Synthesis of 3-β-D-Ribofuranosylwybutine, the Most Probable Structure for the Hypermodified Nucleoside Isolated from Yeast Phenylalanine Transfer Ribonucleic Acids

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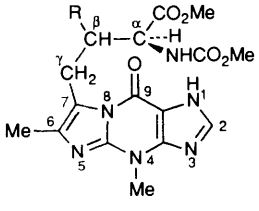
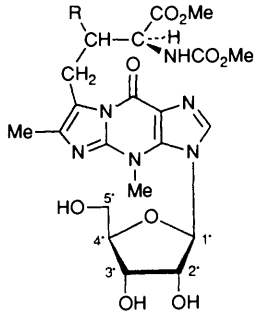
An alternative synthesis of the key intermediate **8** for the synthesis of wybutine **1** has been attained through the Heck reaction between (*S*)-*N*-(methoxycarbonyl)vinylglycine **13** and 1-benzyl-7-iodowye **7**. The nucleoside version of this method using 7-iodo-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)wye **19**, followed by catalytic hydrogenation, afforded a mixture of diastereoisomers **22** and **23**. Separation of isomer **22** by means of high-performance liquid chromatography, followed successively by esterification and deprotection has accomplished the first synthesis of 3-(β-D-ribofuranosyl)wybutine **3**, which is the most probable structure for wybutosine isolated from phenylalanine transfer ribonucleic acids.

Wybutosine, one of the most highly modified members of more than 50 minor nucleosides of transfer ribonucleic acids,[1] was first isolated in 1968 from the next position to the 3′-end of the anticodon of phenylalanine transfer ribonucleic acids ($tRNAs^{Phe}$) of baker's[2] and brewer's yeasts.[3] On mild treatment with acid, wybutosine releases the fluorescent base[3] wybutine **1**,[4] whose two-dimensional structure has been elucidated by Nakanishi's and Zachau's groups.[5] The absolute configuration of wybutine **1** has been established by our chiral synthesis.[6] The structure **1** is apparently a derivative of guanine, which has indeed been shown to be a precursor for the biosynthesis of the condensed tricyclic component of yeast $tRNA^{Phe}$.[7] It follows that wybutosine should be a derivative of guanosine. Thus, 3-(β-D-ribofuranosyl)wybutine **3** has long been accepted as the most probable structure for wybutosine. Nevertheless, rigorous identification of wybutosine, especially the position of glycosylation and the structure of the sugar moiety, has had to await chemical synthesis because of the extremely minute amount available. We report here a full account of the first synthesis of compound **3**.[8]

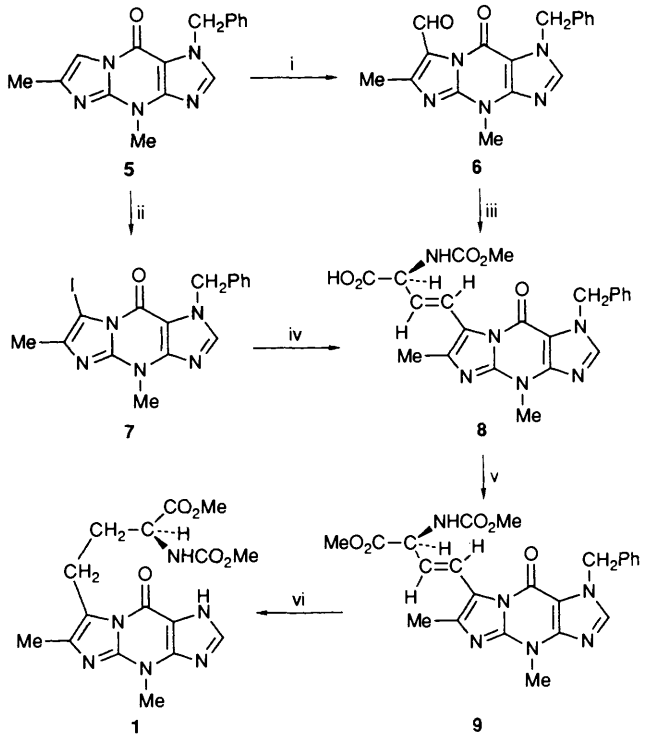


1 R = H
2 R = OH



3 R = H
4 R = OH

The only chiral synthesis of compound **1** has been accomplished by us through the Wittig reaction between 1-benzyl-7-formylwye **6** and (*R*)-{2-carboxy-2-[(methoxycarbonyl)amino]ethyl}triphenylphosphonium chloride as the key step (Scheme 1).[6] Contrary to our expectation, the reaction at the nucleoside level using 7-formyl-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)wye[9] did not afford the desired olefin. Among other possible reactions for an approach to compound **3**, the Heck reaction[10] warranted our attention. Being encouraged by recent reports on the Heck reaction at comparatively low



Scheme 1 *Reagents:* i, $POCl_3$, DMF; ii, I_2, $NaHCO_3$; iii, (*R*)-[2-carboxy-2-[(methoxycarbonyl)amino]ethyl]triphenylphosphonium chloride, BuLi; iv, **13**, $Pd(OAc)_2$, $Bu_4N^+ Cl^-$, $NaHCO_3$; v, Me_3SiCHN_2, MeOH; vi, Pd–C, H_2

temperatures[11] as well as by syntheses of optically active vinylglycine,[12] we started with an alternative synthesis of compound **8** as a model experiment.

Results and Discussion

The requisite aryl iodide **7** was easily obtained by treatment of 1-benzylwye **5**[4] with iodine in dichloromethane in the presence of sodium hydrogen carbonate. As an olefinic unit, we preferred (*S*)-*N*-(methoxycarbonyl)vinylglycine **13** over its methyl ester because esters of N-protected β,γ-unsaturated amino acids are usually susceptible to isomerization[12a] and/or racemization[6,13] under basic conditions. Methoxycarbonylation of (*S*)-vinylglycine hydrochloride[12b] followed by

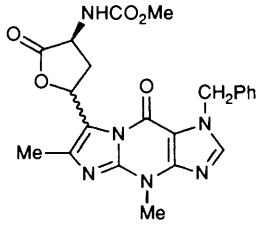
Table 1 Heck reaction of iodide **19** with amido acid **13** at various temperatures

Reaction conditions		Yield (%) of compounds **20** and **21**	$[\alpha]_D/10^{-1}$ deg cm^2 g^{-1} (*c* 0.20, MeOH) of **1**[a]
Temp. (*T*/°C)	Time (*t*/h)		
30	264	21	−25
45	24	37	−32
60	2	48	−33
80	0.7	39	−32

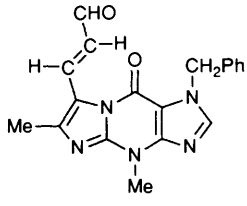
[a] Compound **1** was prepared from the mixture of butenoic acids **20** and **21** according to the procedure described in the text.

recrystallization three times from benzene gave compound **13** of 97% enantiomeric excess (ee).

The Heck reaction between substrates **7** and **13** was conducted according to Jeffery's procedure[11a] at 45 °C to afford crude compound **8**. Esterification of this product furnished diester **9**. Compound **9** of optical purity comparable to that of the sample from the Wittig reaction[6] was obtained in 24% yield after recrystallization from methanol. No evidence was found for the formation of the *Z*-isomer of compound **8**. Although acidic ester **8** is amphoteric, an alternative, inner-salt structure can be ruled out on the basis of the similarity of the ^{1}H NMR spectrum to that of compound **9**.[6] We obtained starting material **5**, and compounds **10** and **11** (9% yield) as by-products.

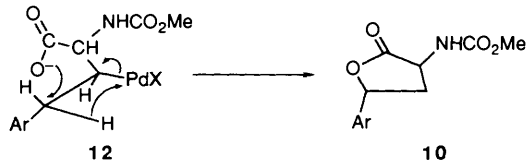


10



11

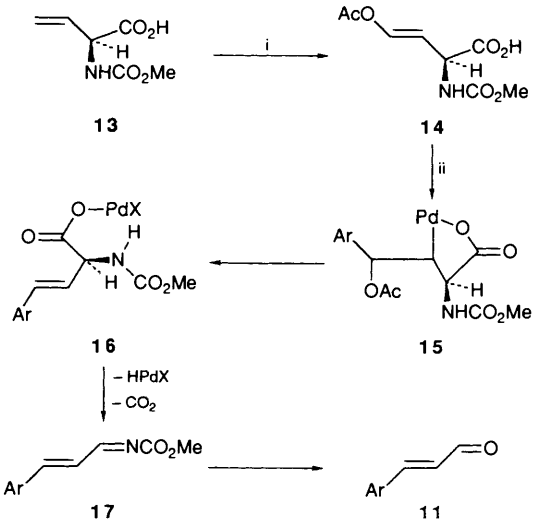
The correctness of the propenal structure **11** was established by an alternative synthesis from iodide **7** and acrolein. Because compound **8** was stable under conditions similar to those employed for its preparation,* we supposed that lactone **10** was formed competitively with compound **8** from the intermediate **12** through intramolecular nucleophilic attack of the carboxylate group on the γ-position and displacement of HPdX as shown in Scheme 2. Compound **11** might be formed through



12 **10**

Scheme 2

the Heck reaction with compound **14**, which should be generated by oxidation of the glycine **13** with palladium(II).[10] Indeed, the use of a stoicheiometric amount of palladium(II) acetate increased the yield of the propenal **11** up to 23%. As shown in Scheme 3, the electron-withdrawing acetoxy group would suppress the normal *cis*-elimination of HPd species from the intermediate **15**, while it would leave to produce the palladium carboxylate **16**. Decarboxylative elimination of



13 **14** **16** **15** **17** **11**

Scheme 3 *Reagents:* i, $Pd(OAc)_2$; ii, ArPdX

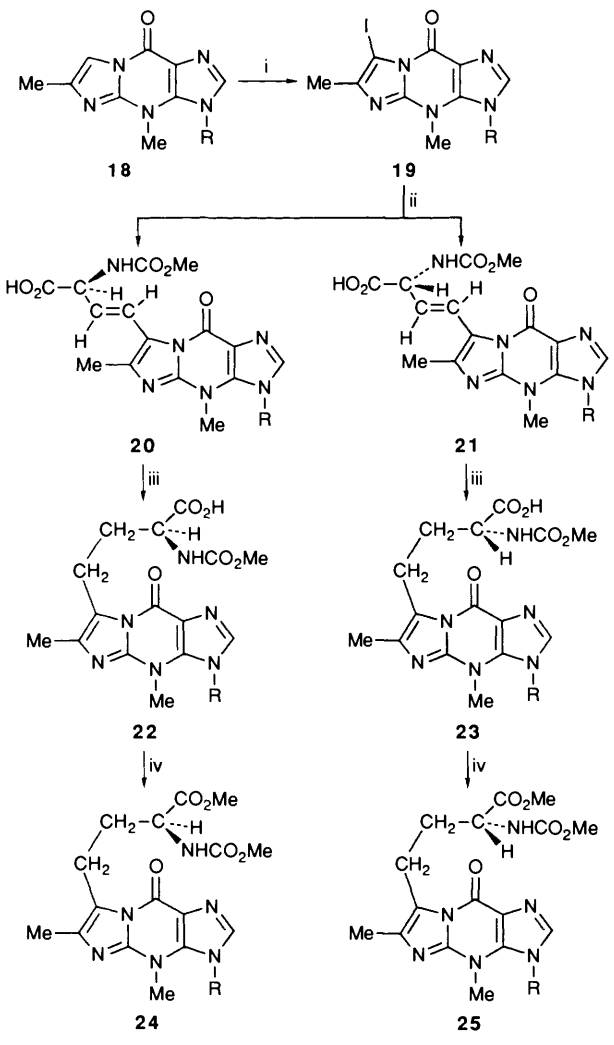
HPdX from the salt **16** would then afford the carbamate **17**, which should be hydrolysed to the propenal **11**. The reaction's features depend largely on what solvent is used: replacement of DMF by acetonitrile afforded mainly compound **5** instead of monoester **8**. We appreciate the present method of synthesis of compound **8** over our previous one[6] from the viewpoints of experimental facility, yield, and reproducibility.†

Having secured an alternative synthesis of the key intermediate **8**, we turned to the Heck reaction at the nucleoside level. The substrate we adopted was the protected nucleoside **19** rather than the unprotected one in view of its solubility in organic solvents and the stability of the glycosyl bond.[15] Compound **19**‡ was produced in 97% yield by iodination of compound **18**[9,17] in a manner similar to that employed for the preparation of compound **7**. The Heck reaction between substrates **19** and **13** was conducted at 45 °C under conditions similar to those employed for the model experiment to afford the desired product as a glass in 37% yield (Scheme 4). This product was suggested to be a mixture of the diastereoisomers **20** and **21** by ^{1}H NMR spectroscopy. Partial epimerization at the amino acid moiety was confirmed by means of the specific rotation after the products were transformed into wybutine **1**.[6] The results summarized in Table 1 indicate that the reaction at ~60 °C gave the maximum yield of the diastereoisomeric mixture although it offered no advantages in diastereoisomeric excess (de). Variation of reaction time at 60 °C also did not affect the isomer ratio. All attempts to separate the diastereoisomers by medium-pressure column, flash or thin-layer chromatography (TLC) using silica gel, octylated or octadecylated silica gel went unrewarded. Similar efforts to separate them after they were converted into a mixture of aminobutanoates **22** and **23** or a mixture of diesters **24** and **25** were unsuccessful. Enzymic hydrolysis might have a chance of separating these diastereoisomers. As had been reported,[18] (*S*)-*N*-(methoxycarbonyl)-alanine stereospecifically underwent hydrolysis catalysed by acylase I at pH 7.0 and 38 °C. Neither *S*-diastereoisomer **20** nor **22**, however, underwent hydrolysis under these conditions. We expected that they might be digested if the methoxycarbonyl group were to be replaced by an acetyl group. Unfortunately, the Heck reaction of iodide **19** with *N*-acetylvinylglycine[19] took place only slowly at 60 °C and afforded a mixture too complex

* Neither lactone **10** nor aldehyde **11** was formed when acid **8** was treated with a mixture of the glycine **13**, iodobenzene, palladium(II) acetate, tetrabutylammonium chloride (TBACl), sodium hydrogen carbonate and dimethylformamide (DMF) at 45 °C for 24 h.

† Utility of this reaction has been exemplified in chiral synthesis of various β,γ-unsaturated amino acid derivatives.[14]

‡ Synthesis of this compound by iodination with a combination of iodine and silver trifluoroacetate has been reported.[16]



Scheme 4 *Reagents:* i, I_2, $NaHCO_3$; ii, **13**, $Pd(OAc)_2$, Bu_4N^+ Cl^-, $NaHCO_3$; iii, Pd–C, H_2; iv, Me_3SiCHN_2, MeOH

to allow recognition of the presence of the desired olefin. When the reaction was conducted with vinylglycine hydrochloride, the iodide **19** was rapidly reduced to its precursor **18** (62% yield).

Getting these discouraging results, we finally focused our efforts on separation of the diastereoisomeric mixture of compounds **20** and **21** by high-performance liquid chromatography (HPLC). The columns tested were of silica gel, octylated silica gel and octadecylated silica gel. Partial separation was achieved only when a column of octadecylated silica gel was used. The best result was obtained when acetonitrile–0.02 mol dm^{-3} aq. sodium dihydrogen phosphate (85:15, v/v) was used as eluent. The separation depended largely on the concentration of the phosphate salt. Thus, we obtained isomers **20** (6 mg) and **21** (2 mg) through a 30 mg injection of the isomeric mixture onto a semi-preparative column (column diameter, 10 mm) using a recycling mode. Successful separation of *S*-isomer **20** is noteworthy because we envisage this compound as a key intermediate for access to compound **4**,[20] the most probable structure for the fluorescent nucleoside of rat liver $tRNA^{Phe}$.

Catalytic hydrogenation of butenoic acids **20** and **21** over palladium on carbon gave the butanoic acids **22** and **23**, respectively. These two were more easily separable by HPLC. We thus obtained pure *S*-isomer **22** in 22% and *R*-isomer **23** in 8% yield based on iodide **19**. These were separately led to diesters **24** and **25** in the usual manner in quantitative yields. Comparison of the ^1H NMR spectra of diastereoisomers **24** and **25** with those of monoesters **22** and **23** support the nondissociative structures for these carboxylic acids. Deacetylation of *S*-isomer **24** by short treatment with sodium methoxide in methanol* accomplished the synthesis of stereochemically pure compound **3** for the first time. The structure of compound **3** thus obtained was supported by the self-consistent synthetic route through which it was obtained, the reasonable ^1H NMR spectrum, and the mild hydrolysis that afford optically pure wybutine **1**.[6]

In conclusion, we have accomplished the first synthesis of compound **3** by utilising the Heck reaction as the key step. Although the lack of a sample of wybutosine prevents the establishment of its ultimate structure at present, the present synthesis of compound **3** should help toward the efficient isolation and identification of wybutosine.

Experimental

All m.p.s were determined by using a Yamato MP-1 or Büchi 530 capillary melting point apparatus and are corrected. UV and mass spectra were recorded on a Hitachi 320 UV spectrophotometer and a Hitachi M-80 mass spectrometer. NMR spectra were measured with JEOL JNM-FX-100, JEOL JNM-EX-270 and JEOL JNM-GX-400 NMR spectrometers. Unless otherwise stated, they were recorded at 100 MHz and 25 °C in $CDCl_3$ with tetramethylsilane as internal standard; *J* values are given in Hz. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1 dm sample tube and are given in 10^{-1} deg cm^2 g^{-1}. The HPLC system was a Waters model 204 ALC which included a 6000A pump, a U6K injector and a model 440 absorbance detector operating at 254 nm. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. Pre-coated silica gel plates with a fluorescent indicator (Merck) were used for analytical (0.25 mm) and preparative (0.5 mm) TLC (PLC). Flash chromatography was performed according to the reported procedure.[21] The pHs were measured roughly using Universal test papers (Toyo Roshi Co.).

(S)-2-[(*Methoxycarbonyl*)*amino*]*but*-3-*enoic Acid* **13**.—(*S*)-2-[(Benzyloxycarbonyl)amino]but-3-enoic acid methyl ester[12b] (1.50 g, 6 mmol) was hydrolysed with 6 mol dm^{-3} hydrochloric acid[12a] to afford (*S*)-vinylglycine hydrochloride (550 mg, 66%), m.p. 158–159 °C (decomp.); $[\alpha]_D^{15}$ +77.8 (*c* 0.500, water). A mixture of the whole amount of this product, sodium hydrogen carbonate (1.55 g, 18.4 mmol), methyl chloroformate (0.68 g, 7.2 mmol) and water (50 cm^3) was stirred at room temperature for 1 h. The resulting solution was brought to pH 1 with 10% hydrochloric acid and was then extracted with dichloromethane using a continuous extractor for 8 h. The extracts were dried over magnesium sulfate and concentrated under reduced pressure to leave title compound **13** (618 mg, 65%) as a solid. Recrystallization of crude acid **13** three times from benzene gave scales (355 mg, 37%), m.p. 92–93 °C; $[\alpha]_{365}^{17}$ +59.6 (*c* 0.504, MeOH). Further recrystallization from benzene gave an analytical sample of *acid* **13** with unchanged melting point (Found: C, 45.2; H, 5.6; N, 8.8. $C_6H_9NO_4$ requires C, 45.3; H, 5.7; N, 8.8%); $[\alpha]_{365}^{14}$ +59.7 (*c* 0.200, MeOH); δ_H[270 MHz; $(CD_3)_2SO$] 3.55 (3 H, s, Me), 4.59 (1 H, m, $CHCO_2H$), 5.20 (1 H, ddd, *J* 1.7, 1.3 and 10.2) and 5.31 (1 H, dd, *J* 1.3 and 17) (together CH_2=), 5.91 (1 H, ddd, *J* 5.9, 10.2 and 17, CH_2=C*H*),

* No racemization was observed with methyl esters of (*S*)-*N*-(methoxycarbonyl)leucine and (*S*)-*N*-(methoxycarbonyl)phenylalanine on this treatment.

7.27 (0.1 H, br) and 7.67 (0.9 H, d, *J* 7.6) (together NH)* and 12.76 (1 H, br, CO_2H). Optical purity of this sample was determined to be 97% ee by means of chiral HPLC according to the reported procedure.[19]

1-Benzyl-7-iodo-4,6-dimethyl-4,9-dihydro-1H-imidazo[1,2-a]-purin-9-one **7**.—Compound **5**[4] (6.68 g, 22.8 mmol) was iodinated in a manner similar to that described below for the preparation of the nucleoside **19** to afford *title compound* **7** (7.54 g, 79%) as scales, m.p. ~160 °C (decomp.; from ethanol). Further recrystallization from ethanol gave an analytical sample with unchanged m.p. (Found: C, 45.9; H, 3.3; N, 16.8%; M^+, 419. $C_{16}H_{14}IN_5O$ requires C, 45.8; H, 3.4; N, 16.7%; M, 419); λ_{max}(95% EtOH)/nm 244 (ε/dm^3 mol^{-1} cm^{-1} 34 400), 260sh (7200) and 319 (5500); δ_H 2.34 (3 H, s, CMe), 3.90 (3 H, s, NMe), 5.60 (2 H, s, CH_2), 7.36 (5 H, s, Ph) and 7.63 (1 H, s, 2-H).

7-Iodo-4,6-dimethyl-3-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-4,9-dihydro-3H-imidazo[1,2-a]purin-9-one **19**.—A solution of iodine (1.07 g, 4.22 mmol) in dichloromethane (30 cm^3) was added dropwise to a stirred mixture of compound **18**[9,17] (1.60 g, 3.47 mmol), sodium hydrogen carbonate (2.94 g, 35 mmol), dichloromethane (30 cm^3) and water (30 cm^3) at room temperature over a period of 30 min. The mixture was stirred for a further 40 min, washed successively with water (2 × 50 cm^3), 5% aq. sodium thiosulfate (50 cm^3) and water (50 cm^3), dried over magnesium sulfate, and then concentrated under reduced pressure to leave slightly brown needles (1.97 g, 97%), m.p. 140–141 °C (decomp.). Recrystallization of crude *iodide* **19** from ethanol gave an analytical sample as needles, m.p. 145–146 °C (decomp.) (Found: C, 40.6; H, 3.8; N, 11.7%; M^+, 587. $C_{20}H_{22}IN_5O_8$ requires C, 40.9; H, 3.8; N, 11.9%; M, 587); $[\alpha]_D^{23}$ −23.4 (*c* 0.522, MeOH); λ_{max}(95% EtOH)/nm 242 (ε/dm^3 mol^{-1} cm^{-1} 29 600), 278 (6500) and 297 (6800); δ_H 2.10 (3 H, s, Ac), 2.18 (6 H, s, 2 × Ac), 2.28 (3 H, s, 6-Me), 4.14 (3 H, s, NMe), 4.30 (2 H, d, *J* 3, 5′-H_2), 4.49 (1 H, dt, *J* 3.5 and 3, 4′-H), 5.48 (1 H, dd, *J* 3.5 and 5, 3′-H), 5.89 (1 H, dd, *J* 5 and 6, 2′-H), 6.23 (1 H, d, *J* 6, 1′-H) and 7.64 (1 H, s, 2-H).

(E)-3-(1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1H-imidazo-[1,2-a]purin-7-yl)propenal **11**.—Acrolein (116 mg, 2.07 mmol) was added to a mixture of iodide **7** (422 mg, 1.01 mmol), palladium(II) acetate (7.1 mg, 0.032 mmol), sodium hydrogen carbonate (262 mg, 3.12 mmol), a 0.15 mol dm^{-3} TBACl solution in DMF (6.6 cm^3, 0.99 mmol), and DMF (10 cm^3). The whole was stirred at room temperature for 24 h and then at 30 °C for a further 55 h. After water (40 cm^3) had been added, the resulting mixture was extracted with chloroform (4 × 40 cm^3). The organic layers were combined, dried over magnesium sulfate, and concentrated under reduced pressure to leave a brown oil (0.59 g). This was purified by flash chromatography. The column was first eluted with ethyl acetate and then with chloroform–methanol (19:1, v/v) to afford starting material **7** (0.14 g recovery) and a mixture of compounds **7** and **11** (0.30 g). The mixture was again purified by flash chromatography [benzene–ethyl acetate–ethanol (8:8:1, v/v)] to afford a second crop of starting material **7** (0.06 g; the total recovery was 47%), a mixture of compounds **7** and **11** (0.08 g), and title compound **11** (0.12 g). The mixture was further purified by flash chromatography using the same solvent to provide a second crop of compound **11** (0.04 g; the total yield was 46%). Recrystallization of crude compound **11** from ethanol afforded an analytical sample as *yellow needles*, m.p. 247–247.5 °C (decomp.) (Found: C, 65.6; H, 4.7; N, 20.2%; M^+, 347. $C_{19}H_{17}N_5O_2$ requires C, 65.7; H, 4.9; N, 20.2%; M, 347); λ_{max}(95% EtOH)/nm† 239, 260 and 367; δ_H(400 MHz) 2.53 (3 H, s, CMe), 3.97 (3 H, s, NMe), 5.63 (2 H, s, CH_2), 6.40 (1 H, dd, *J* 16.2 and 7.6, =C*H*CHO), 7.36 (5 H, m, Ph), 7.74 (1 H, s, 2-H), 8.86 (1 H, d, *J* 16.2, C*H*=CHCHO) and 9.62 (1 H, d, *J* 7.6, CHO).

(S)-(E)-4-(1-Benzyl-4,6-dimethyl-9-oxo-4,9-dihydro-1H-imidazo[1,2-a]purin-7-yl)-2-[(methoxycarbonyl)amino]but-3-enoic Acid **8**.—The iodide **7** (126 mg, 0.3 mmol), sodium hydrogen carbonate (76 mg, 0.9 mmol) and a 0.2 mol dm^{-3} solution of TBACl (1.5 cm^3, 0.3 mmol) in DMF were added to a solution of palladium(II) acetate (2.5 mg, 0.011 mmol) in DMF (3 cm^3) and the mixture was stirred at 45 °C for 10 min. The olefin **13** (57 mg, 0.36 mmol) was then added to the mixture and the whole was stirred at 45 °C for 24 h. The resulting slightly brown solution was diluted with water (15 cm^3), brought to pH 3–4 with 10% aq. phosphoric acid and extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure to leave a brown glass (0.26 g). This was purified by flash chromatography [chloroform–methanol–water (20:7:1, v/v)]. Fractions containing a polar substance were combined, and concentrated under reduced pressure to ~5 cm^3. The residue was brought to pH 3–4 with 10% aq. phosphoric acid and extracted with dichloromethane (3 × 10 cm^3). The extracts were dried over magnesium sulfate and concentrated under reduced pressure to leave title compound **8** as a yellowish amorphous solid (54 mg). The ^{1}H NMR spectrum [δ_H 2.37 (3 H, s, CMe), 3.73 (3 H, s, OMe), 3.89 (3 H, s, NMe), 5.08 (1 H, br, α-H), 5.57 (2 H, s, CH_2), 5.84 (1 H, dd, *J* 6 and 16, β-H), 7.33 (5 H, s, Ph), 7.63 (1 H, d, *J* 16, γ-H) and 7.64 (1 H, s, 2-H) indicated that this sample was contaminated with a tetrabutylammonium halide to the extent of ~20 mol%.

The earlier fractions containing several products were combined, and concentrated under reduced pressure to give a caramel (0.09 g). This was purified by flash chromatography [chloroform–methanol (30:1, v/v)] and the crude material (0.04 g) obtained from the earlier fractions was purified by repeated PLC on silica gel [1,2-dichloroethane–ethanol (10:1, v/v)] to afford crude compound **11** (9 mg, 9%) as a higher-R_f substance, and compound **5** (18 mg, 20%). Recrystallization of compound **11** from ethanol gave yellowish needles, m.p. 240 °C (decomp.), identical (^{1}H NMR) with an authentic sample described above.

From the polar fractions of the second flash chromatography a fluorescent substance (17 mg, 13%) was obtained as a slightly yellow glass, δ_H 2.35 (3 H, s, overlapped with a one-proton multiplet due to one of 3′-H_2, CMe), 3.01 (1 H, m, one of 3′-H_2), 3.76 (3 H, s, OMe), 3.91 (3 H, s, NMe), 4.85 (1 H, m, 4′-H), 5.48 and 5.60 (1 H each, d, *J* 15, PhCH_2), 5.81 (1 H, dd, *J* 8.5 each, 2′-H), 7.34 (5 H, s, Ph) and 7.73 (1 H, s, 2-H). The ^{1}H NMR spectrum suggested that this was a single diastereoisomer of 1-benzyl-7-{4-[(methoxycarbonyl)amino]-5-oxotetrahydrofuran-2-yl}-4,6-dimethyl-4,9-dihydro-1*H*-imidazo[1,2-*a*]purin-9-one **10**. Further purification of this compound was unsuccessful because of its instability.

* The observed pattern of the NH signal is probably due to *cis–trans* isomerism caused by restricted rotation about the central C–N bond in the carbamate group.[19]

† Optical densities rapidly changed probably owing to photochemical isomerization to the *Z*-isomer. After a dilute solution of compound **11** in 95% aq. ethanol had been stored in a light room for several hours, about one tenth of the original amount of compound **11** was shown to be changed into the *Z*-isomer by silica gel TLC [benzene–acetone (1:1, v/v)] and ^{1}H NMR spectroscopy, δ_H(270 MHz) 2.30 (3 H, s, CMe), 3.95 (3 H, s, NMe), 5.56 (2 H, s, CH_2), 6.14 (1 H, dd, *J* 11 and 7.9, =C*H*CHO), 7.72 (1 H, s, 2-H), 8.12 (1 H, d, *J* 11, C*H*=CHCHO) and 9.65 (1 H, d, *J* 7.9, CHO).

(S)-(E)-4-(1-*Benzyl*-4,6-*dimethyl*-9-*oxo*-4,9-*dihydro*-1H-*imidazo*[1,2-a]*purin*-7-*yl*)-2-[(*methoxycarbonyl*)*amino*]*but*-3-*enoic Acid Methyl Ester* **9**.—Crude acid **8** (47 mg) described above was dissolved in benzene–methanol (7:2, v/v; 7 cm^3). A 1.5 mol dm^{-3} solution of trimethylsilyldiazomethane[22] (0.7 cm^3) was added to the solution, followed by addition of acetic acid (one drop) after 1.5 min. The resulting solution was concentrated under reduced pressure to leave diester **9** as a yellowish solid. Recrystallization of crude product **9** from methanol afforded slightly yellow needles (30 mg, 24% based on aldehyde **6**), m.p. 176–178 °C; $[\alpha]_D^{14}$ +47.7 (*c* 0.373, MeOH). This sample was identical (^{1}H NMR and IR spectra, and chromatographic behaviour) with an authentic sample.[6]

The Heck Reaction between Iodide **19** *and Compound* **13** *at* 45 °C.—The iodide **19** (294 mg, 0.5 mmol), sodium hydrogen carbonate (126 mg, 1.5 mmol) and a 0.2 mol dm^{-3} solution of TBACl in DMF (2.5 cm^3, 0.5 mmol) were added to a solution of palladium(II) acetate (4.8 mg, 0.022 mmol) in DMF (5 cm^3) and the mixture was stirred at 45 °C for 10 min. The olefin **13** (96 mg, 0.6 mmol) was then added to the mixture and the whole was stirred at 45 °C for 24 h. The resulting mixture was brought to pH 3–4 by addition of water (10 cm^3) and 10% aq. phosphoric acid, and was then extracted with dichloromethane (4 × 10 cm^3). The organic phases were dried over magnesium sulfate and concentrated under reduced pressure to leave a brown oil (0.69 g). This was purified by flash chromatography [chloroform–methanol–water (20:7:1, v/v)]. The fractions containing polar substances were combined and concentrated to ~10 cm^3. This was brought to pH 3–4 with aq. phosphoric acid and extracted with dichloromethane (7 × 15 cm^3). The organic phases were combined, dried over magnesium sulfate, and concentrated under reduced pressure to leave a mixture of diastereoisomers **20** and **21** as a slightly yellow glass (115 mg, 37%). Catalytic hydrogenation of the mixture, followed successively by methylation, deacetylation and acidic hydrolysis in the manner similar to those described below, afforded compound **1**, $[\alpha]_D^{13}$ −32 (*c* 0.204, MeOH) {lit.,[6] $[\alpha]_D^{23}$ −45 (*c* 0.130, MeOH)}.

The earlier fraction (30 cm^3) of the eluate, which contained all of the less polar products, was concentrated to a small volume and extracted with dichloromethane. The organic phase was dried over magnesium sulfate and concentrated to leave a brown oil (101 mg). This was purified by flash chromatography [chloroform–methanol (19:1, v/v)]. The last eluate contained highly fluorescent substances (16 mg) with the same R_f-value. The NMR spectrum suggested that they were diastereoisomers of 7-{4-[(methoxycarbonyl)amino]-5-oxotetrahydrofuran-2-yl}-4,6-dimethyl-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4,9-dihydro-3*H*-imidazol[1,2-*a*]purin-9-one, δ_H 2.07, 2.11, 2.13, 2.16 and 2.17 (a total of 9 H, each s, 3 × Ac), 2.29 and 2.33 (a total of 3 H, each s, 6-Me), 2.4–3.2 (2 H, m, CH_2 of the tetrahydrofuran ring), 3.71 and 3.72 (a total of 3 H, each s, OMe), 4.14 (3 H, s, NMe), 4.34 (2 H, m, 5′-H_2), 4.51 (1 H, m, 4′-H), 4.6–5.1 (1 H, m, C*H*NH), 5.47 (1 H, m, 3′-H), 5.7–6.1 (2 H, m, OCH of the tetrahydrofuran ring and 2′-H), 6.29 (1 H, d, *J* 5, 1′-H) and 7.73 (1 H, br s, 2-H). The earlier fractions showed two major spots on a silica gel plate [chloroform–methanol (19:1, v/v)]. These compounds were further purified by PLC on silica gel (the same solvent). The higher-R_f compound, isolated as a yellowish glass (17 mg), was the starting material **19**. From the lower-R_f zone a yellow glass (31 mg) was obtained and it was suggested by ^{1}H NMR spectroscopy to be an almost equimolar mixture of compound **18** and (*E*)-3-{4,6-dimethyl-9-oxo-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4,9-dihydro-3*H*-imidazo[1,2-*a*]purin-7-yl}propenal, δ_H 2.10, 2.17 and 2.18 (a total of 9 H, 3 × Ac), 2.46 (3 H, s, 6-Me), 4.21 (3 H, s, NMe), 4.31 (2 H, d, *J* 3, 5′-H_2), 4.51 (1 H, m, 4′-H), 5.50 (1 H, dd, *J* 5 and 4, 3′-H), 5.93 (1 H, dd, *J* 5 and 6, 2′-H), 6.28 (1 H, d, *J* 6, 1′-H), 6.35 (1 H, dd, *J* 16 and 8, =C*H*CHO), 7.75 (1 H, s, 2-H), 8.80 (1 H, d, *J* 16, C*H*=CHCHO) and 9.61 (1 H, d, *J* 8, CHO).

(S)-(E)- **20** *and* (R)-(E)-4-{4,6-*Dimethyl*-9-*oxo*-3-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*[1,2-a]*purin*-7-*yl*}-2-[(*methoxycarbonyl*)*amino*]*but*-3-*enoic Acid* **21**.—Compound **19** (587 mg, 1 mmol) was allowed to react with compound **13** (239 mg, 1.5 mmol) in the presence of palladium(II) acetate (8.3 mg, 0.037 mmol), a 0.15 mol dm^{-3} solution of TBACl in DMF (6.7 cm^3, 1 mmol), sodium hydrogen carbonate (252 mg, 3 mmol) and DMF (8 cm^3) in a manner similar to that described above except at 60 °C for 7.5 h to afford a mixture of diastereoisomers **20** and **21** (310 mg, 50%) as a slightly yellow foam. A portion (60 mg) of this sample was further purified by PLC on silica gel [chloroform–methanol–water (20:7:1, v/v)], followed by addition of water (8 cm^3) and 10% aq. phosphoric acid to pH 3. The whole was extracted with dichloromethane (2 × 10 cm^3). The organic phases were dried over magnesium sulfate and concentrated under reduced pressure to leave a slightly yellow glass (51 mg). A portion (10 mg) of this sample was dissolved in a mixture of 0.02 mol dm^{-3} aq. sodium dihydrogen phosphate and acetonitrile (2:1, v/v) (0.75 cm^3). The solution was submitted to preparative HPLC in one portion and the column [Hibar RT 250-10 LiChrosorb RP-18 (7 μm)] was eluted with 0.02 mol dm^{-3} aq. sodium dihydrogen phosphate–acetonitrile (85:15, v/v) at the flow rate of 4.4 cm^3 min^{-1}. The first portion (4.4 cm^3) of the eluate containing isomer **20** and the last portion having absorbance < 2 were collected separately. The rest of the eluate was recycled through the column. Shaving of the head and the tail parts was repeated during each cycle until complete separation was attained. After six more recycling operations, all the fractions containing isomer **20** were combined, and concentrated under reduced pressure to ~20 cm^3, brought to pH 3 with 10% aq. phosphoric acid, and extracted with dichloromethane (3 × 10 cm^3). The organic layers were combined, dried over magnesium sulfate, and concentrated under reduced pressure to leave pure *S*-isomer **20** (6 mg) as a glass, δ_H 2.12 (3 H, s, Ac), 2.21 (6 H, s, 2 × Ac), 2.30 (3 H, s, 6-Me), 3.80 (3 H, s, OMe), 4.13 (3 H, s, NMe), 4.28 (2 H, br, 5′-H_2), 4.48 (1 H, m, 4′-H), 5.32 (2 H, br, α-H and CO_2H), 5.48 (1 H, dd, *J* 4 and 5, 3′-H), 5.70 (1 H, d, *J* 8, NH), 6.01 (1 H, dd, *J* 6 and 16, β-H), 6.07 (1 H, dd, *J* 5 and 6, 2′-H), 6.29 (1 H, d, *J* 6, 1′-H), 7.43 (1 H, d, *J* 16, γ-H) and 7.53 (1 H, s, 2-H).

Similar treatment of the eluate containing the *R*-isomer **21** afforded the pure compound (2 mg) as a glass, δ_H 2.14 (6 H, s, 2 × Ac), 2.23 (3 H, s, Ac), 2.29 (3 H, s, 6-Me), 3.85 (3 H, s, OMe), 4.19 (3 H, s, NMe), 4.32 (2 H, br, 5′-H_2), 4.50 (1 H, m, 4′-H), 5.25 (2 H, m, α-H and CO_2H), 5.50 (1 H, m, 3′-H), 5.95 (1 H, dd, *J* 5 and 16, β-H), 6.05 (1 H, dd, *J* 6 each, 2′-H), 6.32 (1 H, d, *J* 6, 1′-H), 6.88 (1 H, br, NH), 7.54 (1 H, s, 2-H) and 7.59 (1 H, d, *J* 6, γ-H).

(S)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-3-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*[1,2-a]*purin*-7-*yl*}*butanoic Acid* **22**.—Compound **20** (8 mg, 0.013 mmol) was hydrogenated in methanol (3 cm^3) over 10% palladium on carbon (8 mg) at room temperature for 6 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by PLC on silica gel [chloroform–methanol–water (20:7:1, v/v)] and dissolved in water (10 cm^3). The solution was brought to pH 3 by addition of 10% aq. phosphoric acid and was then extracted with dichloromethane (2 × 10 cm^3). The organic layers were combined, dried over magnesium sulfate, and concentrated to afford title compound **22** (6 mg, 75%) as a solid. This sample was

identical (^{1}H NMR and HPLC) with that obtained by separation of a mixture of diastereoisomers **22** and **23** (*vide infra*).

(R)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-3-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*-[1,2-a]*purine*-7-*yl*}*butanoic Acid* **23**.—Hydrogenation of compound **21** (2 mg, 0.003 mmol) was conducted in a manner similar to that described for the preparation of *S*-isomer **22** to afford the *R*-diastereoisomer **23** (1.8 mg) as a glass, identical (^{1}H NMR and HPLC) with a sample of compound **23** obtained by separation of a mixture of diastereoisomers **22** and **23** (*vide infra*).

Separation of a Mixture of Diastereoisomers **22** *and* **23**.—A solution of the mixture (250 mg) of compounds **20** and **21**, which was obtained in the Heck reaction at 60 °C (*vide supra*), in methanol (15 cm^3) was hydrogenated over 10% palladium on carbon (250 mg) at room temperature and atmospheric pressure for 2 h, followed by filtration. The catalyst was washed with hot methanol (50 cm^3). The filtrate and washings were combined, and concentrated under reduced pressure to afford a mixture of diastereoisomers **22** and **23** (231 mg, 92%) as a slightly yellow glass. A portion (212 mg) of this sample was dissolved in 0.01 mol dm^{-3} aq. sodium dihydrogen phosphate–acetonitrile (85:15, v/v) (2.5 cm^3). This solution was applied to the HPLC system as described for the separation of diastereoisomers **20** and **21** in six portions. The earliest part of the eluate (30 cm^3) containing *S*-isomer **22** was withdrawn and the rest was recycled through the column. During the second and the third cycles, the head eluates (65 cm^3 each) containing *S*-isomer **22** were collected. Complete separation was obtained after the fourth cycle. All the fractions containing *S*-isomer **22** were combined, and concentrated under reduced pressure to ~20 cm^3. The resulting aqueous solution was extracted with dichloromethane (3 × 20 cm^3) after being brought to pH 3 with 10% aq. phosphoric acid. The organic layers were combined, dried over magnesium sulfate, and concentrated under reduced pressure to leave *S*-isomer **22** (101 mg, 22% based on iodide **19**) as a solid, m.p. 155–158 °C; δ_H[$(CD_3)_2SO$] 1.9 (2 H, br, β-H_2), 1.98 (3 H, s, Ac), 2.08 [3 H, s (sharpened on irradiation at δ 3.05), 6-Me], 2.10 and 2.11 (a total of 6 H, 2 × Ac), 3.05 (2 H, m, γ-H_2), 3.55 (3 H, s, OMe), 3.75 (1 H, m, α-H), 4.00 (3 H, s, NMe), 4.32 (2 H, m, 5′-H_2), 4.45 (1 H, m, 4′-H), 5.46 (1 H, dd, *J* 5 and 6, 3′-H), 5.84 (1 H, dd, *J* 6 and 5, 2′-H), 6.43 (1 H, d, *J* 5, 1′-H), 7.48 (1 H, d, *J* 8, NH), 8.14 (1 H, s, 2-H) and 12.45 (1 H, br, CO_2H).

The eluates containing *R*-isomer **23** were combined, concentrated under reduced pressure to ~10 cm^3, brought to pH 3 with 10% aq. phosphoric acid, and then extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to leave *R*-isomer **23** as a glass (37 mg, 8% yield based on iodide **19**), δ_H[$(CD_3)_2SO$] 1.9 (2 H, br, β-H_2), 1.99 (3 H, s, Ac), 2.10 and 2.11 (a total of 9 H, 2 × Ac and 6-Me), 3.05 (2 H, m, γ-H_2), 3.55 (3 H, s, OMe), 3.74 (1 H, m, α-H), 4.00 (3 H, s, NMe), 4.32 (2 H, m, 5′-H_2), 4.43 (1 H, m, 4′-H), 5.45 (1 H, dd, *J* 5 and 6, 3′-H), 5.83 (1 H, dd, *J* 6 and 5, 2′-H), 6.41 (1 H, d, *J* 5, 1′-H), 7.47 (1 H, d, *J* 8, NH), 8.14 (1 H, s, 2-H) and 12.36 (1 H, br, CO_2H).

(S)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-3-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*-[1,2-a]*purin*-7-*yl*}*butanoic Acid Methyl Ester* **24**.—Compound **22** (69 mg, 0.11 mmol) was dissolved in methanol–benzene (2:7, v/v) (0.5 cm^3) and then a 1.8 mol dm^{-3} trimethylsilyldiazomethane[22] solution in hexane (0.1 cm^3) was added. The resulting solution was concentrated under reduced pressure to leave *ester* **24** (71 mg, 100%) as a foam, δ_H 1.89 (1 H, m) and 2.0 (1 H, br) (together β-H_2), 2.11, 2.15 and 2.18 (3 H each, s, 3 × Ac), 2.20 (3 H, s, 6-Me), 2.75–3.50 (2 H, m, γ-H_2), 3.70 (6 H, s, 2 × OMe), 4.12 (3 H, s, NMe), 4.32 (2 H, d, *J* 3, overlapping with a broad one-proton signal due to α-H, 5′-H_2), 4.50 (1 H, dt, *J* 3 each, 4′-H), 5.50 (1 H, dd, *J* 3 and 5, 3′-H), 5.86 (1 H, dd, *J* 5 and 6, overlapping with a one-proton signal due to NH, 2′-H), 6.21 (1 H, d, *J* 6, 1′-H) and 7.71 (1 H, s, 2-H); δ_H[270 MHz; $(CD_3)_2SO$] 1.86 and 2.1 (1 H each, br, β-H_2), 1.98, 2.08, 2.10 and 2.11 (3 H each, s, 3 × Ac and 6-Me), 2.82–3.20 (2 H, m, γ-H_2), 3.56 and 3.58 (3 H each, s, 2 × OMe), 3.88 (1 H, br, α-H), 4.00 (3 H, s, NMe), 4.30 (2 H, m, 5′-H_2), 4.46 (1 H, m, 4′-H), 5.46 (1 H, dd, *J* 5 and 6, 3′-H), 5.84 (1 H, dd, *J* 5 and 6, 2′-H), 6.42 (1 H, d, *J* 5, 1′-H), 7.66 (1 H, d, *J* 7.9, NH) and 8.14 (1 H, s, 2-H) (Found: M$^+$, 634.2232. $C_{27}H_{34}N_6O_{12}$ requires M, 634.2232).

(R)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-3-(2,3,5-*tri*-O-*acetyl*-β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*-[1,2-a]*purin*-7-*yl*}*butanoic Acid Methyl Ester* **25**.—Compound **23** (14 mg, 0.023 mmol) was treated with trimethylsilyldiazomethane[22] in a manner similar to that described for the preparation of *S*-isomer **24** and the product was purified by PLC on silica gel [chloroform–methanol (5:1, v/v)] to afford R-*isomer* **25** (14 mg, 100%) as a foam, δ_H 2.04 (2 H, m, β-H_2), 2.11, 2.14 and 2.18 (3 H each, s, 3 × Ac), 2.20 (3 H, s, 6-Me), 2.78–3.55 (2 H, m, γ-H_2), 3.70 (6 H, s, 2 × OMe), 4.12 (3 H, s, NMe), 4.32 (2 H, d, *J* 3, overlapping with a one-proton broad signal due to α-H, 5′-H_2), 4.51 (1 H, dt, *J* 3 each, 4′-H), 5.49 (1 H, dd, *J* 3 and 5, 3′-H), 5.84 (1 H, dd, *J* 5 and 6, overlapping with a one-proton signal due to NH, 2′-H), 6.21 (1 H, d, *J* 6, 1′-H) and 7.74 (1 H, s, 2-H); δ_H[270 MHz; $(CD_3)_2SO$] 1.9 and 2.1 (1 H each, br, β-H_2), 1.99, 2.08, 2.10 and 2.11 (3 H each, s, 3 × Ac and 6-Me), 2.8–3.3 (2 H, m, γ-H_2), 3.56 and 3.58 (3 H each, s, 2 × OMe), 3.86 (1 H, br, α-H), 4.00 (3 H, s, NMe), 4.32 (2 H, m, 5′-H_2), 4.45 (1 H, m, 4′-H), 5.45 (1 H, dd, *J* 6 and 5, 3′-H), 5.83 (1 H, dd, *J* 5 and 6, 2′-H), 6.42 (1 H, d, *J* 6, 1′-H), 7.66 (1 H, d, *J* 7.9, NH) and 8.15 (1 H, s, 2-H) (Found: M$^+$, 634.2238. $C_{27}H_{34}N_6O_{12}$ requires M, 634.2232).

(S)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-3-(β-D-*ribofuranosyl*)-4,9-*dihydro*-3H-*imidazo*[1,2-a]*purin*-7-*yl*}-*butanoic Acid Methyl Ester* **3**.—Compound **24** (57 mg, 0.09 mmol) was dissolved in 0.1 mol dm^{-3} sodium methoxide in methanol (4.7 cm^3), which was previously cooled in an ice-bath, and the resulting solution was kept at that temperature for 5 min. The whole was poured into cold, 0.1 mol dm^{-3} aq. sodium dihydrogen phosphate (9.5 cm^3). Then the mixture was concentrated to dryness under reduced pressure and the residue was purified by PLC on silica gel [chloroform–methanol–water (20:7:1, v/v)]. The main UV-absorbing zone was extracted with ethyl acetate–ethanol (5:1, v/v) and the extracts were concentrated, and were then dried at 2 mmHg and 45 °C for 8 h to afford compound **3** (36 mg, 78%) as a foam, $[\alpha]_D^{23}$ −53.6 (*c* 0.344, MeOH); δ_H[$(CD_3)_2SO$] 1.95 (2 H, m, β-H_2), 2.08 (3 H, s, 6-Me), 3.05 (2 H, m, γ-H_2), 3.56 and 3.58 (3 H each, s, overlapping with a two-proton multiplet due to 5′-H_2, 2 × OMe), 4.03 (3 H, s, overlapping with multiplets due to 4′-H and α-H, NMe), 4.14 (1 H, m, 3′-H), 4.44 (1 H, m, 2′-H), 5.14 and 5.59 (a total of 3 H, br, 3 × OH), 6.09 (1 H, d, *J* 5, 1′-H), 7.64 (1 H, d, *J* 8, NH) and 8.19 (1 H, s, 2-H).

(S)-4-{α-[(*Methoxycarbonyl*)*amino*]-4,6-*dimethyl*-9-*oxo*-4,9-*dihydro*-1H-*imidazo*[1,2-a]*purin*-7-*yl*}*butanoic Acid Methyl Ester* **1**.—A solution of compound **3** (10 mg, 0.02 mmol) in 0.1 mol dm^{-3} hydrochloric acid (2 cm^3) was kept at room temperature for 1 h, brought to pH 7 by addition of 0.2 mol dm^{-3} aq. disodium hydrogen phosphate (2 cm^3) and extracted

with dichloromethane (5 × 5 cm^3). The organic phases were combined, dried over magnesium sulfate, and concentrated under reduced pressure to leave compound **1** (7 mg, 100%) as a solid, m.p. 216–218 °C (decomp.). This sample was shown to be optically pure by HPLC analysis using a chiral column[6] and identical with authentic compound **1**[6] in terms of ^1H NMR, UV and MS spectroscopy, and chromatographic behaviour.

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