

Synthesis of Spiropyrimidodiazepines and Spirodiazepinopurines by Tandem Nitroso-ene/*Diels*–*Alder* Reactions

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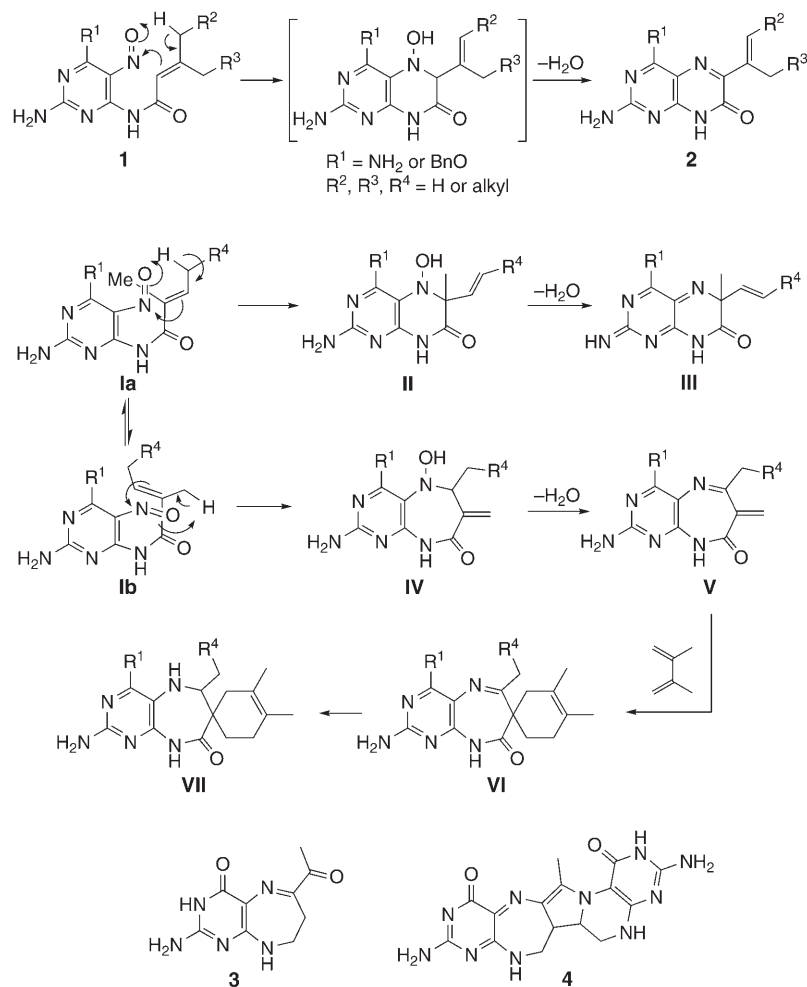
New spirocyclic heterocycles **8**, **16**, **19/20**, **25**, **27**, and **30** derived from pyrimido[4,5-*b*][1,4]diazepin-8'(9'*H*)-one were synthesised by a tandem nitroso-ene/*Diels*–*Alder* reaction of 4-(alkenoylamino)-5-nitrosopyrimidines. The crystal structure of **16** was established by X-ray analysis. It is characterised by four pairs of intermolecular H-bonds linking every two molecules in the unit cell. Sequential imine reduction and intramolecular condensation of the *C*(4')-(acylamino)-pyrimido[4,5-*b*][1,4]diazepines **27** and **30** led to the [1,4]diazepino[1,2,3-*gh*]purines **28/29** and **31**, respectively.

Introduction. – The nitroso-ene reaction of 4-(alkenoylamino)-5-nitrosopyrimidines **1** generates allylic hydroxylamines, and is followed by *in situ* elimination of H₂O, leading in high yield to *C*(6)-substituted pteridinones **2** [1]. We wondered about the ene reaction of the 4-(acylamino)-5-nitrosopyrimidines **I** (*Scheme 1*), possessing an *N*-alkenoyl group substituted at *C*(2) rather than at *C*(3). The ene reaction of **I** may lead either to 6,6-disubstituted pteridinones **II**, *via* the reacting conformer **Ia**, or to pyrimido[4,5-*b*][1,4]diazepines **IV**, *via* conformer **Ib**. Dehydration of the initial ene products should generate the quinonoid **III** and/or lead to pyrimido[4,5-*b*][1,4]diazepines **V**. The expected high reactivity of the intermediates and products suggested intercepting them. We planned to do so by combining the nitroso-ene reaction with a cycloaddition. The cycloaddition of **V** to 2,3-dimethylbuta-1,3-diene is expected to lead to spiropyrimidodiazepines **VI**. This imine, or the presumably more stable amine **VII**, should facilitate the analysis of the regioselectivity of the ene reaction, and lead to a new ring system. No issue of regioselectivity is expected for the ene reaction of 4-(alkenoylamino)-5-nitrosopyrimidines **I** that lack the CH₂R⁴ substituent. Their tandem ene/*Diels*–*Alder* reaction was thought to lead exclusively to pyrimido[4,5-*b*][1,4]diazepines, and appeared particularly attractive.

Two pyrimido[4,5-*b*][1,4]diazepines, 6-acetyl-2-amino-7,8-dihydro-9*H*-pyrimido[4,5-*b*][1,4]diazepin-4(3*H*)-one (PDA, **3**) and drosopterin (**4**), occur in nature. PDA is the biogenetic precursor of drosopterin, aurodrosopterin, and neodrosopterin, red eye pigments of *Drosophila melanogaster* [2]. There is considerable interest in these heterocycles on account of the biological activity of analogous compounds, such as benzodiazepines [3][4], pyridino-1,4-diazepines [5], and pyrimido-azepine-based folates [6].

Most pyrimido[4,5-*b*][1,4]diazepines were prepared by condensing 4,5-diaminopyrimidines with 1,3-dicarbonyl compounds, or with α,β -unsaturated ketones [7][8]. As a rule, the products possessing different substituents at *C*(6) and *C*(8) are obtained as

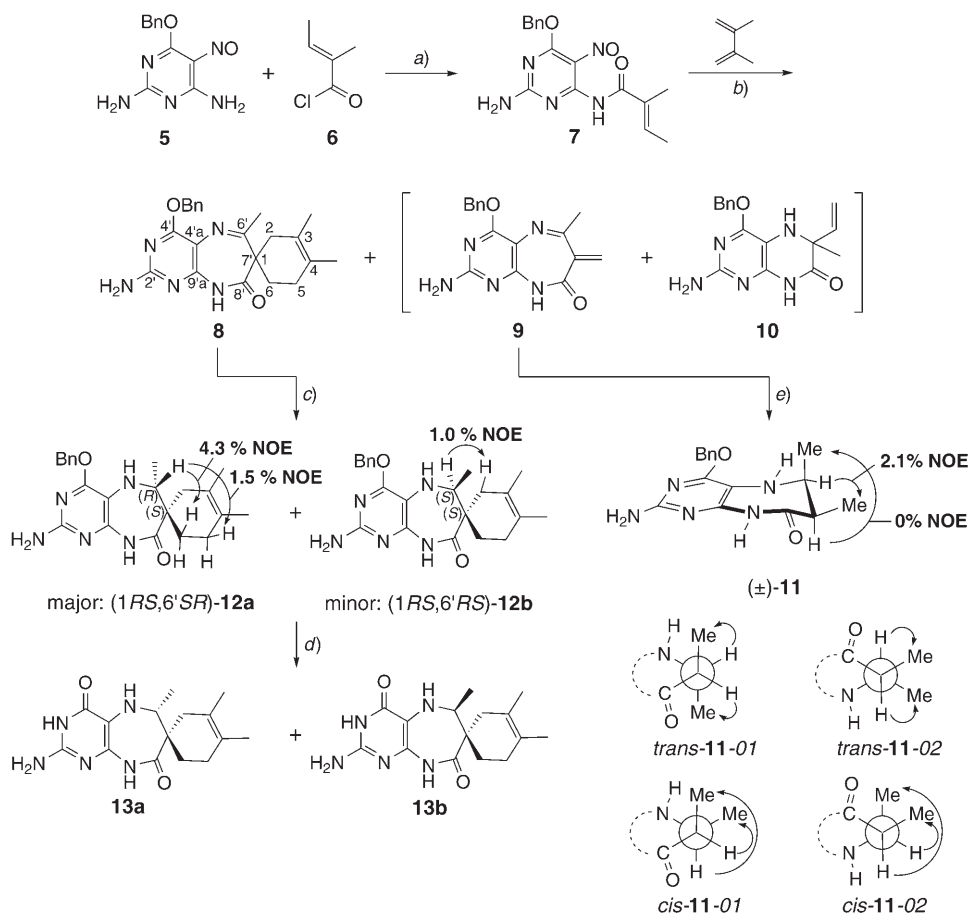
Scheme 1



mixtures of regioisomers, a disadvantage that is avoided by condensing 4-chloro-5-nitropyrimidines with β -amino ketones (*Polonovski–Boon*-type reactions) [9][10]. Only a few examples of spirobenzodiazepines are known [4][11][12] and, to the best of our knowledge, no synthesis of spiropyrimido[4,5-*b*][1,4]diazepines has been reported. We planned to study the nitroso-ene/*Diels–Alder* reaction of the tigloylamide **7** (see *Scheme 2* below), the simplest amide with a substituent corresponding to CH_2R^4 , of the methacryloyl derivative **15** (see *Scheme 3* below), lacking this substituent, and of the amides **24** and **26**, possessing a 6-amino, or a 6-(acylamino) instead of a benzyloxy group (see *Scheme 4* below).

Results and Discussion. – Acylating 2,4-diamino-6-(benzyloxy)-5-nitrosopyrimidine (**5**) [13] with tigloyl chloride (**6**; *Scheme 2*) yielded 54% of the tigloyl amide **7**.

Scheme 2



a) K_2CO_3 , -18° , THF; 54%. *b*) 120° (sealed V-vial), toluene; 50% of **8**. *c*) NaBH_4 , MeOH; 82%.
d) Me_3SiCl (TMSCl), LiBr, MeCN; 81%. *e*) NaBH_4 , MeOH; < 5%.

Similarly as reported for related compounds, the moderate yield of **7** is due to its insufficient stability under acylating conditions (*cf.* [1]). Heating **7** in toluene in the presence, or absence, of a *Lewis* acid such as $\text{Sc}(\text{OTf})_3$ provided a multitude of products. Considering the high reactivity of the initially formed hydroxylamine [1][14] and of the expected dehydration product **9**, we heated **7** in the absence of a *Lewis* acid, but in the presence of excess 2,3-dimethylbuta-1,3-diene. HPLC-MS of the product evidenced the formation of the imines **8** (M_r 391) and **9** (M_r 309), and of the dihydropteridinone **10** (M_r 311). Flash chromatography of the crude provided 50% of **8**, besides small amounts of a mixture **9/10**. The formation of **9** is supported by the isolation, after reduction of **9/10** with NaBH_4 , of less than 5% of the *cis*-configured **11**. The ^1H -NOE difference spectra evidence a different distance between the two Me

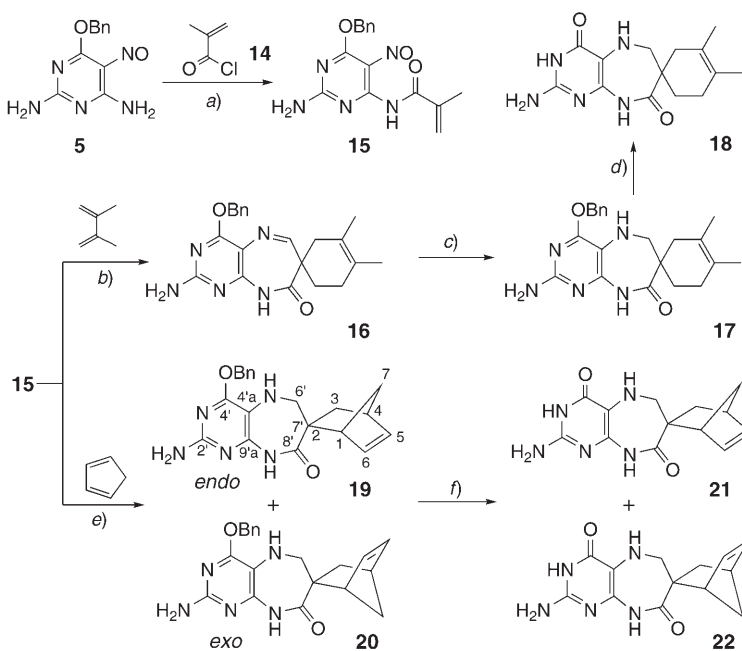
groups to either H–C(6) or H–C(7) and thus, for a chair-like conformer, the *cis*-configuration as in *cis*-**11-02** (Scheme 2). The dihydropteridinone **10** was not isolated; it is thought to arise (by disproportionation?) from precursor **II** (Scheme 1). Addition of butadiene subsequent to the disappearance of the blue colour of **7** resulted in a lower yield of **8**.

The ^1H -NMR spectrum of **8** in CDCl_3 shows conspicuous signals of the allylic CH_2 group linked to the spiro centre ($2d$ at 2.78 and 2.52 ppm, $J = 17.1$), and of the Me group at C(6') (s at 2.21 ppm). The spiro center is revealed by a ^{13}C s at 55.70 ppm.

Reduction of the imine **8** by NaBH_4 led to a mixture **12a/12b** of diastereoisomers (major/minor 3:1; Scheme 2). The ^1H -NOE difference spectrum in deuteriated benzene of the two separated *quintuplets* of H–C(6') evidences the (1*RS*,6'*SR*) configuration of the major component **12a** and the (1*RS*,6'*RS*)-configuration of the minor **12b**. Debenzylation of the mixture **12a/12b** with *in situ* generated Me_3SiBr (TMSBr) yielded 81% of a 3:1 mixture of the spiropyrimido[4,5-*b*][1,4]diazepines **13a** and **13b**.

The methacryloyl amide **15** was obtained in a yield of 45% by acylating **5** with methacryloyl chloride (**14**; Scheme 3). Heating **15** in the presence of 2,3-dimethylbuta-1,3-diene provided the spirodiazepine **16** in a yield of 68%. It was reduced with $\text{NaBH}(\text{OAc})_3$ to the amine **17** (97%) that was debenzylated with TMSBr to **18** that precipitated from solution, and was isolated in a yield of 92%. Heating **15** in the

Scheme 3



a) K_2CO_3 , -18° , THF; 45%. b) 110° (sealed V-vial), 0.5 h, toluene; 68%. c) $\text{NaBH}(\text{OAc})_3$, AcOH , CH_2Cl_2 ; 97%. d) TMSCl, LiBr, MeCN; 92%. e) 110° (sealed V-vial), 0.5 h, toluene; 85%, then $\text{NaBH}(\text{OAc})_3$, AcOH , CH_2Cl_2 ; 94%. f) CF_3COOH (TFA), Et_3SiH ; 90%.

presence of cyclopentadiene [15] resulted in a 7:3 mixture of imines (85%) that were directly reduced to a mixture of the *endo*-amine **19** and its *exo*-isomer **20**¹⁾.

The amines **19/20** were separated by preparative HPLC (NH₂-phase silica gel), and their configuration was deduced on the basis of the H_{a,b}–C(3) signals appearing at 1.70 (*d*, *J* = 11.4, 1 H) and 1.40 ppm (*dd*, *J* = 11.4, 3.0, 1 H) for the *endo*-isomer **19** ($\Delta\delta_{a,b}$ = 0.30 ppm), and at 2.35 (*dd*, *J* = 11.6, 3.0, 1 H) and 0.87 ppm (*d*, *J* = 11.6, 1 H) for the *exo*-isomer **20** ($\Delta\delta_{a,b}$ = 1.48 ppm), revealing the combined effect of the deshielding C(8')=O group and the shielding C(5)=C(6) bond on H₂C(3) [16]. Debenzylation of **19** and **20** with TMSBr gave rise to a considerable amount of by-products, while debenzylation with TFA and Et₃SiH led in high yields to the pyrimidinones **21** and **22**.

The structure of the imine **16** was established by X-ray analysis of crystals that were obtained by slow evaporation of a solution in ^tBuOH/CH₂Cl₂ (2:1; *Fig.*). In the unit

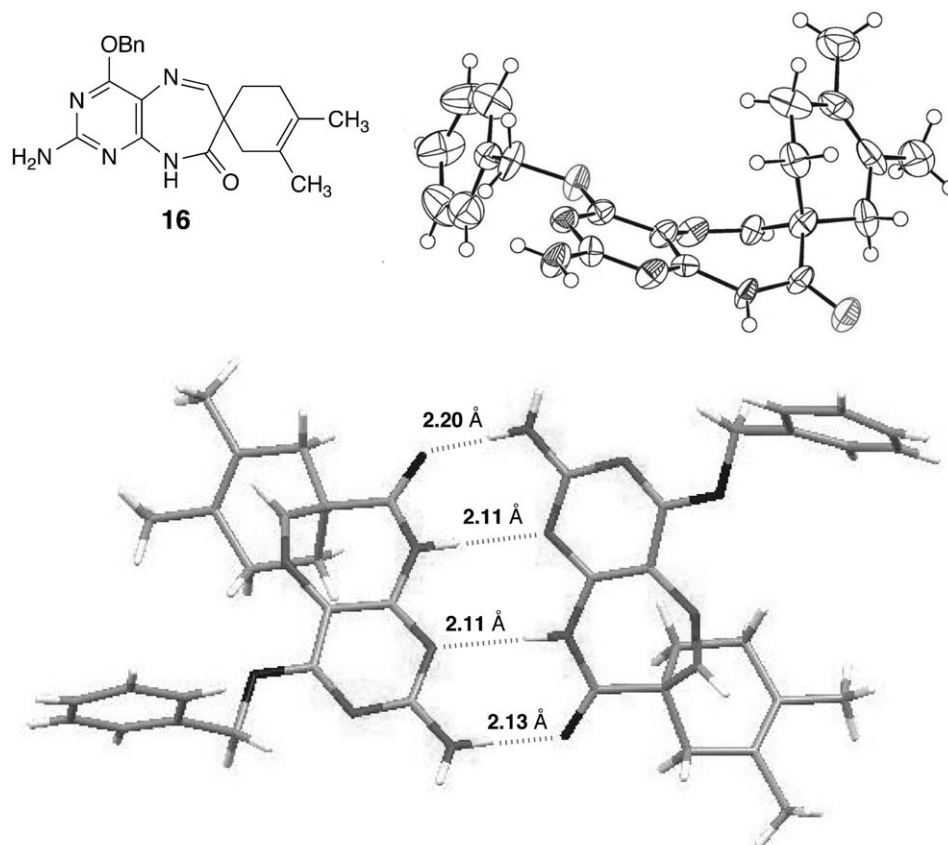


Figure. Crystal structure of **16** showing the conformation and the intermolecular H-bonds

¹⁾ The *endo/exo* configuration refers to the orientation of C(8')=O. Heating **15** in the presence of cyclohexa-1,3-diene afforded mainly an unstable product of an intermolecular nitroso-Diels–Alder cycloaddition.

cell, there are four symmetrically independent molecules of **16** and at least two solvent (CH_2Cl_2) molecules, of which only one could be localised completely. Four pairs of intermolecular H-bonds (compare [17]) link the $\text{H}_2\text{N}-\text{C}=\text{N}$ and $\text{O}=\text{C}-\text{NH}$ groups of two molecules, with $\text{H}\cdots\text{N/O}$ distances in the range of 2.09–2.20 Å. The seven-membered diazepine ring in **16** adopts a $B_{4a,7,9a}$ boat conformation [7].

The transformation of **16** to **17** is evidenced by the disappearance of the $\text{N}=\text{CH}$ *s* at 6.94 ppm and the $\text{N}=\text{CH}$ *d* at 154.84 ppm, and by the appearance of new signals for NHCH_2 at 4.72–4.69 ppm (*m*, D_2O exchangeable, 1 H); for NHCH_2 at 3.06 ppm (*dd*, $J = 13.7, 5.6, 1$ H) and 2.88 ppm (*dd*, $J = 13.7, 3.2, 1$ H), and by a NHCH_2 *t* at 46.17 ppm. The UV spectrum of **17** is characterised by a maximum at 337 nm ($\log \varepsilon = 3.71$) with a shoulder at 273 nm ($\log \varepsilon \approx 3.62$), while **16** shows a maximum at 305 nm ($\log \varepsilon = 4.02$). This may be rationalized by an impaired conjugation of **16** in a $B_{4a,7,9a}$ conformation, as it is found in the solid state (45–50° deviation between the π -planes of the pyrimidine and both the amido moieties), whereas full conjugation is found for the half-chair conformation ($^6\text{H}_7$ and/or $^7\text{H}_6$) of **17**. The UV spectrum of the debenzylated **18** is characterised by a maximum at 344 nm ($\log \varepsilon = 3.81$), and its IR spectrum shows $\text{C}=\text{O}$ bands at 1631 and 1611 cm^{-1} . The UV spectra of **19** and **20** are similar to the one of **17**, and those of **21** and **22** are similar to the one of **18**.

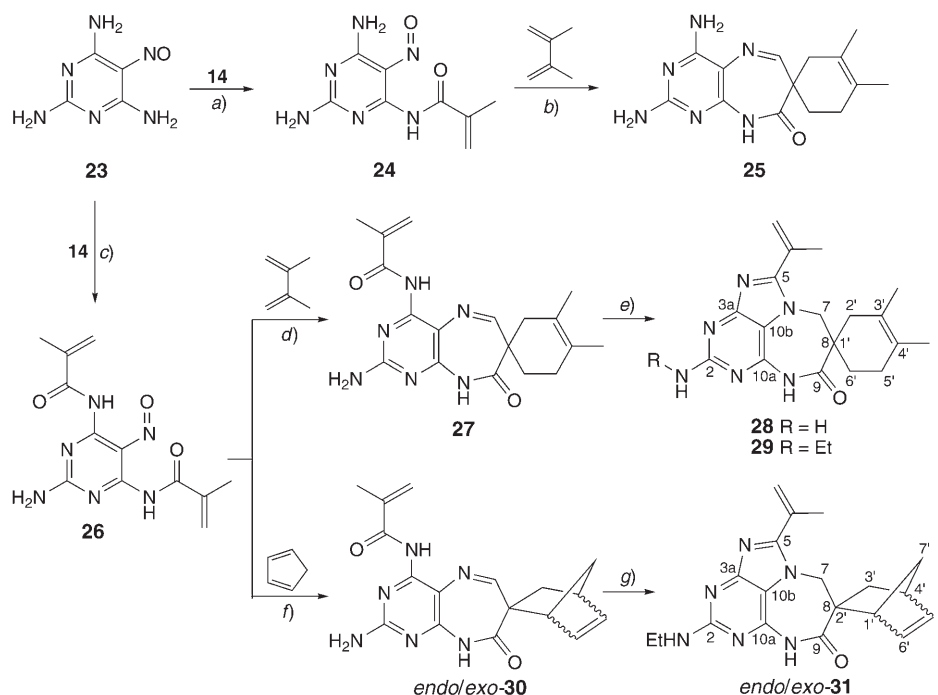
To test the effect on the ene reaction of substituting the benzyloxy by an amino or an acylamino group, we acylated the poorly soluble 2,4,6-triamino-5-nitrosopyrimidine (**23**) [18] with methacryloyl chloride (**14**), and obtained a mixture **24/26** of mono- and diacylated products that were difficult to separate (*Scheme 4*). Acylation of **23** with 1.3 equiv. of **14** at -18° in DMF yielded 40% of the mono-amide **24** as the major product, while acylation with 2.2 equiv. of **14** at -5 to -10° in THF provided mainly the diamide **26** (38%). The modest yield of the amides is again due to the insufficient stability of the nitroso compounds under acylating conditions.

Heating the mono-amide **24** to 155° and the diamide **26** to 110° , both in the presence of 2,3-dimethylbuta-1,3-diene, provided the imines **25** (94%) and **27** (97%), respectively (*Scheme 4*). The higher temperature required for the transformation of **24** may reflect its lower electrophilicity. Reduction of the imine **27** with $\text{NaBH}(\text{OAc})_3$ and AcOH was accompanied by a condensation, as in the *Traube* synthesis of purines [19][20], leading to the spiro[1,4]diazepino[1,2,3-*gh*]purine **28** (41%) and its *N*-ethyl analogue **29** (37%; *Scheme 4*). The 2-ethylamino derivative **29** is presumably formed by reductive alkylation of **28**, with $\text{NaBH}(\text{OAc})_3$ as the source of the Et group. As *ca.* 10% starting material remained when **27** was treated with 5 equiv. $\text{NaBH}(\text{OAc})_3$ and 50 equiv. AcOH, we increased the amount of reducing agent, but only observed the formation of a higher percentage of the 2-ethylamino derivative **29**.

The structure of the condensed purine **28** is confirmed by a high-resolution (HR) MS, and by HSQC and HMBC spectra, and by elemental analysis. The difference between the NMR spectra of the starting material **27** and product **28** shows that an imino group was transformed into an $\text{N}-\text{CH}_2$ rather than into the expected NHCH_2 group, and that one amide NH signal disappeared. The HMBC spectrum shows cross-peaks between the *singlet* of $\text{CH}_2(7)$ and $\text{C}(2')$, $\text{C}(6')$, $\text{C}(5)$, $\text{C}(8)$, $\text{C}(9)$, and $\text{C}(10b)$, evidencing the structure of **28**.

Heating **26** in the presence of cyclopentadiene (*Scheme 4*) yielded 84% of a presumably *endo/exo*-mixture **30** of the expected imines (7:3). Treatment of **30** with

Scheme 4



a) K_2CO_3 , -18° , DMF; 40%. b) 155° (sealed V-vial), toluene; 94%. c) K_2CO_3 , -5 to -10° , THF; 38%. d) 110° (sealed V-vial), toluene; 97%. e) $\text{NaBH}(\text{OAc})_3$, AcOH; 41% of **28** and 37% of **29**. f) 110° (sealed V-vial), toluene; 84%. g) $\text{NaBH}(\text{OAc})_3$, AcOH, CH_2Cl_2 ; 47%.

excess $\text{NaBH}(\text{OAc})_3$ and AcOH provided an *endo/exo*-mixture of the purines **31** (47%) resulting from reduction, condensation, and *N*-ethylation.

The spiro[1,4]diazepino[1,2,3-*gh*]purines **28**, **29**, and **31** are representatives of a new ring system. The only naturally occurring [1,4]diazepino[1,2,3-*gh*]purines are the asmarines A–F, cytotoxic marine alkaloids isolated by *Kashman* and co-workers from the Red Sea sponge *Raspailia* sp. [21]. A few syntheses of [1,4]diazepino[1,2,3-*gh*]purines are known; they proceed by annulating the diazepine ring onto a purine. Thus, *Suzuki et al.* reported the synthesis of a [1,4]diazepino[1,2,3-*gh*]purin-2-one by cyclization *via* silylation and amination of 7-(aminoalkyl)-3-propylpurine-2,4-diones [22]. The *Kashman* group reported the synthesis of 9-substituted tetrahydro[1,4]diazepino[1,2,3-*gh*]purines by intramolecular alkylation at N–C(6) of an C(6)-(benzyloxy)aminoadenine in view of a synthesis of asmarines A–F [23][24], and *Ohba* and *Tashiro* proceeded towards the same goal by cyclization of the 6-chloro-7-[3-(hydroxyamino)propyl]purine [25].

In summary, the tandem nitroso-ene/*Diels–Alder* reaction and the ensuing reduction/condensation offers a rapid and convenient approach to spiropyrimido[4,5-*b*]-[1,4]diazepines and spiro[1,4]diazepino[1,2,3-*gh*]purines.

We thank the *ETH Zürich* and *F. Hoffmann-La Roche AG*, Basel, for generous support, Dr. *Bruno Bernet* for checking the analytical data, Dr. *W. Bernd Schweizer* for the X-ray analysis, Prof. Dr. *Bernhard Jaun* for a critical discussion of the NOE assignments, Prof. Dr. *W. Pfeleiderer* for stimulating discussions about the UV spectra, and *Brigitte Brandenburg* and *Chao Zou* for the NMR spectra.

Experimental Part

General. See [26]. Flash chromatography (FC): *Merck* silica gel 60 (0.063–0.200 mm). FT-IR Spectra: neat (ATR), absorption in cm^{-1} . UV Spectra: in MeOH, λ_{max} (log ϵ). HR-MALDI-MS: in 3-hydroxytycolinic acid (3-HPA) matrix.

(E)-N-[2-Amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]-2-methylbut-2-enamide (**7**). A suspension of **5** (368 mg, 1.5 mmol) in THF (60 ml) was treated with K_2CO_3 (1.7 g, 12 mmol), cooled to -18° , and treated with **6** (0.26 ml, 2.2 mmol) within 2 h (addition *via* a syringe pump). The mixture was stirred for 0.5 h, diluted with CH_2Cl_2 (100 ml), washed with cold H_2O (2×50 ml) and brine (50 ml), dried (MgSO_4), and evaporated. The green residue was washed with $\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 2:1 (20 ml). Filtration gave **7** (265 mg, 54%). Blue powder. M.p. $>139^\circ$ (dec.). R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) 0.50. UV: 204 (4.39), 259 (4.14), 350 (4.33). IR (ATR): 3375w, 3319m, 3236m, 1712m, 1649s, 1634s, 1591s, 1579m, 1519s, 1497m, 1456s, 1435s, 1402s, 1352s, 1329m, 1310m, 1255s, 1188s, 1145s, 1129s, 1076s, 1042s, 1017m, 979m, 939w, 879m, 851w, 827m. $^1\text{H-NMR}$ (300 MHz, $(\text{D}_6)\text{DMSO}$): 13.10 (br. s, NH); 8.78, 8.72 (2 br. s, NH_2); 7.57–7.37 (m, 5 arom. H); 6.67 (br. q, $J = 5.4$, H–C(3)); 5.63 (s, PhCH_2); 1.88 (br. s, 2 Me). $^{13}\text{C-NMR}$ (75 MHz, $(\text{D}_6)\text{DMSO}$): 166.24 (s, C=O); 164.17 (s, C(6')); 139.08 (s, C(4')); 135.53 (s); 135.29 (d, C(3)); 132.41 (s, C(2)); 128.45 (2d); 128.33 (2d); 128.17 (d); 68.31 (t, PhCH_2); 14.29, 11.81 (2q, 2 Me); signals of C(2') and C(5') not visible due to coalescence. HR-MALDI-MS: 328.1409 (40, $[M+H]^+$, $\text{C}_{16}\text{H}_{18}\text{N}_5\text{O}_3^+$; calc. 328.1410), 350.1219 (100, $[M+Na]^+$, $\text{C}_{16}\text{H}_{17}\text{N}_5\text{NaO}_3^+$; calc. 350.1224).

(1*RS*)-2'-Amino-4'-(benzyloxy)-3,4,6'-trimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]diazepin]-8'(9'H)-one ((±)-**8**). A mixture of **7** (32.7 mg, 0.1 mmol) and 2,3-dimethylbuta-1,3-diene (0.09 ml, 0.8 mmol) in toluene (5 ml) in a sealed V-vial was rapidly heated to 120° , and stirred for 4 h. The resulting brown suspension was concentrated. FC (cyclohexane/AcOEt 4:1) gave **8** (19 mg, 50%) and a fraction containing **8** and **9**. White powder. M.p. $121-123^\circ$ (dec.). R_f (cyclohexane/AcOEt 1:2) 0.53. UV: 206 (4.50), 217 (4.497), 307 (4.11). IR (ATR): 3480w, 3321w, 3202m, 2925w, 2855w, 1655m, 1625s, 1594s, 1549s, 1482m, 1424s, 1381m, 1345s, 1312m, 1271m, 1236m, 1202w, 1179m, 1153m, 1092m, 1060w, 1041w, 986w, 951w, 909w, 847w, 824w. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 11.85 (br. s, NH); 7.43–7.28 (m, 5 arom. H); 6.20 (br. s, NH_2); 5.63, 5.46 (2d, $J = 12.9$, PhCH_2); 2.78, 2.52 (2d, $J = 17.1$, 2 H–C(2)); 2.21 (s, Me–C(6')); 1.98–1.66, 1.50–1.40 (2m, 2 CH_2); 1.74, 1.59 (2s, 2 Me). $^1\text{H-NMR}$ (300 MHz, $(\text{D}_6)\text{DMSO}$, 353 K): 10.19 (br. s, NH); 7.46–7.30 (m, 5 arom. H); 6.22 (br. s, NH_2); 5.46 (s, PhCH_2); 2.56, 2.32 (2d, $J = 18.9$, 2 H–C(2)); 2.08 (s, Me–C(6')); 1.90–1.70, 1.60–1.50 (2m, 2 CH_2); 1.65, 1.55 (2s, 2 Me). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 169.00 (s, C=O); 164.78 (s, C(4')); 161.65 (s, C(6')); 159.30 (s, C(2')); 146.60 (s, C(9'a)); 136.75 (s); 128.25 (2d); 127.67 (d); 127.51 (2d); 125.74, 124.15 (2s, C(3), C(4)); 111.79 (s, C(4'a)); 68.15 (t, PhCH_2); 55.70 (s, C(1)); 37.77 (t, C(2)); 29.40, 23.12 (2t, C(5), C(6)); 25.58 (q, Me–C(6')); 19.00, 18.33 (2q, 2 Me). $^{13}\text{C-NMR}$ (75 MHz, $(\text{D}_6)\text{DMSO}$): 166.78 (s, C=O); 163.91 (s, C(4')); 160.11 (s, C(6')); 158.96 (s, C(2')); 147.41 (s, C(9'a)); 136.95 (s); 128.32 (2d); 127.91 (2d); 127.78 (d); 125.74, 124.15 (2s, C(3), C(4)); 110.37 (s, C(4'a)); 66.97 (t, PhCH_2); 55.03 (s, C(1)); 37.43 (t, C(2)); 29.06, 22.43 (2t, C(5), C(6)); 25.13 (q, Me–C(6')); 18.98, 18.16 (2q, 2 Me). HR-MALDI-MS: 392.2086 (100, $[M+H]^+$, $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_2^+$; calc. 392.2087), 414.1913 (5, $[M+Na]^+$, $\text{C}_{22}\text{H}_{25}\text{N}_5\text{NaO}_2^+$; calc. 414.1906).

(1*RS*,6'*SR*)- and (1*RS*,6'*RS*)-2'-Amino-4'-(benzyloxy)-3,4,6'-trimethyl-5',6'-dihydrospiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]diazepin]-8'(9'H)-one ((±)-**12a** and (±)-**12b**). A soln. of **8** (43 mg, 0.11 mmol) in MeOH/THF 3:1 (20 ml) was treated with NaBH_4 (42 mg, 1.1 mmol), heated to reflux for 1 h, treated with additional NaBH_4 (2×42 mg, 1.1 mmol) after 1 and 2 h, and diluted with CH_2Cl_2 (60 ml). The org. phase was washed with 1*N* NaOH, H_2O (2×30 ml), and brine (30 ml), dried (MgSO_4), and evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 6:1) gave **12a/12b** (35 mg, 82%). White powder. M.p. $98-100^\circ$ (dec.). R_f ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 2:1) 0.44. UV: 205 (4.45), 269 (3.77), 343 (3.85). IR (ATR): 3311w, 3200w, 2969w, 2912w, 2855w, 1635m, 1572s, 1494m, 1436s, 1407s, 1376m, 1352s, 1284m, 1237m, 1210m, 1173m,

1090s, 1028w, 947w, 909w, 843w. ¹H-NMR (500 MHz, CD₂Cl₂; 3 : 1 mixture of diastereoisomers): 9.44 (s, 0.25 H), 9.33 (s, 0.75 H) (H–N(9')), exchange with D₂O); 7.43–7.33 (m, 5 arom. H); 5.36 (s, PhCH₂); 5.18 (s, 0.5 H), 5.12 (s, 1.5 H) (H₂N–C(2'), exchange with D₂O); 4.06 (br. s, 0.75 H), 4.00 (br. s, 0.25 H) (H–N(5')), exchange with D₂O); 3.33 (m, H–C(6')), addn. of D₂O → q, J = 6.0); 2.72 (d, 0.75 H), 2.19 (d, 0.25 H) (J ≈ 15.0, H–C(2)); 2.13–1.67 (m, H'–C(2), CH₂CH₂); 1.63, 1.59 (2s, 4.5 H), 1.59, 1.54 (2s, 1.5 H) (Me–C(3), Me–C(4)); 1.09 (d, J = 6.0, Me–C(6')). ¹³C-NMR (125 MHz, CD₂Cl₂; 3 : 1 mixture of diastereoisomers): major: 177.24 (s, C=O); 161.47 (s, C(4')); 154.87 (s, C(2')); 140.99 (s, C(9'a)); 137.32 (s); 129.07 (2d); 128.84 (2d); 128.73 (d); 124.66, 123.61 (2s, C(3), C(4)); 108.64 (s, C(4'a)); 69.17 (t, PhCH₂); 51.98 (s, C(1)); 50.00 (d, C(6')); 38.46 (t, C(2)); 29.59, 28.72 (2t, C(5), C(6)); 19.46 (q, Me–C(6')); 18.85, 18.82 (2q, 2 Me); minor: 178.20 (s, C=O); 161.63 (s, C(4')); 155.24 (s, C(2')); 142.05 (s, C(9'a)); 137.36 (s); 128.77 (2d); 128.75 (d); 128.71 (2d); 125.27, 122.98 (2s, C(3), C(4)); 108.60 (s, C(4'a)); 69.08 (t, PhCH₂); 51.40 (s, C(1)); 49.48 (d, C(6')); 38.22 (t, C(2)); 29.36, 28.83 (2t, C(5), C(6)); 19.59 (q, Me–C(6')); 18.90, 18.35 (2q, 2 Me–C(3,4)). HR-MALDI-MS: 394.2239 (100, [M + H]⁺, C₂₂H₂₈N₅O₂⁺; calc. 394.2238), 416.2073 (3, [M + Na]⁺, C₂₂H₂₇N₅NaO₂⁺; calc. 416.2062).

2-Amino-4-(benzyloxy)-6,7-dihydro-6,7-dimethyl-5H-pyrimido[4,5-b][1,4]diazepin-8(9H)-one (**11**).

The pooled by-products obtained by FC of **8** (22 mg) was treated with excess NaBH₄ in MeOH/THF 3 : 1. Workup as for **12a/12b** and chromatography gave **11** (8 mg). White powder. *R*_f (cyclohexane/AcOEt 2 : 1) 0.30. UV: 214 (4.39), 255 (3.88), 323 (3.75). IR (ATR): 3444m, 3380w, 3330w, 3227w, 3083w, 2963w, 2928w, 1664s, 1619s, 1570s, 1497m, 1479s, 1450m, 1438m, 1417s, 1380m, 1368m, 1354s, 1290m, 1270s, 1206w, 1173m, 1145m, 1084m, 1072m, 1053m, 1029w, 1003w, 986w, 954w, 904w, 862w, 801m. ¹H-NMR (300 MHz, (D₆)DMSO): 9.56 (br. s, H–N(9)); 7.49–7.30 (m, 5 arom. H); 5.96 (br. s, NH₂); 5.36 (s, PhCH₂); 4.06 (d, J = 4.5, H–N(5)); 3.67–3.62 (dq, J = 3.0, 5.5, H–C(6), after D₂O exchange); 2.72–2.67 (dq, J = 3.0, 6.0, H–C(7), after D₂O exchange); 1.02 (d, J = 6.0, Me–C(6)); 0.92 (d, J = 6.0, Me–C(7)). ¹³C-NMR (75 MHz, (D₆)DMSO): 174.59 (s, C=O); 161.62 (s, C(4)); 155.84 (s, C(2)); 149.11 (s, C(9a)); 137.05 (s); 128.52 (2d); 128.06 (2d); 127.98 (d); 108.83 (s, C(4a)); 67.17 (t, PhCH₂); 58.12 (d, C(6)); 41.92 (d, C(7)); 18.27, 12.46 (2q, 2 Me). HR-MALDI-MS: 314.1612 (100, [M + H]⁺, C₁₆H₂₀N₅O₂⁺; calc. 314.1612).

(1*RS*,6'*SR*)- and (1*RS*,6'*RS*)-2'-Amino-5',6'-dihydro-3,4,6'-trimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]diazepine]-4',8'(3'H,9'H)-dione ((±)-**13a** and (±)-**13b**). A soln. of anh. LiBr (14.4 mg, 0.16 mmol) in MeCN (1.5 ml) was treated with Me₃SiCl (22 μl, 0.2 mmol), stirred at 23° under Ar for 5 min, treated with dry **12a/12b** (16 mg, 0.04 mmol), stirred at 23°, and treated with Me₃SiCl (2 × 22 μl, 0.2 mmol) after 8 and 24 h. After stirring for a total of 40 h, an off-white fine precipitate was formed. The suspension was cooled to 0°, treated with MeOH (0.1 ml), filtered (washing with Et₂O), and dried *i.v.* to afford **13a/13b** (10 mg, 81%). Off-white powder. M.p. > 245° (dec.). *R*_f (CH₂Cl₂/MeOH 20 : 1) 0.28. UV: 204 (4.15), 223 (4.19), 252 (3.83), 346 (3.76). IR (ATR): 3336w, 3244w, 3135w, 3042w, 2974w, 1697s, 1651s, 1577w, 1530w, 1491w, 1442w, 1384m, 1351w, 1312m, 1281m, 1249w, 1196w, 1131w, 1085w, 1064w, 910w. ¹H-NMR (300 MHz, (D₆)DMSO), 3 : 1 mixture of diastereoisomers): 11.72 (0.25 H), 11.23 (0.75 H) (2 br. s, H–N(3')); 9.48 (0.25 H), 9.27 (0.75 H) (2s, H–N(9')); 7.40 (0.5 H), 7.31 (1.5 H) (2 br. s, NH₂); 5.48 (br. s, H–N(5')); 3.37 (m, H–C(6')); 2.76–2.40, 2.20–1.62 (2m, 6 H–C(2,5,6)); 1.59, 1.56 (2s, 4.5 H), 1.56, 1.54 (2s, 1.5 H) (Me–C(3), Me–C(4)); 1.06 (0.75 H), 0.97 (2.25 H) (2d, J ≈ 6.0, Me–C(6')). ¹³C-NMR (125 MHz, (D₆)DMSO); only signals of the major isomer are assigned): 174.00 (s, C(8')); 157.82 (s, C(4')); 149.20 (s, C(2')); 123.53, 122.54 (2s, C(3), C(4)); 104.72 (s, C(4'a)); 50.87 (s, C(1)); 49.27 (d, C(6')); 37.32 (t, C(2)); 28.67, 27.70 (2t, C(5), C(6)); 18.92 (q, Me–C(6')); 18.43 (q, Me–C(3), Me–C(4)); the signal of C(9'a) was not observed. HR-MALDI-MS: 304.1763 (100, [M + H]⁺, C₁₅H₂₂N₅O₂⁺; calc. 304.1768), 326.1590 (4, [M + Na]⁺, C₁₅H₂₁N₅NaO₂⁺; calc. 326.1587).

N-[2-Amino-6-(benzyloxy)-5-nitrosopyrimidin-4-yl]-2-methylprop-2-enamide (**15**). A suspension of **5** (1 g, 4.1 mmol) in THF (150 ml) was treated with K₂CO₃ (4.6 g, 32.7 mmol), cooled to –18°, treated dropwise with **14** (0.6 ml, 6.1 mmol) within 2 h (addition *via* a syringe pump), stirred for 0.5 h, diluted with CH₂Cl₂ (200 ml), washed with cold H₂O (2 × 100 ml) and brine (100 ml), dried (MgSO₄), and evaporated. FC (CH₂Cl₂/AcOEt 3 : 1) of the green residue gave **15** (568 mg, 45%). Blue powder. M.p. > 150° (dec.). *R*_f (CH₂Cl₂/MeOH 20 : 1) 0.50. UV: 205 (4.35), 261 (4.11), 353 (4.34). IR (ATR): 3481m, 3299w, 3200m, 1712m, 1630s, 1597s, 1543s, 1496m, 1483w, 1450s, 1401m, 1377w, 1346s, 1307s, 1289s, 1268m, 1194s, 1148s, 1100s, 1078m, 1060m, 1029m, 1002m, 946s, 910m, 889w, 845m, 810m. ¹H-NMR

(300 MHz, (D₆)DMSO): 13.15 (br. s, NH); 8.83, 8.76 (2 br. s, NH₂); 7.57–7.35 (*m*, 5 arom. H); 5.97 (br. s, H–C(3)); 5.82 (*d*, *J* = 1.2, H'–C(3)); 5.63 (*s*, PhCH₂); 1.99 (*s*, Me). ¹H-NMR (300 MHz, CDCl₃): 13.22 (br. s, NH); 7.54–7.34 (*m*, 5 arom. H); 7.02, 6.05 (2 br. s, NH₂); 6.16 (br. s, H–C(3)); 5.79 (*d*, *J* = 1.2, H'–C(3)); 5.72 (*s*, PhCH₂); 2.10 (*s*, Me). ¹³C-NMR (75 MHz, CDCl₃): 167.00 (*s*, C=O); 164.45 (*s*, C(6')); 139.80 (*s*, C(4')); 139.43 (*s*, C(2)); 135.16 (*s*); 128.55 (*2d*); 128.40 (*d*); 128.20 (*2d*); 124.30 (*t*, C(3)); 69.53 (*t*, PhCH₂); 18.15 (*q*, Me); signals of C(2') and C(5') not visible due to coalescence. HR-MALDI-MS (low intensity due to ene reaction during measurement): 314.1249 (33, [M+H]⁺, C₁₅H₁₆N₅O₃⁺; calc. 314.1248), 336.1084 (1, [M+Na]⁺, C₁₅H₁₅N₅NaO₃⁺; calc. 336.1067).

(*IRS*)-2'-Amino-4'-(benzyloxy)-3,4-dimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-*b*][1,4]diazepin]-8'(9'H)-one ((±)-**16**). A mixture of **15** (35 mg, 0.11 mmol) and 2,3-dimethylbuta-1,3-diene (0.1 ml, 0.88 mmol) in toluene (6 ml) in a sealed V-vial was put into an oil-bath of 110°, and stirred for 0.5 h. The resulting light-brown suspension was evaporated, and FC (cyclohexane/AcOEt 3:1) gave **16** (29 mg, 68%). White powder. M.p. 203.8–205.0° (dec.). *R*_f (cyclohexane/AcOEt 1:1) 0.38. UV: 210 (4.47), 305 (4.02). IR (ATR): 3400*m*, 3322*m*, 3216*m*, 3038*w*, 2924*m*, 2885*m*, 2855*m*, 2836*m*, 1666*s*, 1638*s*, 1593*s*, 1545*s*, 1508*m*, 1488*s*, 1455*m*, 1425*s*, 1383*m*, 1340*s*, 1307*s*, 1276*m*, 1238*m*, 1224*m*, 1202*w*, 1153*s*, 1132*m*, 1083*s*, 1059*m*, 1031*w*, 946*m*, 909*m*, 883*m*, 849*m*, 819*m*. ¹H-NMR (300 MHz, (D₆)DMSO): 10.60 (br. s, NH); 7.46–7.31 (*m*, 5 arom. H); 6.94 (*s*, N=CH); 6.68 (br. s, NH₂); 5.44, 5.38 (*2d*, *J* = 12.3, PhCH₂); 2.42 (*d*, *J* = 16.8), 2.13 (*d*, *J* = 17.4) (2 H–C(2)); 1.88–1.44 (*m*, CH₂CH₂); 1.60, 1.55 (2*s*, 2 Me). ¹³C-NMR (75 MHz, (D₆)DMSO): 168.08 (*s*, C=O); 164.62 (*s*, C(4')); 159.53 (*s*, C(2')); 154.84 (*d*, C(6')); 147.75 (*s*, C(9'a)); 136.54 (*s*); 128.21 (*2d*); 127.92 (*2d*); 127.75 (*d*); 124.52, 122.85 (2*s*, C(3), C(4)); 109.83 (*s*, C(4'a)); 67.32 (*t*, PhCH₂); 51.52 (*s*, C(1)); 35.98 (*t*, C(2)); 28.40 (*t*, C(5)); 23.81 (*t*, C(6)); 19.21, 18.51 (2*q*, 2 Me). HR-MALDI-MS: 378.1919 (100, [M+H]⁺, C₂₁H₂₄N₅O₂⁺; calc. 378.1925), 400.1745 (4, [M+Na]⁺, C₂₁H₂₃N₅NaO₂⁺; calc. 400.1744). Anal. calc. for C₂₁H₂₃N₅O₂ (377.45): C 66.83, H 6.14, N 18.55; found: C 66.83, H 6.21, N 18.26.

*X-Ray Analysis of 16*²⁾. Slow evaporation of a soln. of **16** in 'BuOH/CH₂Cl₂ (2:1) gave single crystals suitable for X-ray analysis (dimensions: 0.02 × 0.25 × 0.35 mm; colourless). 4(C₂₁H₂₃N₅O₂) · CH₂Cl₂, *M*_r 1679.62, triclinic, *P* $\bar{1}$, *a* = 13.9256(10), *b* = 17.2683(14), *c* = 8.013(2) Å, α = 92.962(3), β = 106.058(3), γ = 90.082(4)°, *V* = 4156.5(6) Å³; *Z* = 4, *D*_{calc} = 1.268 Mg/m³. Intensities were measured on a *Nonius Kappa* CCD diffractometer, with MoK α radiation λ = 0.71073 Å, θ = 3.7–22.8°, μ = 0.150 mm^{−1}, *T* = 223 K. There are four symmetrically independent molecules in the unit cell, which contains also at least two solvent (CH₂Cl₂) molecules, of which only one could be localised completely. In addition, diffraction of small crystal fragments stuck to the target crystal was interfering with intensities, resulting in an impaired agreement factor.

(*IRS*)-2'-Amino-4'-(benzyloxy)-5',6'-dihydro-3,4-dimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-*b*][1,4]diazepin]-8'(9'H)-one ((±)-**17**). A soln. of NaBH(OAc)₃ (22.4 mg, 0.11 mmol) and AcOH (26 μ l, 0.45 mmol) in CH₂Cl₂ (5 ml) at 0° was treated with a soln. of **16** (25 mg, 0.07 mmol) in CH₂Cl₂ (5 ml), stirred at r.t. for 2 h, diluted with CH₂Cl₂ (20 ml), and poured into H₂O (20 ml). After basification by addition of sat. NaHCO₃, the org. phase was washed with H₂O (2 × 20 ml) and brine (20 ml), dried (MgSO₄), and evaporated. FC (cyclohexane/AcOEt 3:1) gave **17** (24.5 mg, 97%). Very hygroscopic white powder. M.p. 87–89° (dec.). *R*_f (CH₂Cl₂/AcOEt 2:1) 0.38. UV: 204 (4.36), 273 (3.62), 337 (3.71). IR (ATR): 3315*w*, 3204*w*, 2921*w*, 2847*w*, 1652*m*, 1628*m*, 1579*s*, 1468*s*, 1429*s*, 1365*s*, 1341*s*, 1316*m*, 1289*m*, 1236*m*, 1159*s*, 1128*m*, 1095*m*, 1029*w*, 958*w*, 912*w*, 847*w*. ¹H-NMR (300 MHz, (D₆)DMSO): 8.88 (br. s, NH); 7.51–7.32 (*m*, 5 arom. H); 5.74 (br. s, NH₂); 5.37, 5.32 (*2d*, *J* = 12.9, PhCH₂); 4.72–4.69 (*m*, NHCH₂); 3.06 (*dd*, *J* = 13.7, 5.6), 2.88 (*dd*, *J* = 13.7, 3.2) (NHCH₂); 2.45 (H–C(2), overlapping with signal of (D₆)DMSO); 2.18–2.02 (*m*, H'–C(2)); 1.82–1.66 (*m*, CH₂CH₂); 1.57 (*s*, 2 Me). ¹³C-NMR (75 MHz, (D₆)DMSO): 177.63 (*s*, C=O); 159.26 (*s*, C(4')); 154.12 (*s*, C(2')); 143.21 (*s*, C(9'a)); 136.61 (*s*); 128.14 (*2d*); 127.77 (*2d*); 127.63 (*d*); 123.37, 122.23 (2*s*, C(3), C(4)); 109.45 (*s*, C(4'a)); 67.15 (*t*, PhCH₂); 46.77 (*s*, C(1)); 46.17 (*t*, NHCH₂); 37.00 (*t*, C(2)); 28.07 (*t*, C(5)); 27.18 (*t*, C(6)); 19.08, 18.67 (2*q*, 2 Me).

²⁾ The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-636601. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

HR-MALDI-MS: 380.2074 (100, $[M+H]^+$, $C_{21}H_{26}N_5O_2^+$; calc. 380.2081), 402.1900 (4, $[M+Na]^+$, $C_{21}H_{25}N_5NaO_2^+$; calc. 402.1900).

(1RS)-2'-Amino-5',6'-dihydro-3,4-dimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]diazepine]-4',8'-(3'H,9'H)-dione ((±)-**18**). A soln. of anh. LiBr (28 mg, 0.32 mmol) in MeCN (2.5 ml) was treated with Me_3SiCl (40 μ l, 0.32 mmol), stirred at 23° under Ar for 5 min, and treated with dry **17** (30 mg, 0.08 mmol). The mixture was treated twice with Me_3SiCl (50 μ l, 0.4 mmol), after stirring at 23° for 8 h and 24 h, resp. An off-white precipitate was formed. The resulting suspension was stirred for 8 h, cooled to 0°, treated with MeOH (0.3 ml), and filtered. The filter content was washed with Et_2O and dried *i.v.* to afford **18** (16.3 mg). Evaporation of the combined filtrate and washing, and FC (AcOEt/MeOH 20:0 $\rightarrow$ 20:1) gave additional **18** (4.8 mg; total yield: 92%). Off-white powder. M.p. > 250° (dec.). R_f (CH_2Cl_2 /MeOH 20:1) 0.25. UV: 203 (4.34), 226 (4.30), 344 (3.81). IR (ATR): 3334w, 3242w, 3148w, 3019w, 2912w, 1704m, 1631s, 1611s, 1542w, 1503w, 1463m, 1389m, 1315m, 1289m, 1213w, 1175w, 1088w, 1043w, 891w, 848w. 1H -NMR (300 MHz, $(D_6)DMSO$): 11.57 (br. s, H–N(3')); 9.11 (s, H–N(9')); 6.65 (br. s, NH_2); 5.95 (br. s, H–N(5')); 3.13, 2.96 (2d, $J = 13.8$, 2 H–C(6')); 2.45 (overlapping with signal of $(D_6)DMSO$, H–C(2)); 2.14–1.98 (m, H'–C(2)); 1.83–1.61 (m, CH_2CH_2); 1.57 (s, 2 Me). ^{13}C -NMR (75 MHz, $(D_6)DMSO$): 176.02 (s, C(8')); 158.29 (s, C(4')); 148.21 (s, C(2')); 123.57, 122.02 (2s, C(3), C(4)); 108.02 (s, C(4'a)); 47.53 (s, C(1)); 46.39 (t, C(6')); 37.04 (t, C(2)); 28.06 (t, C(5)); 27.28 (t, C(6)); 19.97, 18.56 (2q, 2 Me); the signal of C(9'a) not observed. HR-MALDI-MS: 290.1613 (100, $[M+H]^+$, $C_{14}H_{20}N_5O_2^+$; calc. 290.1612). Anal. calc. for $C_{14}H_{19}N_5O_2 \cdot 0.5 H_2O$ (298.34): C 56.36, H 6.76, N 23.47; found: C 56.36, H 6.27, N 23.05.

(1RS,2RS,4RS) (i.e. *endo*)- and (1RS,2SR,4RS) (i.e. *exo*)-2'-Amino-4'-(benzyloxy)-5',6'-dihydrospiro[bicyclo[2.2.1]hept-5-ene-2,7'-pyrimido[4,5-b][1,4]diazepin]-8'-(9'H)-one (**19** and **20**). A mixture of **15** (54 mg, 0.17 mmol) and cyclopenta-1,3-diene (0.12 ml, 1.36 mmol) in toluene (6 ml) in a sealed V-vial was put into an oil-bath of 110°, and stirred for 20 min. The resulting light-brown suspension was evaporated and FC (cyclohexane/AcOEt 4:1) gave the *endo/exo*-imines (53 mg, 85%) as white powder. A soln. of the crude *endo/exo*-imines (30 mg, 0.08 mmol) in CH_2Cl_2 (8 ml) was added to a soln. of $NaBH(OAc)_3$ (27 mg, 0.12 mmol) and AcOH (30 μ l, 0.52 mmol) in CH_2Cl_2 (8 ml) at 0°, stirred at r.t. for 2 h, diluted with CH_2Cl_2 (30 ml), and poured into H_2O (20 ml). After neutralisation with sat. $NaHCO_3$ soln., the org. layer was separated, washed with H_2O (2 $\times$ 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt 4:1) gave a 7:3 mixture **19/20** (28.5 mg, 94%). White powder. R_f (CH_2Cl_2 /AcOEt 2:1) 0.30 (**20**), 0.25 (**19**). UV: 205 (4.44), 261 (3.75), 335 (3.77). IR (ATR): 3494w, 3448w, 3407w, 3337w, 3191w, 3080w, 2969w, 2938w, 2847w, 1616s, 1571s, 1485s, 1454m, 1426s, 1368s, 1343s, 1286m, 1239m, 1216m, 1193m, 1171m, 1141m, 1087m, 1047w, 1030w, 1003w, 957m, 909w, 847m. 1H -NMR (300 MHz, $CDCl_3$; *endo/exo* 7:3): 9.89 (br. s, 0.7 H), 9.49 (br. s, 0.3 H) (H–N(9')); 7.42–7.29 (m, 5 arom. H); 6.28–6.21, 6.12–6.09 (2m, H–C(5), H–C(6)); 5.38 (s, 0.6 H), 5.37 (s, 1.4 H) ($PhCH_2$); 5.37 (br. s, $NHCH_2$); 3.55, 3.43 (2d, $J = 13.2$, 1.4 H), 3.18, 2.98 (2d, $J = 13.2$, 0.6 H) ($NHCH_2$); 2.98, 2.89 (2 br. s, 1.4 H), 3.04, 2.78 (2 br. s, 0.6 H) (H–C(1), H–C(4)); 2.60 (dd, $J = 12.0$, 3.6, 0.3 H), 1.99 (dd, $J = 12.0$, 2.1, 0.7 H) (H–C(3)); 1.67–1.30 (m, 0.7 H'–C(3), 2 H–C(7)); 0.96 (dd, $J = 12.0$, 2.7, 0.3 H'–C(3)); the signal of H_2N –C(2') was not observed. ^{13}C -NMR (75 MHz, $CDCl_3$; *endo/exo* 7:3): major: 176.81 (s, C=O); 160.88 (s, C(4')); 154.17 (s, C(2')); 141.34 (s, C(9'a)); 138.39, 134.19 (2d, C(5), C(6)); 136.02 (s); 128.53 (2d); 128.36 (d); 128.33 (2d); 109.82 (s, C(4'a)); 68.86 (t, $PhCH_2$); 56.24 (s, C(2)); 52.76 (t, C(6')); 47.08 (t, C(7)); 47.08, 42.35 (2d, C(1), C(4)); 36.70 (t, C(3)); minor: 177.66 (s, C=O); 160.67 (s, C(4')); 153.50 (s, C(2')); 141.34 (s, C(9'a)); 139.48, 133.45 (2d, C(5), C(6)); 136.01 (s); 128.53 (2d); 128.36 (d); 128.33 (2d); 110.53 (s, C(4'a)); 68.87 (t, $PhCH_2$); 56.86 (s, C(2)); 49.87 (t, C(6')); 47.57 (t, C(7)); 48.51, 42.04 (2d, C(1), C(4)); 36.22 (t, C(3)). HR-MALDI-MS: 364.1774 (100, $[M+H]^+$, $C_{20}H_{22}N_5O_2^+$; calc. 364.1768).

The soln. of the 7:3 mixture **19/20** (35 mg) in 15 ml of CH_2Cl_2 /AcOEt 75:25 was separated in three batches by prep. HPLC (Lichrospher 100 (250 $\times$ 25 mm), NH_2 phase, 5 μ m, UV detection at 254 nm, 10 ml/min) to yield **20** (11 mg; t_R 55 min) and **19** (21 mg; t_R 74 min).

Data of **19**: M.p. 213–215° (dec.). 1H -NMR (300 MHz, $(D_6)DMSO$): 9.10 (NH, exchange with D_2O); 7.50–7.30 (m, 5 arom. H); 6.14–6.11, 5.94–5.91 (2m, H–C(5), H–C(6)); 5.79 (s, NH_2 , exchange with D_2O); 5.38 (s, $PhCH_2$); 4.67 (br. t, $J = 4.5$, $NHCH_2$, exchange with D_2O); 3.37 (d, $J = 4.5$, 2 H of $NHCH_2$); 2.78, 2.75 (2 br. s, H–C(1), H–C(4)); 1.70 (d, $J = 11.4$, H–C(3)); 1.55 (d, $J = 9.0$, H–C(7)); 1.40 (dd, $J = 11.4$, 3.0, H'–C(3)); 1.27 (d, $J = 9.0$, H'–C(7)). ^{13}C -NMR (125 MHz, $(D_6)DMSO$): 175.22 (s,

C=O); 160.25 (s, C(4')); 154.42 (s, C(2')); 144.03 (s, C(9'a)); 137.75, 134.48 (2d, C(5), C(6)); 136.89 (s); 128.33 (2d); 127.86 (2d); 127.79 (d); 109.32 (s, C(4'a)); 67.17 (t, PhCH₂); 55.73 (s, C(2)); 53.34 (t, C(6')); 46.85, 41.68 (2d, C(1), C(4)); 46.73 (t, C(7)); 36.18 (t, C(3)). HR-MALDI-MS: 364.1762 (100, [M + H]⁺, C₂₀H₂₂N₅O₂⁺; calc. 364.1768).

Data of 20: M.p. 197–200° (dec.). ¹H-NMR (300 MHz, (D₆)DMSO): 9.14 (s, NH, exchange with D₂O); 7.49–7.29 (m, 5 arom. H); 6.28–6.22, 6.16–6.10 (2m, H–C(5), H–C(6)); 5.754, 5.74 (2s, NH₂, exchange with D₂O); 5.37 (s, PhCH₂); 4.55 (br. s, NHCH₂, exchange with D₂O); 3.02 (d, J = 12.6, 1 H), 2.94 (dd, J = 12.6, 4.8, 1 H) (NHCH₂); 2.88, 2.80 (2 br. s, H–C(1), H–C(4)); 2.35 (dd, J = 11.6, 3.0, H–C(3)); 1.46, 1.29 (2d, J = 7.7, 2 H–C(7)); 0.87 (d, J = 11.6, H'–C(3)). ¹³C-NMR (125 MHz, (D₆)DMSO): 176.58 (s, C=O); 159.82 (s, C(4')); 154.09 (s, C(2')); 143.07 (s, C(9'a)); 136.85 (s); 136.59, 133.81 (2d, C(5), C(6)); 128.25 (2d); 127.74 (2d); 127.70 (d); 109.75 (s, C(4'a)); 67.07 (t, PhCH₂); 55.89 (s, C(2)); 50.54 (t, C(6')); 48.16, 41.42 (2d, C(1), C(4)); 46.95 (t, C(7)); 36.12 (t, C(3)). HR-MALDI-MS: 364.1762 (100, [M + H]⁺, C₂₀H₂₂N₅O₂⁺; calc. 364.1768).

(1RS,2RS,4RS) (i.e., *endo*)- and (1RS,2SR,4RS) (i.e., *exo*)-2'-Amino-5',6'-dihydrospiro[bicyclo[2.2.1]hept-5-ene-2,7'-pyrimido[4,5-b][1,4]diazepine]-4',8'(3'H,9'H)-dione (**21** and **22**, resp.). A 7:3 mixture **19/20** (36.3 mg, 0.1 mmol) and Et₃SiH (25 µl, 0.15 mmol) was treated with TFA (0.6 ml) and stirred at 23° for 1.5 h. The mixture was concentrated to ca. 0.1 ml, Et₂O was added, and the resulting off-white precipitate was collected by filtration and recrystallized in MeOH to afford **21/22** 7:3 (24 mg, 90%) as an off-white powder. M.p. > 210° (dec.). R_f (CH₂Cl₂/MeOH 20:1) 0.28. UV: 203 (4.28), 225 (4.30), 340 (3.80). IR (ATR): 3347w, 3179w, 3054w, 2981w, 1714s, 1663m, 1625s, 1569w, 1551w, 1465m, 1431m, 1412m, 1377m, 1328m, 1281m, 1197s, 1178s, 1142s, 1097w, 1066w, 1037w, 1004w, 950w, 834w. ¹H-NMR (300 MHz, (D₆)DMSO; *endo/exo* 7:3): 10.90 (br. s, H–N(3')); 8.73 (br. s, H–N(9')); 6.27–6.25, 6.14–6.12 (2m, 0.6 H), 6.14–6.12, 5.93–5.91 (2m, 1.4 H) (CH=CH); 5.81 (br. s, NH₂); 4.72 (0.7 H), 4.09 (0.3 H) (2 br. s, H–N(5')); 3.26 (s, 1.4 H), 3.16 (s, 0.6 H) (2 H–C(6')); 3.00–2.85 (m, 0.6 H), 2.78 (br. s, 1.4 H) (H–C(1), H–C(4)); 2.37 (d, 0.3 H), 1.66 (d, 0.7 H) (J = 11.4, H–C(3)); 1.55 (d, J = 8.1, 0.7 H–C(7)); 1.44–1.20 (m, 0.7 H'–C(3), 0.3 H–C(7), 1 H'–C(7)); 0.85 (d, J = 11.4, 0.3 H'–C(3)). ¹³C-NMR (125 MHz, (D₆)DMSO; *endo/exo* 7:3): major: 174.72 (s, C(8')); 159.21 (s, C(4')); 146.28 (s, C(2')); 137.44, 134.62 (2d, C(5), C(6)); 135.51 (s, C(9'a)); 112.15 (s, C(4'a)); 56.26 (s, C(2)); 53.48 (t, C(6')); 46.48, 41.74 (2d, C(1), C(4)); 46.65, 35.83 (2t, C(3), C(7)); minor: 175.91 (s, C(8')); 159.08 (s, C(4')); 146.12 (s, C(2')); 138.49, 133.56 (2d, C(5), C(6)); 135.01 (s, C(9'a)); 112.35 (s, C(4'a)); 56.26 (s, C(2)); 50.43 (t, C(6')); 47.83, 41.44 (2d, C(1), C(4)); 47.00, 35.90 (2t, C(3), C(7)). HR-MALDI-MS: 273.1218 (100, M⁺, C₁₃H₁₅N₅O₂⁺; calc. 274.1226), 274.1301 (78, [M + H]⁺, C₁₃H₁₆N₅O₂⁺; calc. 274.1299). Anal. calc. for C₁₃H₁₅N₅O₂ (273.29): C 57.13, H 5.53, N 25.63; found: C 56.81, H 5.71, N 24.27.

Debenzylation of pure **19** and **20** as described above for the mixture led to **21** and **22**, resp.

Data of 21: ¹H-NMR (300 MHz, (D₆)DMSO): 11.20 (br. s, NH); 9.20 (s, NH); 6.47 (br. s, NH₂); 6.14–6.12, 5.95–5.93 (2m, H–C(5), H–C(6)); 4.22 (br. s, NHCH₂, overlapping with signal of H₂O); 3.43 (br. s, NHCH₂); 2.82, 2.78 (2 br. s, H–C(1), H–C(4)); 1.72 (d, J = 11.4, H–C(3)); 1.53 (d, J = 8.1, H–C(7)); 1.44 (dd, J = 11.4, 3.0, H'–C(3)); 1.28 (d, J = 8.1, H'–C(7)).

Data of 22: ¹H-NMR (300 MHz, (D₆)DMSO): 11.18 (br. s, NH); 9.05 (s, NH); 6.26, 6.11 (2 br. s, H–C(5), H–C(6)); 6.18 (br. s, NH₂); 4.59 (br. s, NHCH₂, overlapping with signal of H₂O); 3.01 (br. s, NHCH₂); 2.94, 2.80 (2 br. s, H–C(1), H–C(4)); 2.32 (dd, J = 11.4, 3.0, H–C(3)); 1.38, 1.30 (2d, J = 7.8, 2 H–C(7)); 0.91 (d, J = 11.4, H'–C(3)).

N-(2,6-Diamino-5-nitrosopyrimidin-4-yl)-2-methylprop-2-enamide (**24**). A soln. of 2,4,6-triamino-5-nitrosopyrimidine (**23**, 308 mg, 2.0 mmol) in DMF (50 ml) was treated with K₂CO₃ (1.4 g, 10 mmol), cooled to –18°, treated dropwise with **14** (0.26 ml, 2.6 mmol) within 2 h (addition *via* a syringe pump), stirred for 0.5 h, and poured into cold H₂O (200 ml). After extraction with AcOEt (3 × 100 ml), the org. layer was washed with brine (50 ml), dried (MgSO₄), and evaporated. The green residue was washed with (CH₂Cl₂/THF 4:1) to give pure solid **24** (145 mg). FC (CH₂Cl₂/THF 4:1) of the filtrate gave additional **24** (30 mg, total yield: 40%). Green powder. M.p. > 177° (dec.). R_f (AcOEt) 0.16. UV: 203 (4.20), 217 (4.19), 262 (3.97), 341 (4.27). IR (ATR): 3467w, 3437w, 3321w, 3107m, 1650s, 1627s, 1521s, 1478s, 1461s, 1399m, 1349m, 1312s, 1292m, 1226m, 1145s, 1106m, 1036w, 1004w, 945m, 894w, 820w. ¹H-NMR (300 MHz, (D₆)DMSO; 3:2 mixture of H-bonded isomers [1]): 13.72 (s, 0.6 H), 10.55 (s, 0.4 H) (HN–C(4')); 9.83, 8.17 (2 br. d, J = 3.2, 0.8 H), 8.57, 7.98 (2 br. s, 1.2 H) (H₂N–C(6')); 8.07, 7.80 (2 br. s,

1.2 H), 7.98, 7.88 (2 br. s, 0.8 H) ($\text{H}_2\text{N}-\text{C}(2')$); 5.95, 5.78 (2s, 1.2 H), 5.89, 5.63 (2 br. s, 0.8 H) ($\text{CH}_2=\text{C}$); 1.98 (s, 1.8 H), 1.95 (s, 1.2 H) (Me). ^{13}C -NMR (75 MHz, $(\text{D}_6)\text{DMSO}$): 3:2 mixture of H-bonded isomers): 165.95, 165.25 (2s, $\text{C}=\text{O}$); 165.80, 164.05 (2s, $\text{C}(5')$); 165.04, 162.63 (2s, $\text{C}(4')$); 150.20, 146.23 (2s, $\text{C}(2')$); 140.24, 138.52 (2s, $\text{C}(2)$); 140.12, 136.95 (2s, $\text{C}(6')$); 122.98, 122.10 (2t, $\text{C}(3)$); 18.18, 17.94 (2q, Me). HR-MALDI-MS: 223.0928 (100, $[\text{M} + \text{H}]^+$, $\text{C}_8\text{H}_{11}\text{N}_6\text{O}_2^+$; calc. 223.0938), 245.0756 (14, $[\text{M} + \text{Na}]^+$, $\text{C}_8\text{H}_{10}\text{N}_6\text{NaO}_2^+$; calc. 245.0757).

N,N'-(2-Amino-5-nitrosopyrimidine-4,6-diyl)bis(2-methylprop-2-enamide) (26). A soln. of 2,4,6-triamino-5-nitrosopyrimidine (**23**, 308 mg, 2.0 mmol) in THF (60 ml) was treated with K_2CO_3 (2.2 g, 16 mmol), cooled to -5 to -10° , treated dropwise with **14** (0.44 ml, 4.4 mmol) within 2 h (addition *via* a syringe pump), stirred for 2 h, and poured into cold H_2O (100 ml). After extraction with CH_2Cl_2 (3×100 ml), the combined org. layer was washed with brine (50 ml), dried (MgSO_4), and evaporated. FC ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 1:1) of the green residue gave **26** (222 mg, 38%). Green powder. M.p. $> 149^\circ$ (dec.). R_f (AcOEt) 0.30. UV: 231 (4.29), 279 (4.18), 356 (4.29). IR (ATR): 3313w, 3181m, 2993w, 2957w, 2920w, 1668s, 1637m, 1614m, 1527s, 1473s, 1448s, 1377m, 1340s, 1306s, 1163s, 1127m, 1080s, 1016w, 1002w, 953w, 930m, 907w, 798s. ^1H -NMR (300 MHz, CDCl_3): 13.06 (br. s, NH); 10.74 (br. s, NH); 7.03 (br. s, NH_2); 6.14, 5.96, 5.82, 5.70 (4s, 2 $\text{CH}_2=\text{C}$); 2.10 (s, 2 Me). ^{13}C -NMR (125 MHz, $(\text{D}_6)\text{DMSO}$): 165.67 (s, 2 $\text{C}=\text{O}$); 164.72 (s, $\text{C}(4')$); 139.96 (s, 2 $\text{C}(2)$); 137.95 (s, $\text{C}(6')$); 123.13 (br. t, 2 $\text{C}(3)$); 17.99 (q, 2 Me); signals of $\text{C}(2')$ and $\text{C}(5')$ not visible due to coalescence. HR-MALDI-MS (low intensity due to ene reaction during measurement): 291.1196 (18, $[\text{M} + \text{H}]^+$, $\text{C}_{12}\text{H}_{15}\text{N}_6\text{O}_3^+$; calc. 291.1200), 313.1013 (43, $[\text{M} + \text{Na}]^+$, $\text{C}_{12}\text{H}_{14}\text{N}_6\text{NaO}_3^+$; calc. 313.1020).

(IRS)-2',4'-Diamino-3,4-dimethylspiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]diazepin]-8'(9'H)-one ($\pm$)-25. A mixture of **24** (32 mg, 0.14 mmol) and 2,3-dimethylbuta-1,3-diene (0.16 ml, 1.1 mmol) in toluene (6 ml) in a sealed V-vial was heated for 0.5 h at 155° . The resulting suspension was evaporated, and the residue was washed with CH_2Cl_2 to afford ($\pm$)-**25** (38.8 mg, 94%). Light-brown powder. M.p. $237-239^\circ$ (dec.). R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) 0.38. UV: 220 (4.39), 305 (3.93). IR (ATR): 3473w, 3314w, 3201w, 3100w, 2912w, 2875w, 2827w, 1676m, 1628s, 1603m, 1587m, 1552s, 1520m, 1453m, 1393m, 1374w, 1309m, 1235m, 1218w, 1168w, 1138w, 1082w, 983w, 869m, 822m. ^1H -NMR (300 MHz, $(\text{D}_6)\text{DMSO}$): 10.32 (br. s, NH); 6.85 (s, $\text{HC}=\text{N}$); 6.53, 6.06 (2 br. s, 2 NH_2); 2.46, 2.14 (2d, $J = 16.5$, 2 $\text{H}-\text{C}(2)$); 1.86–1.42 (m, CH_2CH_2); 1.63, 1.56 (2s, 2 Me). ^{13}C -NMR (75 MHz, $(\text{D}_6)\text{DMSO}$): 167.93 (s, $\text{C}(8')$); 161.41 (s, $\text{C}(4')$); 160.64 (s, $\text{C}(2')$); 152.68 (d, $\text{C}(6')$); 145.62 (s, $\text{C}(9'a)$); 124.49, 122.91 (2s, $\text{C}(3)$, $\text{C}(4)$); 107.58 (s, $\text{C}(4'a)$); 50.92 (s, $\text{C}(1)$); 35.98 (t, $\text{C}(2)$); 28.23 (t, $\text{C}(5)$); 23.13 (t, $\text{C}(6)$); 19.06, 18.32 (2q, 2 Me). HR-MALDI-MS: 287.1611 (100, $[\text{M} + \text{H}]^+$, $\text{C}_{14}\text{H}_{19}\text{N}_6\text{O}^+$; calc. 287.1615).

(IRS)-N-(2'-Amino-8',9'-dihydro-3,4-dimethyl-8'-oxospiro[cyclohex-3-ene-1,7'-pyrimido[4,5-b][1,4]-diazepin]-4'-yl)-2-methylprop-2-enamide ($\pm$)-27. A mixture of **26** (43 mg, 0.15 mmol) and 2,3-dimethylbuta-1,3-diene (0.16 ml, 1.2 mmol) in toluene (6 ml) in a sealed V-vial was put into an oil-bath of 110° and stirred for 0.5 h. The resulting off-white suspension was evaporated. FC (AcOEt) gave **27** (50.8 mg, 97%). White powder. M.p. $> 143^\circ$ (dec.). R_f ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) 0.50. UV: 230 (4.45), 326 (4.08). IR (ATR): 3328w, 3218w, 2919w, 2852w, 1715m, 1674m, 1617s, 1549s, 1466s, 1376m, 1299m, 1239m, 1171m, 1114m, 1053w, 1033w, 1003w, 929w, 862w, 818w. ^1H -NMR (300 MHz, CDCl_3): 11.77 (br. s, 2 NH, distinguishable as 10.71 ($\text{N}(9')-\text{H}$) and 9.72 ($\text{HN}-\text{C}(4')$) in $(\text{D}_6)\text{DMSO}$); 9.52 (s, NH_2); 7.01 (s, $\text{HC}=\text{N}$); 5.86 (br. s), 5.56 (d, $J = 1.5$) ($\text{H}_2\text{C}=\text{C}$); 2.69, 2.23 (2d, $J = 17.1$, 2 $\text{H}-\text{C}(2)$); 2.05 (s, Me); 1.98–1.76 (m, CH_2CH_2); 1.68, 1.62 (2s, $\text{Me}-\text{C}(3)$, $\text{Me}-\text{C}(4)$). ^{13}C -NMR (75 MHz, CDCl_3): 169.96 (s, $\text{C}(8')$); 164.83 (s, $\text{C}=\text{O}$); 161.05 (s, $\text{C}(4')$); 156.22 (s, $\text{C}(2')$); 156.16 (d, $\text{C}(6')$); 147.34 (s, $\text{C}(9'a)$); 140.62 (s, $\text{C}=\text{CH}_2$); 125.69, 122.80 (2s, $\text{C}(3)$, $\text{C}(4)$); 121.54 (t, $\text{CH}_2=\text{C}$); 110.13 (s, $\text{C}(4'a)$); 52.16 (s, $\text{C}(1)$); 36.83 (t, $\text{C}(2)$); 28.88 (t, $\text{C}(5)$); 24.51 (t, $\text{C}(6)$); 19.54, 18.84 (2q, $\text{Me}-\text{C}(3)$, $\text{Me}-\text{C}(4)$); 18.62 (q, Me); assignment based on a DEPT and a HMBC spectrum. HR-MALDI-MS: 355.1873 (100, $[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{23}\text{N}_6\text{O}_2^+$; calc. 355.1877); 377.1710 (9, $[\text{M} + \text{Na}]^+$, $\text{C}_{18}\text{H}_{22}\text{N}_6\text{NaO}_2^+$; calc. 377.1696).

(IRS)-2-Amino-7,8,9,10-tetrahydro-3',4'-dimethyl-5-(1-methylethenyl)spiro[cyclohex-3-ene-1',8-[1,4]diazepino[1,2,3-gh]purine]-9-one (28) and (IRS)-2-(Ethylamino)-7,8,9,10-tetrahydro-3',4'-dimethyl-5-(1-methylethenyl)spiro[cyclohex-3-ene-1',8-[1,4]diazepino[1,2,3-gh]purine]-9-one (29). A soln. of $\text{NaBH}(\text{OAc})_3$ (0.21 g, 1.0 mmol) and AcOH (0.57 ml, 10 mmol) in CH_2Cl_2 (15 ml) was cooled to 0° , treated with a soln. of ($\pm$)-**27** (71 mg, 0.2 mmol) in CH_2Cl_2 (10 ml), stirred at r.t. for 34 h, diluted with CH_2Cl_2 (50 ml), and poured into H_2O (30 ml). After neutralisation with sat. NaHCO_3 soln., the org.

layer was separated, washed with H₂O (30 ml) and brine (30 ml), dried (MgSO₄), and evaporated. FC (cyclohexane/AcOEt 3:1 → 0:1) gave a mixture of **29** and **27**. Elution with CH₂Cl₂/MeOH (20:1) gave **28** (28 mg, 41%). Chromatography of the mixture **29/27** on neutral Al₂O₃ (activity IV, AcOEt/MeOH 100:3) afforded **29** (27 mg, 37%), each as a white powder.

Data of (±)-28: M.p. 181–183° (dec.). *R*_f (CH₂Cl₂/MeOH 20:1) 0.35. UV: 199 (4.21), 230 (4.54), 332 (3.91). IR (ATR): 3338w, 3204w, 3125w, 2975w, 2916w, 2861w, 1679m, 1636s, 1585s, 1487m, 1403m, 1364s, 1303m, 1272m, 1231m, 1169w, 1138w, 1101w, 1021w, 923w, 792m, 728w. ¹H-NMR (300 MHz, (D₆)DMSO, 353 K): 10.28 (s, H–N(10)); 5.79 (s, H₂N–C(2)); 5.68 (br. s), 5.35 (d, *J* = 0.9) (CH₂=C); 4.22 (s, 2 H–C(7)); 2.45, 1.97 (2d, *J* = 15, 2 H–C(2')); 2.15 (s, Me); 1.79–1.70 (m, CH₂CH₂); 1.56, 1.53 (2s, Me–C(3'), Me–C(4')). ¹³C-NMR (75 MHz, (D₆)DMSO): 175.02 (s, C(9)); 161.51 (s, C(2)); 160.33 (s, C(3a)); 154.72 (s, C(5)); 144.30 (s, C(10a)); 133.28 (s, C=CH₂); 123.61, 122.20 (2s, C(3'), C(4')); 121.57 (t, CH₂=C); 110.13 (s, C(10b)); 46.97 (t, C(7)); 46.14 (s, C(8)); 36.10 (t, C(2')); 27.71, 26.41 (2t, C(5'), C(6')); 21.69 (q, Me); 18.83, 18.06 (2q, Me–C(3'), Me–C(4')); assignment based on a HSQC and a HMBC spectrum. HR-MALDI-MS: 339.1926 (100, [*M* + H]⁺, C₁₈H₂₃N₆O⁺; calc. 339.1928), 361.1749 (4, [*M* + Na]⁺, C₁₈H₂₂N₆NaO⁺; calc. 361.1747). Anal. calc. for C₁₈H₂₂N₆O (338.41): C 63.89, H 6.55, N 24.83; found: C 63.73, H 6.75, N 24.09.

Data of (±)-29: M.p. 213–215° (dec.). *R*_f (CH₂Cl₂/MeOH 20:1) 0.45. UV: 202 (4.36), 233 (4.52), 337 (3.87). IR (ATR): 3323w, 3204w, 3119w, 2961m, 2925m, 2860m, 1726w, 1674m, 1635s, 1584s, 1507m, 1468m, 1445m, 1403s, 1366s, 1350s, 1324m, 1305m, 1274s, 1221s, 1135m, 1071w, 1043w, 1011w, 919w, 848w. ¹H-NMR (300 MHz, (D₆)DMSO): 10.64 (br. s, H–N(10)); 6.50 (br. t, *J* ≈ 5.7, HN–C(2)); 5.70, 5.33 (2 br. s, CH₂=C); 4.22 (s, 2 H–C(7)); 3.28 (quint., *J* ≈ 7.0, CH₂Me); 2.13 (s, MeC=CH₂); 2.00–1.40 (m, 6 H–C(2',5',6')); 1.54 (br. s, Me–C(3'), Me–C(4')); 1.12 (t, *J* = 7.2, MeCH₂). ¹³C-NMR (75 MHz, (D₆)DMSO): 175.09 (s, C(9)); 161.46 (s, C(2)); 159.53 (s, C(3a)); 154.63 (s, C(5)); 144.27 (s, C(10a)); 133.36 (s, C=CH₂); 123.59, 122.25 (2s, C(3'), C(4')); 121.64 (t, CH₂=C); 108.61 (s, C(10b)); 47.00 (t, C(7)); 46.22 (s, C(8)); 35.54 (t, C(2')); 28.18 (t, MeCH₂); 27.79, 26.53 (2t, C(5'), C(6')); 21.78 (q, MeC=CH₂); 18.95, 18.17 (2q, Me–C(3'), Me–C(4')); 14.81 (q, MeCH₂). HR-MALDI-MS: 367.2247 (100, [*M* + H]⁺, C₂₀H₂₇N₆O⁺; calc. 367.2246), 389.2085 (4, [*M* + Na]⁺, C₂₀H₂₆N₆NaO⁺; calc. 389.2066).

(1*RS*,2*RS*,4*RS*) (i.e., *endo*)- and (1*RS*,2*SR*,4*RS*) (i.e., *exo*)-N-[2'-Amino-8',9'-dihydro-8'-oxospiro[bicyclo[2.2.1]hept-5-ene-2,7'-pyrimido[4,5-b][1,4]diazepin]-4'-yl]-2-methylprop-2-enamide (*endo*-**30** and *exo*-**30**, resp.). A mixture of **26** (50 mg, 0.17 mmol) and cyclopenta-1,3-diene (0.12 ml, 1.36 mmol) in toluene (6 ml) in a sealed V-vial was put into an oil-bath of 110° and stirred for 0.5 h. The resulting suspension was evaporated, and FC (CH₂Cl₂/AcOEt 2:1) gave *endo*-**30**/*exo*-**30** 7:3 (48 mg, 84%). White powder. M.p. > 122° (dec.). *R*_f (CH₂Cl₂/AcOEt 1:1) 0.15. UV: 229 (4.41), 328 (4.02). IR (ATR): 3555w, 3369w, 3306w, 3198w, 3083w, 2973w, 2847w, 1737m, 1704m, 1665m, 1627s, 1616s, 1549s, 1465s, 1450s, 1382s, 1334m, 1310s, 1229m, 1173s, 1118m, 1076w, 1044m, 1026m, 951w, 937w, 870m, 818m. ¹H-NMR (300 MHz, CD₂Cl₂; *endo*/*exo* 7:3): 11.87 (s, 0.3 H), 11.84 (br. s, 0.7 H) (HN–C(8')); 9.38 (br. s, 0.7 H), 9.28 (s, 0.3 H) (HN–C(4')); 7.35 (s, 0.7 H), 7.13 (s, 0.3 H) (H–C(6')); 6.34–6.31 (m, 0.6 H), 6.25 (br. s, 1.4 H) (H–C(5), H–C(6)); 6.25 (br. s, NH₂); 5.83 (br. s, 0.7 H), 5.79 (br. s, 0.3 H) (CHH'=); 5.54 (q, *J* = 1.2, 0.7 H), 5.52 (q, *J* = 1.2, 0.3 H) (CHH'=); 3.51 (s, 0.3 H), 3.28 (br. s, 0.7 H) (H–C(1)); 2.90 (s, 0.3 H), 2.84 (br. s, 0.7 H) (H–C(4)); 2.01 (s, 2.1 H), 1.99 (s, 0.9 H) (Me); 1.69–1.42 (m, 2.8 H), 1.28–1.12 (m, 1.2 H) (2 H–C(3), 2 H–C(7)). ¹H-NMR (300 MHz, (D₆)DMSO; *endo*/*exo* 7:3): 10.71 (s, 0.3 H), 10.62 (s, 0.7 H) (HN–C(8')); 9.88 (s, 0.7 H), 9.74 (s, 0.3 H) (HN–C(4')); 7.33 (br. s, 0.7 H), 7.12 (s, 0.3 H) (H–C(6')); 6.61 (br. s, NH₂); 6.38–6.12 (m, H–C(5), H–C(6)); 5.85 (s, 0.7 H), 5.77 (s, 0.3 H) (CHH'=); 5.56 (s, 0.7 H), 5.51 (s, 0.3 H) (CHH'=); 3.37–3.27 (m, H–C(1)); 2.82–2.73 (m, H–C(4)); 1.89 (s, 2.1 H), 1.86 (s, 0.9 H) (Me); 1.64–1.30 (m, 2 H–C(3), 2 H–C(7)). ¹³C-NMR (75 MHz, CD₂Cl₂; *endo*/*exo* 7:3): 170.95, 169.00 (2s, C(8')); 165.50, 165.42 (2s, C=O); 161.53, 161.48 (2s, C(4')); 159.51, 159.07 (2d, C(6')); 155.99, 155.96 (2s, C(2')); 148.24, 147.73 (2s, C(9'a)); 141.78, 137.63 (2d, C(6)); 136.29, 133.37 (2d, C(5)); 140.74 (s, C=CH₂); 121.91 (t, CH₂=); 111.88, 111.34 (2s, C(4'a)); 61.38, 60.87 (2s, C(2)); 48.76, 48.10 (2t, C(7)); 47.62, 46.50 (2d, C(1)); 42.74, 41.34 (2d, C(4)); 40.54, 38.86 (2t, C(3)); 18.28 (q, Me). HR-MALDI-MS: 339.1558 (34, [*M* + H]⁺, C₁₇H₁₉N₆O₂⁺; calc. 339.1564), 361.1383 (4, [*M* + Na]⁺, C₁₁H₁₈N₆NaO₂⁺; calc. 361.1383). Signals of the ene product (retro-Diels–Alder product): 273.1084 (100, [*M* + H]⁺, C₁₂H₁₃N₆O₂⁺; calc. 273.1095), 295.0914 (5, [*M* + Na]⁺, C₁₂H₁₂N₆NaO₂⁺; calc. 295.0914).

(1'RS,2'RS,4'RS) (i.e., *endo*)- and (1'RS,2'SR,4'RS) (i.e., *exo*)-2-(Ethylamino)-7,8,9,10-tetrahydro-5-(1-methylethenyl)spiro[bicyclo[2.2.1]hept-5-ene-2',8-[1,4]diazepino[1,2,3-gh]purine]-9-one (*endo*-**31** and *exo*-**31**, resp.). A soln. of NaBH(OAc)₃ (0.29 g, 1.3 mmol) and AcOH (0.38 ml, 6.5 mmol) in CH₂Cl₂ (8 ml) was cooled to 0°, treated with a soln. of *endo*-**30**/*exo*-**30** 7:3 (43 mg, 0.13 mmol) in CH₂Cl₂ (8 ml), stirred at r.t. for 2 d, diluted with CH₂Cl₂ (40 ml), and poured into H₂O (20 ml). After neutralisation with sat. NaHCO₃ soln., the org. layer was separated, washed with H₂O (2 × 20 ml) and brine (20 ml), dried (MgSO₄), and evaporated. FC (CH₂Cl₂/AcOEt 2:1 to 0:1) gave *endo*-**31**/*exo*-**31** 7:3 (21 mg, 47%). White powder. M.p. > 173° (dec.). *R*_f (AcOEt) 0.25. UV: 198 (4.16), 237 (4.61), 346 (3.87). IR (ATR): 3320*m*, 3107*w*, 3058*w*, 2972*w*, 2941*w*, 2912*w*, 2872*w*, 1679*s*, 1634*s*, 1587*s*, 1513*m*, 1472*m*, 1401*m*, 1360*s*, 1336*m*, 1317*m*, 1292*w*, 1276*m*, 1252*m*, 1228*s*, 1161*w*, 1139*w*, 1121*w*, 1103*w*, 1071*w*, 1007*w*, 948*w*, 880*w*, 826*w*, 805*m*. ¹H-NMR (300 MHz, CD₂Cl₂; *endo*/*exo* 7:3): 11.06 (br. *s*, H–N(10)); 7.05 (br. *s*, HN–C(2)); 6.34–6.29 (*m*, 0.6 H), 6.23, 6.01 (2 br. *s*, 1.4 H) (CH(5')=CH(6')); 5.74 (0.7 H), 5.68 (0.3 H) (2*s*, CHH'=); 5.34 (0.7 H), 5.26 (0.3 H) (2*s*, CHH'=); 4.41 (*s*, 1.4 H), 4.09 (*s*, 0.6 H) (2 H–C(7)); 3.48–3.40 (*m*, MeCH₂); 3.18–2.48 (*m*, H–C(1'), H–C(4')); 2.27 (*s*, 2.1 H), 2.25 (*s*, 0.9 H) (MeC=CH₂); 2.00–1.40 (*m*, 2 H–C(3'), 2 H–C(7')); 1.27 (*t*, 2.1 H), 1.14 (*t*, 0.9 H) (*J* = 7.2, MeCH₂). ¹³C-NMR (75 MHz, CD₂Cl₂; only peaks of major isomer are assigned): 176.41 (br. *s*, C(9)); 162.82 (*s*, C(2)); 160.42 (*s*, C(3a)); 156.71 (*s*, C(5)); 144.76 (*s*, C(10a)); 140.82, 131.52 (2 br. *d*, C(5'), C(6')); 134.47 (*s*, C=CH₂); 122.14 (*t*, CH₂=); 109.90 (br. *s*, C(10b)); 57.12 (*s*, C(8)); 51.72 (br. *t*, C(3')); 48.35 (*d*, C(1')); 46.98 (*t*, C(7)); 45.85 (br. *t*, C(7')); 42.60 (*d*, C(4')); 36.66 (*t*, MeCH₂); 22.22 (*q*, MeC=CH₂); 14.62 (*q*, MeCH₂). HR-MALDI-MS: 351.1931 (100, [M + H]⁺, C₁₉H₂₃N₆O⁺; calc. 351.1933); 373.1752 (4, [M + Na]⁺, C₁₉H₂₂N₆NaO⁺; calc. 373.1753).

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