Synthesis and properties of 2-nitrosoadenosine

Martin J. Wanner and Gerrit-Jan Koomen*

Laboratory of Organic Chemistry, Institute of Molecular Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, NL-1018 WS Amsterdam, Netherlands.
E-mail: gjk@org.chem.uva.nl; Fax: +31-20-5255670

Received (in Cambridge, UK) 29th March 2001, Accepted 19th June 2001
First published as an Advance Article on the web 26th July 2001

A series of new 2-substituted adenosine derivatives was synthesised *via* addition and condensation reactions with 2-nitrosoadenosine triacetate **4**. The exceptional reactivity of the adenosine nitroso functionality was demonstrated by reaction with, *e.g.*, dienes (4 + 2 cycloaddition), cyclohexene ('ene' reaction), furans (addition/rearrangement) and with anilines (Mills coupling). 2-Nitrosoadenosine triacetate was prepared from 6-chloropurine riboside triacetate *via* nitration at the 2-position followed by reduction/oxidation of the nitro group. The vulnerable nitroso functionality of **4** had to be protected by 4 + 2 cycloaddition with cyclopentadiene to make deacylation of the ribose ring possible. Retro-Diels–Alder reaction of the deacylated product at 95 °C gave the title compound 2-nitrosoadenosine **7**. Dimerisation of the nitroso functionality of triacetate **4** was studied with ^{1}H NMR by changing the temperature, concentration and solvent. In particular, variation of temperature gave control over this dimerisation: 100% monomer at 65 °C gave complete dimerisation at −20 °C.

Introduction

The application of purine derivatives in the research areas of *e.g.*, purinergic receptors, cyclin-dependent protein kinase (CDK) inhibitors, antitumour and antiviral compounds has resulted in a large number of synthetic investigations. Besides substitution at the 6-, 8- and 9-position, modification of the 2-position of the purine ring has received much attention. The 2-position is in general substituted by conversion of an amino group, as it is present in guanine or guanosine derivatives, to halogen substituents *via* alkyl nitrite-catalyzed reactions (Fig. 1).[1–3] Replacement of these halides with, *e.g.*, amines is often sluggish and requires high temperatures. Some recent examples show that substitution with suitable amines using Pd catalysis is effected under milder conditions.[4,5] An alternative strategy for the introduction of amino substituents on the 2-position of the purine ring is based on nitroso chemistry (Fig. 2). We here report the synthesis of the hitherto unknown, but stable, 2-nitrosoadenosine from the corresponding 2-nitropurine ribosides. The required 2-nitronucleosides were prepared *via* selective nitration of the 2-position of 6-chloropurine triacetate with the nitrating mixture tetrabutylammonium nitrate and trifluoroacetic anhydride (TBAN–TFAA) as we described recently.[6,7] The reactivity, dimerisation and in particular the conversion of 2-nitrosoadenosine triacetate to a number of new 2-substituted adenosine derivatives *via* addition and condensation reactions will be discussed in this paper.

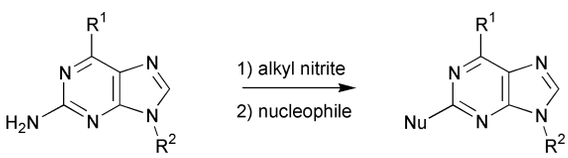


Fig. 1 Substitution of the guanosine C-2 position.

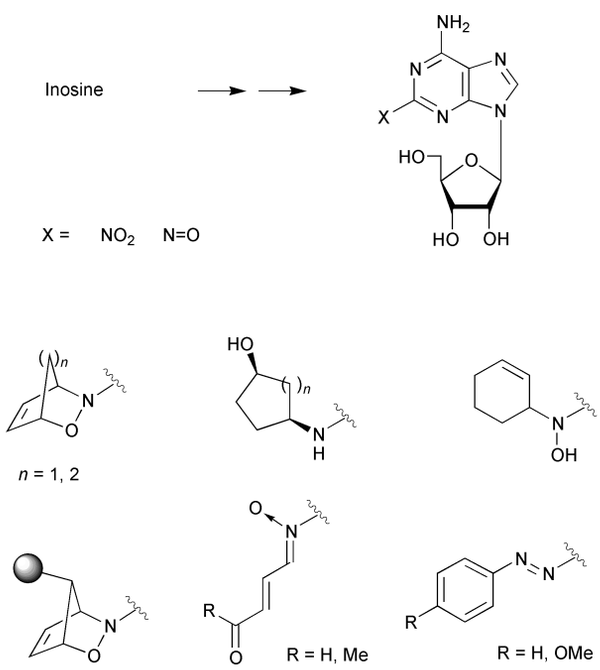


Fig. 2 Substitution of the purine C-2 position based on nitroso chemistry.

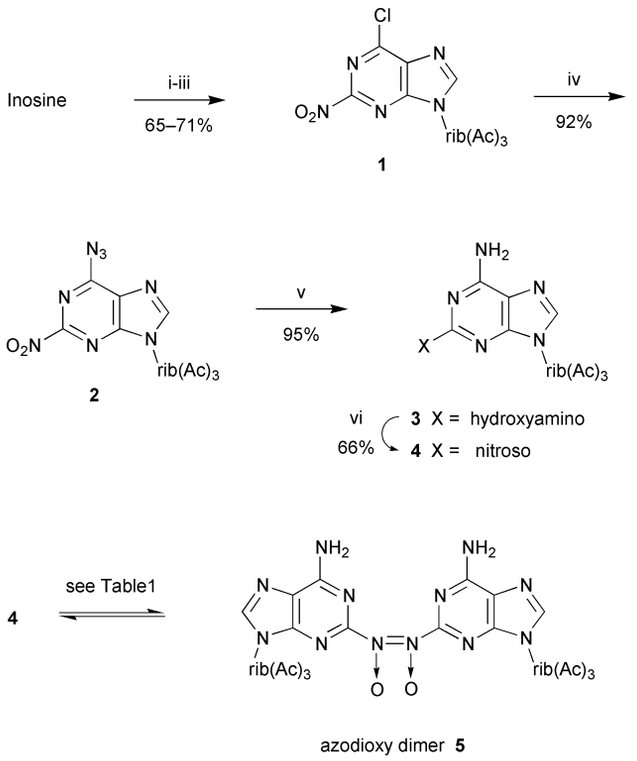
Results and discussion

Synthesis

2-Nitrosoadenosine triacetate. Aromatic nitroso compounds are most conveniently prepared from the corresponding nitro derivatives in a 2-step reduction–oxidation process.[8,9] This reduction–oxidation route towards nitroso compounds is precluded for most electron-deficient heterocycles since electrophilic nitration of these heterocycles to the required nitro compounds is not possible. To circumvent the nitration of pyridines an oxidative sequence was developed to obtain 2- and 3-nitrosopyridines from the corresponding amines.[10] Since purines substituted with a nitro group at the 2-position are now readily available *via* TBAN–TFAA nitration[6,7] we examined the redox conversion of 2-nitro- to 2-nitrosopurines.

TBAN–TFAA nitration of triacetyl-protected 6-chloropurine riboside took place exclusively at the 2-position, as was shown by long-range correlation NMR experiments performed with **1** (Scheme 1).[6] The highly reactive chloride **1** was converted to the corresponding azide **2** with one equivalent of sodium

 DOI: 10.1039/b102897a



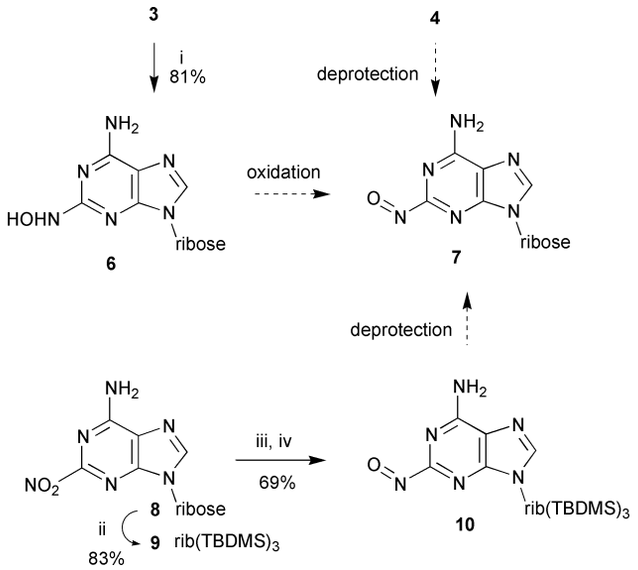
Scheme 1 *Reagents and conditions*: (i) Ac_2O, pyridine; (ii) $POCl_3$, $PhNMe_2$ (ref. 28); (iii) TBAN, TFAA, DCM, 0 °C; (iv) 1.0 eq. NaN_3, DMF, −18 °C; (v) H_2, Pd/C; (vi) $NaIO_4$, EtOAc, water.

azide at −18 °C.[7] Hydrogenation of both the azido and the nitro functionality was accomplished cleanly and selectively using 10% Pd/C. Hydrogen uptake stopped almost completely at the stage of the 2-(hydroxyamino)adenosine **3** and, after removal of the catalyst by filtration, this hydroxylamine was immediately oxidised with an aqueous solution of sodium periodate at 0 °C. 2-Nitrosoadenosine triacetate **4** was obtained as a shelf-stable, yellow solid by trituration with methanol.

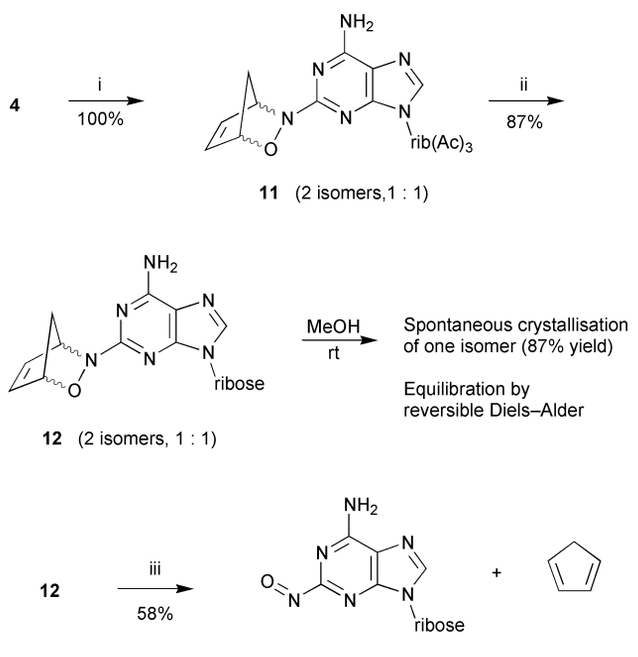
2-Nitrosoadenosine *via* Diels–Alder protection. Deprotection of nitrosoadenosine triacetate **4** to obtain triol **7** provided us with serious problems (Scheme 2). Standard methanolysis of **4** under mild conditions using KCN in methanol resulted in decomposition before the last acetate was removed. To avoid the deprotection step, oxidation of unprotected 2-(hydroxyamino)adenosine **6** was attempted. Oxidation with $NaIO_4$ was not selective, however, since glycol-splitting of the *cis*-diol in the ribose moiety was a competing process. With *tert*-butyl hypochlorite as an oxidant[8] the formation of yellow nitroso compounds was observed, but now as a side reaction, oxidation of the NH_2 substituent at C-6 also occurred. An extra complicating factor for this type of hydroxylamine oxidation is the formation of azoxydimers. These azoxydimers are formed irreversibly by condensation of the starting hydroxylamine with the nitroso product. To avoid this side reaction, fast oxidation reactions are required and the use of more than one equivalent of oxidant is recommended.

In a third approach the reaction sequence of Scheme 1 was repeated with *tert*-butylsilyl (TBS) ethers instead of acetates as protecting groups of the ribose ring. TBDMS-protected 2-nitrosoadenosine **10** was obtained in good overall yield from 2-nitroadenosine **8** but again deprotection to **7** failed. Both acetic acid-catalyzed hydrolysis as well as fluoride-catalyzed deprotection (*e.g.* TBAF, pH 7, or $R_3N{\cdot}HF$) destroyed the nitroso functionality.

To overcome the instability of the nitroso moiety during methanolysis of triacetate **4** we decided to protect the nitroso group *via* a hetero-Diels–Alder reaction with a suitable 1,3-



Scheme 2 *Reagents and conditions*: (i) NH_3 MeOH; (ii) TBDMSCl, imidazole, DMF; (iii) H_2, 10% Pd/C; (iv) $NaIO_4$, EtOAc, water.



Scheme 3 *Reagents and conditions*: (i) cyclopentadiene, DCM, rt; (ii) KCN, MeOH, rt; (iii) DMF, N_2-stream, 95 °C.

diene (Scheme 3).[11–14] It was envisaged that thermal retro-Diels–Alder reaction of the oxazines should restore the nitroso function. In the case of the Diels–Alder reaction between nitrosobenzene and cyclopentadiene, which is reversible at room temperature, the equilibrium constants have been studied.[15] Cyclopentadiene reacted instantly with **4**, producing a 50 : 50 mixture of stable diastereomeric oxazines **11**. No influence of the ribose ring on the diastereoselectivity was observed, and even at −78 °C the same inseparable 50 : 50 mixture was formed according to ^1H NMR. During removal of the acetate protecting groups from **11** with KCN in methanol, one of the two possible diastereomeric nucleosides **12** precipitated from the reaction mixture in pure form and, surprisingly, in more then the theoretical yield of 50%. The dissolved isomer equilibrated *via* a retro-Diels–Alder reaction, thus providing an 86% yield of the crystalline isomer after 48 h.[16] When the methanolysis was stopped after 6 h the filtrate consisted mainly of the other isomer. The occurrence of the retro-Diels–Alder process that is responsible for this isomerisation was nicely

Table 1 ^{1}H NMR dimerisation studies with 2-nitrosoadenosine triacetate **4**. The ratio monomer–dimer is based on the integral of 8-H at δ 8.2 and 8.3, respectively

(a) Concentration effects [a]

Entry	Conc.[b]	Monomer	Dimer
1	0.5	63	37
2	2.0	38	62
3	5.0	25	75

(b) Solvent effects [c]

Entry	Solvent	Monomer	Dimer
4	$CDCl_3$	32	68
5	CD_3OD	21	79
6	d_6-DMSO–D_2O 4 : 1	14	86
7	d_6-DMSO–D_2O 2 : 1	7	93

(c) Temperature effects [c]

Entry	Temp. (θ/°C)	Monomer	Dimer
8	67[d]	100	0
9	−20[e]	0	100

[a] In d_6-DMSO at 27 °C. [b] In mg per 0.5 mL. [c] At 2 mg/0.5 mL, 27 °C. [d] In d_6-DMSO. [e] In $CDCl_3$.

demonstrated by ^{1}H NMR. When a solution of **12** (single isomer) was kept at rt for 40 h in DMSO (1 mg in 0.5 mL), a 60 : 40 mixture of isomers had formed. At 50 °C complete equilibration to a 50 : 50 mixture already occurred within a few minutes, but now also small amounts of the precursors, cyclopentadiene and 2-nitrosoadenosine **7**, were observed. At still higher temperatures (100 °C) the formation of the Diels–Alder precursors was almost complete. Upon cooling to rt the 50 : 50 mixture of cycloaddition products **12** was reproduced in high yield.

To drive the retro-Diels–Alder reaction of **12** to completion in a synthetically useful procedure, it was essential to remove the cyclopentadiene from the reaction mixture. Initially we used dienophiles (*e.g.*, maleimide) to trap the diene, but the C6-amino substituent appeared to react with these reagents. Satisfactory conversion was accomplished by heating cycloadduct **12** in DMF at 95 °C, under a vigorous stream of nitrogen gas. Crystalline 2-nitrosoadenosine **7** was obtained in this way in 58% yield. This compound was stable enough for biological investigations, but for reasons of availability and solubility we preferred to examine the reactivity of the nitroso substituent with the triacetyl-protected derivative **4**.

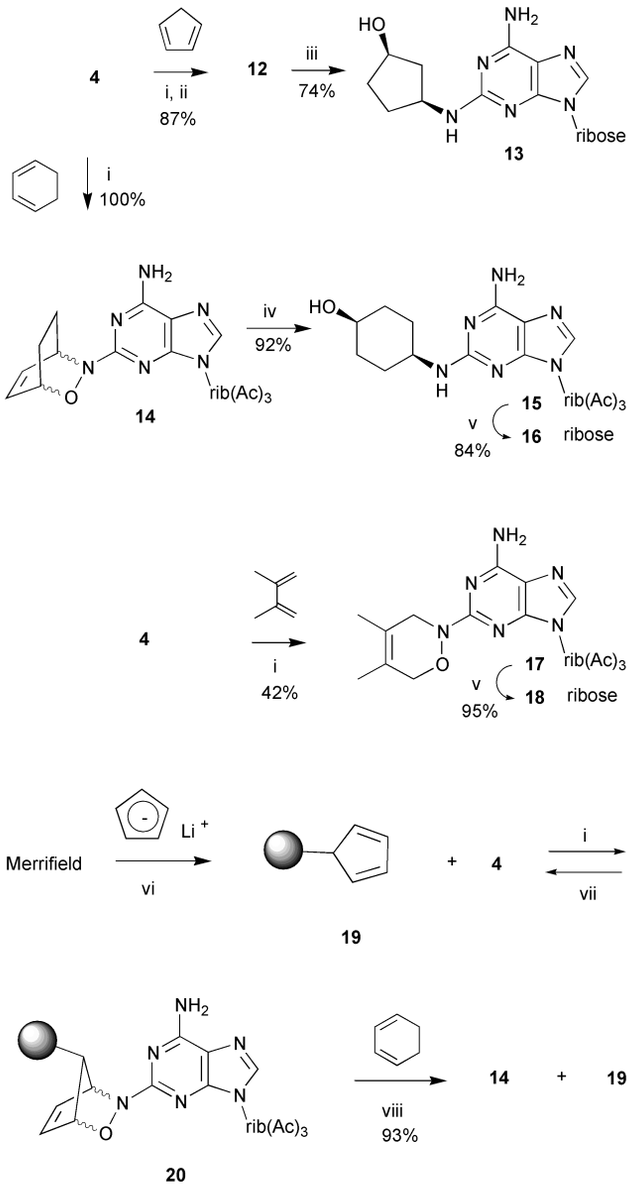
Properties of 2-nitrosoadenosine triacetate 4

Dimerisation studies. Aromatic nitroso compounds show a strong tendency to form azodioxy dimers in a reversible process.[17,18] The amount of dimerisation in solution not only depends on the presence of substituents on the aromatic system but also on concentration, temperature and solvent. The influence of those variables on the dimerisation of **4** to **5** (Scheme 1) was studied using ^{1}H NMR spectroscopy. As can be seen from Table 1, the monomer–dimer equilibrium of **4** is concentration dependent, as expected. Probably the amount of monomer will reach 100% at higher dilution, but NMR does not allow us to measure this. Replacement of $CDCl_3$ for d_6-DMSO did not influence the equilibrium significantly, but a pronounced shift was observed when mixtures of DMSO with deuterium oxide were used. Hydrogen-bond stabilisation of the polar dimer probably plays a role here. This effect was also demonstrated with nitrosobenzene, which is known to be completely in its monomeric form in organic solvents. When we dissolved nitrosobenzene in a 1 : 1 mixture of d_6-DMSO and deuterium oxide (1 mg in 0.5 mL), formation of 21% of the dimer was observed.

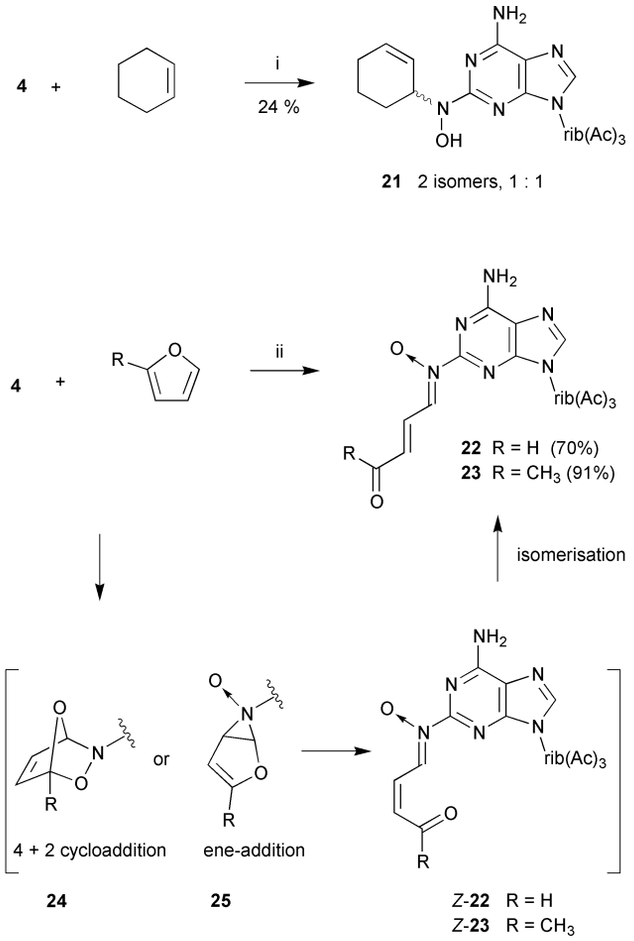
Changing the temperature had the strongest effect on the equilibrium between **4** and **5**: after increasing the temperature to 65 °C in d_6-DMSO, the equilibrium shifted completely to the monomer. On the other hand, when a solution of **4** in $CDCl_3$ was cooled to −20 °C, only the dimer was present. In all examples only one of the *Z*/*E* isomers of dimer **5** was detected in the ^{1}H NMR spectra (>98%). In general, when no *ortho*-substituents are present in the aromatic ring, the *Z*-dimer is preferred in solution. The same tendency towards the formation of *Z*-dimers was observed for 2-nitrosopyridines.[18] In analogy with these data, and in view of the absence of even hydrogen substituents in both *ortho* positions, the azodioxy dimer **5** of 2-nitrosoadenosine triacetate **4** in solution was assumed to be the *Z*-form.

Diels–Alder reactions. Two more dienes were used for cycloaddition with nitrosoadenosine **4** (Scheme 4). Cyclohexa-1,3-diene reacted rapidly and quantitatively to give adduct **14** in the same 50 : 50 ratio of diastereomers as was observed with cyclopentadiene. The acyclic diene 2,3-dimethylbuta-1,3-diene reacted less cleanly to give **17**. Lower abundance of the *s-cis* form in dimethylbutadiene compared with the cyclic dienes probably favour ene-type side reactions. Hydrogenation converted the cycloadducts to the corresponding cyclopentyl and cyclohexylamines. From crystalline cyclopentadiene isomer **12**, obtained as described in Scheme 3, the *cis*-3-aminocyclopentanol **13** (single isomer) was obtained. The absolute configuration of the cyclopentane part of the molecule was not determined. Hydrogenation of **14** and subsequent removal of the acetates produced the symmetrical *cis*-substituted 4-aminocyclohexanol **16**. In **17** both the tetra substituted double bond and the N–O bond resisted hydrogenation, so except for deacetylation of the ribose ring to **18**, cycloadduct **17** was not subjected to further transformations.

An additional example of the versatility of this cycloaddition was obtained from a solid-phase reaction of **4** with resin-bound cyclopentadiene (Scheme 4). In the synthesis of **7** (Scheme 3) removal of cyclopentadiene with a N_2-stream in the retro-Diels–Alder process is the limiting step. If resin-bound cyclopentadiene is used, filtration of a hot Diels–Alder equilibration mixture will be sufficient to remove the cyclopentadiene. Immobilised cyclopentadiene **19** was prepared by the coupling of Merrifield resin with cyclopentadienyl lithium. Although **19** and **20** are depicted as 5-substituted cyclopentadienes in Scheme 4, it should be noted that (base-catalysed) 1,5-hydrogen shifts can also give the 1- and 2-substituted cyclopentadiene isomers. When a solution of **4** in DCM was stirred with resin **19** at rt, the yellow colour of the nitroso compound disappeared and within a few minutes complete cycloaddition to **20** had occurred. The retro-Diels–Alder of **20** in hot DMF could easily be monitored by the development of the yellow colour of the nitroso compound, allowing easy recovery of **4** by filtration and evaporation. The retro-Diels–Alder reaction of **20** in the presence of cyclohexadiene was very efficient, and produced **14** in almost quantitative yield. Although resin-bound cycloadduct **20** was prepared to allow us to obtain unprotected 2-nitrosoadenosine **7**, we have not been successful in removal of the ribose acetates from **20** without destroying the compound. Immobilised cyclopentadiene **19** has potential applications in handling other reactive nitroso compounds such as nitrosyl cyanide[12,19] or *N*-acylnitroso derivatives.[14,20] Often these unstable compounds are captured as cycloadducts with 9,10-dimethylanthracene that can be used as latent sources of the nitroso compound.



Scheme 4 *Reagents and conditions*: (i) DCM, rt, 30 min; (ii) KCN, MeOH, rt; (iii) H_2, 10% Pd/C, EtOH, water; (iv) H_2, 10% Pd/C, EtOH, EtOAc; (v) NH_3, MeOH; (vi) DMF, rt; (vii) DMF, filtration at 95 °C; (viii) 2 eq. cyclohexa-1,3-diene, DMF, 90 °C, 30 min.



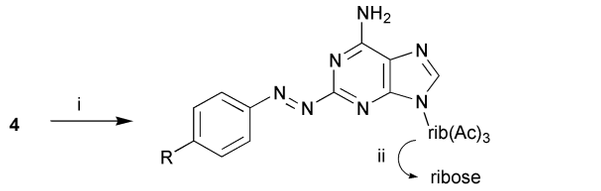
Scheme 5 *Reagents and conditions*: (i) 5 eq. cyclohexene, DCM–MeOH 18 h, rt; (ii) 5 eq. furan or 2-methylfuran, DCM, 18 h, rt.

Ene reaction with cyclohexene. Ene reactions with nitroso compounds are limited to reactive derivatives such as nitrosocarbonyl compounds,[21] *p*-nitronitrosobenzene[22] or pentafluoronitrosobenzene.[23] Also, **4** showed reactivity and with excess of cyclohexadiene the anticipated hydroxylamine **21** was formed in moderate yield, as a 1 : 1 mixture of diastereomers (Scheme 5). This reaction probably proceeds *via* an aziridine *N*-oxide intermediate, followed by hydrogen abstraction.[21] An aziridine *N*-oxide is also suggested as one of the possible intermediates in the rearrangement described in the next paragraph [structure **25** (Scheme 5)].

Addition reactions with furans. Rather unexpected were the addition reactions of **4** with furan and 2-methylfuran (Scheme 5). Only a few reactions of nitroso compounds with furans are known in the literature. *N*-Acylnitroso compounds react in general in a 4 + 2 fashion with the furan system, but in this example the furan ring acts as the dienophile.[24] An intramolecular addition process of a nitrosoarene to the 2- and 5-position of the furan ring has been reported,[25] but the actual cycloadducts were never observed and merely rearranged, and ring-opened products were isolated. From our room-temperature reactions of nitrosoadenosine **4** with excess of furan or 2-methylfuran the moderately stable α, β-unsaturated nitrones **22** and **23** were obtained. To monitor the formation of primary adducts such as **24** or **25** in this reaction, the process was repeated in an NMR tube. 4 + 2 Addition products (**24**) or 'ene' intermediates (**25**) were not observed, however. From this NMR experiment we obtained an explanation for the *E*-geometry of the double bond in **22** and **23** ($J = 16.1$ and 16.3 Hz respectively). The originally formed *Z*-alkenes *Z*-**22** and *Z*-**23** ($J = 11.6$ Hz) were observed but completely isomerised to the *E*-alkenes *E*-**22** and *E*-**23** during the reaction.

Mills coupling with aniline. 2-Phenyldiazo-substituted purine nucleosides such as **28** and **29** (Scheme 6) have not been reported before in the literature. Classical diazonium coupling with phenyldiazonium salts cannot be used since the purine 2-position is not suitable for electrophilic substitution. The alternative route *via* 2-diazonium purines is also impossible since these compounds, as most heterocyclic diazonium salts, are not stable.

Mills coupling between nitrosoaromatics and anilines is a complementary method for the preparation of azo compounds.[26] Acetic acid-catalyzed condensation of **4** with 2 eq. of aniline or *p*-anisidine produced the expected diazo compounds **26** and **27** in 84 and 91% yield, respectively. After deprotection with aq. ammonia in methanol the orange coloured *E*-form of 2-phenylazoadenosine **28** and 2-(4-methoxyphenylazo)-adenosine **29** were obtained. When quickly dissolved in D_2O, the ^1H NMR spectrum of **28** showed only the *E*-form; however, during storage in daylight *E*-**28** was transformed into a mixture of *Z* and *E* isomers. After storage for *ca.* 6 h a photo-stationary phase was reached with $Z : E = 41 : 59$. Irradiation of this D_2O



26 R = H (84%) **27** R = OCH_3 (91%)

28 ribose (86%) **29** ribose (77%)

isomerisation of **28**

	Z	*E*
solid state	0	100
daylight (D_2O)	41	59
350 nm (D_2O)	79	21

Scheme 6 *Reagents and conditions*: (i) $ArNH_2$, CH_3CN–HOAc 5 : 1; rt, 5 h; (ii) NH_3, MeOH.

sample at 350 nm produced predominantly the *Z*-isomer (*Z* : *E* = 79 : 21) and this mixture returned to the stationary state of 41 : 59 after 4–6 h in daylight.

Conclusions

In summary, 2-nitrosoadenosine, and in particular its triacetate, are made readily available from inosine and are presented as versatile precursors for a large number of new, 2-substituted adenosine derivatives. Biological applications of 2-nitrosoadenosine and its derivatives will be described elsewhere.

Experimental

General

All reagents and solvents were used as commercially available, unless indicated otherwise. Flash chromatography refers to purification using the indicated eluents and Janssen Chimica silica gel 60 (0.030–0.075 mm). Mps were measured with a Leitz melting point microscope and are uncorrected. Elemental analyses were performed by Kolbe, Mülheim a. d. Ruhr, Germany. IR spectra were obtained from $CHCl_3$ solutions unless indicated otherwise, using a Bruker IFS 28 FT-spectrophotometer, and wavenumbers are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR; APT) spectra were determined in $CDCl_3$ at 300 K using a Bruker ARX 400 (400 MHz, 100 MHz respectively) spectrometer, unless indicated otherwise. *J*-values are given in Hz. Mass spectra and accurate mass measurements were performed on a JEOL JMS-SX/SX 102 A Tandem Mass Spectrometer using Fast Atom Bombardment (FAB) or Electron Impact (EI). A resolving power of 10 000 (10% valley definition) for high-resolution electron impact or FAB mass spectrometry was used.

6-Chloro-2-nitro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine[6] 1

In the synthesis of 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine[27,28] the work-up of the chlorination reaction was slightly modified: the residue obtained after evaporation of the $POCl_3$ was poured into a stirred mixture of ice and water. This reversed quenching procedure gave the quantitative yield the authors claimed.

A nitrating mixture was prepared at 0 °C by adding TFAA (6.34 mL, 45 mmol) to a solution of tetrabutylammonium nitrate (TBAN, 13.7 g, 45 mmol) in dry DCM (75 mL) during *ca.* 2 min. After being stirred for 10 min this solution was added *via* syringe to an ice-cold solution of 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine (12.39 g, 30 mmol) in DCM (75 mL). The reaction was quenched after 3 h at 0 °C by pouring the reaction mixture into a stirred mixture of saturated aq. $NaHCO_3$ (200 mL), water (200 mL) and diethyl ether (*ca.* 250 mL). The water layer was extracted with a 2 : 1 mixture of diethyl ether and DCM, the combined organic layers were washed successively with dilute aq. $NaHCO_3$ (2 × 30 mL) and water (30 mL), and dried over Na_2SO_4 (sometimes crystallisation of the product occurs during the extraction procedure). The pale yellow product was obtained by trituration with methanol (9.75 g, 71%). An analytical sample was obtained by recrystallisation from EtOAc, mp 170–172 °C (Found: C, 42.02; H, 3.46; N, 15.22. Calc. for $C_{16}H_{16}ClN_5O_9$: C, 41.98; H, 3.52; N, 15.30%); ν_{max}/cm^{-1} (KBr) 3131, 1771, 1745, 1734, 1589, 1560 and 1331; δ_H 8.58 (1H, s, 8-H), 6.30 (1H, d, *J* 5.3, 1′-H), 5.76 (1H, dd, *J* 5.3 and 5.3, 2′-H), 5.57 (1H, m, 3′-H), 4.52 (1H, m, 4′-H), 4.44 (2H, m, 5′-H_2), 2.16, 2.09 and 2.06 (all 3H, s, acetates); δ_C 170.0, 169.4, 169.4, 153.1, 152.7, 151.3, 147.0, 134.8, 87.13, 81.16, 73.53, 70.53, 62.82, 20.56, 20.35 and 20.14; *m*/*z* (FAB$^+$) 458 (7%), 259 (100) and 242 (31) (Found: $M^+ + 1$, 458.0712. $C_{16}H_{17}ClN_5O_9$ requires *m*/*z* 458.0719).

6-Azido-2-nitro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-9*H*-purine 2

Sodium azide (0.65 g, 10 mmol) was added to a solution of **6** (4.58 g, 10 mmol) in DMF (40 mL) at −18 °C (bath temperature). After stirring for 1 h at this temperature, stirring was continued at 0 °C for 2 h. Water (40 mL) was slowly added, resulting in crystallisation of the product. The mixture was kept for 4 h at 0 °C and filtered. The azide was washed with water (3 times) and with 1 : 1 water–methanol (3 times) and dried *in vacuo* (P_2O_5) (4.26 g, 92%). A *pure sample* was obtained by recrystallisation from EtOAc, mp 164–166 °C (Found: C, 41.48; H, 3.49; N, 24.02. $C_{16}H_{16}N_8O_9$ requires C, 41.39; H, 3.47; N, 24.13%); ν_{max}/cm^{-1} (KBr) 2165, 2143, 1746, 1602, 1557 and 1435; δ_H 8.39 (1H, s, 8-H), 6.28 (1H, d, *J* 5.5, 1′-H), 5.76 (1H, dd, *J* 5.3 and 5.3, 2′-H), 5.58 (1H, m, 3′-H), 4.52 (1H, m, 4′-H), 4.46 (2H, m, 5′-H_2), 2.16, 2.12 and 2.09 (all 3H, s, acetates); δ_C 170.4, 169.8, 169.4, 155.0, 153.9, 152.2, 145.0, 127.1, 87.3, 81.7, 73.5, 71.4, 63.2, 20.6, 20.4 and 20.2; *m*/*z* (FAB$^+$) 456 ($M^+ + 1$, 3%) and 259 (100) (Found: $M^+ + 1$, 456.1089. $C_{16}H_{17}N_8O_9$ requires *m*/*z*, 456.1088).

2′,3′,5′-Tri-*O*-acetyl-2-nitrosoadenosine 4 and its dimer 5

A suspension of **2** (1.39 g, 3 mmol) and Pd/C (10%; 0.150 g) in a mixture of EtOAc (50 mL) and EtOH (25 mL) was stirred at 45–50 °C (bath temperature) under hydrogen (1 atm). After 3 h the catalyst was removed by filtration and the mixture was evaporated to leave a glass. The resulting 2′,3′,5′-tri-*O*-acetyl-2-(hydroxyamino)adenosine **3** was used in the next step without purification, δ_H 9.2 (1H, br, NHOH), 8.4 (1H, br, NHOH), 7.71 (1H, s, 8-H), 6.45 (2H, br, NH_2), 6.06 (1H, d, *J* 4.1, 1′-H), 5.98 (1H, dd, *J* 4.1 and 5.3, 2′-H), 5.78 (1H, m, 3′-H), 4.39 (3H, m, 4′-H, 5′-H_2), 2.10, 2.05, 2.02 (all 3H, s, acetates).

To a vigorously stirred solution of crude compound **3** (3 mmol) in EtOAc (50 mL) at 0 °C was added an ice-cold solution of sodium periodate (0.77 g, 3.6 mmol) in 30 mL of water. After 15 min the mixture was warmed to room temperature and stirring was continued for 1 h. The precipitated product was dissolved by adding methanol and additional EtOAc. The layers were separated and the organic layer was dried (Na_2SO_4) and the solvent evaporated off. Trituration with methanol and cooling in ice produced pure **4** (0.792 g, 63% from **2**) as a *yellow solid*, mp 158–159 °C (Found: C, 45.36; H, 4.41; N, 19.82. $C_{16}H_{18}N_6O_8$ requires C, 45.50; H, 4.30; N, 19.90%); λ_{max}/nm(1,4-dioxane) 248, 371; ν_{max}/cm^{-1} (KBr) 1750, 1641, 1600, 1483, 1371 and 1329; δ_H (monomer **4**, obtained from mixtures with its dimer **5**) 8.28 (1H, s, 8-H), 6.5–6.9 (2H, br, NH_2), 6.43 (1H, d, *J* 5.6, 1′-H), 5.89 (1H, t, *J* 5.6, 2′-H), 5.69 (1H, dd, *J* 5.3 and 5.6, 3′-H), 4.6–4.4 (3H, m, 4′-H and 5′-H_2),

2.19, 2.14 and 2.09 (all 3H, s, acetates); δ_H (dimer **5**, obtained from mixtures with its monomer **4**) 8.08 (1H, s, 8-H), 6.34 (1H, d, *J* 6.5, 1′-H), 6.04 (2H, br s, NH_2), 5.58 (1H, dd, *J* 5.8 and 6.5, 2′-H), 5.45 (1H, dd, *J* 2.4 and 5.8, 3′-H), 4.6–4.4 (3H, m, 4′-H and 5′-H_2), 2.22, 2.17 and 2.14 (all 3H, s, acetates).

2-(Hydroxyamino)adenosine 6

Aq. ammonia (25%; 3 mL) was added to a solution of **3** (0.20 g, 0.47 mmol) in methanol (3 mL) and the resulting solution was stirred at rt for 16 h. The mixture was evaporated and the residue was coevaporated twice with ethanol. Trituration with a small amount of ethanol produced **6** (0.114 g, 81%) as a solid, mp 185–195 °C; δ_H (d_6-DMSO) 8.56 (1H, br, NHOH), 8.27 (1H, br, NHOH), 8.03 (1H, s, 2-H), 6.96 (2H, br, NH_2), 5.80 (1H, d, *J* 6.8, 1′-H), 5.39 (1H, d, *J* 6.1, OH), 5.20 (1H, d, *J* 5.0, OH), 5.14 (1H, d, *J* 5.6, OH), 4.59 (1H, dd, *J* 6.8 and 5.3, 2′-H), 4.18 (1H, m, 3′-H), 3.98 (1H, m, 4′-H), 3.60 (2H, m, 5′-H_2); δ_C (d_6-DMSO) 162.8, 156.2, 155.9, 151.0, 137.1, 114.8, 86.9, 85.7, 73.2, 70.8 and 64.9; *m*/*z* (FAB^+) 299 ($M^+ + 1$, 22%), 217 (62), 154 (100) and 136 (87) (Found: $M^+ + 1$, 299.1103. $C_{10}H_{15}N_6O_5$ requires *m*/*z* 299.1104).

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-2-nitroadenosine 9

A solution of 2-nitroadenosine **8** (0.106 g, 0.5 mmol), TBDMSCl (0.377 g, 2.5 mmol) and imidazole (0.198 g, 3.0 mmol) in DMF (3 mL) was stirred for 42 h at room temperature. Extractive work-up using water and diethyl ether followed by trituration with methanol produced **9** (0.271 g, 83%): mp 92–96 °C; ν_{max}/cm^{-1} (KBr) 1490, 1345; δ_H 8.45 (s, 1H, 8-H), 7.39 (br, s, 2H, NH_2), 5.99 (d, 1H, *J* 4.2, H-1′), 4.66 (dd, 1H, *J* 4.2, 4.3, 2′-H), 4.33 (m, 1H, 3′-H), 4.18 (m, 1H, 4′-H), 4.15 (m, 1H, 5′-H^a), 3.83 (m, 1H, 5′-H^b), 0.15, 0.14, 0.09, 0.08, 0.01, −0.10 (6 s, $SiCH_3$); δ_C 152.4, 152.1, 151.1, 148.0, 134.8, 89.6, 85.6, 76.2, 71.1, 61.8, 25.7, 25.4, 18.4, 17.9, −4.10, −4.58, −4.59, −4.76, −5.13 and −5.28.

2′,3′,5′-Tris-*O*-(*tert*-butyldimethylsilyl)-2-nitrosoadenosine 10

A mixture of **9** (0.171 g, 0.261 mmol) and 10% Pd/C (10 mg) in EtOAc (10 mL) was stirred at 45–50 °C (bath temperature) under hydrogen (1 atm). After 3 h the catalyst was removed by filtration and the resulting solution was cooled to 0 °C. An ice-cold solution of sodium periodate (0.075 g, 0.35 mmol) in 30 mL of water was added and the mixture was stirred vigorously for 30 min. Separation of the layers, drying of the organic layer (Na_2SO_4), and trituration of the residue obtained after evaporation produced **10** (0.116 g, 69%) as a yellow solid: mp >180 °C (decomp.); δ_H (mixture of monomer and dimer, selected signals): 8.61 (s, 1H, 8-H monomer), 8.31 (s, 1H, 8-H dimer), 6.32 (d, *J* 4.3, 1′-H monomer), 5.72 (d, *J* 4.1, 1′-H dimer).

2′,3′,5′-Tri-*O*-acetyl-2-(2-oxa-3-azabicyclo[2.2.1]hept-5-en-3-yl)adenosine 11

Cyclopentadiene (30 µL, 0.5 mmol) was added to a suspension of **4** (0.085 g, 0.2 mmol) in DCM (2 mL). After stirring of the mixture for 30 min the volatiles were removed by evaporation, yielding pure **11** (quantitative) as a glass (inseparable 1 : 1 mixture of isomers). The ^{1}H NMR spectrum could not be resolved except for the signals for 8-H, δ_H 7.70 and 7.64; δ_C 170.5, 170.4, 169.5, 169.42, 169.4, 169.3, 162.7, 155.7, 155.6, 150.3, 150.2, 136.0, 135.4, 133.2, 132.9, 116.2, 116.0, 87.39, 86.82, 83.39, 83.37, 79.50, 79.48, 73.10, 72.85, 70.19, 70.17, 65.93, 65.92, 63.15, 62.70, 48.16, 48.02, 20.62, 20.55, 20.43, 20.39 and 20.38.

2-(2-Oxa-3-azabicyclo[2.2.1]hept-5-en-3-yl)adenosine 12

Direct preparation *via* **11**: a suspension of **4** (0.844 g, 2.0 mmol) in methanol (25 mL) was stirred with cyclopentadiene (0.248 mL, 3 mmol) for 1 h until a clear solution of **11** (1 : 1 mixture of isomers) was obtained. KCN (26 mg, 0.40 mmol) was added and after *ca.* 1 h crystallisation started. This KCN-catalysed deprotection was in general complete after 6 h, but filtration of the product at this stage of the reaction gave much lower yields of the crystalline isomer and the filtrate consisted mainly of the second isomer. When stirring was continued for 48 h **12** was obtained as a single isomer by filtration (0.633 g, 87%), mp >200 °C (decomp.) (Found: C, 49.66; H, 4.95; N, 23.08. $C_{15}H_{18}N_6O_5$ requires C, 49.72; H, 5.01; N, 23.19%); δ_H (d_6-DMSO) 8.09 (1H, s, 8-H), 7.16 (2H, s, NH_2), 6.36 (1H, m, 5″-H or 6″-H), 6.24 (1H, m, 6″-H or 5″-H), 5.76 (1H, d, *J* 5.6, 1′-H), 5.40 (1H, d, *J* 6.2, 2′-OH), 5.36 (1H, m, 1″-H or 4″-H), 5.20 (1H, m, 4″-H or 1″-H), 5.15 (1H, d, *J* 4.5, 3′-OH), 5.02 (1H, dd, *J* 7.0 and 4.8, 5′-OH), 4.67 (1H, m, 2′-H), 4.17 (1H, m, 3′-H), 3.93 (1H, m, 4′-H), 3.64 (1H, m, 5′-H^a), 3.55 (1H, m, 5-H^b), 1.93 (1H, d, *J* 8.3, 7″-H^a), 1.71 (1H, d, *J* 8.3, 7″-H^b); *m*/*z* (FAB^+) 363 ($M^+ + 1$, 4%), 307 (33), 289 (27), 154 (100) and 136 (96) (Found: $M^+ + 1$, 363.1413. $C_{15}H_{19}N_6O_5$ requires *m*/*z*, 363.1317).

When this NMR sample was heated for a short time at 50 °C complete isomerisation occurred and a 1 : 1 mixture of two isomers **12** was formed. From the second isomer only two proton signals were observed separately at 500 MHz (d_6-DMSO): δ_H 5.06 (1H, m, 5′-OH) and 4.61 (1H, m, 2′-H).

2-Nitrosoadenosine 7

A vigorous stream of N_2 was led through a solution of **12** (0.2 g, 0.55 mmol) in anhydrous DMF (8 mL) at 95 °C (bath temperature). After 15 min the solvent was evaporated off and the residue was crystallised from water (*ca.* 3 mL) to give **7** (0.072 g) as a yellow crystalline solid. The filtrate was evaporated, and the residue was thermolyzed in DMF (3 mL) as described before to give a combined yield of 0.094 mg of *title compound* **7** (58%), mp >250 °C (decomp.) (Found: C, 40.40; H, 4.10; N, 28.21. $C_{10}H_{12}N_6O_5$ requires C, 40.54; H, 4.08; N, 28.37%); λ_{max}/nm (H_2O) 247, 311, 400; ν_{max}/cm^{-1} (KBr) 1655, 1597, 1492, 1365 and 1330; δ_H monomer (d_6-DMSO; 70 °C, 1 mg in 0.6 mL; monomer : dimer = 1 : 1) 8.68 (1H, s, 2-H), 7.7 (2H, s, NH_2), 6.05 (1H, d, *J* 5.6, 1′-H), 5.33 (1H, d, *J* 5.6, OH), 4.99 (1H, m, OH), 4.87 (1H, m, OH), 4,67 (1H, m, 2′-H), 4.24 (1H, m, 3′-H), 4.02 (1H, m, 4′-H), 3.62–3.75 (2H, m, 5′-H_2); δ_H dimer 8.43 (1H, s, 8-H), 7.8 (2H, br, NH_2), 5.64 (1H, d, *J* 5.6, 1′-H), 5.54 (1H, d, *J* 6.1, OH), 5.17 (1H, m, OH), 5.10 (1H, m, OH), 4.32 (1H, m, 2′-H), 4.09 (1H, m, 3′-H), 3.88 (1H, m, 4′-H), 3.65–3.55 (2H, m, 5′-H_2); distinct ^{13}C NMR spectra of **4** or **5** could not be obtained; with FAB techniques the M^+ or $M^+ + 1$ ion could not be detected.

2-(*cis*-3-Hydroxycyclopentylamino)adenosine 13

A suspension of **12** (0.048 g, 0.13 mmol) and 10% Pd/C (10 mg) in a mixture of ethanol (3 mL) and water (2 mL) was stirred under 1 atm hydrogen for 24 h. Chromatography on silica, and elution with EtOAc–MeOH 4 : 1, gave **13** (0.035 g, 74%) as a white solid, mp 131–151 °C; δ_H (d_6-DMSO) 7.90 (1H, s, 8-H), 6.72 (2H, s, NH_2), 6.01 (1H, d, *J* 8.2, NH), 5.72 (1H, d, *J* 6.0, 1′-H), 5.37 (1H, br, OH), 5.13 (1H, br, OH), 4.64 (1H, m, 2′-H), 4.60 (1H, br, OH), 4.21 (1H, br, OH), 4.13 (2H, m), 3.90 (1H, m, 4′-H), 3.5–3.7 (2H, m, 5′-H_2), 2.10 (1H, m), 1.90 (1H, m), 1.65–1.75 (3H, m), 1.44 (1H, m); *m*/*z* (FAB^+) 367 ($M^+ + 1$, 55%), 235 (25), 154 (100) and 136 (96) (Found: $M^+ + 1$, 367.1735. $C_{15}H_{23}N_6O_5$ requires *m*/*z*, 367.1722).

2′,3′,5′-Tri-*O*-acetyl-2-(*cis*-4-hydroxycyclohexylamino) adenosine 15

Cyclohexa-1,3-diene (19 µL, 0.2 mmol) was added to a suspension of **4** (0.042 g, 0.1 mmol) in DCM (2 mL). After stirring of the mixture for 30 min the volatiles were removed by evaporation, leaving pure 2′,3′,5′-tri-*O*-acetyl-2-(2-oxa-3-azabicyclo-

[2.2.2]oct-5-en-3-yl)adenosine **14** (quantitative) as a glass (inseparable 1 : 1 mixture of isomers). The ^{1}H NMR spectrum of this mixture could not be resolved except for the signals for 8-H: δ_H 7.67 and 7.62; δ_C 170.4, 170.3, 169.4, 169.33, 169.3, 169.25, 162.8, 162.6, 155.7, 155.6, 150.4, 150.2, 132.8, 132.3, 131.6, 131.3, 126.2, 124.1, 115.9, 115.7, 87.30, 86.98, 79.47, 73.11, 72.86, 70.37, 70.14, 70.08, 63.06, 62.76, 51.06, 50.99, 24.05, 23.96, 21.89, 20.56, 20.51, 20.45, 20.39 and 20.34.

A suspension of **14** (50 mg, 0.1 mmol) and 10% Pd/C (10 mg) in a mixture of ethanol (2 mL) and EtOAc (2 mL) was stirred under 1 atm hydrogen for 16 h. Filtration and evaporation of the mixture gave pure **15** (0.046 mg, 92%) as a glass: δ_H 7.58 (1H, s, 8-H), 5.9–6.2 (2H, br, NH_2), 6.06 (1H, m), 5.88 (1H, m), 5.73 (1H, m), 5.5 (1H, br, N-H), 4.42 (1H, m, 5′-H^a), 4.35 (1H, m, 4′-H), 4.25 (1H, m, 5′-H^b), 2.09, 2.07 and 2.02 (all 3H, s, acetates), 1.6–1.8 (8H, m); δ_C 170.4, 169.3, 169.25, 157.7, 155.0, 151.4, 113.9, 110.5, 110.45, 87.00, 79.29, 72.65, 70.25, 66.97, 63.13, 47.49, 30.96, 27.54, 27.43, 20.53, 20.37 and 20.32.

2-(*cis*-4-Hydroxycyclohexylamino)adenosine 16

The acetates were removed from **15** (49 mg, 0.1 mmol) with aq. ammonia (25%; 3 mL) and methanol (3 mL) as described for **6**. Trituration with diethyl ether produced **16** (32 mg, 84%) as a white solid; mp 135–138 °C; δ_H (d_6-DMSO) 7.89 (1H, s, 8-H), 6.69 (2H, s, NH_2), 5.85 (1H, d, *J* 6.7, NH), 5.72 (1H, d, *J* 6.0, 1′-H), 5.4–5.0 (3H, m, 3 × OH), 4.63 (1H, m, 2′-H), 4.3 (2H, m, 2 × OH), 4.16 (1H, m, 3′-H), 3.5–3.9 (6H, m), 1.5–1.7 (8H, m); *m*/*z* (FAB$^+$) 381 (M^+ + 1, 15%), 307 (13), 217 (20), 154 (100) and 136 (92) (Found: M^+ + 1, 381.1848. $C_{16}H_{25}N_6O_5$ requires *m*/*z*, 381.1847).

2′,3′,5′-Tri-*O*-acetyl-2-(4,5-dimethyl-3,6-dihydro-1,2-oxazin-2-yl)adenosine 17

2,3-Dimethylbuta-1,3-diene (20 μL, 0.2 mmol) was added to a suspension of **4** (0.042 g, 0.1 mmol) in DCM (2 mL). After 30 min at rt the reaction mixture was evaporated and the residue was purified by chromatography using 2% methanol in EtOAc as eluent, to yield **17** (21 mg, 42%); mp 190–194 °C; δ_H 7.66 (1H, s, 8-H), 6.02 (1H, m, 2′-H), 5.96 (1H, d, *J* 3.8, 1′-H), 5.91 (2H, s, NH_2), 5.83 (1H, m, 3′-H), 4.44 (1H, dd, *J* 6.1 and 12.0, 5′-H^a), 4.35 (1H, m, 4′-H), 4.33 (2H, m, 3″-H_2 or 6″-H_2), 4.27 (1H, dd, *J* 6.1 and 12.0, 5′-H^b), 4.18 (2H, m, 6″-H_2 or 3″-H_2), 2.11, 2.09 and 2.02 (all 3H, s, acetates), 1.72 (3H, br s, CH_3), 1.58 (3H, br s, CH_3).

2-(4,5-Dimethyl-3,6-dihydro-1,2-oxazin-2-yl)adenosine 18

The acetates were removed from **17** (21 mg, 0.042 mmol) with aq. ammonia (25%; 2 mL) and methanol (2 mL) as described for **6**. Trituration with diethyl ether produced **18** (15 mg, 95%) as a white solid; δ_H (d_6-DMSO) 8.11 (1H, s, 8-H), 7.20 (2H, s, NH_2), 5.79 (1H, d, *J* 6.5, 1′-H), 5.5–5.0 (3H, m, 3 × OH), 4.64 (1H, m), 4.23 (2H, m), 4.15 (1H, m), 4.08 (2H, m), 3.94 (1H, m), 3.5–3.7 (2H, m, 5′-H), 1.70 (3H, br s, CH_3), 1.57 (3H, br s, CH_3); *m*/*z* (FAB$^+$) 381 (M^+ + 1, 8%), 154 (100) and 136 (92) (Found: M^+ + 1, 379.1727. $C_{16}H_{23}N_6O_5$ requires *m*/*z*, 379.1715).

Cyclopentadiene-coupled resin 19

Merrifield resin (1 g; 1.35 mmol g^{-1}) was stirred for 18 h with lithium cyclopentadienide (0.486 g, 6.75 mmol) in DMF (10 mL). The resin was filtered off and washed repeatedly with both DMF–water 9 : 1 and MeOH to remove lithium salts, and finally with DCM and MeOH to give resin **19** (0.59 mmol g^{-1}, as was determined by coupling to excess of **4**; see the next procedure).

Diels–Alder reaction of 4 with 19

Resin **19** (0.75 g, 0.45 mmol; 0.59 mmol g^{-1}) was stirred with **4** (0.169 g, 0.4 mmol) for 30 min in DCM (10 mL) at rt. The resin was washed, filtered off, and dried *in vacuo* to give **20** (0.91 g, 0.44 mmol g^{-1}): ν_{max}/cm^{-1} (KBr) 1754, 1620, 1600 and 1580.

Reaction of 20 with cyclohexadiene

Resin **20** (0.130 g; 0.59 mmol g^{-1}) was stirred with cyclohexa-1,3-diene (0.05 mL) in DMF (2 mL) at 90 °C for 30 min. The resin was filtered off, and washed successively with DMF and diethyl ether. Evaporation of solvents produced pure **14** (27 mg, 93%) as a glass.

Ene reaction of 4 with cyclohexene to give adduct 21

A solution of **4** (0.063 g, 0.15 mmol) in a mixture of DCM (10 mL) and MeOH (10 ml) was stirred with cyclohexene (0.152 mL, 1.5 mmol) for 18 h. Chromatography of the reaction mixture (EtOAc–MeOH 98 : 2) gave **21** (0.018 g, 24%) as a 1 : 1 mixture of isomers; δ_H 7.70 (0.5H, s, 8-H), 7.69 (0.5H, s, 8-H), 6.0–5.9 (3H, m, 1′-H, CH=CH), 5.83 (1H, m, 2′-H), 5.67 (1H, m, 3′-H), 5.59 (2H, br s, NH_2), 5.15 (1H, m, CH N), 4.4–4.25 (3H, m, 4′-H, 5′-H_2), 2.2–1.6 (6H, m), 2.13, 2.11 and 2.06 (all 3H, s, acetates).

Reaction of 4 with furan to give adduct 22

A solution of **4** (3 mg) and furan (5 μL) was stirred in $CDCl_3$ (0.5 mL) for 24 h. ^{1}H NMR after 3 h showed starting material **4** and a mixture of (*Z*)-**22** and (*E*)-**22** in proportions 1 : 1 : 2. After 18 h only the *E*-isomer of **22** was present: ν_{max}/cm^{-1} 1747, 1644, 1593 and 1373; δ_H 9.81 (1H, d, *J* 8.0, CH=O), 9.19 (1H, d, *J* 10.1, CH=N), 8.05 (1H, s, 8-H), 7.93 (1H, dd, *J* 10.1 and 16.1, CH=CCO), 6.90 (1H, dd, *J* 8.0 and 16.1, C=CHCO), 6.2 (2H, br s, NH_2), 6.14 (1H, d, *J* 3.5, 1′-H), 6.01 (1H, m, 2′-H), 5.87 (1H, m, 3′-H), 4.2–4.4 (3H, m, 4′-H and 5′-H), 2.17, 2.14 and 2.02 (all 3H, s, acetates); (*Z*)-**22**: 10.23 (1H, d, *J* 6.0, CH=O), 9.81 (1H, d, *J* 11.6, CH=N), 7.81 (1H, dd, *J* 11.6 and 11.0, CH=CCO), C=CHCO not observed.

Reaction of 4 with 2-methylfuran to give adduct 23

A solution of **4** (3 mg) and 2-methylfuran (5 μL) was stirred in DCM (1.5 mL) for 3 h at rt. The volatiles were removed *in vacuo* at 20 °C, leaving almost pure **23** as a glass: ν_{max}/cm^{-1} 1748, 1720, 1645, 1595 and 1373; δ_H 9.03 (1H, d, *J* 9.8, CH=N), 8.04 (1H, s, 8-H), 7.86 (1H, dd, *J* 9.8 and 16.3, CH=CCO), 6.99 (1H, d, *J* 16.3, C=CHCO), 6.5 (2H, br s, NH_2), 6.12 (1H, d, *J* 3.8, 1′-H), 6.00 (1H, m, 2′-H), 5.76 (1H, m, 3′-H), 4.2–4.4 (3H, m, 4′-H and 5′-H_2), 2.44 (3H, s), 2.16, 2.13 and 2.02 (all 3H, s, acetates); (*Z*)-**23** (recorded after 50 min reaction time, using $CDCl_3$ as solvent): 9.91 (1H, d, *J* 10.6, CH=N).

2′,3′,5′-Tri-*O*-acetyl-2-phenylazoadenosine 26

A mixture of **4** (0.063 g, 0.15 mmol), aniline (18.6 mL, 0.2 mmol) and acetic acid (0.1 mL) was stirred in acetonitrile (1.5 mL). After *ca.* 10 min the starting material had dissolved and from this yellow solution the product started to precipitate. The mixture was stirred at rt for 5 h, cooled in ice, and filtered, producing **26** (0.063 g, 84%) as an orange solid; mp 108–112 °C; ν_{max}/cm^{-1} (KBr) 1751, 1638 and 1593; δ_H 8.10 (1H, s, 8-H), 8.09 (2H, d, *J* 4.6, ArH_{ortho}), 7.5–7.6 (3H, m, $ArH_{meta+para}$), 6.43 (1H, d, *J* 5.8, 1′-H), 5.9 (2H, br s, NH_2), 5.84 (1H, m, 2′-H), 5.66 (1H, m, 3′-H), 4.4–4.5 (3H, m, 4′-H and 5′-H_2), 2.16, 2.15 and 2.07 (all 3H, s, acetates).

2′,3′,5′-Tri-*O*-acetyl-2-(4-methoxyphenylazo)adenosine 27

Condensation of **4** (0.042 g, 0.1 mmol) with *p*-anisidine (0.013 g, 0.11 mmol) was performed as described for **26**. Chromatography (EtOAc–MeOH 95 : 5) yielded **27** (0.048 g,

91%) as an orange glass: ν_{max}/cm^{-1} 1751, 1640 and 1583; δ_H 8.11 (1H, s, 8-H), 8.09 (2H, d, *J* 6.1, ArH_{ortho}), 7.02 (2H, d, *J* 6.1, ArH_{meta}), 6.44 (1H, d, *J* 5.9, 1′-H), 6.26 (2H, br s, NH_2), 5.81 (1H, m, 2′-H), 5.63 (1H, m, 3′-H), 4.4–4.5 (3H, m, 4′-H and 5′-H_2), 3.90 (3H, s, CH_3OAr), 2.15, 2.14 and 2.06 (all 3H, s, acetates).

2-(Phenylazo)adenosine 28

Triacetate **26** (0.050 g, 0.1 mmol) was stirred with methanol (2 mL) and aq. ammonia (25%; 2 mL) for 5 h. Evaporation of the mixture, coevaporation with methanol (3 mL), and trituration with methanol gave **28** (0.032 g, 86%) as an *orange solid*, mp 215–218 °C (Found: C, 51.63; H, 4.73; N, 26.24. $C_{16}H_{17}N_7O_4$ requires C, 51.75; H, 4.61; N, 26.40%); ν_{max}/cm^{-1} (KBr) 1647 and 1597; δ_H (d_6-DMSO) **28** (*E*-isomer) 8.51 (1H, s, 8-H), 7.95 (2H, m, ArH_{ortho}), 7.8 (2H, br s, NH_2), 7.65 (3H, m, $ArH_{meta + para}$), 5.96 (1H, d, *J* 6.6, 1′-H), 5.5 (1H, d, *J* 6.3, OH), 5.2 (2H, m, 2 × OH), 4.66 (1H, m 2′-H), 4.17 (1H, m 3′-H), 4.00 (1H, m 4′-H), 3.70 (1H, m 5′-H[a]), 3.48 (1H, m, 5′-H)[b]; **28** (*Z*-isomer, selected signals) 8.32 (1H, s, 8-H), 7.65 (2H, br s, NH_2), 7.33 (2H, t, *J* 7.3, ArH_{meta}), 7.23 (1H, t, *J* 7.3, ArH_{para}), 6.94 (2H, d, *J* 7.3, ArH_{ortho}), 5.72 (1H, d, *J* 5.8, 1′-H); *m*/*z* (FAB$^+$) 372 ($M^+ + 1$, 10%), 307 (13), 217 (29), 154 (100) and 136 (95) (Found: $M^+ + 1$, 372.1438. $C_{16}H_{18}N_7O_4$ requires *m*/*z*, 372.1420).

2-(4-Methoxyphenylazo)adenosine 29

Deprotection of **27** as described for **26** gave **29** (77%) as an *orange solid*; mp 140–143 °C (Found: C, 51.03; H, 4.84; N, 24.28. $C_{17}H_{19}N_7O_5$ requires C, 50.87; H, 4.77; N, 24.43%); ν_{max}/cm^{-1} (KBr) 3332, 3188, 1668, 1640, 1601, 1581, 1504, 1367 and 1335; δ_H (d_6-DMSO) **29** (*E*-isomer) 8.48 (1H, s, 8-H), 7.96 (2H, d, *J* 8.8, ArH_{ortho}), 7.72 (2H, br s, NH_2), 7.18 (2H, d, *J* 8.8, ArH_{meta}), 5.95 (1H, d, *J* 6.3, 1′-H), 5.5 (1H, br, OH), 5.22 (2H, br, 2 × OH), 4.66 (1H, m, 2′-H), 4.17 (1H, m, 3′-H), 3.99 (1H, m, 4′-H), 3.91 (3H, s, CH_3OAr), 3.6–3.7 (2H, m, 5′-H_2); **29** (*Z*-isomer, selected signals) 8.35 (1H, s, 8-H), 7.7 (2H, br, NH_2), 7.00 (2H, d, *J* 8.8, ArH), 6.89 (2H, d, *J* 8.8, ArH), 5.76 (1H, d, *J* 5.8, 1′-H), 3.74 (3H, s, CH_3OAr); *m*/*z* (FAB$^+$) 402 ($M^+ + 1$, 6%), 154 (100) and 136 (92) (Found: $M^+ + 1$, 401.3783. $C_{17}H_{20}N_7O_5$ requires *m*/*z*, 401.3769).

References

1 M. J. Robins and B. Uznanski, *Can. J. Chem.*, 1981, **59**, 2601.
2 V. Nair and T. B. Sells, *Tetrahedron Lett.*, 1990, **31**, 807.
3 S. A. Adah and V. Nair, *Tetrahedron*, 1997, **53**, 6747.
4 E. A. Harwood, P. B. Hopkins and S. Th. Sigurdson, *J. Org. Chem.*, 2000, **65**, 2959.
5 F. De Riccardis and F. Johnson, *Org. Lett.*, 2000, **2**, 293.
6 P. Y. F. Deghati, M. J. Wanner and G.-J. Koomen, *Tetrahedron Lett.*, 2000, **41**, 1291.
7 M. J. Wanner, J. K. Von Frijtag Drabbe Künzel, A. P. IJzerman and G.-J. Koomen, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2141.
8 M. H. Davey, V. Y. Lee, R. D. Miller and T. J. Marks, *J. Org. Chem.*, 1999, **64**, 4976.
9 S. B. Park and R. F. Standaert, *Tetrahedron Lett.*, 1999, **40**, 6557.
10 E. C. Taylor, C.-P. Tseng and J. B. Rampal, *J. Org. Chem.*, 1982, **47**, 552.
11 S. M. Weinreb and R. R. Staib, *Tetrahedron*, 1982, **38**, 3087.
12 G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1.
13 P. Zuman and B. Shah, *Chem. Rev.*, 1994, **94**, 1621.
14 G. E. Keck and S. A. Fleming, *Tetrahedron Lett.*, 1978, 4763.
15 J. W. Wijnen and J. B. F. N. Engbers, *Liebigs Ann./Recl.*, 1997, 1085.
16 The ^{1}H NMR spectra showed only marginal chemical-shift differences between the 2 isomers. No attempts were made to determine the structure of the crystalline isomer.
17 K. G. Orrell, V. Sik and D. Stephenson, *Magn. Reson. Chem.*, 1987, **25**, 1007.
18 B. G. Gowenlock, M. J. Maidment, K. G. Orrell, V. Sik, G. Mele, G. Vasapollo, M. B. Hursthouse and K. M. A. Malik, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2280.
19 P. Horsewood and G. W. Kirby, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1587; P. Horsewood, G. W. Kirby, R. P. Sharma and J. G. Sweeny, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1802.
20 G. E. Keck, *Tetrahedron Lett.*, 1978, 4767; G. E. Keck and D. G. Nickel, *J. Am. Chem. Soc.*, 1980, **102**, 3632.
21 D. Mackay, L. H. Dao and J. M. Dust, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2408.
22 A. Adam, N. Bottke and O. Krebs, *Org. Lett.*, 2000, **2**, 3293; A. Adam, N. Bottke and O. Krebs, *J. Am. Chem. Soc.*, 2000, **122**, 6791.
23 C. A. Seymour and F. D. Greene, *J. Org. Chem.*, 1982, **47**, 5226.
24 D. Mackay, E. G. Neeland and N. J. Taylor, *J. Org. Chem.*, 1986, **51**, 2351.
25 A. V. Butin, T. A. Stroganova, I. V. Lodina and G. D. Krapivin, *Tetrahedron Lett.*, 2001, **42**, 2031.
26 For recent applications see refs. 8 and 9.
27 J. F. Gerster, J. W. Jones and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 945.
28 I. M. Buck and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2937.