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

by **Fang-Li Zhang** and **Andrea Vasella***

Laboratorium für Organische Chemie, Departement Chemie und Angewandte Biowissenschaften, ETH Zürich, HCI, CH-8093 Zürich

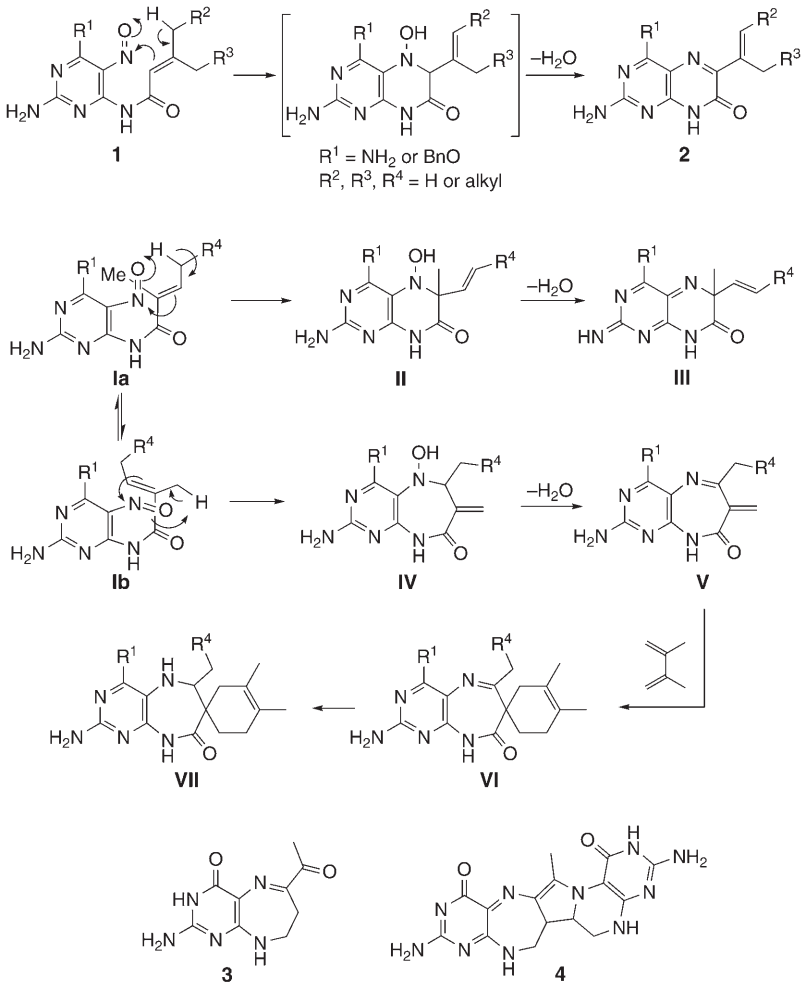
New spirocyclic heterocycles **8**, **16**, **19/20**, **25**, **27**, and **30** derived from pyrimido[4,5-*b*][1,4]diazepin]-8′(9′*H*)-one were synthesised by a tandem nitroso-ene/*Diels–Alder* reaction of 4-(alkenoylamino)-5-nitrosopyrimides. The crystal structure of **16** was established by X-ray 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 H_2O, 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 raction of 4-(alkenoylamino)-5-nitrosopyrimidines **I** that lack the CH_2R^4 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

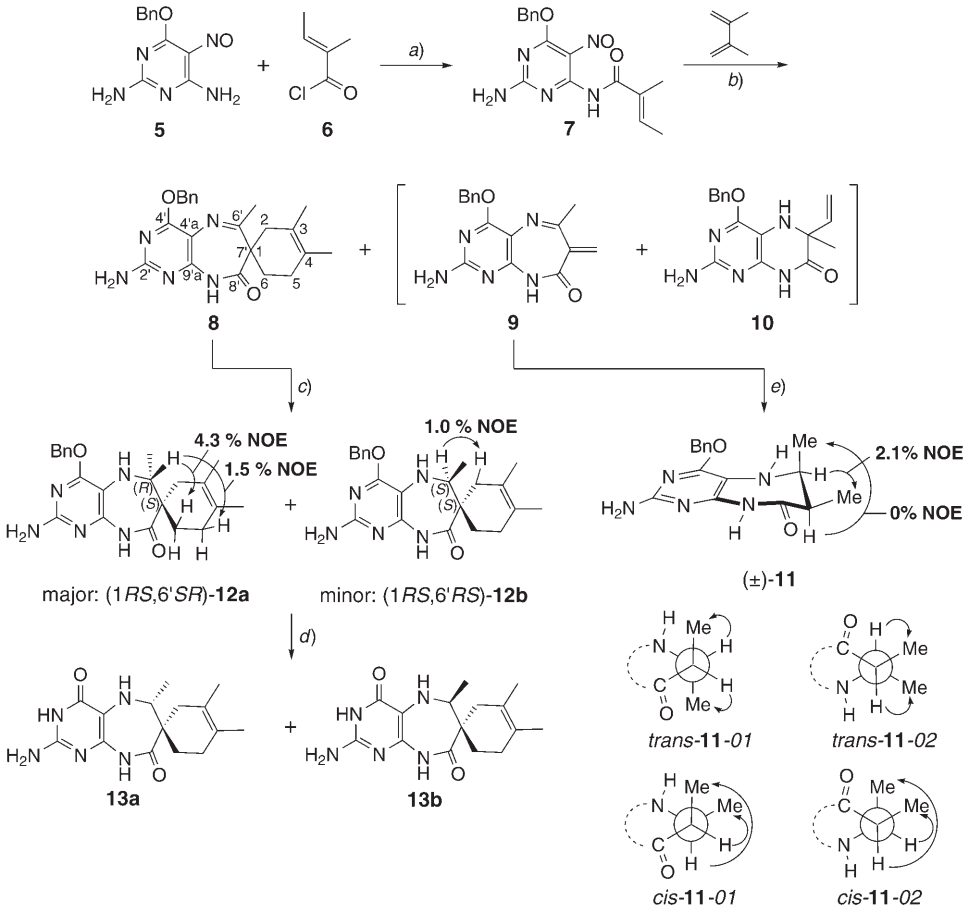
Scheme 1



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 $Sc(OTf)_3$ 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 ^{1}H-NOE difference spectra evidence a different distance between the two Me

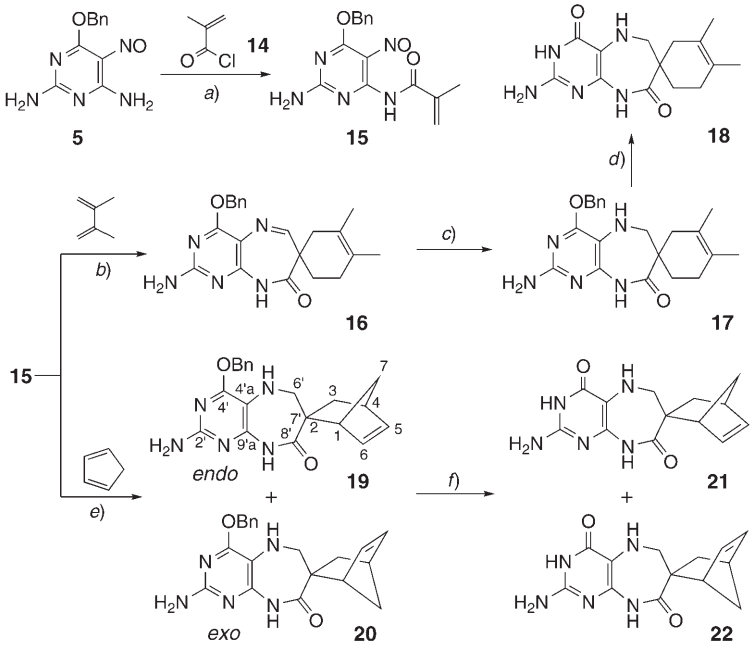
groups to either H–C(6) or H–C(7) and thus, for a chair-like conformer, the *cis*-configuration as in *cis*-**11**-*02* (*Scheme 2*). The dihydropteridinone **10** was not isolated; it is thought to arise (by disproportionation?) from precursor **II** (*Scheme 1*). Addition of butadiene subsequent to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

The ^{1}H-NMR spectrum of **8** in $CDCl_3$ shows conspicuous signals of the allylic CH_2 group linked to the spiro centre (2*d* 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 ^{1}H-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 $NaBH(OAc)_3$ 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*) $NaBH(OAc)_3$, AcOH, CH_2Cl_2; 97%. *d*) TMSCl, LiBr, MeCN; 92%. *e*) 110° (sealed V-vial), 0.5 h, toluene; 85%, then $NaBH(OAc)_3$, 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 (NH_2-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 $H_2C(3)$ [16]. Debenzylation of **19** and **20** with TMSBr gave rise to a considerable amount of by-products, while debenzylation with TFA and Et_3SiH 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 ^{t}BuOH/CH_2Cl_2 (2:1; *Fig.*). In the unit

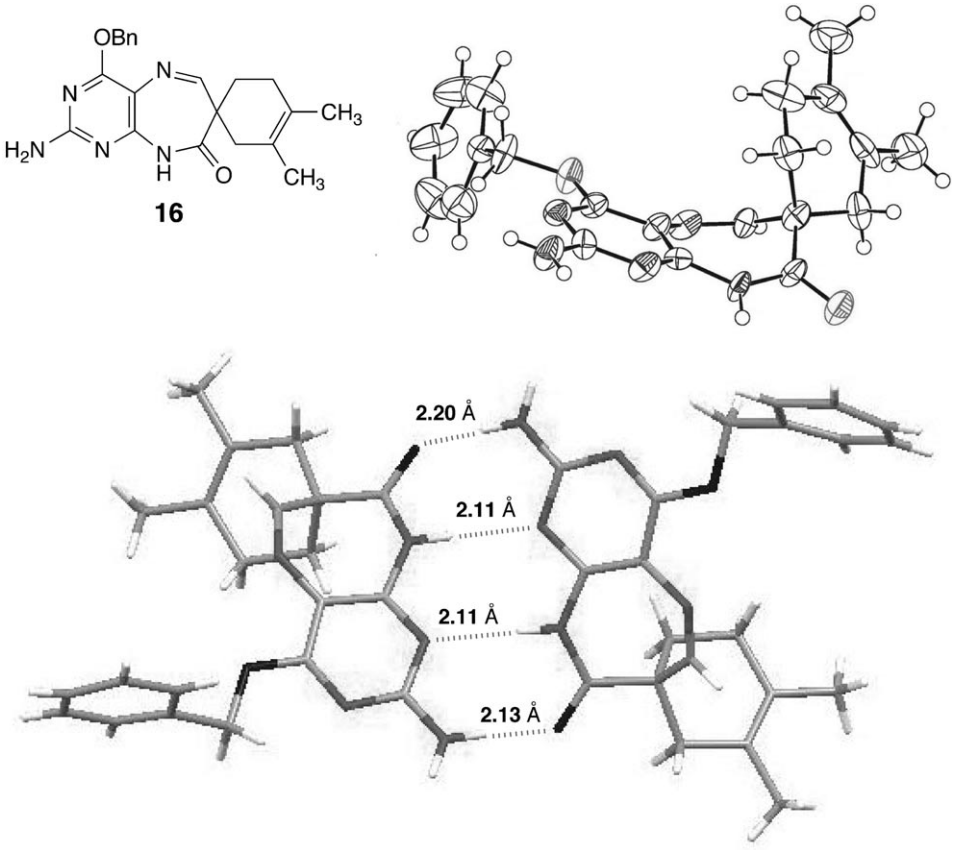


Figure. *Crystal structure of* **16** *showing the conformation and the intermolecular H-bonds*

[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 $H_2N-C=N$ and $O=C-NH$ groups of two molecules, with $H\cdots N/O$ 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 N=C*H s* at 6.94 ppm and the N=*C*H *d* at 154.84 ppm, and by the appearance of new signals for N*H*CH_2 at 4.72–4.69 ppm (*m*, D_2O exchangeable, 1 H); for NHC*H*$_2$ 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 NH*C*H_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 ($^6H_7$ and/or $^7H_6$) 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 C=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**.

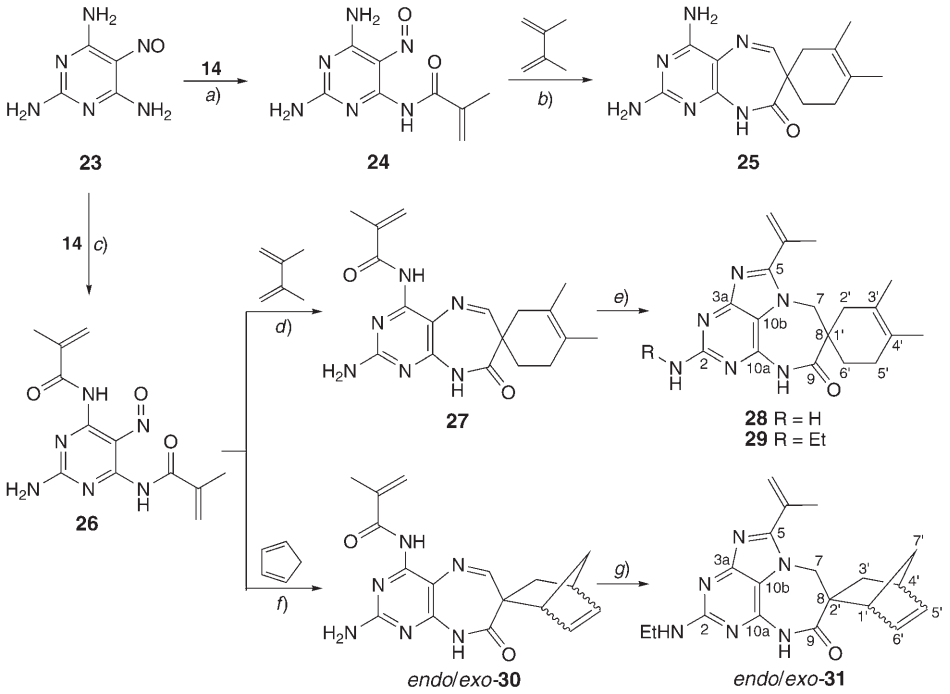
To test the effect on the ene reaction of substituting the benzyloxy by an amino or an acylamino group, we acylated the poorly soluble 2,4,6-triamino-5-nitrosopyrimidine (**23**) [18] with methacryloyl chloride (**14**), and obtained a mixture **24**/**26** of mono- and diacylated products that were 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 $NaBH(OAc)_3$ 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 $NaBH(OAc)_3$ as the source of the Et group. As *ca.* 10% starting material remained when **27** was treated with 5 equiv. $NaBH(OAc)_3$ 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 $N-CH_2$ 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 $CH_2(7)$ and C(2′), C(6′), C(5), C(8), C(9), and 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*) $NaBH(OAc)_3$, AcOH; 41% of **28** and 37% of **29**. *f*) 110° (sealed V-vial), toluene; 84%. *g*) $NaBH(OAc)_3$, AcOH, CH_2Cl_2; 47%.

excess $NaBH(OAc)_3$ 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. Pfleiderer* for stimulating discussions about the UV spectra, and *Brigitte Brandenberg* 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-hydroxypicolinic 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 CH_2Cl_2/AcOEt 2:1 (20 ml). Filtration gave **7** (265 mg, 54%). Blue powder. M.p. $>139°$ (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.50. UV: 204 (4.39), 259 (4.14), 350 (4.33). IR (ATR): 3375*w*, 3319*m*, 3236*m*, 1712*m*, 1649*s*, 1634*s*, 1591*s*, 1579*m*, 1519*s*, 1497*m*, 1456*s*, 1435*s*, 1402*s*, 1352*s*, 1329*m*, 1310*m*, 1255*s*, 1188*s*, 1145*s*, 1129*s*, 1076*s*, 1042*s*, 1017*m*, 979*m*, 939*w*, 879*m*, 851*w*, 827*m*. ^{1}H-NMR (300 MHz, (D_6)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}C-NMR (75 MHz, (D_6)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 (2*d*); 128.33 (2*d*); 128.17 (*d*); 68.31 (*t*, PhCH_2); 14.29, 11.81 (2*q*, 2 Me); signals of C(2′) and C(5′) not visible due to coalescence. HR-MALDI-MS: 328.1409 (40, $[M+H]^+$, $C_{16}H_{18}N_5O_3^+$; calc. 328.1410), 350.1219 (100, $[M+Na]^+$, $C_{16}H_{17}N_5NaO_3^+$; 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° (dec.). R_f (cyclohexane/AcOEt 1:2) 0.53. UV: 206 (4.50), 217 (4.497), 307 (4.11). IR (ATR): 3480*w*, 3321*w*, 3202*m*, 2925*w*, 2855*w*, 1655*m*, 1625*s*, 1594*s*, 1549*s*, 1482*m*, 1424*s*, 1381*m*, 1345*s*, 1312*m*, 1271*m*, 1236*m*, 1202*w*, 1179*m*, 1153*m*, 1092*m*, 1060*w*, 1041*w*, 986*w*, 951*w*, 909*w*, 847*w*, 824*w*. ^{1}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 (2*d*, *J* = 12.9, PhCH_2); 2.78, 2.52 (2*d*, *J* = 17.1, 2 H–C(2)); 2.21 (*s*, Me–C(6′)); 1.98–1.66, 1.50–1.40 (2*m*, 2 CH_2); 1.74, 1.59 (2*s*, 2 Me). ^{1}H-NMR (300 MHz, (D_6)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 (2*d*, *J* = 18.9, 2 H–C(2)); 2.08 (*s*, Me–C(6′)); 1.90–1.70, 1.60–1.50 (2*m*, 2 CH_2); 1.65, 1.55 (2*s*, 2 Me). ^{13}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 (2*d*); 127.67 (*d*); 127.51 (2*d*); 125.74, 124.15 (2*s*, 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 (2*t*, C(5), C(6)); 25.58 (*q*, Me–C(6′)); 19.00, 18.33 (2*q*, 2 Me). ^{13}C-NMR (75 MHz, (D_6)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 (2*d*); 127.91 (2*d*); 127.78 (*d*); 125.74, 124.15 (2*s*, 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 (2*t*, C(5), C(6)); 25.13 (*q*, Me–C(6′)); 18.98, 18.16 (2*q*, 2 Me). HR-MALDI-MS: 392.2086 (100, $[M+H]^+$, $C_{22}H_{26}N_5O_2^+$; calc. 392.2087), 414.1913 (5, $[M+Na]^+$, $C_{22}H_{25}N_5NaO_2^+$; 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 1N NaOH, H_2O (2 × 30 ml), and brine (30 ml), dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/AcOEt 6:1) gave **12a**/**12b** (35 mg, 82%). White powder. M.p. 98–100° (dec.). R_f (CH_2Cl_2/AcOEt 2:1) 0.44. UV: 205 (4.45), 269 (3.77), 343 (3.85). IR (ATR): 3311*w*, 3200*w*, 2969*w*, 2912*w*, 2855*w*, 1635*m*, 1572*s*, 1494*m*, 1436*s*, 1407*s*, 1376*m*, 1352*s*, 1284*m*, 1237*m*, 1210*m*, 1173*m*,

1090*s*, 1028*w*, 947*w*, 909*w*, 843*w*. ^{1}H-NMR (500 MHz, CD_2Cl_2; 3:1 mixture of diastereoisomers): 9.44 (*s*, 0.25 H), 9.33 (*s*, 0.75 H) (H–N(9′), exchange with D_2O); 7.43–7.33 (*m*, 5 arom. H); 5.36 (*s*, PhCH_2); 5.18 (*s*, 0.5 H), 5.12 (*s*, 1.5 H) (H_2N–C(2′), exchange with D_2O); 4.06 (br. *s*, 0.75 H), 4.00 (br. *s*, 0.25 H) (H–N(5′), exchange with D_2O); 3.33 (*m*, H–C(6′), addn. of $D_2O \rightarrow q$, $J = 6.0$); 2.72 (*d*, 0.75 H), 2.19 (*d*, 0.25 H) ($J \approx 15.0$, H–C(2)); 2.13–1.67 (*m*, H′–C(2), CH_2CH_2); 1.63, 1.59 (2*s*, 4.5 H), 1.59, 1.54 (2*s*, 1.5 H) (Me–C(3), Me–C(4)); 1.09 (*d*, $J = 6.0$, Me–C(6′)). ^{13}C-NMR (125 MHz, CD_2Cl_2; 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 (2*d*); 128.84 (2*d*); 128.73 (*d*); 124.66, 123.61 (2*s*, C(3), C(4)); 108.64 (*s*, C(4′a)); 69.17 (*t*, PhCH_2); 51.98 (*s*, C(1)); 50.00 (*d*, C(6′)); 38.46 (*t*, C(2)); 29.59, 28.72 (2*t*, C(5), C(6)); 19.46 (*q*, *Me*–C(6′)); 18.85, 18.82 (2*q*, 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 (2*d*); 128.75 (*d*); 128.71 (2*d*); 125.27, 122.98 (2*s*, C(3), C(4)); 108.60 (*s*, C(4′a)); 69.08 (*t*, PhCH_2); 51.40 (*s*, C(1)); 49.48 (*d*, C(6′)); 38.22 (*t*, C(2)); 29.36, 28.83 (2*t*, C(5), C(6)); 19.59 (*q*, *Me*–C(6′)); 18.90, 18.35 (2*q*, 2 *Me*–C(3,4)). HR-MALDI-MS: 394.2239 (100, $[M+H]^+$, $C_{22}H_{28}N_5O_2^+$; calc. 394.2238), 416.2073 (3, $[M+Na]^+$, $C_{22}H_{27}N_5NaO_2^+$; calc. 416.2062).

*2-Amino-4-(benzyloxy)-6,7-dihydro-6,7-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]diazepin-8(9*H*)-one* (**11**). The pooled by-products obtained by FC of **8** (22 mg) was treated with excess $NaBH_4$ 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): 3444*m*, 3380*w*, 3330*w*, 3227*w*, 3083*w*, 2963*w*, 2928*w*, 1664*s*, 1619*s*, 1570*s*, 1497*m*, 1479*s*, 1450*m*, 1438*m*, 1417*s*, 1380*m*, 1368*m*, 1354*s*, 1290*m*, 1270*s*, 1206*w*, 1173*m*, 1145*m*, 1084*m*, 1072*m*, 1053*m*, 1029*w*, 1003*w*, 986*w*, 954*w*, 904*w*, 862*w*, 801*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 9.56 (br. *s*, H–N(9)); 7.49–7.30 (*m*, 5 arom. H); 5.96 (br. *s*, NH_2); 5.36 (*s*, PhCH_2); 4.06 (*d*, $J = 4.5$, H–N(5)); 3.67–3.62 (*dq*, $J = 3.0, 5.5$, H–C(6), after D_2O exchange); 2.72–2.67 (*dq*, $J = 3.0, 6.0$, H–C(7), after D_2O exchange); 1.02 (*d*, $J = 6.0$, Me–C(6)); 0.92 (*d*, $J = 6.0$, Me–C(7)). ^{13}C-NMR (75 MHz, (D_6)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 (2*d*); 128.06 (2*d*); 127.98 (*d*); 108.83 (*s*, C(4a)); 67.17 (*t*, PhCH_2); 58.12 (*d*, C(6)); 41.92 (*d*, C(7)); 18.27, 12.46 (2*q*, 2 Me). HR-MALDI-MS: 314.1612 (100, $[M+H]^+$, $C_{16}H_{20}N_5O_2^+$; calc. 314.1612).

*(1*RS*,6′*RS*)- 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 Me_3SiCl (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 Me_3SiCl (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 Et_2O), and dried *i.v.* to afford **13a**/**13b** (10 mg, 81%). Off-white powder. M.p. >245° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.28. UV: 204 (4.15), 223 (4.19), 252 (3.83), 346 (3.76). IR (ATR): 3336*w*, 3244*w*, 3135*w*, 3042*w*, 2974*w*, 1697*s*, 1651*s*, 1577*w*, 1530*w*, 1491*w*, 1442*w*, 1384*m*, 1351*w*, 1312*m*, 1281*m*, 1249*w*, 1196*w*, 1131*w*, 1085*w*, 1064*w*, 910*w*. ^{1}H-NMR (300 MHz, (D_6)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) (2*s*, H–N(9′)); 7.40 (0.5 H), 7.31 (1.5 H) (2 br. *s*, NH_2); 5.48 (br. *s*, H–N(5′)); 3.37 (*m*, H–C(6′)); 2.76–2.40, 2.20–1.62 (2*m*, 6 H–C(2,5,6)); 1.59, 1.56 (2*s*, 4.5 H), 1.56, 1.54 (2*s*, 1.5 H) (Me–C(3), Me–C(4)); 1.06 (0.75 H), 0.97 (2.25 H) (2*d*, $J \approx 6.0$, Me–C(6′)). ^{13}C-NMR (125 MHz, (D_6)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 (2*s*, 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 (2*t*, 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, $[M+H]^+$, $C_{15}H_{22}N_5O_2^+$; calc. 304.1768), 326.1590 (4, $[M+Na]^+$, $C_{15}H_{21}N_5NaO_2^+$; 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 K_2CO_3 (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 CH_2Cl_2 (200 ml), washed with cold H_2O (2 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/AcOEt 3:1) of the green residue gave **15** (568 mg, 45%). Blue powder. M.p. >150° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.50. UV: 205 (4.35), 261 (4.11), 353 (4.34). IR (ATR): 3481*m*, 3299*w*, 3200*m*, 1712*m*, 1630*s*, 1597*s*, 1543*s*, 1496*m*, 1483*w*, 1450*s*, 1401*m*, 1377*w*, 1346*s*, 1307*s*, 1289*s*, 1268*m*, 1194*s*, 1148*s*, 1100*s*, 1078*m*, 1060*m*, 1029*m*, 1002*m*, 946*s*, 910*m*, 889*w*, 845*m*, 810*m*. ^{1}H-NMR

(300 MHz, (D_6)DMSO): 13.15 (br. *s*, NH); 8.83, 8.76 (2 br. *s*, NH_2); 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*, PhCH_2); 1.99 (*s*, Me). ^{1}H-NMR (300 MHz, $CDCl_3$): 13.22 (br. *s*, NH); 7.54–7.34 (*m*, 5 arom. H); 7.02, 6.05 (2 br. *s*, NH_2); 6.16 (br. *s*, H–C(3)); 5.79 (*d*, $J = 1.2$, H′–C(3)); 5.72 (*s*, PhCH_2); 2.10 (*s*, Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (2*d*); 128.40 (*d*); 128.20 (2*d*); 124.30 (*t*, C(3)); 69.53 (*t*, Ph*C*H_2); 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, $[M+H]^+$, $C_{15}H_{16}N_5O_3^+$; calc. 314.1248), 336.1084 (1, $[M+Na]^+$, $C_{15}H_{15}N_5NaO_3^+$; calc. 336.1067).

*(1*RS*)-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*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.60 (br. *s*, NH); 7.46–7.31 (*m*, 5 arom. H); 6.94 (*s*, N=C*H*); 6.68 (br. *s*, NH_2); 5.44, 5.38 (2*d*, $J = 12.3$, PhCH_2); 2.42 (*d*, $J = 16.8$), 2.13 (*d*, $J = 17.4$) (2 H–C(2)); 1.88–1.44 (*m*, CH_2CH_2); 1.60, 1.55 (2*s*, 2 Me). ^{13}C-NMR (75 MHz, (D_6)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 (2*d*); 127.92 (2*d*); 127.75 (*d*); 124.52, 122.85 (2*s*, C(3), C(4)); 109.83 (*s*, C(4′a)); 67.32 (*t*, Ph*C*H_2); 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, $[M+H]^+$, $C_{21}H_{24}N_5O_2^+$; calc. 378.1925), 400.1745 (4, $[M+Na]^+$, $C_{21}H_{23}N_5NaO_2^+$; calc. 400.1744). Anal. calc. for $C_{21}H_{23}N_5O_2$ (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 ^{t}BuOH/CH_2Cl_2 (2:1) gave single crystals suitable for X-ray-analysis (dimensions: $0.02 \times 0.25 \times 0.35$ mm; colourless). $4(C_{21}H_{23}N_5O_2) \cdot CH_2Cl_2$, M_r 1679.62, triclinic, $P\bar{1}$, $a = 13.9256(10)$, $b = 17.2683(14)$, $c = 8.013(2)$ Å, $\alpha = 92.962(3)$, $\beta = 106.058(3)$, $\gamma = 90.082(4)°$, $V = 4156.5(6)$ Å^3; $Z = 4$, $D_{calc.} = 1.268$ Mg/m^3. Intensities were measured on a *Nonius Kappa CCD* diffractometer, with MoK_α radiation $\lambda = 0.71073$ Å, $\theta = 3.7–22.8°$, $\mu = 0.150$ mm^{-1}, $T = 223$ K. There are four symmetrically independent molecules in the unit cell, which contains also at least two solvent (CH_2Cl_2) 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.

*(1*RS*)-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 µl, 0.45 mmol) in CH_2Cl_2 (5 ml) at 0° was treated with a soln. of **16** (25 mg, 0.07 mmol) in CH_2Cl_2 (5 ml), stirred at r.t. for 2 h, diluted with CH_2Cl_2 (20 ml), and poured into H_2O (20 ml). After basification by addition of sat. $NaHCO_3$, the org. phase was washed with H_2O (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt 3:1) gave **17** (24.5 mg, 97%). Very hygroscopic white powder. M.p. 87–89° (dec.). R_f (CH_2Cl_2/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*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 8.88 (br. *s*, NH); 7.51–7.32 (*m*, 5 arom. H); 5.74 (br. *s*, NH_2); 5.37, 5.32 (2*d*, $J = 12.9$, PhCH_2); 4.72–4.69 (*m*, N*H*CH_2); 3.06 (*dd*, $J = 13.7$, 5.6), 2.88 (*dd*, $J = 13.7$, 3.2) (NHCH_2); 2.45 (H–C(2), overlapping with signal of (D_6)DMSO); 2.18–2.02 (*m*, H′–C(2)); 1.82–1.66 (*m*, CH_2CH_2); 1.57 (*s*, 2 Me). ^{13}C-NMR (75 MHz, (D_6)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 (2*d*); 127.77 (2*d*); 127.63 (*d*); 123.37, 122.23 (2*s*, C(3), C(4)); 109.45 (*s*, C(4′a)); 67.15 (*t*, Ph*C*H_2); 46.77 (*s*, C(1)); 46.17 (*t*, NH*C*H_2); 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).

*(1*RS*)-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 µl, 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 µl, 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 → 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): 3334*w*, 3242*w*, 3148*w*, 3019*w*, 2912*w*, 1704*m*, 1631*s*, 1611*s*, 1542*w*, 1503*w*, 1463*m*, 1389*m*, 1315*m*, 1289*m*, 1213*w*, 1175*w*, 1088*w*, 1043*w*, 891*w*, 848*w*. ^{1}H-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 (2*d*, *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 (2*s*, 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 (2*q*, 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.

*(1*RS*,2*RS*,4*RS*)* (*i.e. endo*)- *and (1*RS*,2*SR*,4*RS*)* (*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 µl, 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 × 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): 3494*w*, 3448*w*, 3407*w*, 3337*w*, 3191*w*, 3080*w*, 2969*w*, 2938*w*, 2847*w*, 1616*s*, 1571*s*, 1485*s*, 1454*m*, 1426*s*, 1368*s*, 1343*s*, 1286*m*, 1239*m*, 1216*m*, 1193*m*, 1171*m*, 1141*m*, 1087*m*, 1047*w*, 1030*w*, 1003*w*, 957*m*, 909*w*, 847*m*. ^{1}H-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 (2*m*, H–C(5), H–C(6)); 5.38 (*s*, 0.6 H), 5.37 (*s*, 1.4 H) (PhCH_2); 5.37 (br. *s*, N*H*CH_2); 3.55, 3.43 (2*d*, *J* = 13.2, 1.4 H), 3.18, 2.98 (2*d*, *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 (2*d*, C(5), C(6)); 136.02 (*s*); 128.53 (2*d*); 128.36 (*d*); 128.33 (2*d*); 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 (2*d*, 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 (2*d*, C(5), C(6)); 136.01 (*s*); 128.53 (2*d*); 128.36 (*d*); 128.33 (2*d*); 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 (2*d*, 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 × 25 mm), NH_2 phase, 5 µm, 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.). ^{1}H-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 (2*m*, 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, N*H*CH_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 (2*d*, C(5), C(6)); 136.89 (*s*); 128.33 (2*d*); 127.86 (2*d*); 127.79 (*d*); 109.32 (*s*, C(4′a)); 67.17 (*t*, Ph*C*H$_2$); 55.73 (*s*, C(2)); 53.34 (*t*, C(6′)); 46.85, 41.68 (2*d*, C(1), C(4)); 46.73 (*t*, C(7)); 36.18 (*t*, C(3)). HR-MALDI-MS: 364.1762 (100, $[M+H]^+$, $C_{20}H_{22}N_5O_2^+$; calc. 364.1768).

Data of **20**: M.p. 197–200° (dec.). ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 9.14 (*s*, NH, exchange with D$_2$O); 7.49–7.29 (*m*, 5 arom. H); 6.28–6.22, 6.16–6.10 (2*m*, H–C(5), H–C(6)); 5.754, 5.74 (2*s*, NH$_2$, exchange with D$_2$O); 5.37 (*s*, Ph*CH*$_2$); 4.55 (br. *s*, N*H*C*H*$_2$, exchange with D$_2$O); 3.02 (*d*, *J* = 12.6, 1 H), 2.94 (*dd*, *J* = 12.6, 4.8, 1 H) (NHC*H*$_2$); 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 (2*d*, *J* = 7.7, 2 H–C(7)); 0.87 (*d*, *J* = 11.6, H′–C(3)). ^{13}C-NMR (125 MHz, (D$_6$)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 (2*d*, C(5), C(6)); 128.25 (2*d*); 127.74 (2*d*); 127.70 (*d*); 109.75 (*s*, C(4′a)); 67.07 (*t*, Ph*C*H$_2$); 55.89 (*s*, C(2)); 50.54 (*t*, C(6′)); 48.16, 41.42 (2*d*, C(1), C(4)); 46.95 (*t*, C(7)); 36.12 (*t*, C(3)). HR-MALDI-MS: 364.1762 (100, $[M+H]^+$, $C_{20}H_{22}N_5O_2^+$; calc. 364.1768).

*(1*RS*,2*RS*,4*RS*) (i.e., endo)- and (1*RS*,2*SR*,4*RS*) (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 Et$_3$SiH (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, Et$_2$O 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 (CH$_2$Cl$_2$/MeOH 20:1) 0.28. UV: 203 (4.28), 225 (4.30), 340 (3.80). IR (ATR): 3347*w*, 3179*w*, 3054*w*, 2981*w*, 1714*s*, 1663*m*, 1625*s*, 1569*w*, 1551*w*, 1465*m*, 1431*m*, 1412*m*, 1377*m*, 1328*m*, 1281*m*, 1197*s*, 1178*s*, 1142*s*, 1097*w*, 1066*w*, 1037*w*, 1004*w*, 950*w*, 834*w*. ^{1}H-NMR (300 MHz, (D$_6$)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 (2*m*, 0.6 H), 6.14–6.12, 5.93–5.91 (2*m*, 1.4 H) (CH=CH); 5.81 (br. *s*, NH$_2$); 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)). ^{13}C-NMR (125 MHz, (D$_6$)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 (2*d*, (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 (2*d*, C(1), C(4)); 46.65, 35.83 (2*t*, C(3), C(7)); minor: 175.91 (*s*, C(8′)); 159.08 (*s*, C(4′)); 146.12 (*s*, C(2′)); 138.49, 133.56 (2*d*, 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 (2*d*, C(1), C(4)); 47.00, 35.90 (2*t*, C(3), C(7)). HR-MALDI-MS: 273.1218 (100, M^+, $C_{13}H_{15}N_5O_2^+$; calc. 274.1226), 274.1301 (78, $[M+H]^+$, $C_{13}H_{16}N_5O_2^+$; calc. 274.1299). Anal. calc. for $C_{13}H_{15}N_5O_2$ (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**: ^{1}H-NMR (300 MHz, (D$_6$)DMSO): 11.20 (br. *s*, NH); 9.20 (*s*, NH); 6.47 (br. *s*, NH$_2$); 6.14–6.12, 5.95–5.93 (2*m*, H–C(5), H–C(6)); 4.22 (br. *s*, N*H*C*H*$_2$, overlapping with signal of H$_2$O); 3.43 (br. *s*, NHC*H*$_2$); 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**: ^{1}H-NMR (300 MHz, (D$_6$)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*, NH$_2$); 4.59 (br. *s*, N*H*C*H*$_2$, overlapping with signal of H$_2$O); 3.01 (br. *s*, NHC*H*$_2$); 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 (2*d*, *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 K$_2$CO$_3$ (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 H$_2$O (200 ml). After extraction with AcOEt (3 × 100 ml), the org. layer was washed with brine (50 ml), dried (MgSO$_4$), and evaporated. The green residue was washed with (CH$_2$Cl$_2$/THF 4:1) to give pure solid **24** (145 mg). FC (CH$_2$Cl$_2$/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): 3467*w*, 3437*w*, 3321*w*, 3107*m*, 1650*s*, 1627*s*, 1521*s*, 1478*s*, 1461*s*, 1399*m*, 1349*m*, 1312*s*, 1292*m*, 1226*m*, 1145*s*, 1106*m*, 1036*w*, 1004*w*, 945*m*, 894*w*, 820*w*. ^{1}H-NMR (300 MHz, (D$_6$)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) (H$_2$N–C(6′)); 8.07, 7.80 (2 br. *s*,

1.2 H), 7.98, 7.88 (2 br. *s*, 0.8 H) ($H_2N-C(2')$); 5.95, 5.78 (2*s*, 1.2 H), 5.89, 5.63 (2 br. *s*, 0.8 H) ($CH_2=C$); 1.98 (*s*, 1.8 H), 1.95 (*s*, 1.2 H) (Me). ^{13}C-NMR (75 MHz, (D_6)DMSO; 3:2 mixture of H-bonded isomers): 165.95, 165.25 (2*s*, C=O); 165.80, 164.05 (2*s*, C(5′)); 165.04, 162.63 (2*s*, C(4′)); 150.20, 146.23 (2*s*, C(2′)); 140.24, 138.52 (2*s*, C(2)); 140.12, 136.95 (2*s*, C(6′)); 122.98, 122.10 (2*t*, C(3)); 18.18, 17.94 (2*q*, Me). HR-MALDI-MS: 223.0928 (100, $[M+H]^+$, $C_8H_{11}N_6O_2^+$; calc. 223.0938), 245.0756 (14, $[M+Na]^+$, $C_8H_{10}N_6NaO_2^+$; 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 (CH_2Cl_2/AcOEt 1:1) of the green residue gave **26** (222 mg, 38%). Green powder. M.p. >149° (dec.). R_f (AcOEt) 0.30. UV: 231 (4.29), 279 (4.18), 356 (4.29). IR (ATR): 3313*w*, 3181*m*, 2993*w*, 2957*w*, 2920*w*, 1668*s*, 1637*m*, 1614*m*, 1527*s*, 1473*s*, 1448*s*, 1377*m*, 1340*s*, 1306*s*, 1163*s*, 1127*m*, 1080*s*, 1016*w*, 1002*w*, 953*w*, 930*m*, 907*w*, 798*s*. ^{1}H-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 (4*s*, 2 $CH_2=C$); 2.10 (*s*, 2 Me). ^{13}C-NMR (125 MHz, (D_6)DMSO): 165.67 (*s*, 2 C=O); 164.72 (*s*, C(4′)); 139.96 (*s*, 2 C(2)); 137.95 (*s*, C(6′)); 123.13 (br. *t*, 2 C(3)); 17.99 (*q*, 2 Me); signals of C(2′) and C(5′) not visible due to coalescence. HR-MALDI-MS (low intensity due to ene reaction during measurement): 291.1196 (18, $[M+H]^+$, $C_{12}H_{15}N_6O_3^+$; calc. 291.1200), 313.1013 (43, $[M+Na]^+$, $C_{12}H_{14}N_6NaO_3^+$; calc. 313.1020).

*(1*RS*)-2′,4′-Diamino-3,4-dimethylspiro[cyclohex-3-ene-1,7′-pyrimido[4,5-*b*][1,4]diazepin]-8′(9′*H*)-one* ((±)-**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 (±)-**25** (38.8 mg, 94%). Light-brown powder. M.p. 237–239° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.38. UV: 220 (4.39), 305 (3.93). IR (ATR): 3473*w*, 3314*w*, 3201*w*, 3100*w*, 2912*w*, 2875*w*, 2827*w*, 1676*m*, 1628*s*, 1603*m*, 1587*m*, 1552*s*, 1520*m*, 1453*m*, 1393*m*, 1374*w*, 1309*m*, 1235*m*, 1218*w*, 1168*w*, 1138*w*, 1082*w*, 983*w*, 869*m*, 822*m*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.32 (br. *s*, NH); 6.85 (*s*, HC=N); 6.53, 6.06 (2 br. *s*, 2 NH_2); 2.46, 2.14 (2*d*, $J=16.5$, 2 H–C(2)); 1.86–1.42 (*m*, CH_2CH_2); 1.63, 1.56 (2*s*, 2 Me). ^{13}C-NMR (75 MHz, (D_6)DMSO): 167.93 (*s*, C(8′)); 161.41 (*s*, C(4′)); 160.64 (*s*, C(2′)); 152.68 (*d*, C(6′)); 145.62 (*s*, C(9′a)); 124.49, 122.91 (2*s*, C(3), C(4)); 107.58 (*s*, C(4′a)); 50.92 (*s*, C(1)); 35.98 (*t*, C(2)); 28.23 (*t*, C(5)); 23.13 (*t*, C(6)); 19.06, 18.32 (2*q*, 2 Me). HR-MALDI-MS: 287.1611 (100, $[M+H]^+$, $C_{14}H_{19}N_6O^+$; calc. 287.1615).

*(1*RS*)-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* ((±)-**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° (dec.). R_f (CH_2Cl_2/MeOH 20:1) 0.50. UV: 230 (4.45), 326 (4.08). IR (ATR): 3328*w*, 3218*w*, 2919*w*, 2852*w*, 1715*m*, 1674*m*, 1617*s*, 1549*s*, 1466*s*, 1376*m*, 1299*m*, 1239*m*, 1171*m*, 1114*m*, 1053*w*, 1033*w*, 1003*w*, 929*w*, 862*w*, 818*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.77 (br. *s*, 2 NH, distinguishable as 10.71 (N(9′)–H) and 9.72 (HN–C(4′)) in (D_6)DMSO); 9.52 (*s*, NH_2); 7.01 (*s*, HC=N); 5.86 (br. *s*), 5.56 (*d*, $J=1.5$) ($H_2C=C$); 2.69, 2.23 (2*d*, $J=17.1$, 2 H–C(2)); 2.05 (*s*, Me); 1.98–1.76 (*m*, CH_2CH_2); 1.68, 1.62 (2*s*, Me–C(3), Me–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.96 (*s*, C(8′)); 164.83 (*s*, C=O); 161.05 (*s*, C(4′)); 156.22 (*s*, C(2′)); 156.16 (*d*, C(6′)); 147.34 (*s*, C(9′a)); 140.62 (*s*, *C*=CH_2); 125.69, 122.80 (2*s*, C(3), C(4)); 121.54 (*t*, *C*H_2=C); 110.13 (*s*, C(4′a)); 52.16 (*s*, C(1)); 36.83 (*t*, C(2)); 28.88 (*t*, C(5)); 24.51 (*t*, C(6)); 19.54, 18.84 (2*q*, *Me*–C(3), *Me*–C(4)); 18.62 (*q*, Me); assignment based on a DEPT and a HMBC spectrum. HR-MALDI-MS: 355.1873 (100, $[M+H]^+$, $C_{18}H_{23}N_6O_2^+$; calc. 355.1877); 377.1710 (9, $[M+Na]^+$, $C_{18}H_{22}N_6NaO_2^+$; calc. 377.1696).

*(1*RS*)-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 (1*RS*)-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 $NaBH(OAc)_3$ (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 (±)-**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 H_2O (30 ml) and brine (30 ml), dried ($MgSO_4$), and evaporated. FC (cyclohexane/AcOEt 3:1 → 0:1) gave a mixture of **29** and **27**. Elution with CH_2Cl_2/MeOH (20:1) gave **28** (28 mg, 41%). Chromatography of the mixture **29**/**27** on neutral Al_2O_3 (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 (CH_2Cl_2/MeOH 20:1) 0.35. UV: 199 (4.21), 230 (4.54), 332 (3.91). IR (ATR): 3338*w*, 3204*w*, 3125*w*, 2975*w*, 2916*w*, 2861*w*, 1679*m*, 1636*s*, 1585*s*, 1487*m*, 1403*m*, 1364*s*, 1303*m*, 1272*m*, 1231*m*, 1169*w*, 1138*w*, 1101*w*, 1021*w*, 923*w*, 792*m*, 728*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO, 353 K): 10.28 (*s*, H–N(10)); 5.79 (*s*, H_2N–C(2)); 5.68 (br. *s*), 5.35 (*d*, J = 0.9) (CH_2=C); 4.22 (*s*, 2 H–C(7)); 2.45, 1.97 (2*d*, J = 15, 2 H–C(2′)); 2.15 (*s*, Me); 1.79–1.70 (*m*, CH_2CH_2); 1.56, 1.53 (2*s*, Me–C(3′), Me–C(4′)). ^{13}C-NMR (75 MHz, (D_6)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*=CH_2); 123.61, 122.20 (2*s*, C(3′), C(4′)); 121.57 (*t*, *C*H_2=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 (2*t*, C(5′), C(6′)); 21.69 (*q*, Me); 18.83, 18.06 (2*q*, *Me*–C(3′), *Me*–C(4′)); assignment based on a HSQC and a HMBC spectrum. HR-MALDI-MS: 339.1926 (100, $[M+H]^+$, $C_{18}H_{23}N_6O^+$; calc. 339.1928), 361.1749 (4, $[M+Na]^+$, $C_{18}H_{22}N_6NaO^+$; calc. 361.1747). Anal. calc. for $C_{18}H_{22}N_6O$ (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 (CH_2Cl_2/MeOH 20:1) 0.45. UV: 202 (4.36), 233 (4.52), 337 (3.87). IR (ATR): 3323*w*, 3204*w*, 3119*w*, 2961*m*, 2925*m*, 2860*m*, 1726*w*, 1674*m*, 1635*s*, 1584*s*, 1507*m*, 1468*m*, 1445*m*, 1403*s*, 1366*s*, 1350*s*, 1324*m*, 1305*m*, 1274*s*, 1221*s*, 1135*m*, 1071*w*, 1043*w*, 1011*w*, 919*w*, 848*w*. ^{1}H-NMR (300 MHz, (D_6)DMSO): 10.64 (br. *s*, H–N(10)); 6.50 (br. *t*, $J \approx 5.7$, HN–C(2)); 5.70, 5.33 (2 br. *s*, CH_2=C); 4.22 (*s*, 2 H–C(7)); 3.28 (*quint.*, $J \approx 7.0$, *C*H_2Me); 2.13 (*s*, *Me*C=CH_2); 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, *Me*CH_2). ^{13}C-NMR (75 MHz, (D_6)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*=CH_2); 123.59, 122.25 (2*s*, C(3′), C(4′)); 121.64 (*t*, *C*H_2=C); 108.61 (*s*, C(10b)); 47.00 (*t*, C(7)); 46.22 (*s*, C(8)); 35.54 (*t*, C(2′)); 28.18 (*t*, Me*C*H_2); 27.79, 26.53 (2*t*, C(5′), C(6′)); 21.78 (*q*, *Me*C=CH_2); 18.95, 18.17 (2*q*, *Me*–C(3′), Me–C(4′)); 14.81 (*q*, *Me*CH_2). HR-MALDI-MS: 367.2247 (100, $[M+H]^+$, $C_{20}H_{27}N_6O^+$; calc. 367.2246), 389.2085 (4, $[M+Na]^+$, $C_{20}H_{26}N_6NaO^+$; 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 (CH_2Cl_2/AcOEt 2:1) gave *endo*-**30**/*exo*-**30** 7:3 (48 mg, 84%). White powder. M.p. >122° (dec.). R_f (CH_2Cl_2/AcOEt 1:1) 0.15. UV: 229 (4.41), 328 (4.02). IR (ATR): 3555*w*, 3369*w*, 3306*w*, 3198*w*, 3083*w*, 2973*w*, 2847*w*, 1737*m*, 1704*m*, 1665*m*, 1627*s*, 1616*s*, 1549*s*, 1465*s*, 1450*s*, 1382*s*, 1334*m*, 1310*s*, 1229*m*, 1173*s*, 1118*m*, 1076*w*, 1044*m*, 1026*m*, 951*w*, 937*w*, 870*m*, 818*m*. ^{1}H-NMR (300 MHz, CD_2Cl_2; *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*, NH_2); 5.83 (br. *s*, 0.7 H), 5.79 (br. *s*, 0.3 H) (C*H*H′=); 5.54 (*q*, J = 1.2, 0.7 H), 5.52 (*q*, J = 1.2, 0.3 H) (CH*H*′=); 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)). ^{1}H-NMR (300 MHz, (D_6)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*, NH_2); 6.38–6.12 (*m*, H–C(5), H–C(6)); 5.85 (*s*, 0.7 H), 5.77 (*s*, 0.3 H) (C*H*H′=); 5.56 (*s*, 0.7 H), 5.51 (*s*, 0.3 H) (CH*H*′=); 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)). ^{13}C-NMR (75 MHz, CD_2Cl_2; *endo*/*exo* 7:3): 170.95, 169.00 (2*s*, C(8′)); 165.50, 165.42 (2*s*, C=O); 161.53, 161.48 (2*s*, C(4′)); 159.51, 159.07 (2*d*, C(6′)); 155.99, 155.96 (2*s*, C(2′)); 148.24, 147.73 (2*s*, C(9′a)); 141.78, 137.63 (2*d*, C(6)); 136.29, 133.37 (2*d*, C(5)); 140.74 (*s*, *C*=CH_2); 121.91 (*t*, CH_2=); 111.88, 111.34 (2*s*, C(4′a)); 61.38, 60.87 (2*s*, C(2)); 48.76, 48.10 (2*t*, C(7)); 47.62, 46.50 (2*d*, C(1)); 42.74, 41.34 (2*d*, C(4)); 40.54, 38.86 (2*t*, C(3)); 18.28 (*q*, Me). HR-MALDI-MS: 339.1558 (34, $[M+H]^+$, $C_{17}H_{19}N_6O_2^+$; calc. 339.1564), 361.1383 (4, $[M+Na]^+$, $C_{11}H_{18}N_6NaO_2^+$; calc. 361.1383). Signals of the ene product (retro-*Diels–Alder* product): 273.1084 (100, $[M+H]^+$, $C_{12}H_{13}N_6O_2^+$; calc. 273.1095), 295.0914 (5, $[M+Na]^+$, $C_{12}H_{12}N_6NaO_2^+$; 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 CH_2Cl_2 (8 ml) was cooled to 0°, treated with a soln. of *endo*-**30**/*exo*-**30** 7:3 (43 mg, 0.13 mmol) in CH_2Cl_2 (8 ml), stirred at r.t. for 2 d, diluted with CH_2Cl_2 (40 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 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated. FC (CH_2Cl_2/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*. ^{1}H-NMR (300 MHz, CD_2Cl_2; *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*, C*H*H′=); 5.34 (0.7 H), 5.26 (0.3 H) (2*s*, CH*H*′=); 4.41 (*s*, 1.4 H), 4.09 (*s*, 0.6 H) (2 H–C(7)); 3.48–3.40 (*m*, MeCH_2); 3.18–2.48 (*m*, H–C(1′), H–C(4′)); 2.27 (*s*, 2.1 H), 2.25 (*s*, 0.9 H) (*Me*C=CH_2); 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, *Me*CH_2). ^{13}C-NMR (75 MHz, CD_2Cl_2; 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*=CH_2); 122.14 (*t*, CH_2=); 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*, Me*C*H_2); 22.22 (*q*, *Me*C=CH_2); 14.62 (*q*, *Me*CH_2). HR-MALDI-MS: 351.1931 (100, $[M+H]^+$, $C_{19}H_{23}N_6O^+$; calc. 351.1933); 373.1752 (4, $[M+Na]^+$, $C_{19}H_{22}N_6NaO^+$; calc. 373.1753).

REFERENCES

[1] F.-L. Zhang, W. B. Schweizer, M. Xu, A. Vasella, *Helv. Chim. Acta* **2007**, *90*, 521.
[2] S. Taghavi-Moghadam, R. Stumpf, H. Fischer, W. Pfleiderer, *Collect. Czech. Chem. Commun.* **1999**, *64*, 313.
[3] O. H. Drummer, *Forensic Sci. Rev.* **2002**, *14*, 1.
[4] O. Lack, R. E. Martin, *Tetrahedron Lett.* **2005**, *46*, 8207.
[5] B. L. De Corte, *J. Med. Chem.* **2005**, *48*, 1689.
[6] E. C. Taylor, J. E. Dowling, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 453.
[7] V. A. Chebanov, S. M. Desenko, O. V. Shishkin, N. N. Kolos, S. A. Komykhov, V. D. Orlov, H. Meier, *J. Heterocycl. Chem.* **2003**, *40*, 25.
[8] B. Insuasty, H. Insuasty, J. Quiroga, C. Saitz, C. Jullian, *J. Heterocycl. Chem.* **2000**, *37*, 401.
[9] P. H. Boyle, E. M. Hughes, H. A. Khattab, R. J. Lockhart, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2071.
[10] D. C. Pike, M. T. Hora, S. W. Bailey, J. E. Ayling, *Biochemistry* **1986**, *25*, 4762.
[11] A. M. El-Sayed, H. Abdel-Ghany, A. M. M. El-Saghier, *Synth. Commun.* **1999**, *29*, 3561.
[12] J. K. Chakrabarti, T. M. Hotten, D. E. Tupper, *J. Heterocycl. Chem.* **1978**, *15*, 705.
[13] W. Pfleiderer, R. Lohrmann, *Chem. Ber.* **1961**, *94*, 12.
[14] W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131.
[15] R. B. Moffett, *Org. Synth., Coll. Vol.* **1963**, *4*, 238.
[16] Y. Hayashi, J. J. Rohde, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 5502.
[17] M. Melguizo, A. Sanchez, M. Nogueras, J. N. Low, R. A. Howie, G. Andrei, E. Declercq, *Tetrahedron* **1994**, *50*, 13511.
[18] M. F. Mallette, E. C. Taylor, C. K. Cain, *J. Am. Chem. Soc.* **1947**, *69*, 1814.
[19] B. Traube, *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3035.
[20] G. W. Shaw, *Compr. Heterocycl. Chem.* **1984**, *5*, 567.
[21] T. Yosief, A. Rudi, Y. Kashman, *J. Nat. Prod.* **2000**, *63*, 299.
[22] H. Suzuki, H. Sawanishi, K. Yamamoto, K. Miyamoto, *Chem. Pharm. Bull.* **1999**, *47*, 1322.
[23] D. Pappo, S. Shimony, Y. Kashman, *J. Org. Chem.* **2005**, *70*, 199.
[24] D. Pappo, Y. Kashman, *Tetrahedron* **2003**, *59*, 6493.
[25] M. Ohba, T. Tashiro, *Heterocycles* **2002**, *57*, 1235.
[26] J. Pabba, B. P. Rempel, S. G. Withers, A. Vasella, *Helv. Chim. Acta* **2006**, *89*, 635.

Received November 6, 2007