rac*-**14**, CCDC-111527 for *rac*-**15**, and CCDC-111528 for *rac*-**17c**. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21E2, UK (fax: +44 (1223) 336033; e-mail: deposit@ccdc.cam.ac.uk).

1. *Preparation of Monomer Building Blocks*. 1.1. *Common Route to Iodo Lactams of Type 12a* (Scheme 1). 1.1.1. *(1S)*-3-[(Cyclohex-3-en-1-yl)carbonyl]-1,3-oxazolidin-2-one (**7**)¹⁹. To an oven-dried, 2-l, three-necked, round-bottomed flask, equipped with an efficient mechanical stirrer, a thermometer, and, a pressure-equalizing addition funnel with an Ar inlet were added (i-PrO)₂TiCl₂ (9.79 g; 41.5 mmol) in anh. xylene (800 ml; distilled from CaH₂ and stored over 4-Å molecular sieves) and **6** [16] (24.1 g, 45.6 mmol). The mixture was stirred at r.t. for 1 h. Then, **5** [16]²⁰ (35.3 g, 0.25 mmol), powdered 4-Å molecular sieves (1.90 g), and heptane (800 ml; distilled from CaH₂ and stored over 4-Å molecular sieves) were added. The ivory suspension was stirred at r.t. for 15 min and then cooled down to 10–15° with an ice-bath. Buta-1,3-diene (**4**; 130 g; 2.4 mmol) from a commercial cylinder controlled by a needle valve with gentle flow was introduced into the suspension. Afterwards, the mixture, which gradually became viscous, was stirred at r.t. for 5 d. H₂O (300 ml) was added, the mixture effectively stirred for 15 min, and filtered through *Celite*. The remaining solid material was washed, first with H₂O (250 ml) and then with Et₂O (250 ml). The aq. soln. was extracted twice with Et₂O (400 ml each), and the combined Et₂O extracts were dried (MgSO₄) and evaporated. FC (petroleum ether/AcOEt 2:1) yielded

¹⁹) The mixture (**7**/*ent*-**7** >> 1) was prepared by a modified version of the Ti-TADDOLate mediated *Diels-Alder* reaction of **4** with **5** [16].

²⁰) The acryloylation of oxazolidin-2-one was performed according to [32].

crude TADDOL **3** (26.6 g) which, by FC (hexane/AcOEt 20:1 + 30% CH₂Cl₂) could be purified for further use, and **4/ent-4** (ratio $\gg 1$; 42.5 g; 87%), which, without decrease in ee, could be purified by a bulb-to-bulb distillation (180°/0.25 Torr). TLC (hexane/AcOEt 1:1): $R_f = 0.42$. $[\alpha]_{589}^{23} = -20.8$; $[\alpha]_{578}^{23} = -21.5$; $[\alpha]_{346}^{23} = -23.6$; $[\alpha]_{336}^{23} = -32.4$; $[\alpha]_{365}^{23} = -31.9$ ($c = 1.76$, CH₂Cl₂; [14]); $[\alpha]_{589}^{23} = -20.2$ ($c = 1.75$, CH₂Cl₂; 89% ee; with reference to [14] the optical purity amounted to 92%). Determination of ee by HPLC (*Daicel OD-H Chiralcel*, hexane/EtOH 50:1, 1.0 ml/min, 210 nm): $> 92\%$. IR (KBr): 3025*m* (=C–H); 2917*s*, 2839*m* (–C–H); 1789*s*, 1778*s*, 1770*s*, 1694*s* (C=O); 1651*m* (C=C). ¹H-NMR: 1.59–1.75 (*m*, H–C(6')); 1.93–2.01 (*m*, H'–C(6')); 2.04–2.36 (*m*, 2 H–C(2'), 2 H–C(5')); 3.74 (*m*, H–C(1')); 4.00–4.14 (*m*, 2 H–C(4)); 4.38–4.45 (*m*, 2 H–C(5)); 5.69–5.71 (*m*, H–C(3'), H–C(4')). The signals were assigned by a ¹H,¹H-COSY spectrum. Cross signals between 1.59–1.75/1.93–2.36; 1.59–1.75/3.74; 1.93–2.01/2.04–2.36; 1.93–2.01/3.74; 2.04–2.36/3.74; 2.04–2.36/5.69–5.71; 4.00–4.14/4.38–4.45. ¹³C-NMR: 24.6, 27.1 (C(2'), C(5')); 25.5 (C(6')); 38.1 (C(1')); 42.8 (C(4)); 61.9



(Fig. 4)

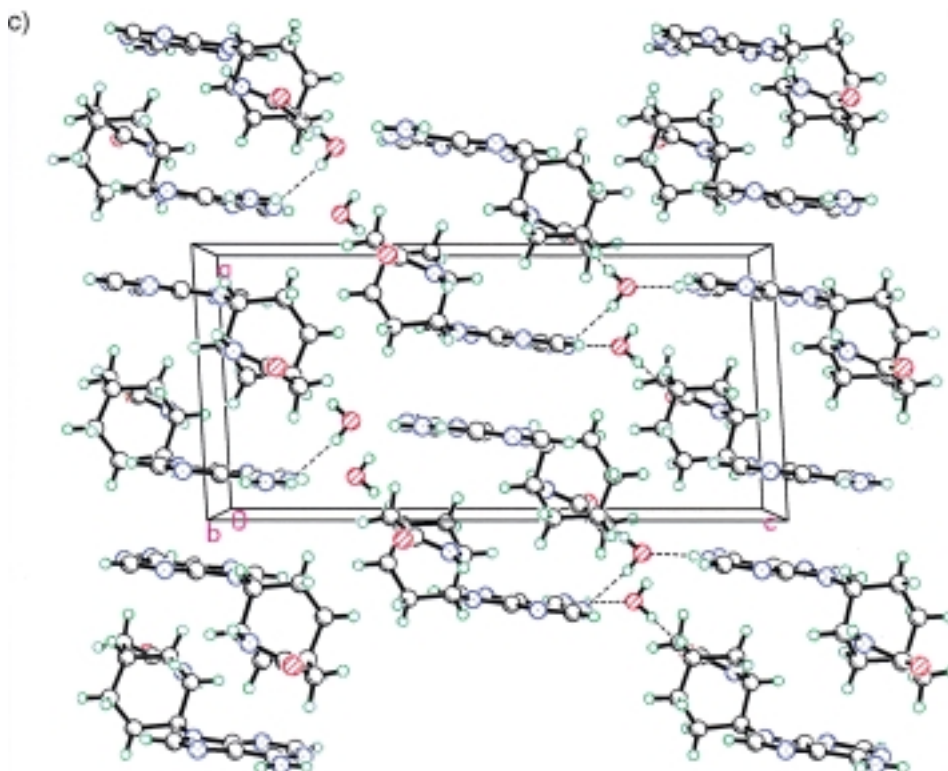


Fig. 4. Representation of the crystal structure of rac-15 (Exper. 1.2.2.2). a) Molecular structure; b) H-bonded chains in the *b* direction; c) crystal packing viewed down *b*.

(C(5)); 125.0, 126.6 (C(3'), C(4')); 153.2, 176.4 (C(2), C(7')). The signals were assigned by a ^1H , ^{13}C -COSY spectrum. Cross signals between 1.59–2.04/25.5; 1.93–2.36/24.6; 1.93–2.36/27.1; 3.74/38.1; 4.00–4.14/42.8; 4.38–4.45/61.9; 5.69–5.71/125.0; 5.69–5.71/126.6. Anal. calc. for $\text{C}_{10}\text{H}_{13}\text{NO}_3$ (195.22): C 61.53, H 6.71, N 7.17; found: C 61.24, H 6.73, N 7.10.

(IR)-3-[(Cyclohex-3-enyl)carbonyl]-1,3-oxazolidin-2-one (*ent*-7; 7*ent*-7 $\gg$ 1; 90%): $[\alpha]_{\text{D}}^{25} = +21.1$; $[\alpha]_{\text{D}}^{33} = +21.8$; $[\alpha]_{\text{D}}^{346} = +23.9$; $[\alpha]_{\text{D}}^{23} = +32.9$; $[\alpha]_{\text{D}}^{365} = +32.8$ ($c = 1.5$, CH_2Cl_2 ; with reference to [16] the optical purity amounted to 93%). Determination of ee by HPLC (*vide supra*): > 92%.

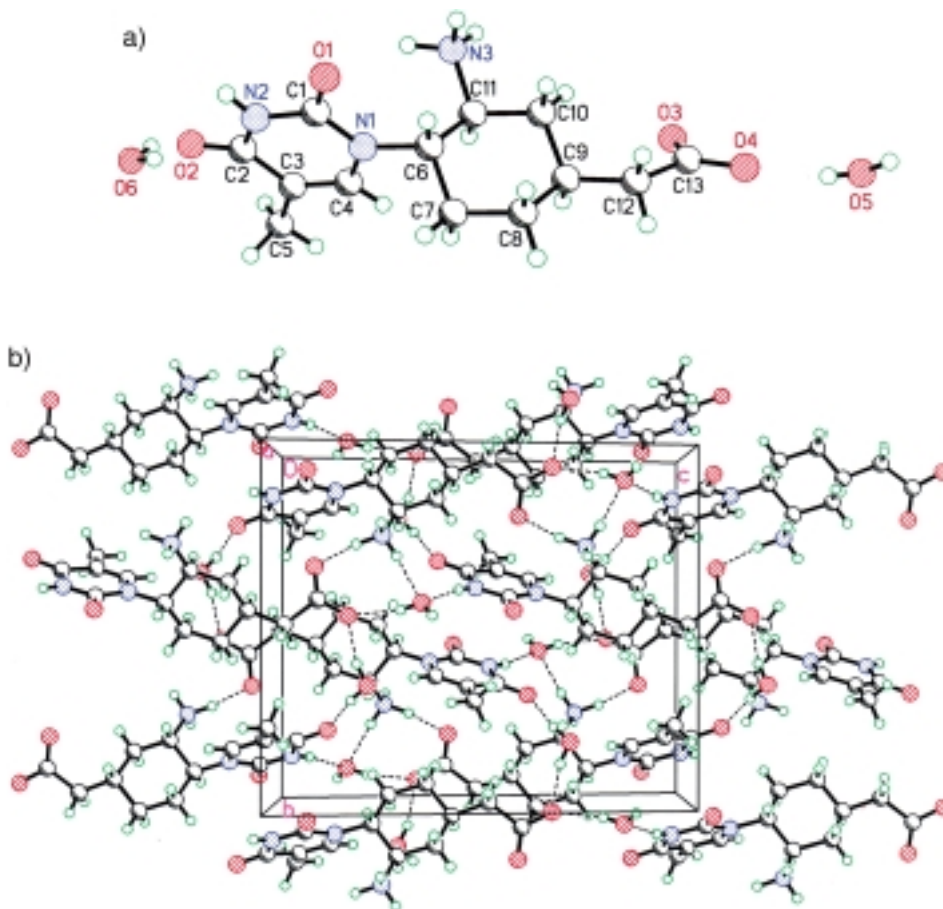
1.1.2. Methyl (1*S*)-Cyclohex-3-ene-1-carboxylate (**8b**)²¹. A 1-l, three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser fitted with an anh. CaSO_4 filled drying tube, and a pressure-equalizing dropping funnel was charged with Mg turnings (814 mg, 33.5 mmol) and anh. MeOH (375 ml) and stirred overnight. A soln. of 7*ent*-7 $\gg$ 1 (64.1 g, 328 mmol; see Exper. 1.1.1) in anh. Et_2O (150 ml) was added over 15 min under stirring. The pale yellow soln., after stirring for another 30 min, was distributed between sat. aq. NH_4Cl soln. (200 ml) and CH_2Cl_2 (200 ml). The aqueous phase was extracted twice with CH_2Cl_2 (150 ml each), and the combined organic soln. was washed with sat. aq. NaCl soln., dried (Na_2SO_4) and evaporated (50°/350 Torr). Bulb-to-bulb distillation (100°/15 Torr) yielded **8b**/*ent*-**8b** as a clear oil (42.9 g, 93%); TLC (hexane/AcOEt 1:1): R_f 0.71. $[\alpha]_{\text{D}}^{23} = -82.2$; $[\alpha]_{\text{D}}^{33} = -85.9$; $[\alpha]_{\text{D}}^{23} = -97.7$; $[\alpha]_{\text{D}}^{436} = -167.2$; $[\alpha]_{\text{D}}^{23} = -260.6$ ($c = 0.94$, in CH_2Cl_2) [33]: $[\alpha]_{\text{D}}^{33} = -86.3$ ($c = 1.00$, CHCl_3). With reference to [33]: optical purity 91%. IR (film): 3027s

²¹) The $\text{Mg}(\text{OMe})_2$ mediated conversion of 7*ent*-7 $\gg$ 1 into **8b**/*ent*-**8b** $\gg$ 1 has been described for a similar case [16].

(=C–H); 2951s, 2929s, 2842s (–C–H); 1736s (ester); 1654s (C=C). ¹H-NMR: 1.60–1.77 (*m*, H–C(6)); 1.95–2.13 (*m*, H'–C(6), 2 H–C(5)); 2.23–2.28 (*m*, 2 H–C(2)); 2.51–2.63 (*m*, H–C(1)); 3.69 (*s*, MeO); 5.63–5.70 (*m*, H–C(3), H–C(4)).

Methyl (1R)-Cyclohex-3-ene-1-carboxylate (ent-8b; 8b/ent-8b < 1; 93%): [α]₃₈₉²⁵ = +80.4 (*c* = 1.06 in CHCl₃); [33]: +86.5 (*c* = 1.05, in CH₂Cl₂); with reference to [28], the optical purity amounted to 86%.

1.1.3. *(1S)-Cyclohex-3-enemethanol (9a)*. An oven-dried, 1-l, three-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a pressure-equalizing dropping funnel was purged with dry Ar and charged with anh. THF (300 ml) and LiAlH₄ (17.4 g; 458 mmol) in limited portions at 0° (ice-bath) under stirring. To the cooled mixture, a soln. of **8b/ent-8b** (42.5 g; 303 mmol; see *Exper. 1.1.2*) in anh. THF (120 ml) was added under vigorous stirring at such a rate that the temp. did not rise above 20°. After 90 min stirring at 0°, THF/H₂O 5:1 was carefully added until gas production has ceased. The mixture was transferred to a 2-l separatory funnel, and H₂SO₄ (15% aqueous soln.) was added until the precipitate was dissolved. Ice was added to bring the temp. down to r.t., and the aq. soln. was extracted with Et₂O (3 × 250 ml). The Et₂O extracts were combined, washed with sat. aq. NaHCO₃ soln., dried (MgSO₄), and evaporated (50°/100 Torr) to yield a faintly yellow oil (42.5 g), which, after bulb-to-bulb distillation (120°/36 Torr), afforded **9a/ent-9a** >> 1 (33.9 g, 99%). [α]₃₈₉²³ = –90.1; [α]₃₇₈²³ = –94.1; [α]₃₄₆²³ = –107.1; [α]₃₃₆²³ = –183.7; [α]₃₆₅²³ = –287 (*c* = 1.7, MeOH). [34]: [α]₃₈₉²³ = –100.4 (*c* = 1.71, MeOH; with reference to [29], the optical purity amounted to 90%). IR (film): 3332s (OH);



(Fig. 5)

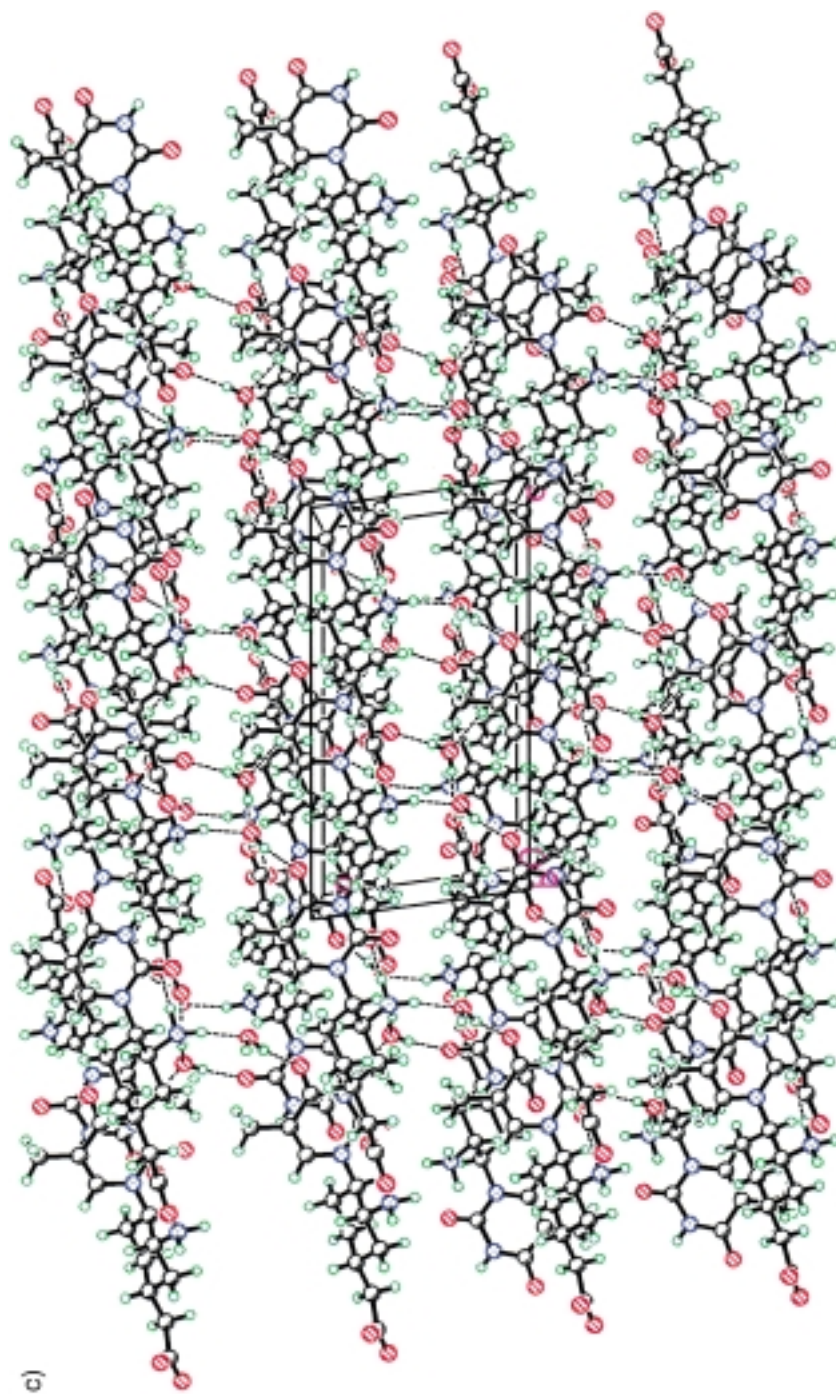


Fig. 5. Representation of the crystal structure of rac-**17c** (*Exper. 12.1.5*). *a*) Molecular structure; *b*) H-bonding in a layer parallel to the *bc* plane; *c*) crystal packing viewed down *b*.

3022s (=C–H); 291s, 2838s (–C–H); 1652s (C=C). ¹H-NMR: 1.24–1.40 (*m*, H–C(1')); 1.41 (*br. s*, partially superimposed, exchangeable on treatment with D₂O, OH); 1.69–1.86, 2.05–2.16 (*2m*, 2 H–C(2'), 2 H–C(5'), 2 H–C(6')); 3.53 (*ψd*, *J*(H–C(1), H'–C(1)) = 5.9, H–C(1)); 3.55 (*ψd*, *J*(H'–C(1), H–C(1)) = 5.9, H'–C(1)); 5.67–5.69 (*m*, H–C(3'), H–C(4')). Anal. calc for C₇H₁₂O (112.17): C 74.95, H 10.78; found: C 74.74, H 10.89.

(*IR*)-Cyclohex-3-enemethanol (*ent-9a*). The mixture **9a**/*ent-9a* ≪ 1 (99%): [α]_D²² = +91.2; [α]_D²²₇₇₈ = +95.1; [α]_D²²₃₄₆ = +108.3; [α]_D²²₃₆₅ = +185.9; [α]_D²²₅₄₆ = +290.4 (*c* = 1.6, MeOH). [35]: [α]_D²² = +96.0 (*c* = 3, MeOH). [31]: [α]_D²² = +87.9; [α]_D²²₇₇₈ = +91.3; [α]_D²²₅₄₆ = +103.5; [α]_D²²₄₃₆ = +168.7; [α]_D²²₃₆₅ = +202.4 (*c* = 0.9, MeOH); [α]_D²² = +95.9; [α]_D²²₇₇₈ = +106.1; [α]_D²²₃₄₆ = +120.5; [α]_D²²₄₃₆ = +205.4; [α]_D²²₃₆₅ = +324.6 (*c* = 6.0, CHCl₃). [34]: *ent-9a* [α]_D²² = +100.4 (*c* = 1.71, MeOH). With reference to [34], the optical purity amounts to 91%.

1.1.4. (*IS*)-Cyclohex-3-eneacetonitril (**10**). An oven-dried, 500-ml, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel capped with a gas outlet, a thermometer, and gas inlet was purged with dry Ar, and charged at 0° (bath temp.) with anh. pyridin (210 ml) and freshly distilled MsCl (33.9 ml, 428 mmol). A soln. of **9a**/*ent-9a* ≫ 1 (32.7 g, 292 mmol; see *Exper. 1.1.3*) in anh. pyridin (110 ml) was added under stirring at such a rate that the temp. did not exceed 10°. The resulting orange suspension, after stirring for 2 h at 0°, was transferred to a 2-l separatory funnel halfly filled with ice-water (600 g). By careful addition of conc. aq. HCl, the soln. was acidified (pH ≈ 1–2) and extracted with Et₂O (3 × 300 ml). The combined extracts were washed first with sat. aq. NaHCO₃ soln., and then with H₂O, dried (MgSO₄), and evaporated to yield a clear oil (55 g), which was used without purification for the preparation of **10**/*ent-10* ≫ 1 (*vide infra*). From a similarly obtained batch the crude product was purified by a bulb-to-bulb distillation (130°/0.1 Torr) to afford (*S*)-cyclohex-3-en-1-yl methanesulfonate (**9b**/*ent-9b* ≫ 1), which showed the following properties: TLC (hexane/AcOEt 1:1): *R*_f 0.49. [α]_D²⁰₅₈₉ = –63.0; [α]_D²⁰₅₇₈ = –65.7; [α]_D²⁰₅₄₆ = –74.8; [α]_D²⁰₄₃₆ = –128.7; [α]_D²⁰₃₆₅ = –201.8° (*c* = 1.1, CH₂Cl₂). IR (film): 3026s (=C–H); 2920s, 2841s (–C–H); 1652m (C=C); 1355s, 1175s (S=O). ¹H-NMR: 1.33–1.42 (*m*, H–C(1)); 1.78–1.89 (*m*, 2 H–C(6)); 2.02–2.22 (*m*, 2 H–C(2), 2 H–C(5)); 3.01 (*s*, Me); 4.12 (*ψd*, *J*(H–C(7), H–C(1)) = 6.5, 2 H–C(7)); 5.62–5.74 (*m*, H–C(3), H–C(4)). Anal. calc. for C₈H₁₄O₃S (190.26): C 50.50, H 7.42; found: C 50.60, H 7.52.

NaCN (21.5 g; 438 mmol) was slowly dissolved, at ca. 80°, in anh. DMSO (320 ml) placed in a 1-l, three-necked, round-bottomed flask equipped with a magnetic stirring bar, a condenser fitted with a MgSO₄-filled drying tube, and a pressure-equalizing dropping funnel. A soln. of the crude material containing **9b**/*ent-9b* ≫ 1 (*vide supra*) in DMSO (160 ml) was slowly added. After the mixture had been heated at 110–120° for 90 min, it was poured into ice-water. The soln. was extracted with Et₂O (3 × 250 ml), and the combined extracts were washed with sat. aq. NaCl soln., dried (MgSO₄), and evaporated to yield a pale yellow oil (35.6 g), which was purified by bulb-to-bulb distillation (120°/10 Torr) to give **10**/*ent-10* ≫ 1 (33.1 g, 94%) with an unpleasant smell. TLC (hexane/AcOEt 1:1): *R*_f 0.58. [14]: [α]_D²⁰₅₈₉ = –92.9; [α]_D²⁰₅₇₈ = –97.0; [α]_D²⁰₅₄₆ = –110.8; [α]_D²⁰₄₃₆ = –191.3; [α]_D²⁰₃₆₅ = –301.1 (*c* = 1.0, CH₂Cl₂). IR (film): 3026s (=C–H); 2920s, 2840s (–C–H); 2246s, (C≡N); 1652m (C=C). ¹H-NMR: 1.37–1.52 (*m*, H–C(1')); 1.56–2.30 (*m*, 2 H–C(2'), 2 H–C(5'), 2 H–C(6')); 2.34 (*ψd*, *J*(H–C(2), H–C(1')) = 6.9, 2 H–C(2)); 5.60–5.73 (*m*, H–C(3'), H–C(4')).

(*IR*)-Cyclohex-3-eneacetonitril (*ent-10*). The mixture **10**/*ent-10* ≪ 1 (95%): [α]_D²⁰ = +92.3; [α]_D²⁰₅₇₈ = +96.5; [α]_D²⁰₃₄₆ = +110.2; [α]_D²⁰₃₃₆ = +190.3; [α]_D²⁰₃₆₅ = +300.0 (*c* = 1.1, CH₂Cl₂).

1.1.5. (*IS*)-Cyclohex-3-eneacetamide (**11**)²². A 1-l, four-necked, round-bottomed flask equipped with a gas inlet, a condenser capped with a gas outlet, a mechanical stirrer, and a thermometer was purged with dry Ar and charged with an aq. suspension of Cu (60 g; *Raney*-Cu, 50% aq. suspension; *Fluka*), degassed H₂O (325 ml), and a soln. of **7**/*ent-7* ≫ 1 (32.7 g, 270 mmol; *Exper. 1.1.4*) in anh. DMSO (130 ml). The stirred mixture was heated under Ar for 17 h at 95–105°. The catalyst was filtered off and washed with hot H₂O (2 × 80 ml). From the filtrate, first at r.t. and then at 4°, the product crystallized. The crystals were filtered off and washed with cyclohexane (160 ml). Mother liquor and cyclohexane phase were combined, sat. with NaCl, and extracted with CH₂Cl₂ (5 × 160 ml). The combined org. phases were dried (MgSO₄) and evaporated to give an oily residue, which was purified by bulb-to-bulb distillation (100°/15 Torr). The resulting solid material was crystallized from H₂O (50 ml), and the filtered crystals were washed with cyclohexane (30 ml). The combined crystal fractions (37.6 g) were freed from traces of solvent to give a solid, which was recrystallized from hot CCl₄ to furnish (**11**/*ent-11* ≫ 1) (33.2 g, 88%). M.p. 143–145° (H₂O). TLC (hexane/AcOEt 1:1): *R*_f 0.05; (CH₂Cl₂/acetone 1:1): *R*_f 0.45. [α]_D²⁰₅₈₉ = –74.9; [α]_D²⁰₅₇₈ = –78.4; [α]_D²⁰₅₄₆ = –89.3; [α]_D²⁰₄₃₆ = –153.0; [α]_D²⁰₃₆₅ = –239.1° (*c* = 1.0, CH₂Cl₂; with reference to *Exper. 2.1*, the optical purity amounted to 94%). IR (KBr): 3353s, 3178s (N–H); 3025m (=C–H); 2917m (–C–H); 1664s, 1628s (amide). ¹H-NMR: 1.22–1.40 (*m*, H–C(1')); 1.71–1.84 (*m*, 2 H–C(6')); 2.03–

²²) The Cu⁰-catalyzed hydration of **10** to **11** was performed, by and large, according to a general method [37].

2.23 (*m*, 2 H–C(2'), 2 H–C(5'), 2 H–C(2)); 5.30 (br. *s*, exchangeable on treatment with D₂O, NH₂); 5.63–5.68 (*m*, H–C(3'), H–C(4')). Anal. calc. for C₈H₁₃NO (139.20): C 69.03, H 9.41, N 10.06; found: C 68.88, H 9.34, N 10.02.

(*1R*)-Cyclohex-3-eneacetamide (*ent*-**11**; **11/ent-11** ≪ 1; 86%): M.p. 143° (H₂O). $[\alpha]_D^{20} = +76.1$; $[\alpha]_{578}^{20} = +79.6$; $[\alpha]_{346}^{20} = +90.6$; $[\alpha]_{436}^{20} = +155.3$; $[\alpha]_{365}^{20} = +242.8$ (*c* = 1.0, CH₂Cl₂). An authentic sample of *ent*-**11**, which had been obtained by a sequence of transformations (*Exper. 2.1.2*), preceded by a resolution of *rac*-**8a** (*Exper. 2.1.1*) [32], showed the following data for optical rotation: $[\alpha]_D^{20} = +80.0$; $[\alpha]_{578}^{20} = +83.2$; $[\alpha]_{346}^{20} = +94.6$; $[\alpha]_{436}^{20} = +162.6$; $[\alpha]_{365}^{20} = +254.0$ (*c* = 1.026 in CH₂Cl₂; with reference to the latter the optical purity amounted to 95%).

(*1R*)-Cyclohex-3-eneacetamide (*rac*-**11**)²³: M.p. 142–143° (acetone). TLC (CH₂Cl₂/acetone 2:5): *R*_f = 0.43. IR: (KBr) 3347*s* (NH), 3177*m* (NH), 3016*w* (=CH), 2905*w*, 2825*w* (–CH), 1664*s*, 1624*s* (C=O, amide). ¹H-NMR (CDCl₃): 1.28–1.40 (*m*, H–C(1')); 1.68–1.84 (*m*, 2 H–C(6')); 2.06–2.23 (*m*, 2 H–C(2'), 2 H–C(5')); 5.30–5.40 (br. *s*, 2 H, amide NH, D₂O); 5.60–5.70 (*ψdt*, H–C(3'), H–C(4')). Anal. calc. for C₈H₁₃NO (139.2): C 69.03, H 9.41, N 10.06; found: C 68.83, H 9.13, N 10.36.

1.1.6. (*1S,5S,8S*)-8-Iodo-2-azabicyclo[3.3.1]nonan-3-one (**12a**)²⁴. An oven-dried, 500-ml, three-necked, round-bottomed flask equipped with magnetic stirrer bar, septum, and a glass stopper was purged with dry Ar, and charged with **11/ent-11** ≫ 1 (18.4 g, 132 mmol; see *Exper. 1.1.5*) in dry pentane (140 ml) and anh. Et₃N (46.0 ml, 330 mmol; added *via* syringe). To the stirred soln. trimethylsilyl trifluoromethanesulfonate (59.6 ml, 330 mmol) was added *via* syringe. The rapidly stirred mixture was cooled (ice-bath), as soon as 1/5 of the reagent was added. After the addition, the mixture was stirred for 1 h at r.t. When the stirring was stopped, the glass stopper was substituted by a septum, and two layers formed were allowed to separate.

A second, dry, 500-ml, three-necked, round-bottomed flask was equipped with magnetic stirring bar, septum, glass stopper, and vacuum-pump connection. The top-pentane layer from the first flask, which contained the bis(trimethylsilyl) imidate, was carefully transferred to the second flask by cannula, maintaining the Ar atmosphere and leaving the oily trimethylammonium trifluoromethanesulfonate layer behind. This remaining salt was triturated with pentane/Et₂O 2:1 (50 ml) by stirring for 15 min, allowing the layers to separate, then transferring the extract to the second flask as before. The trituration was repeated with anh. Et₂O (50 ml), and the combined extracts in the second flask were concentrated with stirring. Excessive solvents and reagents were removed by thorough evaporation.

A third, dry, 1-l, three-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, and septum was purged with dry Ar and charged with I₂ (100.6 g; 396 mmol) in anh. Et₂O (250 ml). The mixture was stirred for 1 h. The concentrated org. extract in the second flask was now added to the I₂ soln. under effective stirring and cooling (ice-bath). Anh. Et₂O (130 ml) was used to transfer the rest in flask two to flask three. After the addition, funnel was substituted by a glass stopper, the mixture was stirred for another 3 h under Ar. Near the end of the procedure, part of the mixture solidified, and the solid residue was gently broken up using a spatula. The reaction is quenched by removing the addition funnel and stopper, and by slowly (vigorous gas evolution!) adding, alternatively, sat. aq. NaHCO₃ and Na₂SO₃ solns. The mixture separated into a faintly yellow org. layer, an intensive yellow aq. layer, and a white precipitate. It is extracted with CH₂Cl₂ (1 × 500 and 2 × 250 ml portions). The combined extracts were washed with sat. aq. Na₂SO₃ and NaHCO₃ solns. (100 ml each), dried (MgSO₄), and evaporated to yield **12a/ent-12a** ≫ 1 as a yellow solid (32 g). A sample, after semi-prep. HPLC (dioxane/AcOMe 10:4) gave a solid with $[\alpha]_{589}^{20} = -14.8$ (*c* = 1.0 in CH₂Cl₂); $[\alpha]_{578}^{20} = -15.8$; $[\alpha]_{346}^{20} = -19.6$; $[\alpha]_{436}^{20} = -50.8$; $[\alpha]_{365}^{20} = -118.8^\circ$. According to specific rotation of a recrystallized sample (from THF/cyclohexane), the optical purity amounted to 93%. According to HPLC (*Daicel OD-H* 250 × 4.6; hexane/*i*-PrOH 7:3; 1.5 ml/min; 228 nm) the ee amounted to 92%.

Recrystallization from THF (330 ml) and cyclohexane (165 ml) furnished colorless needles (*Fraction 1*: 17.8 g; 51%). Concentration of the mother liquor afforded another 3.19 g (*Fraction 2*: 9%) and 3.84 g (*Fraction 3*: 11%). *Fractions 2* and *3* were combined and recrystallized (80 ml of THF, 40 ml of cyclohexane) to furnish 4.38 g (*Fraction 4*: 13%). The ee of *Fractions 1* and *4* were determined by HPLC (*vide supra*) to be > 99%. M.p. 198–199°. TLC (CH₂Cl₂/acetone 1:1): *R*_f 0.47. $[\alpha]_{589}^{23} = -15.7$; $[\alpha]_{578}^{23} = -16.7$; $[\alpha]_{346}^{23} = -20.9$; $[\alpha]_{436}^{23} = -54.5$; $[\alpha]_{365}^{23} = -129.8$ (*c* = 1.0, CH₂Cl₂). IR (KBr): 3474*m*, 3185*s* (N–H); 2940*s*, 2929*s*, 2861*s* (–C–H); 1667*s*

²³) Prepared by following the route described in [38] *via rac*-**9a**, *rac*-**9b**, and *rac*-**10**. An authentic sample of *rac*-**11** was prepared according to [39].

²⁴) The iodolactamization of (**11/ent-11** ≫ 1) followed as close as possible the detailed procedure for the conversion of another γ,δ-unsaturated amide into the corresponding iodolactame [26].

(amide). $^1\text{H-NMR}$: 1.54–1.57 (*m*, H–C(7)); 1.77–1.90 (*m*, H–C(4), H–C(6)); 1.93–2.13 (*m*, H'–C(7), H–C(9)); 2.19–2.26 (*m*, H–C(5), H'–C(6)); 2.54–2.59 (*m*, H'–C(9)); 2.68 (*dd*, $J(\text{H'–C(4), H–C(4)}) = 18.6$, $J(\text{H'–C(4), H–C(5)}) = 7.2$, H'–C(4)); 3.73 (*s*, H–C(1)); 4.37 (*s*, H–C(8)); 7.03 (*br. s.*, exchangeable on treatment with D_2O , H–N(2)). The signals were assigned by a $^1\text{H}, ^1\text{H-COSY}$ spectrum. Cross signals between 1.54–1.57/1.77–1.90, 1.93–2.13, 2.19–2.26, 4.37; 1.77–1.90/1.93–2.13, 2.19–2.26, 2.54–2.59, 3.74, 4.37; 1.93–2.13/2.19–2.26, 2.68, 4.37; 2.19–2.26/2.54–2.59, 2.68; 2.54–2.59/3.74; 3.74/4.37, 7.03. $^{13}\text{C-NMR}$: 25.90 (C(6)); 25.93 (C(9)); 26.4 (C(4)); 27.5 (C(7)); 31.6 (C(8)); 37.5 (C(5)); 53.0 (C(1)); 173.7 (C(3)). The signals were assigned by a $^1\text{H}, ^{13}\text{C-COSY}$ spectrum. Cross signals between: 1.54–1.57/27.5; 1.77–2.26/ 25.90, 26.4; 1.93–2.13/ 25.93, 27.5; 2.68/26.4; 3.73/53.0; 4.37/31.6. Anal. calc. for $\text{C}_8\text{H}_{12}\text{INO}$ (265.09): C 36.25, H 4.56, N 5.28; found: C 36.31, H 4.59, N 5.24.

Crystal Structure Analysis of 12a (see Fig. 2). Suitable crystals (orthorhombic) were obtained from THF/cyclohexane at $+4^\circ$. Space group $P2_12_12_1$ (No. 19); cell: $a = 7.958(2)$ Å; $b = 9.998(2)$ Å; $c = 11.535(2)$ Å; $V = 917.8(5)$ Å³; $Z = 4$; $D_c = 1.918$ g · cm^{−3}. Octant up to $2\theta_{\text{max}} = 140^\circ$. 2598 reflections, 1655 independent reflections, 1648 reflections with $I > 1$ of a colorless, transparent crystal (size 0.05×0.52 mm). Number of variables: 101. The final difference density was less than $0.5 \text{ e} \cdot \text{Å}^{-3}$, in the vicinity of the I-atom $1.3 \text{ e} \cdot \text{Å}^{-3}$.

(*1R,5R,8R*)-8-Iodo-2-azabicyclo[3.3.1]nonan-3-one (*ent-12a*)²⁵. A 2-l, four-necked, round-bottomed flask equipped with a mechanical stirrer, a 500-ml pressure-equalizing dropping funnel, a thermometer, and a glass stopper was purged with dry Ar and charged with **11**/*ent-11* $\ll$ 1 (104.4 g, 0.75 mol; see *Exper. 1.1.5*) and a soln. of anhyd. Et_3N (265 ml, 1.9 mol) in pentane (800 ml). To the stirred soln., trimethylsilyl trifluoromethanesulfonate (500 ml, 1.83 mol) was added at such a rate (within 5 min), that the temp. – with the help of an ice-bath – was kept at $32\text{--}35^\circ$. After cooling to r.t., stirring was continued for 1 h and then stopped. The glass stopper was substituted by a septum. The mixture separated into two layers, and the top layer was transferred *via* a Teflon tube into a 2-l, three-necked, round-bottomed flask equipped with a magnetic stirring bar, reflux condenser, vacuum pump connection, and a septum. The bottom layer of the first flask was mixed with pentane (250 ml) under stirring, and the separated pentane layer was sucked into the second flask. The last procedure was repeated twice. The combined pentane solns. were evaporated at $40\text{--}60^\circ$ under reduced pressure (300–15 mbar), and the oily residue was stirred for 1 h under heating (bath temp. 60°) and reduced pressure (0.5 mbar). The concentrate was dissolved in dry Et_2O (750 ml), and the soln. was passed into a pressure-equalizing 1-l dropping funnel, which was put to a 6-l three-necked, round-bottomed flask, additionally equipped with a mechanical stirrer and a glass stopper, and charged with a soln. of I_2 (571.3 g; 2.25 mol) in Et_2O (1.4 l). The content of the dropping funnel, at 10° (cooling with an ice-bath), was passed into the stirred soln. in the flask as rapidly as possible (within 5–10 min), and the mixture was stirred for 1 h at r.t. The mixture was carefully (gas evolution!) treated successively with sat. aq. solns. of NaHCO_3 and Na_2SO_3 (5×300 ml each). Decolorization occurred, and a precipitation was formed, which was collected by suction filtration. The Et_2O soln. was concentrated, the resulting solid was combined with that obtained before and dissolved in CH_2Cl_2 . The soln. was washed successively with sat. aq. solns. of NaHCO_3 , Na_2SO_3 , and NaCl, and dried (MgSO_4). After evaporation, a solid material (180 g) remained, which was crystallized from MeCN to furnish 150.5 g (75.5%) of **12a**/*ent-12a* $\ll$ 1. M.p. $197\text{--}198^\circ$ (THF/cyclohexane). $[\alpha]_{\text{D}}^{20} = +14.9$ ($c = 1.145$ in CH_2Cl_2). According to specific rotation of a recrystallized sample (*vide infra*), the optical purity amounted to 94%. According to HPLC (*Dacel* OD-H 250×4.6 ; hexane/*i*-PrOH 7:3; 1.5 ml/min; 228 nm), ee amounted to 95%. After recrystallisation: *ent-12a*. $[\alpha]_{\text{D}}^{20} = +15.8$; $[\alpha]_{\text{D}}^{20} = +17.1$; $[\alpha]_{\text{D}}^{20} = +21.3$; $[\alpha]_{\text{D}}^{20} = +56.1$; $[\alpha]_{\text{D}}^{20} = +133.10$ ($c = 1.0$ in CH_2Cl_2). No **12a** was detectable by HPLC on chiral column.

(*1R,5RS,8RS*)-8-Iodo-2-azabicyclo[3.3.1]nonan-3-one (*rac-12*): M.p. $185^\circ\text{--}186^\circ$ (THF/hexane). TLC (CH_2Cl_2 /acetone 1:1): R_f 0.26. IR: (KBr) 3174m , 3056m (NH lactam), 2944m , 2913s , 2853m (CH), 1671s , 1651s (C=O), 1407s , 1182s , 1091s , 830m , 769m , 555m . $^1\text{H-NMR}$ (CDCl_3): 1.50–1.59 (*m*, H–C(6)); 1.78–1.92 (*m*, H'–C(9), H'–C(7)); 1.99–2.11 (*m*, H–C(7), H–C(6)); 2.20–2.24 (*m*, H'–C(4), H–C(5)); 2.55–2.58 (ψd , H–C(9)); 2.64–2.70 (*dd*, $J(\text{H–C(4), H–C(5)}) = 7$); 3.74 (*m*, H–C(1)); 4.37 (*m*, H–C(8)); 7.10–7.27 (*br.*, NH, exchangeable with D_2O). $^{13}\text{C-NMR}$ (CDCl_3): 25.99 (C(5)); 26.03 (C(7)); 26.48 (C(9)); 27.63 (C(6)); 31.69 (C(8)); 37.59 (C(4)); 53.07 (C(1)); 173.75 (C=O). Anal. calc. for $\text{C}_8\text{H}_{12}\text{INO}$ (265.09): C 36.25, H 4.56, N 5.28; found: C 36.16, H 4.53, N 5.43.

²⁵) Prepared by Dr. Dieter Reuschling of Aventis Research and Technology as part of a scale-up performance: solvents used here were used without further purification.

In the presence of triethylammonium trifluoromethanesulfonate the intermediately formed *N,O*-bis(tri-methylsilyl) derivative preceding iodolactamization was iodinated forming finally diiodo lactams of type **12b**.

(1*S*,4*R*,5*S*,8*S*)-4,8-Diiodo-2-azabicyclo[3.3.1]nonan-3-one (**12b**²⁶); see Scheme 1): M.p. 215–217° (THF/cyclohexane; dec.). TLC (CH₂Cl₂/acetone 1:1): *R*_f 0.74. [α]_D²⁰ = +7.7; [α]_D³⁰ = +7.8; [α]_D²⁴ = +8.1; [α]_D²⁰ = +3.8 (*c* = 1.0, CH₂Cl₂). IR (KBr): 3450*w*, 3180*m*, 3084*m* (NH); 2933*m*, 2848*w* (–C–H); 1674*s*, 1624*s* (C=O). ¹H-NMR: 1.76–2.12 (*m*, 4 aliph. H); 2.46–2.50 (*m*, 3 aliph. H); 3.84 (*ψs*, H–C(1)); 4.28–4.29 (*m*, H–C(8)); 4.61–4.62 (*m*, H–C(4)); 5.97 (br. *ψs*, exchangeable on treatment with D₂O, NH). Anal. calc. for C₈H₁₁I₂NO (390.98): C 24.58, H 2.84, N 3.58; found: C 24.70, H 2.82, N 3.54. IR and ¹H-NMR spectra of **12b/ent-12b** ≫ 1 identical with those of *rac*-**12b**.

(1*R*,5*R*,5*R*,8*R*)-4,8-Diiodo-2-azabicyclo[3.3.1]nonan-3-one (*rac*-**12b**): M.p. 204–206° (CHCl₃/hexane). TLC (hexane/AcOEt 1:2): *R*_f 0.5. IR (KBr): 3170*m*, 3061*m* (NH lactam), 2933*m*, 2911*m*, 2883*w* (–C–H), 1646*s* (C=O), 1475*m*, 1411*m*, 1331*m*, 1198*m*, 1173*m*, 1091*s*, 970*s*, 829*s*, 774*s*. ¹H-NMR: 1.76–1.84 (*m*, H–C(7), H–C(6)); 1.92–2.17 (*ψqt*, H–C(7'), H–C(6')); 2.44–2.53 (*m*, H–C(9), H–C(5)); 3.80–3.85 (*m*, H–C(1)), 4.25–4.3 (*m*, H–C(8)); 4.60 (*ψd*, H–C(4)); 6.60–6.65 (br., HN, exchangeable on treatment with D₂O). ¹³C-NMR: 22.65 (C(9)); 25.23 (C(4)); 25.28 (C(7)); 27.34 (C(6)); 30.53 (C(8)); 38.98 (C(5)); 53.43 (C(1)); 172.10 (C=O). Anal. calc. for: C₈H₁₁I₂NO: C 24.58, H 2.84, N 3.58; found: C 24.75, H 2.98, N 3.49.

Crystal-Structure Analysis of rac-12b (see Fig. 6)²⁷. Suitable crystals (triclinic) were obtained from CHCl₃/hexane at r.t.; space group *P*₁ (No. 2); cell: *a* = 6.548(2) Å; *b* = 8.702(3) Å; *c* = 9.653(1) Å; α = 92.55(2)°; β = 102.18(1)°; γ = 96.61(3)°; *V* = 532.7(5) Å³; *Z* = 2; *D*_c = 2.437 g · cm^{–3}. Sphere up to $\Theta_{\max}$ = 120°. 2847 reflections, 1577 independent reflections, 1571 reflections with *I* > 0 of a colorless, transparent crystal (size 0.17 × 0.20 × 0.30 mm). Number of variables 109. *R*(*F*) = 0.086; *wR*(*F*) = 0.115.

The heterocyclic ring has a conformation between a chair and a half chair. The lactam group is slightly non-planar with a torsion angle C(3)–N–C(1)–C(2) of 13(2)°. The carbocyclic ring has an almost regular chair conformation. Both I-atoms are in an axial or pseudo-axial orientation (Fig. 6, *a*). The crystal structure contains centrosymmetric pairs of molecules connected by H-bonds between the two lactam groups (Fig. 6, *b* and *c*). The dimensions of the H-bonds are: N–H...O (symmetry code: 1 – *x*; – *y*; 1 – *z*), N–H: 1.00 Å, H...O: 1.91 Å, N...O: 2.91(1) Å and angle N–H–O: 177°. A number of intermolecular distances approach the *van der Waals* contact distances: I(1)...I(2): 4.170(1) Å (*x*, *y*, *z* – 1), I(1)...O: 3.40(1) Å (*x*, *y*, *z* – 1), I(2)...O: 3.38(1) Å (*x* – 1, *y*, *z*), I(1)...H_b–C(7): 3.23 Å (1 – *x*, 1 – *y*, – *z*) and I(2)...H_a–C(7): 3.23 Å (*x* – 1, *y*, *z*).

1.2. *Separate Routes to Individual Monomers*. 1.2.1. *Thymine Monomer Building Blocks of Type 17* (Scheme 3). 1.2.1.1. 3-*f*-(Benzyloxy)methyl]-5-methyl-1-*[(1S,5S,8S)-3-oxo-2-azabicyclo[3.3.1]nonan-8-yl]pyrimidine-2,4(1H,3H)-dione* (**16b**). NaH (148 mg of a 65% dispersion in mineral oil; 4.0 mmol) was placed in a dry, 50-ml Löwenthal flask and washed free of mineral oil with three portions of pentane. Remaining pentane was evaporated, and the flask was purged with dry N₂ prior to adding anh. DMF (20 ml) and 3-(benzyloxymethyl)thymine [26] (493 mg, 2.0 mmol; in several portions). After the evolution of H₂, ceased, **12a** (Exper. 1.1.6; 530 mg; 2.0 mmol; in several portions) was added. The mixture was stirred for 20 min and left overnight at r.t. NH₄Cl (1 ml of a sat. aq. soln.) was added. The resulting soln. was concentrated under reduced pressure first with a rotary evaporator and then by bulb-to-bulb distillation (70°/0.5 Torr) to yield an orange oil (1.71 g). FC (150 g of silica gel; CH₂Cl₂/MeOH 30:1 → 15:1) furnished a solid residue, which was digested with Et₂O, filtered, and ground. Traces of solvent were removed under reduced pressure to leave a colorless powder (405 mg, 53%). A sample was crystallized to show the following properties: m.p. 160–162° (THF/cyclohexane)²⁸. TLC (CH₂Cl₂/MeOH 15:1): *R*_f 0.41. [α]_D²³ = –43.3 (*c* = 1.10, CH₂Cl₂). UV (MeCN): $\lambda_{\max}$ 274.2 (9623). IR (KBr): 3447*w*, 3189*w*, 3090*w*, 2949*m*, 2906*m*, 1703*s*, 1652*s*, 1464*s*, 1405*s*, 1357*s*, 1270*s*, 1076*s*. ¹H-NMR: 1.59 (*m*_c, H–C(4'), 2 H–C(9')); 1.85 (*m*_c, H–C(3')); 1.88 (*s*, Me); 2.00–2.14 (*m*, H'–C(3'), H'–C(4'), H–C(6')); 2.20 (br. *s*, H–C(5')); 2.47 (*dd*, *J*(H'–C(6'), H–C(6')) = 18.5, *J*(H'–C(6'), H–C(5')) = 7.5, H'–C(6')); 3.58 (br. *m*, H–C(1')); 4.22 (br. *m*, H–C(2')); 4.60 (*s*, PhCH₂O); 5.35 (*m*_c, 2 H, OCH₂N); 7.22–7.35 (*m*, 5 arom. H); 7.54 (*s* with f.s., H–C(6)); 7.99 (*d*, *J*(H–N(8'), H–C(1')) = 4.6, H–N(8')). The signals were assigned by a ¹H, ¹H-COSY spectrum. ¹³C-NMR: 12.75 (Me); 17.90 (C(3')); 23.82 (C(9')); 24.66 (C(5')); 27.47 (C(4')); 37.15 (C(6')); 47.27 (C(1')); 55.55 (C(2')); 70.45 (OCH₂N); 71.06 (PhCH₂O); 107.82 (C(5)); 127.06,

²⁶) The X-ray crystal-structure determination of *rac*-**12b** (*vide infra*) revealed pseudo-axial orientation of the I-atom at C(4). Identity of IR and ¹H-NMR spectra of **12b** with those of *rac*-**12b** then indicated (4*R*) configuration of **12b**.

²⁷) For the numbering of atoms, see Fig. 6, *a*.

²⁸) M.p. of *rac*-**16b**: 186–188° (THF/cyclohexane).

127.29, 128.03 (5 arom. C); 137.40 (C(6)); 138.18 (C_{ipso}); 151.04 (C(2)); 162.67 (C(4)); 170.83 (C(7)). The signals were assigned by a ^1H , ^{13}C -COSY spectrum. ESI-MS: 767.8 ($[2M+H]^+$), 384.5 ($[M+H]^+$). Anal. calc. for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4$ (383.45): C 65.78, H 6.57, N 10.96; found: C 65.68, H 6.64, N 10.84.

1.2.1.2. 3-[(*Benzoyloxy*)methyl]-2-[[*(tert-butoxy)carbonyl*]amino]-5-methyl-1-[(1*S*,5*S*,8*S*)-3-oxo-2-azabicyclo[3.3.1]nonan-8-yl]pyrimidine-2,4(1*H*,3*H*)-dione (**16c**). A dry, 500-ml, three-necked, round-bottomed flask equipped with a magnetic stirring bar, glass stopper, and pressure-equalizing dropping funnel was charged with a soln. of **16b** (Exper. 1.2.1.2; 8.75 g, 22.8 mmol) in anhyd. THF (100 ml). Successively, anhyd. Et_3N (6.3 ml, 45.6 mmol) and $(\text{Boc})_2\text{O}$ (15.0 g, 68.4 mmol) were added to the stirred soln. Subsequently, DMAP (5.6 g; 45.6 mmol) was added in several portions, and the yellow soln. was stirred for 3 h at r.t. Solvents and excessive reagents were removed by evaporation under reduced pressure to give a sticky residue, which was dissolved in CH_2Cl_2 (100 ml) and successively washed with 1*N* aq. HCl and sat. aq. NaHCO_3 soln. The org. phase was dried (MgSO_4) and evaporated under reduced pressure to give a brown oil (15.6 g)²⁹, which was chromatographed (275 g of silica gel; AcOEt/heptane 2:1) to afford a pale yellow solid (10.4 g), which, after crystallization from THF (50 ml)/cyclohexane (100 ml) furnished colorless crystals (9.52 g, 86%) of **16c**. M.p. 124–126° (THF/cyclohexane)³⁰. TLC (AcOEt/heptane 2:1): R_f : 0.13. $[\alpha]_{\text{D}}^{25} = -10.3$ ($c = 1.37$, CH_2Cl_2). UV (MeCN): λ_{max} 273.6 (10200). IR (KBr): 3447w, 2934w, 1744s, 1701m, 1663s, 1448m, 1363m, 1260s, 1153m, 1078m. ^1H -NMR: 1.49 (s, *t*-Bu); 1.52–1.63, 1.74–2.13 (2*m*, 2 H–C(3'), 2 H–C(4'), 2 H–C(9')); 1.88 (s, Me–C(5)); 2.33 (br. s, H–C(5')); 2.38 (*d*, $J(\text{H}–\text{C}(6'), \text{H}'–\text{C}(6')) = 18.2$, H–C(6')); 2.70 (*dd*, $J(\text{H}'–\text{C}(6'), \text{H}–\text{C}(6')) = 18.2$, $J(\text{H}'–\text{C}(6'), \text{H}–\text{C}(5')) = 6.7$, H'–C(6')); 4.27 (*m*, H–C(1')); 4.40 (*m*, H–C(2')); 4.65 (s, PhCH_2O); 5.45 (*m*, OCH_2N); 7.14–7.32 (*m*, H–C(6), 5 arom. H). The signals were assigned by a ^1H , ^1H -COSY spectrum. ^{13}C -NMR: 13.39 (Me–C(5)); 19.63 (C(3')); 24.90 (C(9')); 25.37 (C(5')); 27.39 (C(4')); 27.84 (Me_3C); 41.03 (C(6')); 53.36 (C(1')); 57.71 (C(2')); 70.80 (OCH_2N); 72.25 (PhCH_2O); 89.97 (Me_3C); 109.73 (C(5)); 127.55, 128.20 (5 arom. C); 137.17 (C(6)); 138.16 (C_{ipso}); 151.19, 152.15 (COON , C(2)); 163.30 (C(4)); 170.45 (C(7')). The signals were assigned by a ^1H , ^{13}C -COSY spectrum. ESI-MS: 501.7 ($[M+H]^+$), 384.5 ($[M+H–\text{Boc}]^+$). Anal. calc. for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_6$ (483.56): C 64.58, H 6.88, N 8.69; found: C 64.45, H 6.91, N 8.59.

1.2.1.3. (1*S*,3*S*,4*S*)-4-{3-[(*Benzoyloxy*)methyl]-1,2,3,4-tetrahydro-5-methyl-2,4-dioxypyrimidin-1-yl}-3-[[*(tert-butoxy)carbonyl*]amino]cyclohexane)acetic Acid (**17a**). A 500-ml, round-bottomed flask was charged with a soln. of **16c** (Exper. 1.2.1.3; 7.81 g, 16.2 mmol) in THF (225 ml) and H_2O (50 ml). To the cooled (ice-bath) soln.,

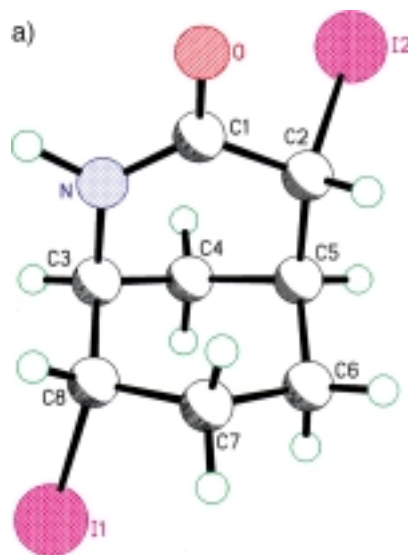


Fig. 6. Representation of the crystal structure of rac-**12b** (Exper. 1.1.6). a) Molecular structure; b) H-bonded pairs; c) crystal packing viewed down a.

²⁹) The oil without purification may be directly submitted to ring opening (see Exper. 1.2.1.3).

³⁰) M.p. of rac-**16c**: 125–127° (THF/cyclohexane).

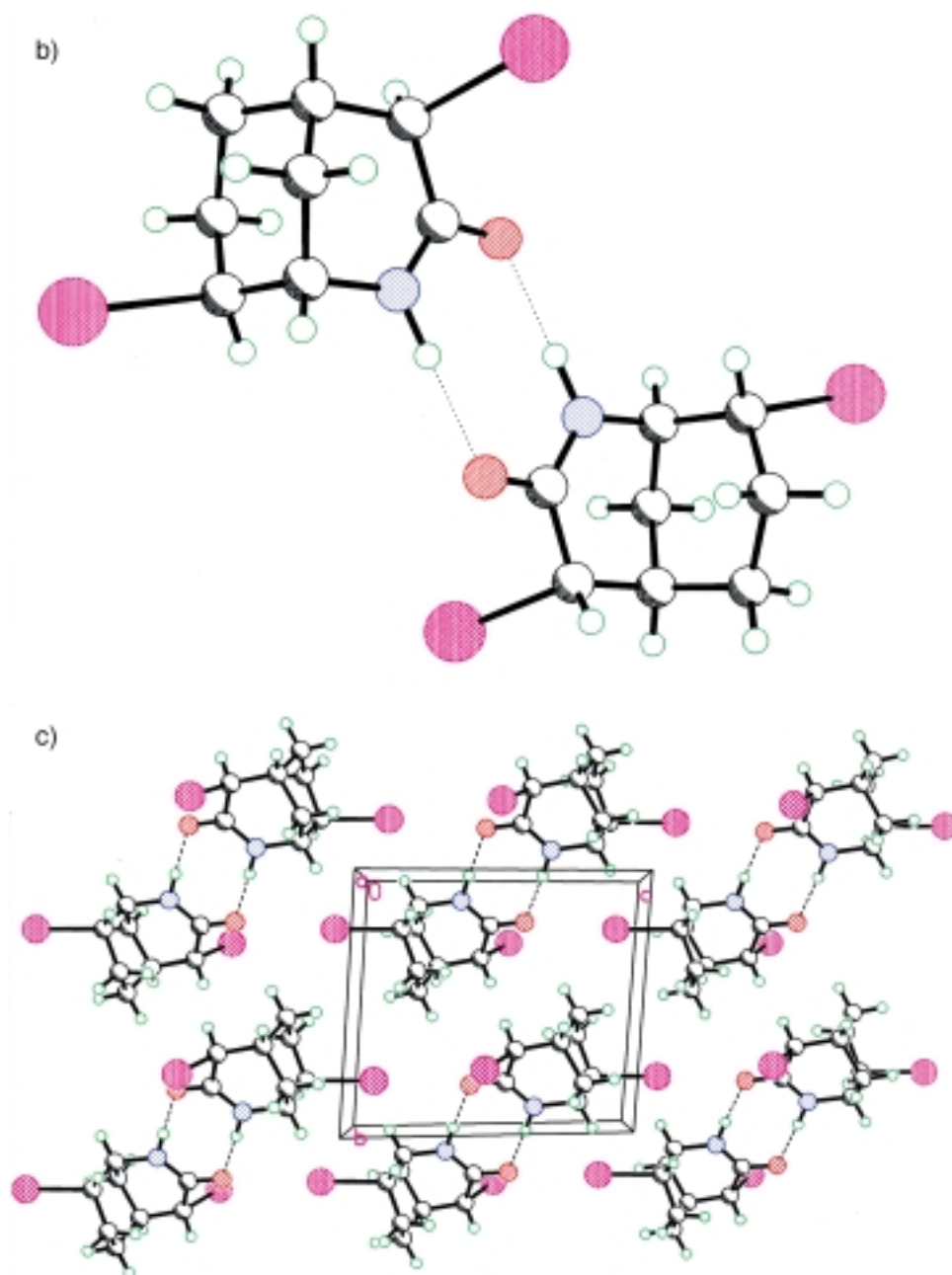


Fig. 6 (cont.)

H_2O_2 (7.33 g of a 30% aq. soln.; 64.8 mmol) and LiOH (1.36 g of $\text{LiOH} \cdot \text{H}_2\text{O}$ in 25 ml of H_2O ; 32.3 mmol) were added successively. The opaque soln. was allowed to warm to r.t. and stirred for 45 min. Na_2SO_3 (25 ml of a 1.5M aq. soln.) and NaHCO_3 (75 ml of a sat. aq. soln.) were added, and the soln. was concentrated under reduced

pressure (up to 50°/75 Torr). The concentrate was diluted with H₂O (350 ml) and made alkaline (pH > 12) with aq. 2N NaOH. The milky suspension was extracted with CH₂Cl₂ (3 × 350 ml), the extracts were combined, dried (MgSO₄), and evaporated under reduced pressure to yield crude **16b**, which was purified by crystallization (THF/cyclohexane 1:2) to give 1.55 g of **16b**. The aq.-alkaline phase was acidified (pH 1–2) using half-conc. HCl, extracted with AcOEt (3 × 350 ml), dried (Na₂SO₄), and evaporated under reduced pressure to give **17a** (5.09 g, 63%) as a fine-crystalline solid. M.p. 89–91° (after washing with Et₂O)³¹. TLC (CH₂Cl₂/MeOH 15:1): R_f 0.37. $[\alpha]_{D}^{25} = -24.0$ (*c* = 0.99, MeOH). UV (MeCN): $\lambda_{\max}$ 273.2 (10890). IR (KBr): 3373*m*, 2974*m*, 2932*m*, 1706*s*, 1691*s*, 1664*s*, 1647*s*, 1534*m*, 1469*m*, 1452*m*, 1365*m*, 1290*m*, 1255*m*, 1175*m*. ¹H-NMR: 0.88–1.30 (*m*, H–C(4), H–C(6)); 1.19 (*s*, *t*-Bu); 1.66–2.00 (*m*, 2 H–C(3), H'–C(4), H–C(5), H'–C(6)); 1.80 (*s*, Me–C(5')); 2.16 (*m_c*, CH₂CO₂H); 3.79 (*m_c*, H–C(1)); 4.27 (*m_c*, H–C(2)); 4.58 (*s*, PhCH₂O); 5.34 (*s*, OCH₂N); 6.86 (*d*, J(NH, H–C(1)) = 9.6, NH); 7.23–7.37 (*m*, 5 arom. H); 7.68 (*br. s*, H–C(6')); 12.09 (*br. s*, CH₂CO₂H). The signals were assigned by a ¹H,¹H-COSY spectrum. ¹³C-NMR: 13.09 (Me–C(5')); 28.11 (Me₃C); 30.13 (C(3)); 31.07 (C(4)); 33.38 (C(5)); 39.23 (C(6)); 40.18 (CH₂CO₂H); 51.38 (C(1)); 58.19 (C(2)); 70.83 (OCH₂N); 72.17 (PhCH₂O); 80.05 (Me₃C); 110.06 (C(5')); 127.62, 127.69, 128.27 (5 arom. C); 135.46 (C(6')); 138.00 (*C_{ipso}*); 152.72, 155.43 (COON, C(2')); 163.20 (C(4')); 176.30 (CH₂CO₂H). The signals were assigned by a ¹H,¹³C-COSY spectrum. ESI-MS: 519.7 ([*M* + H + H₂O]⁺). Anal. calc. for C₂₆H₃₅N₃O₇ (501.58): C 62.26, H 7.03, N 8.38; found: C 62.00, H 6.96, N 8.17.

1.2.1.4. (1*S*,2*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-4-[1,2,3,4-tetrahydro-5-methyl-2,4-dioxypyrimidin-1-yl]cyclohexanecetic Acid (**17b**). A soln. of **17a** (Exper. 1.2.1.4; 2.01 g, 4.0 mmol) in THF (90 ml) was hydrogenated using Pd/C (300 mg; 10%). The catalyst was removed by filtration of the mixture through *Celite*, and the solvent was evaporated to yield a colorless foam (1.96 g), which was dissolved in a soln. of MeONa (454 mg, 8.40 mmol) in anh. MeOH (90 ml). The mixture was kept overnight excluding air moisture. NH₄Cl (6 ml of a sat. aq. soln.) was added, and the soln. was concentrated under reduced pressure. The concentrate was poured into H₂O (50 ml), and the resulting soln. was acidified (pH 1–2) with 2N aq. HCl and extracted with AcOEt (4 × 50 ml). The combined extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residual foam was digested with Et₂O (20 ml), filtered, and dried (*in vacuo*) to give **17b** (1.43 g, 94%) as a colorless solid. An anal. sample, after recrystallization, showed the following properties: m.p. 235–237° (MeOH/H₂O; dec.)³². TLC (CH₂Cl₂/MeOH 5:1): R_f 0.38. $[\alpha]_{D}^{25} = -21.9$ (*c* = 0.57, MeOH). UV (H₂O): $\lambda_{\max}$ 272.4 (11450). IR (KBr): 3374*s*, 3187*w*, 2978*w*, 2935*w*, 1702*s*, 1648*s*, 1522*s*, 1394*w*, 1366*w*, 1282*s*, 1254*m*, 1170*m*. ¹H-NMR: 0.85–1.38 (*m*, H–C(4), H–C(6)); 1.27 (*s*, *t*-Bu); 1.62–2.00 (*m*, 2 H–C(3), H'–C(4), H–C(5), H'–C(6)); 1.73 (*s*, Me–C(5')); 2.15 (*m_c*, CH₂CO₂H); 3.75 (*m_c*, H–C(1)); 4.19 (*m_c*, H–C(2)); 6.77 (*d*, J(NH, H–C(1)) = 9.6, NH); 7.56 (*s*, H–C(6')); 11.09 (*s*, H–N(3')); 12.08 (*br. s*, CH₂CO₂H). Low-intensity signals in the region of 6.00–10.0 disappear on heating up to 80°. The signals were assigned by a ¹H,¹H-COSY spectrum. ¹³C-NMR (75.5 MHz, (D₆)DMSO): 12.03 (Me–C(5')); 27.90 (Me₃C); 29.16 (C(3)); 30.72 (C(4)); 32.72 (C(5)); 38.06 (C(6)); 40.30 (CH₂CO₂H); 49.71 (C(1)); 57.05 (C(2)); 77.51 (Me₃C); 107.65 (C(5')); 138.32 (C(6')); 151.28, 154.79 (COON, C(2')); 163.60 (C(4')); 173.35 (CH₂CO₂H). The signals were assigned by a ¹H,¹³C-COSY spectrum. ESI-MS: 382.3 ([*M* + H]⁺). Anal. calc. for C₁₈H₂₇N₃O₆ (381.43): C 56.68, H 7.13, N 11.02; found: C 56.45, H 7.16, N 10.80.

1.2.1.5. (1*S*,3*S*,4*S*)-3-Amino-4-(1,2,3,4-tetrahydro-5-methylpyrimidin-1-yl)cyclohexanecetic Acid (**17c**). A 50-ml, round-bottomed flask was charged with **17b** (Exper. 1.2.1.5; 1.42 g, 3.72 mmol) and 2N aq. HCl (25 ml). The suspension was slowly heated to 95°, when a clear soln. arose. This temp. was kept for 45 min. Then, TLC control (CH₂Cl₂/MeOH 5:1) showed no educt left behind. Solvent was removed under reduced pressure, the residue was suspended in AcOEt (20 ml), filtered, and dried (*h.v.*) to give the hydrochloride of **17c** (1.08 g). A soln. of the hydrochloride in 1N aq. NaOH (6.9 ml) was passed through a column of ion exchange resin (35 g of *Amberlite IR-120*; washed with 2N aq. HCl and then washed free from chlorides with H₂O; a test portion of the effluent should be neutral). The amino acid was eluted with 1N aq. ammonia soln. The collected soln. was concentrated under reduced pressure to yield **17c** (737 mg, 70%) as a colorless solid. Instead of showing a sharp melting interval, it sintered above 200° and decomposed above 250°. An anal. sample was crystallized from H₂O³³. TLC (i-PrOH/H₂O/NH₃ 14:2:1): R_f 0.29. $[\alpha]_{D}^{25} = -143$ (*c* = 0.61, H₂O). UV (H₂O): $\lambda_{\max}$ 269.0 (8750). IR (KBr): 3369*s*, 2973*m*, 2934*m*, 1691*s*, 1665*s*, 1648*s*, 1539*s*, 1470*m*, 1452*s*, 1176*m*. ¹H-NMR: 1.26 (*m_c*, H–C(4)); 1.41 (*m_c*, H–C(6)); 1.80–2.07 (*m*, 2 H–C(3), H'–C(4), H–C(5)); 1.91 (*s*, Me); 2.09–2.31 (*m*, CH₂CO₂; H'–C(6)); 3.65 (*br. s*, H–C(1)); 4.62 (*br. s*, H–C(2)); 7.62 (*s*, H–C(6')). The signals were assigned by a ¹H,¹H-

³¹) M.p. of *rac*-**17a**: 168–170° (THF/cyclohexane).

³²) M.p. of *rac*-**17b**: 231–233° (MeOH/H₂O; dec.).

³³) M.p. of *rac*-**17c**: 172–174° (H₂O; dec.).

COSY spectrum. ^{13}C -NMR: 14.35 (Me); 31.93 (C(3)); 33.17 (C(4)); 35.99 (C(5)); 38.47 (C(6)); 46.77 (CH_2CO_2); 54.45 (C(1)); 58.43 (C(2)); 115.04 (C(5')); 140.67 (C(6')); 155.53 (C(2')); 169.12 (C(4')); 184.25 (CH_2CO_2). The signals were assigned by a ^1H , ^{13}C -COSY spectrum. ESI-MS: 282.2 ($[\text{M} + \text{H}]^+$). Anal. calc. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_4 \cdot 2\text{H}_2\text{O}$ (317.34): C 49.20, H 7.30, N 13.24; found: C 48.96, H 7.32, N 13.15.

Crystal-Structure Analysis of rac-17c (see Fig. 5). Suitable crystals (monoclinic) are obtained from H_2O . Space group $P2_1/c$ (No. 14). Cell: $a = 7.845(1) \text{ \AA}$; $b = 12.809(3) \text{ \AA}$; $c = 14.987(2) \text{ \AA}$; $\beta = 97.97(1)^\circ$; $V = 1491.5(4) \text{ \AA}^3$. $Z = 4$; $D_c = 1.413 \text{ g} \cdot \text{cm}^{-3}$. Sphere up to $2\theta_{\text{max}} = 57^\circ$; 22063 reflections, 3526 independent reflections, 3409 reflections with $I > 0$ of a colorless, transparent crystal (size: $0.14 \times 0.18 \times 0.20 \text{ mm}^3$). Number of variables: 292. $R_F = 0.106$; $wR(F) = 0.059$; $S = 1.00$.

1.2.2. *Adenine Monomer Building Blocks of Type 19* (Scheme 4). 1.2.2.1. *(1S,5S,8S)-8-(6-Benzamido-9H-purin-9-yl)-2-azabicyclo[3.3.1]nonan-3-one (18a)*. A 500-ml, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, an Ar inlet adapter, and an oil bubbler was purged with Ar and charged with dry DMF (180 ml) and NaH (2.25 g of a 64% suspension in mineral oil; 60 mmol). 6-*N*-benzoyladenine [27] (7.18 g, 30 mmol) was added portionwise, and the mixture was stirred, until gas evolution ceased. After 15 min, **12a** (7.95 g, 30 mmol) was added, and the soln. was stirred in the dark for 22 h. The soln., cooled down 0° and neutralized by addition of aq. HCl (24 ml of a 1M soln.), was evaporated under reduced pressure ($60^\circ/0.3 \text{ Torr}$). The resulting residue was dissolved in MeOH (100 ml) and preabsorbed onto silica gel (15 g). FC on silica gel ($7 \times 15 \text{ cm}$ filling; $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 12:1) yielded a yellow oil (17 g), which was crystallized from MeOH (15 ml) to give **18a** (8.2 g, 73%) as a colorless solid, pure enough for further reaction. For anal. purposes, a small sample was recrystallized from MeOH/Et₂O. M.p. $269-271^\circ$ (dec.³⁴). TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): R_f 0.28. $[\alpha]_D^{20} = +35.9$ (c 1.03, MeOH). UV (MeOH): λ_{max} 280 (20330). IR: 3500–3000s, 2938m, 1685m, 1654s, 1610s, 1542w, 1508w, 1490m, 1458s, 1400m, 1341m, 1286s, 1254s, 1168w, 1098m, 799w, 713m, 643w. ^1H -NMR (d_6 -DMSO): 1.53–1.72 (*m*, 3 H); 2.08–2.32 (*m*, 5 H); 2.48–2.58 (*m*, 1 H); 4.27 (br. *m*, H–C(1')); 4.63 (br. *m*, H–C(2')); 7.52–7.58 (*m*, 2 arom. H); 7.62–7.68 (*m*, 1 arom. H); 8.04–8.08 (*m*, 2 arom. H); 8.14 (*d*, $J(\text{H}–\text{N}(8'), \text{H}(\text{C}(1')) = 4.3$, H–N(8')); 8.70, 8.75 (2s, H–C(2); H–C(8)); 11.18 (*s*, H–NC(6)). ^{13}C -NMR ((D_6) -DMSO): 18.89, 24.21, 27.27 (C(3'), C(4'), C(9')); 25.15 (C(5')); 36.95 (C(6')); 47.44 (C(1')); 54.21 (C(2')); 125.32 (C(5)); 128.34, 132.28, 133.34 (Ph); 143.05 (C(8)); 150.17 (C(4)); 151.12 (C(2)); 152.59 (C(6)); 165.49 (Bz C=O); 171.39 (lactam C=O). ESI-MS: 377 (100, $[\text{M} + \text{H}]^+$). Anal. calc. for $\text{C}_{20}\text{H}_{20}\text{N}_6\text{O}_2$: C 63.83, H 5.32, N 22.34; found: C 63.90, H 5.45, N 22.14.

1.2.2.2. *(1S,5S,8S)-8-(6-Amino-9H-purin-9-yl)-2-azabicyclo[3.3.1]nonan-3-one (18b = 15; Schemes 4 and 2)*. A 500-ml, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser fitted with a CaCl_2 -filled drying tube was charged with **18a** (8.2 g; 22 mmol) and dry MeOH (250 ml). The suspension was heated until **18a** was completely dissolved, and a soln. of NaOMe (1.62 g) in MeOH (5.5 ml) was added, and the mixture was stirred for 19 h at r.t. The resulting suspension was filtered, and the precipitate was washed with Et₂O. The filtrate was neutralized by adding ion-exchange resin (*Amberlite IR-120*, H^+ form; activated with 1M HCl, washed with H_2O until the filtrate became neutral). The resin was filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (4 ml), precipitated by adding Et₂O (30 ml), and the precipitate was filtered off. The combined precipitates were dried *in vacuo* to give **18b** (5.8 g, 97%), which was pure enough for further reactions. An anal. sample is recrystallized from MeOH/ H_2O . M.p. $300-302^\circ$ (dec.). TLC (MeOH): R_f 0.35. $[\alpha]_D^{20} = +42.8$ ($c = 0.40$, MeOH). UV (MeOH): λ_{max} 260 (16375). IR: 3367s, 3179s, 3101m, 2926m, 2864w, 1651s, 1600s, 1563m, 1470m, 1337m, 1296m, 1258m, 1229m, 1166w, 1107w, 1005w, 802w, 724w, 668w. ^1H -NMR ((D_6) -DMSO): 1.48–1.67 (*m*, 3 H); 2.04–2.24 (*m*, 5 H); 2.46–2.54 (*m*, 1 H); 4.20 (br. *m*, H–C(1')); 4.46 (br. *m*, H–C(2')); 7.26 (*s*, NH_2); 8.06 (*d*, $J(\text{H}–\text{N}(8'), \text{H}–\text{C}(1')) = 4.3$, H–N(8')); 8.14, 8.35 (2s, H–C(2), H–C(8)). ^{13}C -NMR ((D_6) -DMSO): 18.94, 24.15, 27.36 (C(3'), C(4'), C(9')); 25.20 (C(5')); 37.03 (C(6')); 47.47 (C(1')); 53.85 (C(2')); 118.75 (C(5)); 139.18 (C(8)); 149.70 (C(4)); 152.15 (C(2)); 156.03 (C(6)); 178.91 (lactam C=O). ESI-MS: 273 (100, $[\text{M} + \text{H}]^+$). Anal. calc. for $\text{C}_{13}\text{H}_{16}\text{N}_6\text{O} \cdot \text{H}_2\text{O}$: C 53.78, H 6.25, N 28.95; found: C 53.65, H 6.24, N 29.12.

Crystal Structure Analysis of rac-15 (see Fig. 4). Suitable crystals (monoclinic) were obtained from MeOH/ H_2O . Space group $P2_1/n$ (No. 14); cell: $a = 9.5482(8) \text{ \AA}$; $b = 7.2199(6) \text{ \AA}$; $c = 19.763(1) \text{ \AA}$; $\beta = 93.30(1)^\circ$; $V = 1360.1(3) \text{ \AA}^3$; $Z = 4$; $D_c = 1.418 \text{ g} \cdot \text{cm}^{-3}$. Hemisphere up to $2\theta_{\text{max}} = 130^\circ$. 4521 reflections, 2316 independent reflections, 2286 reflections with $I > 0$. Number of variables: 263. $R(F) = 0.036$, $\omega R(F) = 0.052$.

1.2.2.3. *(1S,5S,8S)-8-(6-[[Dimethylamino]methylidene]amino]-9H-purin-9-yl)-2-azabicyclo[3.3.1]nonan-3-one (18c)*. A 500-ml, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser fitted

³⁴) M.p. of *rac*-**18a**: $280-283^\circ$ (dec.).

with a CaCl₂-filled drying tube was charged with **18b** (5.58 g, 20 mmol), dry DMF (200 ml), and dimethylformamid diethylacetale (17.1 ml, 100 mmol; *Fluka*). The mixture was kept for 3 h at 80°. The resulting clear soln. was concentrated under reduced pressure (60°/0.4 Torr) to give crude **18c** (6.9 g)³⁵, which was used without further purification. TLC (Al₂O₃; CH₂Cl₂/MeOH 20:1): *R*_f 0.75. ¹H-NMR: 1.58–1.79 (*m*, 2 H); 1.89–1.93 (*m*, 1 H); 2.16–2.28 (*m*, 2 H); 2.38–2.51 (*m*, 3 H); 2.69–2.78 (*m*, 1 H); 3.23, 3.28 (2*s*, 2 Me); 4.38 (br. *m*, H–C(1′)); 4.68 (br. *m*, H–C(2′)); 6.62 (*d*, *J*(H–N(8′), H(C(1′))) = 4.3, H–N(8′)); 8.13, 8.54 (2*s*, H–C(2)); 8.97 (*s*, 1 H, formamidine H). ESI-MS: 328 (100, [*M* + H]⁺).

1.2.2.4. (1*S*,5*S*,8*S*)-2-[*(tert*-Butoxy)carbonyl]-8-[6-[(*dimethylamino*)methyliden]amino]-9H-purin-9-yl]-2-azabicyclo[3.3.1]nonan-3-one (**18d**). A 250-ml, round-bottomed flask, equipped with a magnetic stirring bar and a CaCl₂-filled drying tube was charged with crude **18c** ((6.9 g; 20 mmol) and dry CH₂Cl₂ (100 ml). Under stirring, Et₃N (2.8 ml, 20 mmol) was added, followed by (Boc)₂O (8.7 g; 40 mmol) and DMAP (2.44 g, 20 mmol). The soln. was stirred for 16 h at r.t., when TLC (silica gel; CH₂Cl₂/MeOH 1:1) showed no starting material and only one product. The solvent was removed under reduced pressure, and the resulting residue was purified by FC (7 × 16 cm silica gel filling; CH₂Cl₂/MeOH 2:1) to give 8.2 g of a yellow solid, which was transferred to a 100-ml, round-bottomed flask. Et₂O (50 ml) was added, and the mixture was sonicated for 2 h under reflux. After cooling to r.t., the mixture was filtered, and the precipitate was treated with Et₂O and ultrasound once again. Filtration gave **18d** (6.66 g, 78%) as a pale yellow solid, which was pure enough for further reaction. TLC (CH₂Cl₂/MeOH 1:1): *R*_f 0.66. ¹H-NMR: 1.54 (*s*, *t*-Bu); 1.84–2.36 (*m*, 7 H); 2.44 (*d*, *J* = 18.5, 1 H); 2.77 (*dd*, *J* = 7.0, 18.5, 1 H); 3.14, 3.20 (2*s*, 2 formamidine Me); 4.80 (br. *m*, H–C(1′)); 5.23 (br. *m*, H–C(2′)); 8.04, 8.48 (2*s*, H–C(2)); 8.87 (*s*, 1 formamidine H). ESI-MS: 428 (100, [*M* + H]⁺).

1.2.2.5. (1*S*,5*S*,8*S*)-2-[*(tert*-Butoxy)carbonyl]-8-[6-*(4-amino-9H-purin-9-yl)*-2-azabicyclo[3.3.1]nonan-3-one (**18e**). A 250-ml, round-bottomed flask, equipped with a magnetic stirring bar and a CaCl₂-filled drying tube was charged with **18d** (6.64 g; 15.5 mmol) and dry CH₂Cl₂ (150 ml). Then, *p*-toluenesulfonohydrazide (11.55 g; 62.0 mmol) was added, followed by TsOH (1.47 g, 7.75 mmol), and the soln. was stirred at r.t. for 44 h. After addition of CH₂Cl₂ (150 ml), the soln. was washed with H₂O three times (pH > 12, adjusted by addition of 2*M* NaOH). The combined aq. washings were re-extracted with 100 ml of CH₂Cl₂, and the combined org. layers were dried (MgSO₄). After filtration, the solvent was removed under reduced pressure, and the resulting residue was purified by FC (5.2 × 20 cm silica-gel filling; CHCl₃/MeOH 30:1) to give **18e** (4.96 g; 86%), which was pure enough for further reaction. An anal. sample was recrystallized from THF/cyclohexane. M.p. 211° (gas evol.), 300–302° (dec.)³⁶. TLC: (CHCl₃/MeOH 30:1): *R*_f 0.23. [*α*]_D²⁰ = +80.6 (*c* = 1.32, CH₂Cl₂). UV (MeCN/H₂O 1:9): λ_{max} 260 (14136). IR: 3406*m*, 3328*m*, 3206*m*, 2941*w*, 1756*s*, 1724*s*, 1701*m*, 1668*s*, 1645*s*, 1597*s*, 1570*m*, 1479*m*, 1414*w*, 1304*m*, 1273*s*, 1251*s*, 1228*m*, 1145*s*, 1034*w*, 996*w*, 853*w*, 760*w*. ¹H-NMR (300 MHz, CDCl₃): 1.62 (*s*, *t*-Bu); 1.81–1.89 (*m*, 3 H); 2.19–2.37 (*m*, 4 H); 2.54 (*d*, *J* = 18.5, 1 H); 2.86 (*dd*, *J* = 7.0, 18.5, 1 H); 4.86 (br. *m*, H–C(1′)); 5.28 (br. *m*, H–C(2′)); 5.64 (*s*, NH₂); 8.06, 8.38 (2*s*, H–C(2); H–C(8)). ¹³C-NMR (75 MHz, (D₆)DMSO): 19.93, 25.45, 27.23 (C(3′), C(4′), C(9′)); 25.97 (C(5′)); 28.01 (Me₃C); 40.24 (C(6′)); 52.65 (C(1′)); 53.68 (C(2′)); 84.12 (Me₃C); 119.82 (C(5)); 139.20 (C(8)); 150.59 (C(4)); 152.58 (C(2)); 155.55 (C(6)); 158.46 (Boc C=O); 171.14 (lactam C=O). ESI-MS: 373 (100, [*M* + H]⁺). Anal. calc. for: C₁₈H₂₄N₆O₃: C 58.05, H 6.50, N 22.57; found: C 58.13, H 6.51, N 22.85.

1.2.2.6. (1*S*,5*S*,8*S*)-2-[*(tert*-Butoxy)carbonyl]-8-[6-(4-methoxybenzamido)-9H-purin-9-yl]-2-azabicyclo[3.3.1]nonan-3-one (**18f**). A 100-ml, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a pressure-equalizing dropping funnel, and a CaCl₂-filled drying tube was charged with **18e** (4.96 g, 13.3 mmol) and dry CH₂Cl₂ (60 ml). Then, dry pyridine (5.35 ml, 66.5 mmol) was added, followed by DMAP (1.59 g, 1.3 mmol). After cooling to 0°, 4-methoxybenzoyl chloride (5.4 ml, 39.9 mmol) was added dropwise, and the mixture was stirred at 0° for 15 min. The ice bath was removed and the mixture was stirred at r.t. for 22 h. The mixture was then again cooled to 0°, and 35 ml of MeOH were added dropwise. After 30 min at 0°, 80 ml of a sat. soln. of NH₃ in MeOH was added dropwise. A white precipitate was formed, which dissolved after the addition was complete. After 30 min, the ice-bath was removed, and the mixture was stirred at r.t. for further 2 h. The solvent was removed under reduced pressure, and the resulting residue was dissolved in 200 ml of CH₂Cl₂. The soln. was successively washed with 150 ml sat. NaHCO₃ soln. and aq. citric acid (20%, 2 × 100 ml), dried (MgSO₄), filtered, and concentrated *in vacuo*. The resulting residue was purified by FC (5.2 × 18 cm silica gel; AcOEt/MeOH 40:3) to give 5.93 g **18f** (88%). M.p. 110–112° (dec.)³⁷. TLC: (CH₂Cl₂/MeOH 40:1): *R*_f 0.44.

³⁵) Verbindung *rac*-**18c** (93%), recrystallized from CH₂Cl₂/AcOEt, was used without further purification.

³⁶) M.p. of *rac*-**18e** (THF/cyclohexane): 164–167° (dec.).

³⁷) M.p. of *rac*-**18f**: 172–175° (dec.).

$[\alpha]_D^{20} = +58.3$ ($c = 1.32$, CH_2Cl_2). UV (MeOH): λ_{max} 288 (30459). IR: 3600–3050m, 2940m, 1757s, 1707m, 1671m, 1604s, 1577m, 1506s, 1458m, 1402m, 1342m, 1251s, 1168m, 1145s, 1100m, 1024m, 893w, 848m, 794w, 761m, 644w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.63 (s, *t*-Bu); 1.84–1.91 (*m*, 3 H); 2.24–2.40 (*m*, 4 H); 2.55 (*d*, $J = 18.5$, 1 H); 2.88 (*dd*, $J = 7.0$, 18.5, 1 H); 3.92 (s, MeO); 4.95 (br. *m*, H–C(1')); 5.28 (br. *m*, H–C(2')); 7.01–7.04 (*m*, 2 arom. H); 8.01–8.04 (*m*, 2 arom. H); 8.26, 8.81 (2s, H–C(2), H–C(8)); 8.91 (s, H–NC(6)). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 19.95, 25.55, 27.24 (C(3'), C(4'), C(9')); 25.95 (C(5')); 28.06 (Me_3C); 40.28 (C(6')); 52.61 (C(1')); 53.99 (C(2')); 55.54 (MeO); 84.27 (Me_3C); 114.08 (arom. C); 123.12 (C(5)); 126.24 (arom. C); 130.03 (arom. C); 141.58 (C(8)); 149.87 (C(4)); 152.00 (C(2)); 152.31 (C(6)); 152.54, 163.31, 164.02 (arom. C, benzoyl C=O, Boc–C=O); 171.14 (lactam–C=O). ESI-MS: 507 (100, $[M+H]^+$). Anal. calc. for: $\text{C}_{26}\text{H}_{30}\text{N}_6\text{O}_5$: C 61.66, H 5.93, N 16.60; found: C 61.75, H 6.01, N 16.69.

1.2.2.7. (1*S*,2*S*,4*S*)-3-[[*tert*-Butoxy]carbonyl]amino]-4-[6-(4-methoxybenzamido)-9H-purin-9-yl]cyclohexanecarboxylic Acid (**19**). A 500-ml, two-necked, round-bottomed flask, equipped with a magnetic stirring bar and a pressure-equalizing dropping funnel was charged with 5.25 g of **18f** (10.36 mmol) and 200 ml of THF. After cooling to 0°, a soln. of 2.17 g of $\text{LiOH} \cdot \text{H}_2\text{O}$ (51.8 mol) in 50 ml of H_2O was added dropwise over a period of 20 min. Then, 30 ml of MeOH were added, the ice bath was removed, and the mixture was stirred at r. t. for 1 h. Ion-exchange resin (Amberlite IR-120, H^+ form) was added until pH reached 7. The resin was removed by filtration, and the soln. was concentrated under reduced pressure to a volume of 100 ml. 200 ml of H_2O were added, and pH 2 was adjusted by addition of 1M aq. HCl. The soln. was extracted with AcOEt (3×200 ml), and the combined org. extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in 25 ml of hot MeOH. The product was precipitated by addition of 10 ml of H_2O . The precipitate was filtered, washed with H_2O , and dried (P_4O_{10}) to give 1.95 g of **19**. Another 0.57 g could be obtained from the mother liquor and washings to give a total yield of 46%. M.p. 238–239°³⁸. TLC. ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): R_f 0.39. $[\alpha]_D^{20} = +19.9$ ($c = 0.55$, MeOH). UV (MeCN/ H_2O): λ_{max} 290 (22722). IR: 3368m, 2939w, 1710m, 1683s, 1608s, 1577m, 1528m, 1507m, 1458m, 1306m, 1250s, 1175s, 1030w, 842w, 761w. $^1\text{H-NMR}$ (300 MHz, (D_6)-DMSO): 1.08 (s, *t*-Bu); 1.09–1.40 (*m*, 2 H); 1.80–2.35 (*m*, 7 H); 3.86 (s, MeO); 4.07, 4.36 (2 br. *m*, H–C(1'), H–C(1''), H–C(2'')); 6.87 (br. s, NHBoc); 7.06–7.09 (*m*, 2 arom. H); 8.00–8.05 (*m*, 2 arom. H); 8.42, 8.86 (2s, H–C(2), H–C(8)); 10.88 (s, C(6)–NH). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 27.73 (Me_3C); 30.35, 30.46, 37.95 (C(3'), C(5'), C(6'')); 32.89 (C(4'')); 40.32 ($\text{CH}_2\text{CO}_2\text{H}$); 51.30 (C(2'')); 55.38 (MeO); 77.45 (Me_3C); 113.55 (arom. C); 125.24 (C(5)); 125.63 (arom. C); 131.41 (arom. C); 143.48 (C(8)); 150.03 (C(4)); 150.69 (C(2)); 152.38 (C(6)); 154.53, 162.38, 164.77 (arom. C, benzoyl C=O, Boc C=O); 173.36 (CO_2H). MS: 525 (100, $[M+H]^+$). Anal. calc. for: $\text{C}_{26}\text{H}_{32}\text{N}_6\text{O}_6$: C 59.53, H 6.15, N 16.02; found: C 59.35, H 6.32, N 15.89.

2. Reference and Model Compounds³⁹). – 2.1. Preparation of Reference Compound ent-**11** (Scheme 1). 2.1.1. Preparation of ent-**8a** by Resolution of rac-**8a**. A mixture of rac-**8a** (25.0 g; 198 mmol) and acetone (150 ml) was placed in a 250-ml Erlenmeyer flask and heated to boiling. To the hot soln., a soln. of (*S*)-phenylethylamine (24.0 g; 198 mmol) in acetone (150 ml) was added dropwise under stirring. The resulting soln. was allowed to cool. The formed salt separated as white needles, which were collected on a filter and dried under reduced pressure to give a mixture of diastereoisomeric salts (25.4 g, 52%). Recrystallization (350 ml acetone) yielded 12.0 g (24%). $[\alpha]_{589}^{25} = +21.8$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +22.8$; $[\alpha]_{546}^{25} = +25.8$; $[\alpha]_{436}^{25} = +42.8$; $[\alpha]_{365}^{25} = +63.7$. Recrystallization from acetone (150 ml) afforded white needles (6.2 g, 13%): $[\alpha]_{589}^{25} = +30.7$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +32.2$, $[\alpha]_{546}^{25} = +36.4$; $[\alpha]_{436}^{25} = +60.5$; $[\alpha]_{365}^{25} = +90.4$. Recrystallization from acetone (60 ml) gave white needles (4.0 g, 8.2%): $[\alpha]_{589}^{25} = +34.8$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +36.2$; $[\alpha]_{546}^{25} = +40.9$; $[\alpha]_{436}^{25} = +68.1$; $[\alpha]_{365}^{25} = +101.9$. Recrystallization from acetone (50 ml) provided white needles (2.3 g, 4.7%): $[\alpha]_{589}^{25} = +38.5$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +40.0$; $[\alpha]_{546}^{25} = +45.4$; $[\alpha]_{436}^{25} = +75.6$; $[\alpha]_{365}^{25} = +113.4$. Recrystallization from acetone (25 ml) led to white needles (2.6 g, 3.3%): $[\alpha]_{589}^{25} = +39.6$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +41.2$; $[\alpha]_{546}^{25} = +46.8$; $[\alpha]_{436}^{25} = +77.7$; $[\alpha]_{365}^{25} = +115.9$. Recrystallization from acetone (15 ml) furnished white needles (1.15 g; 2.3%): $[\alpha]_{589}^{25} = +40.1$ ($c = 1$, MeOH); $[\alpha]_{578}^{25} = +41.7$; $[\alpha]_{546}^{25} = +47.3$; $[\alpha]_{436}^{25} = +79.2$; $[\alpha]_{365}^{25} = +119.2$; [2]: $[\alpha]_{589}^{25} = +40.5$ ($c = 1$, MeOH). A mixture of the purified salt (11.5 g) and H_2O (50 ml) was slightly acidified with 1N aq. HCl soln. The resulting mixture was shaken with CH_2Cl_2 (5×25 ml). After the combined org. extracts had been washed with sat. aq. NaCl soln. (30 ml) and dried (MgSO_4), the solvent was distilled, and the residual liquid was used directly for further reaction.

2.1.2. From ent-**8a** to ent-**11**. An oven-dried, 100-ml, two-necked Loewenthal flask equipped with a magnetic stirring bar, rubber septum, and reflux condenser was charged under Ar with a suspension of LiAlH_4

³⁸) M.p. of rac-**19**: 236–239°.

³⁹) Prepared by Dr. Wolfgang Döring.

(212 mg, 5.6 mmol) in dry THF (20 ml). A soln. of *ent-8a* (587 mg; 4.6 mmol) in dry THF (10 ml) was added at 0° *via* syringe. The mixture was stirred at r.t. for 3 h, quenched by ice-water and shaken with Et₂O (4 × 20 ml each). The combined Et₂O extracts were dried (MgSO₄) and concentrated on a rotary evaporator. The IR spectrum of the residual oil (522 mg) proved to be identical with that one of *rac-9a* (*Exper. 1.1.3*).

A 25-ml, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a pressure-equalizing condenser, and a septum, was charged with a soln. of *ent-9* (522 mg, 4.6 mmol) in dry pyridine (5 ml) and cooled to 0°. After MsCl (430 µl, 5.6 mmol) had been added dropwise by syringe while stirring, the mixture was left for 3 h at r.t., and afterwards distributed between 1N aq. HCl and CH₂Cl₂. The aq. layer is shaken thrice with CH₂Cl₂. The combined org. phases were washed successively with 1N aq. HCl and aq. NaHCO₃ soln., dried (MgSO₄), and distilled (bulb-to-bulb; oven temp. *ca.* 140°/0.15 Torr), after evaporation of solvent, to give *ent-6b* (806 mg, 91%). The IR spectrum of the colorless oil was identical with that of *rac-9b*.

A 25-ml, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, a pressure-equalizing condenser, and a septum was charged with a soln. of NaCN (250 mg, 5.0 mmol) in dry DMSO (10 ml) and heated to 90° while stirring. After *ent-9b* (800 mg, 4.2 mmol) had been added dropwise by syringe, the red mixture was stirred for 3 h at 120° and 15 h at r.t. The mixture was poured into a slurry of H₂O and ice, and extracted four times with Et₂O. The combined org. phases are dried (MgSO₄) and concentrated under reduced pressure to furnish *ent-10* (433 mg; 85%) as a colorless oil, the IR spectrum of which is identical with that of *rac-10*.

Into a 25-ml, two-necked *Loewenthal* flask, equipped with a magnetic stirring bar and a septum was placed CuSO₄·5H₂O (807 mg, 3.3 mmol) in H₂O (8 ml) under Ar. A soln. of NaBH₄ (136 mg, 3.3 mmol) and NaOH (129 mg, 3.3 mmol) in H₂O (5 ml), while stirring, was added through the septum within 30 min under external cooling with an ice-bath. The mixture was stirred for another h at this temp. The formed precipitate was filtered through a *Schlenck* fritte, washed with H₂O until the washings were neutral, and transferred into a 50-ml *Schlenck* flask, equipped with a pressure-equalizing condenser. A soln. of *ent-10* (400 mg, 3.3 mmol) in DMSO (5 ml) was added. The mixture was heated under Ar for 24 h at 90°, and the catalyst was filtered off (using a *Schlenck* fritte) and washed with hot H₂O. The filtrate was allowed to cool to r.t. and shaken with Et₂O (4 times). The combined Et₂O extracts were evaporated under reduced pressure to give *ent-11* (367 mg, 80%). M.p. 138–140° (H₂O). TLC(CH₂Cl₂/acetone 2:5): *R_f* 0.4. [α]₃₈₉²⁰ = +80.0 (*c* = 1.026, CH₂Cl₂); [α]₃₇₈³⁰ = +83.20; [α]₃₄₆³⁰ = +94.6; [α]₄₃₆²⁰ = +162.6; [α]₃₆₅²⁰ = +254.0. IR(KBr): 3348s, 3175m (NH); 3014w (=C–H); 2907w, 2828w (–C–H); 1665s, 1622s (C=O, amide I,II). ¹H-NMR (CDCl₃): 1.24–1.39 (*m*, H–C(1′)); 1.69–1.85 (*m*, 2 H–C(6′)); 2.03–2.22 (*m*, 2 H–C(2), 2 H–C(2′), 2 H–C(5′)); 5.49 (br. s, with D₂O exchangeable, NH); 5.59–5.71 (*m*, H–C(3′), H–C(4′), ¹H with D₂O exchangeable, NH). Anal. calc. for: C₈H₁₃NO (139.20): C 69.03, H 9.41, N 10.06; found: C 69.05, H 9.12, N 10.01. IR and ¹H-NMR spectra were identical with those of *rac-11* [7].

2.2. Preparation of (1*R*,5*R*,8*R*)-8-(2,6-diamino-9H-purin-9-yl)-2-azabicyclo[3.3.1]nonan-3-one (*rac-13*). To a soln. of 2,6-diaminopurine (75 mg, 0.5 mmol) in anh. DMF (10 ml), NaH (30 mg of a 80% suspension; 1.0 mmol) was added. The resulting suspension was stirred for 1 h at r.t. The white suspension was treated with *rac-12a* (133 mg; 0.5 mmol) and the mixture was stirred for 15 h. The solvent was removed under reduced pressure (bulb-to-bulb distillation, 50°/0.1 Torr). The residue was dissolved in boiling H₂O (10 ml). The soln. was filtered through cotton-wool to give white crystals (115 mg, 80%) of *rac-13*. M.p. > 250°. TLC: (reversed phase SiO₂; MeOH/H₂O 1:1 + 1% TFA): *R_f* 0.5. UV (MeOH): $\lambda_{\max}$ 258.0 (9600); 281.5 (11600). IR (KBr): 3414s, 3319s (NH, amine); 3195s (NH, lactam); 2932m, 2866m (–C–H); 1662s, 1654s, 1640s, 1626s, 1616s, 1603s, 1594s, 1588s, 1508m (C=O, C=N, C=C). ¹H-NMR ((D₆)DMSO): 1.61 (*ψ*s, H–C(16), 2 H–C(18)); 1.97–2.14 (*m*, H–C(14), H–C(15), H′–C(16), 2 H–C(17)); 2.44–2.54 (*m*, H′–C(14)); 3.32 (*s*, H₂O); 4.19 (*ψ*s, H–C(11)); 4.27 (*ψ*s, H–C(10)); 5.63 (*s*, NH₂); 6.69 (*s*, NH₂); 7.88 (*d*, *J*(H–N(12), H–C(11)) = 4.3, H–N(12)); 7.92 (*s*, H–C(8)). The signals were assigned by ¹H,¹H-COSY spectrum. Cross signals between: 1.61/1.97–2.14; 1.61/4.19; 2.05–2.14/2.44–2.54; 1.97–2.14/4.27; 4.19/4.27; 4.19/7.88 ppm. Relative configuration at C(10)–C(11) follows from a ROESY spectrum. Cross signals between: 1.61/1.97–2.14; 2.05–2.14/2.44–2.54; 1.97–2.14/4.27; 1.97–2.14/7.92; 4.19/4.27; 4.19/7.88; 4.27/7.88. Anal. calc. for C₁₃H₁₇N₇O·H₂O (305.34): C 51.14, H 6.27, N 32.11; found: C 51.32, H 6.25, N 32.04.

Crystall-Structure Analysis of ent-13 (see Fig. 2). Suitable crystals of *ent-13*⁴⁰⁾ (needles; orthorhombic) were obtained from EtOH/H₂O. Space group: *P*₂₁₂₁₂₁ (No. 19); cell: *a* = 9.267(2) Å; *b* = 10.960(1) Å; *c* = 14.058(2) Å; *V* = 1427.9(7) Å³; *Z* = 4; *D_c* = 1.420 g cm^{–3}. Hemisphere up to 2 $\theta_{\max}$ = 130°. 3938 reflections, 2314 independent reflections, 2305 reflections with *I* > 0. Number of variables: 276. *R*(*F*) = 0.028; ωR (*F*) = 0.038.

⁴⁰⁾ Spontaneous resolution has taken place on crystallization.

2.3. 5-Methyl-1-[(1*R*,5*R*,8*R*)-3-oxo-2-azabicyclo[3.3.1]nonan-8-yl]pyrimidine-2,4(1*H*,3*H*)-dione (*rac*-**14a** = *rac*-**14**; Scheme 2). NaH (3.69 g of a 65% dispersion in mineral oil; 100 mmol) was placed in a dry, 500-ml, three-necked, round-bottomed flask equipped with a magnetic stirring bar, Ar inlet, outlet, and pressure-equalizing dropping funnel, and washed with pentane (2 × 30 ml each). The flask was purged with dry Ar prior to adding anhyd. DMSO (250 ml) and thymine (6.31 g, 50.0 mmol). After stirring for 5 min at r.t., *rac*-**12a** (13.3 g; 50.0 mmol) was added. The mixture was stirred for 48 h at r.t., NH₄Cl (20 ml of a sat. aq. soln.) was added, and the solvent was evaporated (70°/1 Torr). The oily residue was adsorbed on silica gel (20 g) and filtered through silica gel (200 g; 3 l of AcOEt; 1 l of Et₂O; 1.6 l of CH₂Cl₂/MeOH 15:1; 1.1 l of CH₂Cl₂/MeOH 10:1; 1.2 l of CH₂Cl₂/MeOH 5:1). The residue of the concentrated eluate (18 g) was dissolved in a small amount of MeOH, and to the resulting soln., CH₂Cl₂ was added under stirring. The colorless precipitate formed was filtered and dried (P₂O₅ in a vacuum desiccator) to give *rac*-**13a** (4.49 g, 34%). The mother liquor was concentrated, traces of solvent were removed by a bulb-to-bulb distillation (120°/0.3 Torr), and the residue was purified by FC (150 g; CH₂Cl₂/MeOH 15:1) to afford additional product (1.20 gm, 9%), hereby increasing the overall yield to 41%. M.p. 304–306° (MeOH/H₂O). TLC (CH₂Cl₂/MeOH 10:1): *R*_f 0.22. UV (H₂O): λ_{max} 273.0 (11470). IR (KBr): 3611m, 3432s, 3257s, 3190s, 2944s, 2812s, 1704s, 1663s, 1621s, 1486s, 1430s, 1398s, 1365s, 1268s, 1116s. ¹H-NMR ((D₆)-DMSO): 1.42, 1.65 (*m*, H–C(4'), 2 H–C(9')); 1.69–1.88 (*m*, H–C(3'), Me); 1.89–2.05 (*m*, H'–C(3'), H'–C(4'), H–C(6')); 2.10 (*br. s.*, H–C(5')); 2.42 (*dd*, *J*(H'–C(6'), H–C(6')) = 18.0, *J*(H'–C(6'), H–C(5')) = 7.5, H'–C(6')); 3.58 (*br. m.*, H–C(1')); 4.15 (*br. m.*, H–C(2')); 7.52 (*s.*, H–C(6)); 7.97 (*d.*, exchangeable on treatment with D₂O, *J*(H–N(8), H–C(1)) = 4.5, H–N(8)); 11.29 (*s.*, exchangeable on treatment with D₂O, H–N(3)). ¹³C-NMR (50 MHz, (D₆)-DMSO): 12.18 (Me); 17.99 (C(3')); 23.76 (C(9')); 24.64 (C(5')); 27.48 (C(4')); 37.13 (C(6')); 47.40 (C(1')); 54.63 (C(2')); 108.64 (C(5)); 138.12 (C(6)); 151.00 (C(2)); 163.70 (C(4)); 171.19 (C(7')). The signals were assigned by DEPT and ¹H, ¹³C-COSY spectra. ESI-MS: 264.3 ([M + H]⁺). Anal. calc. for C₁₃H₁₇N₃O₃·H₂O (281.31): C 55.51, H 6.81, N 14.94; found: C 55.64, H 6.83, N 15.08.

Crystal-Structure Analysis of rac-**16a** (see Fig. 3). Suitable crystals (monoclinic) were obtained from MeOH·H₂O. Space group *C2/c* (No. 15); cell: *a* = 21.472(3) Å; *b* = 11.304(1) Å; *c* = 14.028(3) Å; β = 127.81(1); *V* = 2689(1) Å³; *Z* = 8; *D*_c = 1.389 g·cm^{−3}. Hemisphere up to 2θ_{max} = 130°. 4779 reflections, 2289 independent reflections, 2254 reflections with *I* > 0. Number of variables: 250. *R*(*F*) = 0.054, ω*R*(*F*) = 0.074.

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