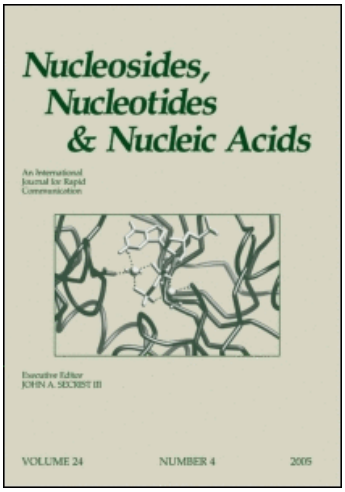


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Synthesis of the Potent A_2 Selective Adenosine Agonist N^6-[2-(3,5-Dimethoxyphenyl)-2-(2-Methylphenyl)Ethyl]Adenosine, and Its 5'-N-Ethyl Ribofuranuronamide Derivative

Alexander J. Bridges[a]
[a] Departments of Chemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Mi

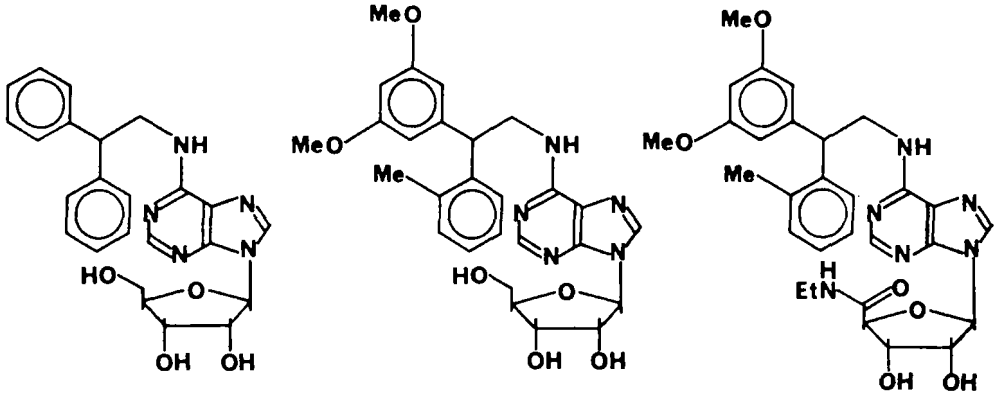
To cite this Article Bridges, Alexander J.(1989) 'A Synthesis of the Potent A_2 Selective Adenosine Agonist N^6-[2-(3,5-Dimethoxyphenyl)-2-(2-Methylphenyl)Ethyl]Adenosine, and Its 5'-N-Ethyl Ribofuranuronamide Derivative', Nucleosides, Nucleotides and Nucleic Acids, 8: 3, 357 — 366
To link to this Article: DOI: 10.1080/07328318908054181
URL: http://dx.doi.org/10.1080/07328318908054181

NUCLEOSIDES & NUCLEOTIDES, 8(3), 357-366 (1989)

A SYNTHESIS OF THE POTENT A_2 SELECTIVE ADENOSINE AGONIST N^6-[2-(3,5-DIMETHOXYPHENYL)-2-(2-METHYLPHENYL)ETHYL]ADENOSINE, AND ITS 5'-N-ETHYL RIBOFURANURONAMIDE DERIVATIVE .

Alexander J. Bridges, Department of Chemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Mi 48105.

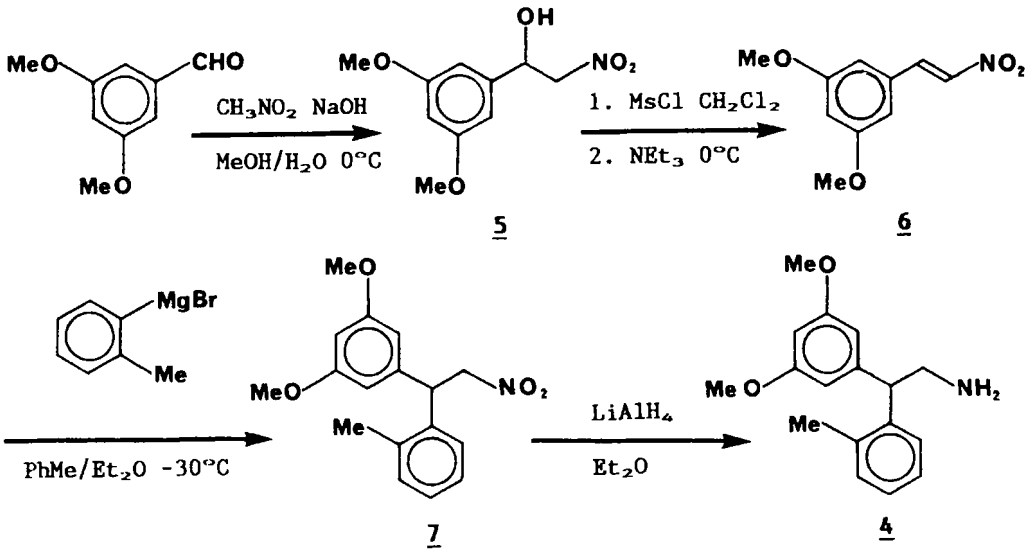
Abstract. A detailed experimental procedure for the synthesis and resolution of 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine, and its conversion into the titled adenosine reference agonists is given.



1 2 3

In a recent communication[1] we reported that suitably modified derivatives of N^6(2,2-diphenylethyl)adenosine 1[2] are very potent adenosine receptor agonists with a previously unachieved degree of selectivity for the high affinity A_{2a} adenosine receptor. The best of these agonists, N^6-[(RS)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine 2, its separated diastereoisomers 2A and 2B, and the corresponding N-ethyluronamide (NECA) derivative 3, all had K_i affinities for the A_{2a} adenosine receptor in the 3-6nM range and at least 25-fold weaker affinity at the A_1 receptor, with isomer 2A being the most potent A_{2a} receptor agonist yet revealed (K_i = 3.1nM) as well as the most selective for that receptor (38-fold). We believe that these compounds will find use in adenosine pharmacology as reference agents for the exploration of the A_{2a} receptor, and the purpose of this paper is to provide the fully documented synthetic procedures for 2 and 3.

Initial exploration of the N^6-(2,2-diarylethyl)adenosine series revealed the need for a short and straightforward synthesis of substituted 2,2-diarylethylamines, which can then be coupled with 6-chloropurine riboside



Scheme 1. Synthesis of Diarylethylamine 4 via Nitrostyrene 6.

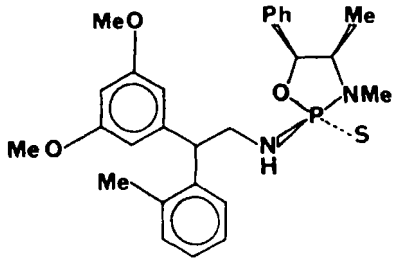
to make the desired adenosines. The best published synthesis[3] involved the initial condensation of an aryl aldehyde with ethyl cyanoacetate. Michael addition of an aryl Grignard reagent to the highly activated double bond of the intermediate benzylidene derivative was followed by a vigourous hydrolysis-decarboxylation to give a 3,3-diarylpropionic acid, which could be chain-shortened to the desired ethylamine by Curtius-Schmidt rearrangement. We reasoned that the route could be simplified, and the potentially hazardous acyl azide intermediate avoided, by the use of one nitro group to activate the benzylidene double bond to Michael addition. The major advantage of such an approach is that it does not introduce any extra carbon atoms, which require subsequent removal.

Scheme 1 shows the sequence used to prepare 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine 4. The experimental procedure described in this paper was used, essentially without modification, to produce more than 60 diarylethylamines[4], usually, and most conveniently, on a 5-20 mmol scale. Condensation of 3,5-dimethoxybenzaldehyde with nitromethane using NaOH, followed by quenching with dilute hydrochloric acid[5], gave close to a 1:1 mixture of the simple adduct, nitroalcohol 5, and its dehydration product, nitrostyrene 6. Although it is reported[5] that this sequence gives nitrostyrenes directly, we always obtained mixtures of nitroalcohol and nitrostyrene. With electron deficient aldehydes, we found that the mixtures contained only 10-20% of the nitrostyrene, but electron rich aldehydes produced up to 60% nitrostyrene. The crude mixture of 5 and 6 was assayed by nmr, dissolved in CH_2Cl_2 at 0°C and 1.05 equivalents of mesyl chloride[6], (based on the determined nitroalcohol content), was

added dropwise, followed by 2.2 equivalents of NEt_3[7]. Aqueous workup gave the nitrostyrene 6 in >90% crude yield, pure enough to be used in the next step if so desired, although in this particular case it was found to be advantageous to recrystallize 6 from EtOH. Addition of base to the mixture before the mesyl chloride decreased yields as a retroaldol process reformed some starting aldehyde. Although this is a two step process, it can produce 6 in less than 3 hours, and we found it to be generally more reliable and easier than trying to follow any of the one-step literature preparations.

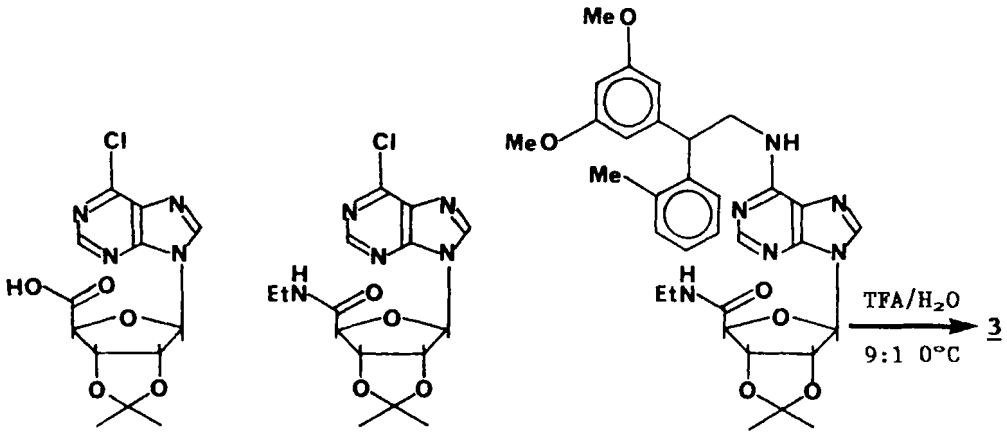
Addition of 2-methylphenyl magnesium bromide in ether to a partial solution of nitrostyrene 6 in toluene at -30°C gave a cloudy orange-red solution. Acid quenching gave a quantitative yield of the crude diaryl-nitroethane 7. In this addition THF could be substituted for ether and aryl lithium agents could be substituted for Grignard reagents, but CuI addition decreased yields. Additionally, temperature control did not appear to be crucial, as addition temperatures between 0 and -40°C made little difference to yields. However, the use of toluene as the major solvent appeared to be crucial for two reasons. Yields were much higher in toluene, and no residual nitrostyrene was present at the end of the reaction. (Unreacted nitrostyrene led to 2-arylethylamine contaminant at the end of the sequence, causing purification problems.) The sequence was completed by adding an ethereal solution (or, in the case of 7, a slurry) of the nitroethane to three molar equivalents of $LiAlH_4$ in ether. Acid extraction gave the desired diarylethylamines in better than 90% purity, as yellow oils. Amine 4 was atypical, in that it solidified readily, and could be further purified by recrystallization from toluene. Recrystallized amine 4 was obtained in 51% overall yield using this procedure. Usually, electron rich aldehydes gave 40-65% overall yields of diarylethylamines in this process, whereas electron deficient aldehydes gave lower overall yields (15-35%), probably mainly due to extensive polymerization during the Michael addition. Additionally, some aryl substituents, such as carbonyl, nitro and amino were not compatible with the process. Several other aromatic systems such as 2-furanyl, 2- and 3-thienyl and 1- and 2-naphthyl could be introduced into the final amine[4].

Amine 4 was resolved by repeated crystallization of its dibenzoyl tartrate salt from absolute ethanol. On a small scale 10 recrystallizations were required to obtain salt with an EE of greater than 90%, and the overall efficiency was very low. However, on a larger scale, optimal control of concentrations, and the use of high EE seed crystals during crystallization, allowed the resolution to be shortened to five recrystallizations. Using (-)-D-dibenzoyl tartaric acid (-)-4 was obtained in 11.8% yield and 94% EE. Liberation of the free amine from the mother liquors of the first crystallization, followed by three recrystallization with (+)-L-dibenzoyl tartaric acid gave (+)-4 in 13.5% yield and 87% EE. Enantiomeric excess determinations could be carried out by proton nmr after formation of the chiral cyclic phosphoramidate derivative 8[8,9] (at room temperature). Alternately, a reverse phase hplc analysis on a cyclodextrin stationary phase[1,10] allowed for enantiomeric excesses of 4 to be measured directly.



8

Amine 4 and both of its resolved enantiomers coupled readily with 6-chloropurine riboside[10] in refluxing EtOH containing two equivalents of NEt_3. Adenosine 2, and its individual diastereoisomers 2A and 2B, were all crystalline solids, which could be recrystallized from EtOH in good yields. The diastereoisomeric excesses of these compounds could be determined using reverse phase cyclodextrin hplc analysis[11]. Adenosine 2 crystallized as a 49:51 mixture of diastereoisomers. It was very unusual for adenosines in this series to crystallize, and most were purified by removal of the solvent, partitioning between EtOAc and water, and flash chromatography on silica gel, eluting with 5% MeOH in $CHCl_3$ or CH_2Cl_2, as described in the experimental section for 3.



9 10 11

Coupling of amine 4 with the protected chloropurinyl ribofuranuronic acid derivative 9[12], followed by DCC/hydroxybenzotriazole[13] coupling with $EtNH_2$, or with the N-ethyluronamide 10[12,14] gave 11, the isopropylidene of 3, in good yield. Deprotection of the ketal with 9:1 TFA/water at 0°C, followed by chromatographic purification gave the uronamide 3 in 62% yield from 4. However, when DCC was used in either procedure, the final product 3 contained some DCC related impurities even after chromatography and we found that N-methyl-2-fluoropyridinium tosylate (MFPT)[15] was a superior coupling agent for amidation of ribofuranuronic acids including the cases described above.

Experimental

Materials and Methods

6-Chloropurine riboside was obtained from Parke-Davis, Holland, Michigan. All other reagents were commercial reagent grade samples, and were used without further purification. All solvents were used directly from newly opened bottles of ACS certified grade. Melting points were obtained on an Electrothermal melting point apparatus, and are uncorrected. NMR spectra were obtained on a Varian XL200 nmr spectrometer. IR spectra were obtained on a Nicolet MX-1 FT IR. Mass spectra were obtained on a VG Analytical 7070E/HF mass spectrometer using electron impact at 70eV or fast atom bombardment using 1 milliampere of 7kV xenon as the target gas. Rotations were obtained on a Perkin-Elmer 240 polarimeter. HPLC[11] determinations of the enantiomeric excess of amine 4 were carried out on a Cyclobond 1 column (250 x 4.6 mm) eluting at 1.5 mL/min with MeOH:H_2O (20:80) containing 0.5% formic acid adjusted to pH 4.3 with NH_3, when the enantiomers had retention times of 32 and 37 min. HPLC determinations of diastereoisomeric excess for adenosine 2 were carried out in the same system, except that the MeOH:H_2O ratio was 45:55, when the isomers had retention times of 14 and 21 min.

E,2-(3,5-Dimethoxyphenyl)nitroethene 6.

Aqueous NaOH solution (5 M, 135 mL) was added dropwise over 40 min to a partial suspension of 3,5-dimethoxybenzaldehyde (107.4 g, 0.65 mol) in MeOH (400 mL) containing nitromethane (42 g, 0.67 mol), stirred under N_2 at 0°C. After a further 20 min the light yellow solution was poured onto dil HCl (1.5 M, 0.5 L), and the bright yellow slurry was extracted with CH_2Cl_2 (3 X 250 mL). The combined extracts were washed with water (2 X 250 mL), saturated brine (250 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude nitroalcohol (144.1 g) as a partially crystalline yellow oil. (Nmr analysis showed a 1:4:6 ratio of starting aldehyde:nitrostyrene:nitroalcohol). The material was dissolved in stirred CH_2Cl_2 (1 L) under N_2 at 0°C and mesyl chloride (46 g, 0.4 mol) was added, followed by dropwise addition of NEt_3 (81 g, 0.8 mol) over 45 min. After a further 45 min at 0°C, the orange-brown slurry was poured onto dil HCl (1 M, 0.8 L), the layers were separated, and the residual yellow solid was extracted from the aqueous layer with CH_2Cl_2 (0.6 L). The combined organic extracts were washed with water (0.5 L) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give crude nitrostyrene (190 g) as a somewhat dirty yellow solid, which was recrystallized from EtOH (4 L) to give **nitrostyrene 6** (104.3 g, 2 crops, 77.4%) as yellow needles mp 129-31°C. $C_{10}H_{11}NO_4$ requires: C, 57.42; H, 5.26; N, 6.70%. Found: C, 57.19; H, 5.22; N, 6.58%. IR (KBr) 1637, 1599, 1510, 1428, 1344, 1310, 1290, 1210, 1165, 1154, 1062, 1057, 970, 966, 834 cm^{-1}. NMR ($CDCl_3$) 7.93 (1H, d, J = 13.6 Hz), 7.55 (1H, d, J = 13.6 Hz), 6.67 (2H, d, J = 2.2 Hz), 6.59 (1H, t, J = 2.2 Hz), 3.83 (6H, s) ppm. Mass spectrum (EI) m/e 209 (100, M^+).

2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)nitroethane 7.

A solution of 2-methylphenyl magnesium bromide, prepared from 2-methylbromobenzene (136.8 g, 0.8 mol) and Mg turnings (19.2 g, 0.8 gm atom) in ether (300 mL), was added over 75 min to a partial suspension of E,2-(3,5-dimethoxyphenyl)nitroethene (104.6 g, 0.5 mol) in toluene (2 L)

stirred under N_2 at -30°C. After a further 15 min the cloudy red-brown solution was blown through a catheter onto ice (1 L) and dilute HCl (1 M, 1 L). [On a smaller scale, reactions were quenched by addition of 1 M HCl to the -30° reaction mixture with no detriment.] The layers were separated and the aqueous layer was extracted with toluene (0.5 L). The combined organic layers were washed with saturated brine (0.5 L) and dried ($MgSO_4$). The solvent was removed rigorously under reduced pressure to give the crude **diarylnitroethane** 7 (154.6 g, 99%) as an orange-brown oil. IR (LF) 1607, 1597, 1555, 1462, 1431, 1378, 1206, 1160, 1070 cm^{-1}. NMR ($CDCl_3$) 7.24, 7.22 (2H, 2H, ABq, J = 3.6 Hz), 6.39 (3H, s), 5.09 (1H, d of d, J = 9.3, 7.1 Hz), 4.96, 4.94 (1H, 1H, 2d, J = 7.1, 9.3 Hz), 3.76 (6H, s), 2.36 (3H, s) ppm. Mass spectrum (EI) m/e 301 (100, M^+).

[R,S]-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine 4.
CAUTION! This procedure calls for the use and aqueous quench of a large quantity of $LiAlH_4$. It is **strongly** recommended that those unfamiliar with handling $LiAlH_4$ carry this reaction out on one tenth or less of the scale described here.
A solution of 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) nitroethane 7 (154.6 g, 0.5 mol) in ether (1 L) was added dropwise over 2h to a slurry of $LiAlH_4$ (55.5 g, 1.5 mol) in ether (1.5 L), stirred under N_2 using an icebath to keep the temperature below 25°C. Vigourous gas evolution! After a further 14h, stirring at 25°C the reaction mixture was put on an icebath, and water (50 mL), dilute NaOH solution (2.5 M, 50 mL), and water (150 mL) were added in a cautious, sequential, dropwise fashion over three hours. Vigourous gas evolution! [On a smaller scale the reactions were run for 3h, without cooling]. The slurry was Buchner-filtered, and the residue rinsed with ether (2 X 500 mL). The combined filtrates were extracted with dilute HCl (0.1 M, 4 X 1 L, 0.5 L). The combined acid extracts were washed with ether (2 X 500 mL) and made basic with NaOH pellets (24 g, 0.6 mol). The yellow oil was extracted with ether (5 X 500 mL), and the ethereal solution was washed with water (2 X 500 mL), saturated brine (500 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude diarylethylamine (110.8 g 82%) as a light yellow solid. [This was the only amine in the series which crystallized.] The amine was recrystallized from toluene (200 mL) to give diarylethylamine 4 (92.1 g, 66.8%, 2 crops) as a pale yellow crystalline solid mp 89-91°C. $C_{17}H_{21}NO_2$ requires: C, 75.28; H, 7.75; N, 5.17%. Found: C, 75.46; H, 7.86; N, 5.03%. IR (KBr) 1606, 1593, 1461, 1430, 1203, 1158, 1145, 1067, 844, 746, 702 cm^{-1}. NMR ($CDCl_3$) 7.35-7.1 (4H, m), 6.38 (2H, d, J = 2.3 Hz), 6.31 (1H, t, J = 2.3 Hz), 4.12 (1H, t, J = 7.5 Hz), 3.75 (6H, s), 3.28 (2H, d, J = 7.5 Hz), 2.30 (3H, s), 1.27 (2H, brs) ppm. Mass spectrum (EI) m/e 272 (100, MH^+).

N^6-{[RS]-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl}adenosine 2.
A suspension of 6-chloropurine riboside (74.62 g, 0.26 mol) and 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (70.46 g, 0.26 mol) were refluxed under N_2 in stirring EtOH (1.5 L) containing NEt_3 (52.5 g, 0.52 mol) for 22h. The solvent was removed under reduced pressure from the clear light yellow solution, and the residual gummy foam was partitioned between EtOAc (1 L) and water (0.5 L). The layers were separated, and the aqueous layer was extracted with further EtOAc (0.25 L). The combined organic phases were washed with saturated brine (0.5 L), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow gum which slowly solidified. [This was the only example in the entire

series where this was observed.] The material was recrystallized from the minimum of EtOH (4.5 L), to give the **adenosine 2** (97.9 g, 72.4%, 1st crop; 22.8 g, 16.3% subsequent crops) as white needles mp 183-84°C. $C_{27}H_{31}N_5O_6$ requires: C, 62.19; H, 5.95; N, 13.44%. Found: C, 62.15; H, 5.99; N, 13.11%. IR (KBr) 1622, 1604, 1596, 1480, 1462, 1428, 1352, 1335, 1315, 1297, 1196, 1155, 1126, 1087, 1072, 1063, 1040, 981, 907, 864, 848, 835, 741 cm^{-1}. NMR (DMSO) 8.34, 8.30 (1H, 1H, 2s), 7.93 (1H, brs), 7.37 (1H, d, J = 7 Hz), 7.2-7.05 (3H, m), 6.42 (2H, d, J = 2.2 Hz), 6.33 (1H, t, J = 2.2 Hz), 5.90 (1H, d, J = 6.0 Hz), 5.46 (1H, d, J = 6.0 Hz), 5.41 (1H, d of d, J = 7.0, 4.7 Hz), 5.20 (1H, d, J = 4.6 Hz), 4.79 (1H, sl brt, J = 6 Hz), 4.61 (1H, approx q, J = 5.5 Hz), 4.20-3.95 (4H, m), 3.75-3.50 (2H, ABq of ds of ds), 3.67 (6H, s), 2.31 (3H, sl brs) ppm. CMR (DMSO) 19.5, 43.5, 44.1, 55.0, 61.6, 70.6, 73.5, 85.9, 87.9, 97.7, 106.7, 119.6, 126.0, 126.2, 126.8, 130.3, 136.2, 139.7, 140.5, 144.7, 148.3, 152.4, 154.4, 160.3 ppm. Mass spectrum (FAB) m/e 522 (100, MH^+), 521 (6, M^+).

Resolution of 2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine 4. (±)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine 4 (40.65 g, 0.15 mol) and [2R,3R]-di-O-benzoyltartaric acid monohydrate (56.4 g, 0.15 mol) were recrystallized from refluxing EtOH (700 mL), seeding with crystals of 94% EE optically enriched (-)-amine salt, (produced by 10 recrystallizations of a small sample). The solid was recrystallized four further times at similar concentrations to give 5.78g of salt mp 175.5-177°C, $[\alpha]_D^{23}$ (MeOH)-93.5°. The salt (5.0 g) was partitioned between dilute NaOH solution (1N, 30 mL) and ether (50 mL). The layers were separated, and the aqueous layer was extracted with ether (25 mL). The combined ethereal extracts were washed with water (2 X 25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the **(-)-amine** (2.08 g, 11.8%) as a cloudy pale yellow oil $[\alpha]_D^{23}$ (MeOH) -57.4°, EE 93.4%. The mother liquors from the first recrystallization were evaporated to dryness, and the residual solid partitioned between dilute NaOH solution (0.4 M, 0.5 L) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2 X 100 mL). The combined extracts were washed with dilute NaOH solution (0.25 M, 100 mL), water (100 mL), saturated brine (100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 17.2 g of oil, which was combined with [2S,3S]-di-O-benzoyltartaric acid monohydrate (23.88 g, 63.5 mmol), and was recrystallized three times from EtOH, using the same procedure as described above to give 6.60 g of salt mp 169-171°C. The salt (5.0 g) was neutralized as described above to give the **(+)-amine** (2.09 g, 13.5%) as a cloudy pale yellow oil $[\alpha]_D^{23}$ (MeOH) +53.3°, EE 87%.

N^6-{(-)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl}adenosine 2A. (-)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.02 g, 7.45 mmol), 6-chloropurine riboside (2.16 g, 7.5 mmol) and NEt_3 (1.51 g, 15 mmol) were refluxed under N_2 in stirring EtOH (70 mL) for 18h. On cooling the **(-)-nucleoside 2A** (3.53 g, 90%) crystallized as white needles mp 195-197°C, $[\alpha]_D^{23}$ (DMSO) -78.1°. Diastereoisomeric excess 90.3%. $C_{27}H_{31}N_5O_6$ requires: C, 62.19; H, 5.95; N, 13.44%. Found: C, 61.86; H, 6.03; N, 13.22%. All spectra identical to 2.

N^6-{(+)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl}adenosine 2B. (+)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.03 g, 7.5

mmol) 6-chloropurine riboside (2.16 g, 7.5 mmol) and NEt_3 (1.51 g, 15 mmol) were refluxed in stirring EtOH (75 mL) under N_2 for 18h. The solvent was removed under reduced pressure and the residual gum was partitioned between water (50 mL) and EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (25 mL). The combined extracts were washed with water (25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH (25 mL) at 0°C to give **(+)-nucleoside 2B** (2.86 g, 74%) as white needles mp 168-169°C, $[\alpha]_D^{23}$ (DMSO) -5.5°. Diastereoisomeric excess 80.2%. $C_{27}H_{31}N_5O_6$ requires: C, 62.19; H, 5.95; N, 13.44%. Found: C, 61.83; H, 5.94; N, 13.31%. All spectra identical to 2.

1-Deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamino]-9H-purin-9-yl}-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronic acid.
A solution of 1-(6-chloro-9H-purin-9-yl)-1-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronic acid (3.41 g, 10 mmol), 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.71 g, 10 mmol) and NEt_3 (3.03 g, 30 mmol) were refluxed in stirred EtOH (100 mL) under N_2 for 18h. The solvent was removed under reduced pressure and the residue was dissolved in dilute NaOH solution (0.25 M, 50 mL). The aqueous phase was washed with EtOAc (2 X 25 mL), acidified with concentrated HCl, and extracted with EtOAc (3 X 30 mL). The combined extracts were washed with water (2 X 25 mL) saturated brine (25 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the **adenosine uronic acid** (4.94 g, 82%) as a light yellow solid foam mp 113-121°C, containing 33 mol% EtOAc. IR (KBr) 1735?, 1680, 1624, 1609, 1598, 1463, 1207, 1158, 1100, 1070 cm^{-1}. NMR (DMSO) 13.2-11.7 (1H, brs), 8.23 (2H, s), 7.84 (1H, brs), 7.36 (1H, d, J = 7 Hz), 7.18-7.11 (3H, m), 6.41 (2H, sl brs), 6.34 (2H, sl brs), 5.50 (1H, d of ds, J_{AB} = 6.0 Hz, J_d = 1.6 Hz), 5.46 (1H, d, J_{AB} = 6.0 Hz), 4.8-4.7 (1H, m), 4.70 (1H, d, J = 2 Hz), 4.13-3.90 (2H, brs), 3.67 (6H, s), 2.30 (3H, s), 1.52, 1.35 (3H, 3H, 2s) ppm. CMR (DMSO) 19.4, 25.9, 26.4, 43.0, 55.0, 83.4, 83.7, 85.4, 89.5, 97.7, 106.6, 112.7, 119.3, 125.9, 126.2, 126.7, 130.3, 136.2, 140.2, 140.5, 144.7, 148.0, 152.0, 154.5, 160.3, 170.6 ppm. Mass spectrum (EI) m/e 575 (17, M^+), 148 (100).

N-Ethyl-1-(6-chloro-9H-purin-9-yl)-1-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronamide 10.
Triethylamine (1.01 g, 10 mmol) was added to a stirred suspension of 1-(6-chloro-9H-purin-9-yl)-1-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronic acid (1.70 g, 5 mmol) and N-methyl-2-fluoropyridinium tosylate[14] (2.12 g, 7.5 mmol) in CH_2Cl_2 (25 mL) under N_2 at 0°C. After 10 min ethylamine (1 mL, 15 mmol) was added to the clear yellow solution. After a further 1h, the reaction mixture was poured onto dilute HCl (1 M, 25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were washed with water (25 mL), saturated brine (25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (125 g) eluting with EtOAc/hexanes (1:1, 0.75 L, 3:2, 1.25 L) to give the desired **ribofuranuronamide 10** (1.20 g, 65%) as a white solid foam mp 73-80°C. $C_{15}H_{18}ClN_5O_4$ requires: C, 48.98; H, 4.90; N, 19.05; Cl, 9.66%. Found: C, 48.91; H, 4.94; N, 18.98; Cl, 9.62%. IR (KBr) 1670, 1594, 1565, 1385, 1340, 1204, 1161, 1142, 1097, 940, 886, 638 cm^{-1}. NMR ($CDCl_3$) 8.74, 8.24 (1H, 1H, 2s), 6.21 (1H, 1H,

sl brs, d, J = 2.2 Hz), 5.52, 5.44 (1H, 1H, ABq of ds, J_{AB} = 6.2 Hz, J_d = 2.2, 2 Hz), 4.72 (1H, d, J = 2 Hz), 2.99 (2H, m, J = 6.3 Hz), 1.61, 1.39 (3H, 3H, 2s), 0.67 (3H, t, J = 6.3 Hz) ppm. Mass spectrum (FAB) m/e 370 (31, $^{37}ClMH^+$), 369 (23, $^{35}Cl^{13}CMH^+$), 368 (100, $^{35}ClMH^+$).

N-Ethyl-1-deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethylamino]-9H-purin-9-yl}-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronamide 11.

Dicyclohexylcarbodiimide (0.52 g, 2.5 mmol) was added to a suspension of 1-hydroxybenzotriazole (0.27 g, 2.0 mmol) and 1-deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamino]-9H-purin-9-yl}-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronic acid 10 (1.15 g, 2.0 mmol) in stirred CH_2Cl_2 (20 mL) under N_2 at 0°C. After 10 min ethylamine (0.27 mL, 4 mmol) was added in one portion via precooled syringe. After 16h at 0°C the solution was filtered, and the residue rinsed with CH_2Cl_2 (10 mL). The combined filtrates were concentrated under reduced pressure to give the crude **ribofuranuronamide 11** (1.29 g, quant) as a light yellow solid foam. NMR ($CDCl_3$) 8.23, 7.65 (1H, 1H, 2s), 7.35-7.05 (4H, m), 6.98 (1H, t, J = 5 Hz), 6.35 (2H, d, J = 2 Hz), 6.26 (1H, t, J = 2 Hz), 5.96 (1H, s), 5.90 (1H, t, J = 6 Hz), 5.20 (2H, s), 4.62 (1H, s), 4.6-4.1 (2H, m), 3.67 (3H, s), 3.07 (2H, quintet, J = 6 Hz), 2.23 (3H, s), 1.60 (3H, s), 1.37 (3H, s), 0.88 (3H, t, J = 5 Hz) ppm.

Conversion of N-Ethyl-1-(6-chloro-9H-purin-9-yl)-1-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronamide 10 into N-Ethyl-1-deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethylamino]-9H-purin-9-yl}-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronamide 11.

N-Ethyl-1-(6-chloro-9H-purin-9-yl)-1-deoxy-2,3-di-O-(1-methylethylidene)-β-D-ribofuranuronamide (0.22 g, 0.6 mmol) 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (0.17 g, 0.6 mmol) and NEt_3 (0.12 g, 1.2 mmol) were refluxed under N_2 in stirring EtOH (6 mL) for 20h. The solvent was removed under reduced pressure to give crude **ribofuranuronamide 11** as a light yellow gum, which could be converted to uronamide 3 as described below.

N-Ethyl-1-deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl) ethylamino]-9H-purin-9-yl}-β-D-ribofuranuronamide 3.

N-Ethyl-1-deoxy-1-{6-[N,2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl amino]-9H-purin-9-yl}-2,3-di-O-(1-methylethylidene) - β -D-ribofuranuronamide 10 (1.29 g, 2.0 mmol) was dissolved in aqueous TFA (1:9, 10 mL), stirring under N_2 at 0°C. After 75 min the purple solution was diluted with EtOAc (100 mL) and washed with dilute NaOH solution (1 M, 100 mL), saturated Na_2CO_3 solution (50 mL, emulsion!), saturated brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual yellow solid foam (1.00 g) was purified by flash chromatography on silica gel (100 g) eluting with 5% MeOH in $CHCl_3$, and the solvent was removed under reduced pressure at 80°C, to give **ribofuranuronamide 3** (0.86 g, 76%) as a pale yellow glass mp 103-112°C. Calculated for $C_{29}H_{34}N_6O_6.0.4\ H_2O$: C, 61.14; H, 6.11; N, 14.76%. Found: C, 61.50; H, 6.49; N, 14.41%. IR (KBr) 3600-2600, 1675, 1621, 1610, 1463, 1337, 1296, 1206, 1157, 1056 cm^{-1}. NMR (DMSO) 8.88 (1H, t, J = 5.5 Hz), 8.36, 8.33 (1H, 1H, 2s), 8.00 (1H, brt), 7.34 (1H, d, J = 6.9 Hz), 7.20-7.03 (3H m), 6.39 (2H, d, J = 1.9 Hz), 6.31 (1H, t, J = 1.9 Hz), 5.94 (1H, d, J = 7.7 Hz), 5.73 (1H, d, J = 4.2 Hz), 5.56 (1H, d, J = 7.3 Hz), 4.77 (1H, brt), 4.65-4.50 (1H, m), 4.29 (1H, s), 4.12-3.90 (3H, m),

3.65 (6H, s), 3.21 (2H, quintet, J = 6.5 Hz), 2.29 (3H, s), 1.16 (3H, t, J = 6.5 Hz) ppm. Mass spectrum (EI) m/e 562 (50, M^+), 254 (100).

REFERENCES

1. Bridges, A. J.; Bruns, R. F.; Ortwine, D. F.; Priebe, S. R.; Szotek, D. L.; Trivedi, B. K. J. Med. Chem. **1988**, 31, 1282.

2. Bridges, A. J.; Moos, W. H.; Szotek, D. L.; Trivedi, B. K.; Bristol, J. A.; Heffner, T. G.; Bruns, R. F.; Downs, D. A. J. Med. Chem. **1987**, 30, 1709.

3. Zuccarello, W. A.; Blank, B.; Frishmuth, G. J.; Cohen, S. R.; Scaricaciottola, D.; Owings, F. F. J. Med. Chem. **1969**, 12, 9.

4. Bridges, A. J.; Bruns, R. F.; Ortwine, D. F.; Priebe, S. R.; Szotek, D. L.; Trivedi, B. K. Ms. in preparation.

5. Worrall, D. E. Org. Syn. Coll. Vol. 1 Ed. Gilman, H., J. Wiley, New York, 1943, 413.

6. Crossland, R. K.; Servis, K. L. J. Org. Chem. **1970**, 35, 3195.

7. Banks, B. J.; Barrett, A. G. M.; Russell, M. A. J. Chem. Soc. Chem. Commun. **1984**, 670.

8. Johnson, C. R.; Elliott, R. C.; Penning, T. D. J. Amer. Chem. Soc. **1984**, 106, 5019.

9. Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. J. Chem. Soc. Perkin 1 **1977**, 1969.

10. Priebe, S. R. Ms in preparation.

11. Fleysher, M. H. J. Med. Chem. **1972**, 15, 187.

12. Bridges, A. J. in Nucleic Acid Chemistry Part 4 Ed. Townsend, L. B.; Tipson, R. S., Wiley, New York, in press.

13. Konig, W.; Geiger, R. Chem. Ber., **1970**, 103, 788.

14. Olsson, R. A.; Kusachi, S.; Thompson, R. D.; Ukena, D.; Padgett, W.; Daly, J. W. J. Med. Chem. **1986**, 29, 1683.

15. Mukaiyama, T.; Usui, M.; Shimida, E.; Saigo, K. Chem. Lett., **1975**, 1045, 1163.

Received April 27, 1988.