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SYNTHESIS OF NEW CARBOCYCLIC OXETANOCIN ANALOGUES.

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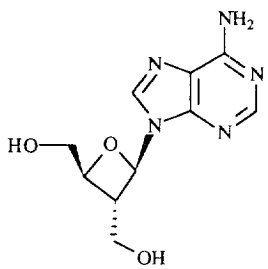
Abstract: Carbocyclic oxetanocin analogues containing 3-fluoro or 3-hydroxy cyclobutyl moieties and different natural bases, have been prepared from the olefinic precursors either by direct fluoro-iodination (AgF-I_2) or by DAST fluorination of the bromhydrin.The latter allowed the synthesis of the corresponding phosphonate derivatives as well.

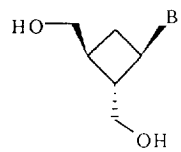
INTRODUCTION

Oxetanocin A (**1**) is the first and so far unique example of a natural four-membered ring nucleoside. This compound has stimulated a great synthetic effort since its discovery by Shimada and co-workers in 1986.[1] In particular, the discovery in 1990[2,3] that carbocyclic analogues of oxetanocin A **2** and **3** exhibit more potent anti-herpes activities than **1**, as well as anti-HIV activity, led numerous groups to investigate original syntheses of carbocyclic oxetanocin and related substances (Figure 1).[4-7]

Figure 1



1 Oxetanocin A

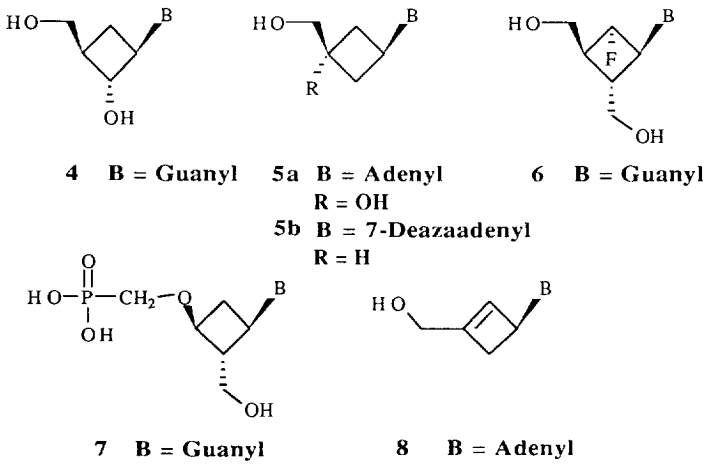


2 B = Adenyl (Cyclobut-A)

3 B = Guanyl (Cyclobut-G)

Among these compounds, SQ-32,829 (**4**),[8] **5**,[9,10] fluoro-derivative **6**,[12] phosphonate derivative **7**[13] and cyclobutene **8**[11] have been synthesized and some of them exhibit potent anti-viral activities (Figure 2).

Figure 2

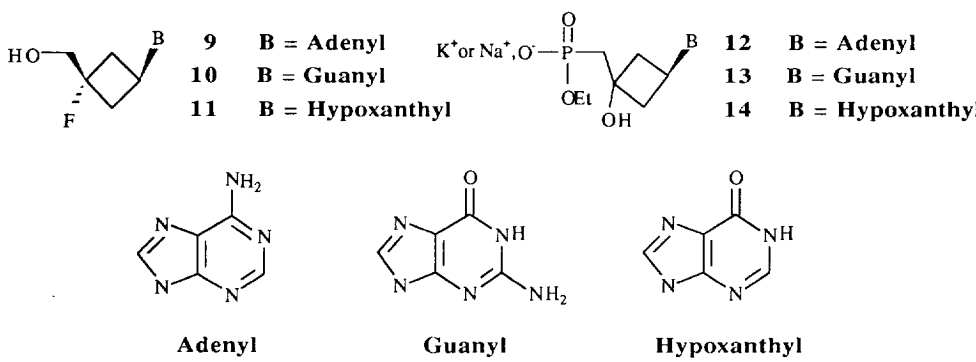


4 B = Guanyl **5a** B = Adenyl R = OH **5b** B = 7-Deazaadenyl R = H **6** B = Guanyl

7 B = Guanyl **8** B = Adenyl

This article describes our synthesis of the previously unknown 3'-fluoro-cyclobutyl derivatives of **9**, **10** and **11** as well as the phosphonate derivatives **12**, **13** and **14** (Figure 3).

Figure 3



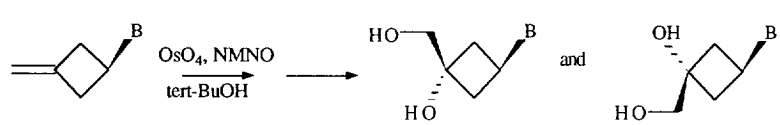
9 B = Adenyl **10** B = Guanyl **11** B = Hypoxanthyl **12** B = Adenyl **13** B = Guanyl **14** B = Hypoxanthyl

Adenyl **Guanyl** **Hypoxanthyl**

RESULTS AND DISCUSSION

For this purpose, we started from olefin intermediates **15** and **16** synthesized previously.[9] The latter were dihydroxylated in good yields with osmium tetroxide (OsO_4) leading to diols **5** and their isomers **17** and **18**.[9]

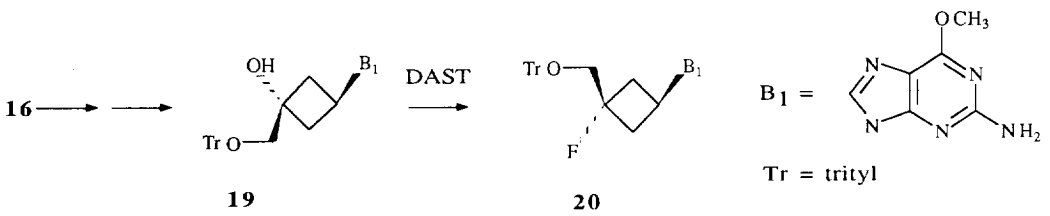
Scheme 1



15 B = 6-chloropurinyl **16** B = 2-amino-6-chloropurinyl **5 a** B = Adenyl **5 c** B = Guanyl **17** B = Adenyl **18** B = Guanyl

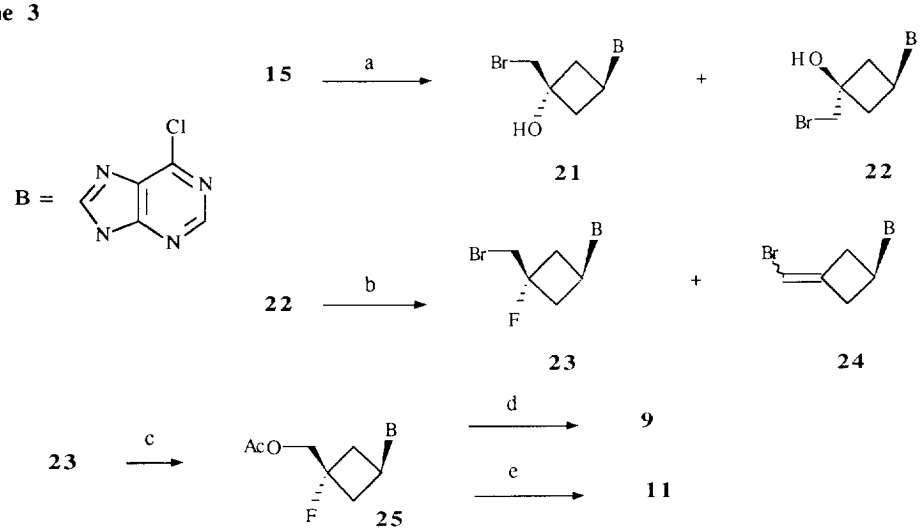
However, as observed recently, direct fluorination of **17** and **18** with diethylaminosulfur trifluoride (DAST) led to decomposition[14] of the starting materials; the same fluorination of the protected precursor **19** led also to extensive decomposition and to a low yield of the target derivative **20** (Scheme 2). This compound was detected by the presence of a doublet at 3.41 ppm with a characteristic coupling constant of 18.38 Hz for $^3J_{CH2\text{-}F}$ in the ^1H NMR spectrum of the reaction mixture.

Scheme 2



We then focussed on bromohydrins **21** and **22** which were obtained in good yield with aqueous N-bromosuccinimide (NBS),[15] under phase transfer conditions and which advantageously replaced diols **17** or **18** by avoiding the protection-deprotection steps. Isomer **22** was fluorinated with DAST in CH_2Cl_2 at O°C. As expected[16] inversion of configuration was observed according to NMR data and led to **23**. A byproduct **24**, isolated in low yield, resulted from a competitive "intramolecular elimination reaction" of O=SFNEt$_2$ group and HF (Scheme 3). Accordingly, treatment of alcohols **21** or **22** with thionyl chloride or phosphorus oxychloride in pyridine afforded **24** in high yield.[12]

Scheme 3



reagents and conditions: a : NBS (1.2 eq.)/KOH (1.2 eq.), AcOEt/H_2O, 15min., 97%ratio cis/trans = 55/45. b : DAST, CH_2Cl_2, 0°C, 15 min., 79% of **23**. c : KOAc , cat. 18-crown-6, DMF, 25°C, 4 h; 95%. d: liq. NH_3- EtOH , 40°C, 24 h; 66%. e : HCl; H_2O; reflux; 2h; 91%.

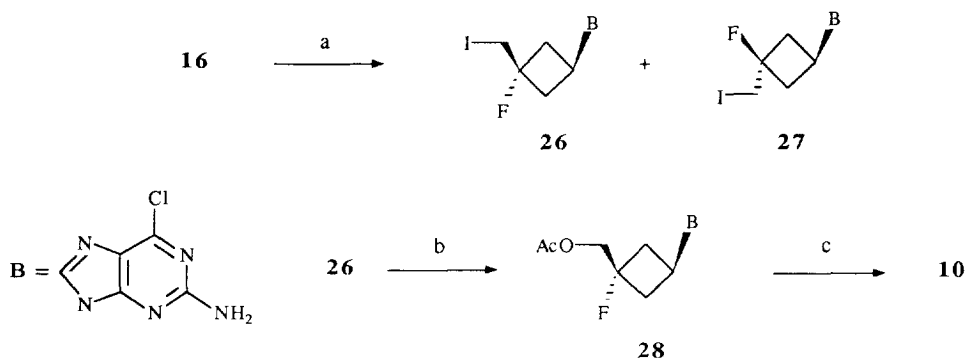
Nucleophilic substitution of the bromine atom in **23** was then performed with potassium acetate in N,N-dimethylformamide (DMF) and treatment of resulting **25** with liquid ammonia led to adenine derivative **9**

whereas chlorine hydrolysis in **25** afforded hypoxanthine derivative **11**. However, the same methodology could not be used for the preparation of the guanyl derivative **10** owing to interference of DAST with the amino group of guanine precursor as observed previously in similar cases.[17,18]

An alternative route for introduction of the 3'-fluoro moiety in the cyclobutane derivatives of adenine and guanine appeared to be the addition of iodine fluoride to the suitable 3'-methylene precursor (**15, 16**). This procedure was used by Moffatt and co-workers[19] in the synthesis of Nucleocidin and, in the present case, did not require any protection of the amino group of the guanine precursor. Thus, fluoro iodination of **16** proceeded in good yield and the ratio of **26**: **27** was always between 7/3 and 6/4 (Scheme 4).

This method has been also successfully carried out from **15**. In each case the mixture of *cis-trans* isomers obtained was separated by column chromatography.

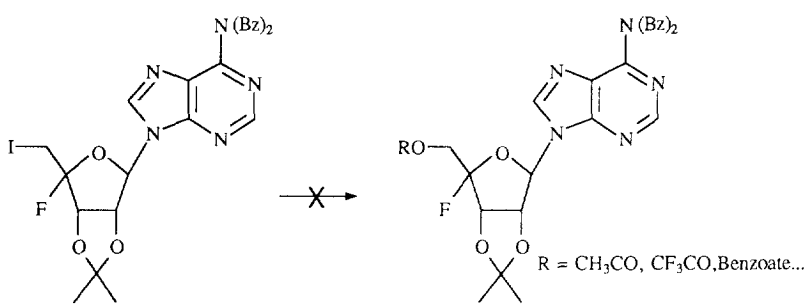
Scheme 4



reagents and conditions: a: I_2; AgF; CH_2Cl_2; r.t.; 65 %. b: KOAc; DMF; 100°C; 5 hours. c: HCl 1N; H_2O; 100°C;

Substitution of the iodine moiety in compound **26** was achieved by dry potassium acetate in DMF under the same conditions as substitution of bromine group in **23**. This substitution turned out to be much easier than the substitution of iodine in the case of N^6,N^6-dibenzoyl-5'-deoxy-4'-fluoro-5'-iodo-2',3'-o-isopropylidene adenosine **29**[19] where the resistance of the iodine function toward substitution was interpreted by the strong deactivating effect of an α fluorine atom due to its high electronegativity (Figure 4).

Figure 4

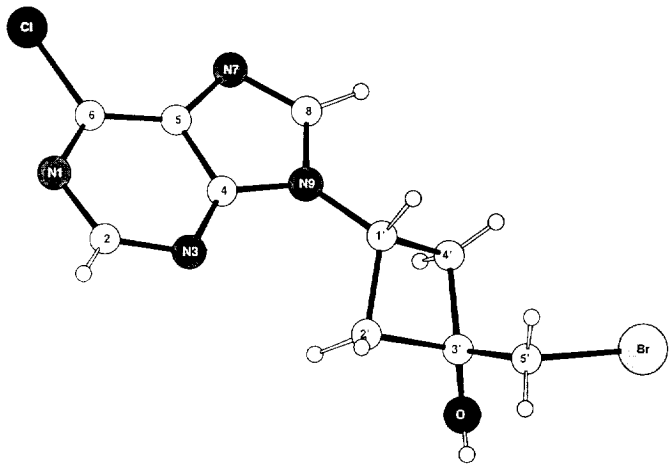


The present example illustrates that electronegative α-substituents exert a cumulative deactivating effect upon attempted displacement of iodine from **29** since fluorine by itself does not prevent nucleophilic substitution of the halogen atom in **23** or in **26**. In addition, it should be mentioned here that catalytic amount of 18-crown-6

ether accelerated this substitution by a factor of four as shown by the substitution of bromine or iodine by acetate ion in **23** and **26**, with or without crown ether, respectively.

Assignment of structure **22** was unambiguously resolved by x-ray crystallography. Its crystal structure

Figure 5



X-ray structure of **22**

(Figure 5) shows the *cis* position of the hydroxyl moiety with respect to the base, and the *gauche* conformation of the CH_2Br substituent.

A summary of the ^1H NMR data concerning H-1 proton of the different couples of isomers is presented in Table 1. In the case of fluoro iodo cyclobutane derivative **27**, a split quintet was observed for H-1 proton in the ^1H NMR spectrum in different solvents (DMSO-d_6, $CDCl_3$). This doubled quintet in **27** can be explained by a long-range W coupling (^4J= 3Hz) of H-1 to the *trans* fluorine atom. This long-range coupling was not observed in the case of the *trans* fluoro isomer **26** where H-1 and F-3 are in *cis*. The quintet observed for H-1 in the latter case (**26**) as well as in the *trans* hydroxylated isomer **21** indicates equivalence of coupling constants of H-1 to both H-2 and H-4 protons. The H-1 signal in the *trans* hydroxylated isomers **21**, **35** and *trans* fluoro isomer **26**, always appeared as a quintet at lower field than in the *cis* hydroxylated isomers **22**, **36** and *cis* fluoro isomer **27** which appeared as a more complex multiplet.

Table 1

Compound	**21**	**22**	**26**	**27**	**35**	**36**
H-1[a]	q	m	q	dq	q	m
δ	5.25	4.85	5.09	4.62	5.01	4.55
$^3J_{H1-H2/4}$	8.50		8.32		8.42	
$^4J_{H1-F}$	-	-	-	3	-	-

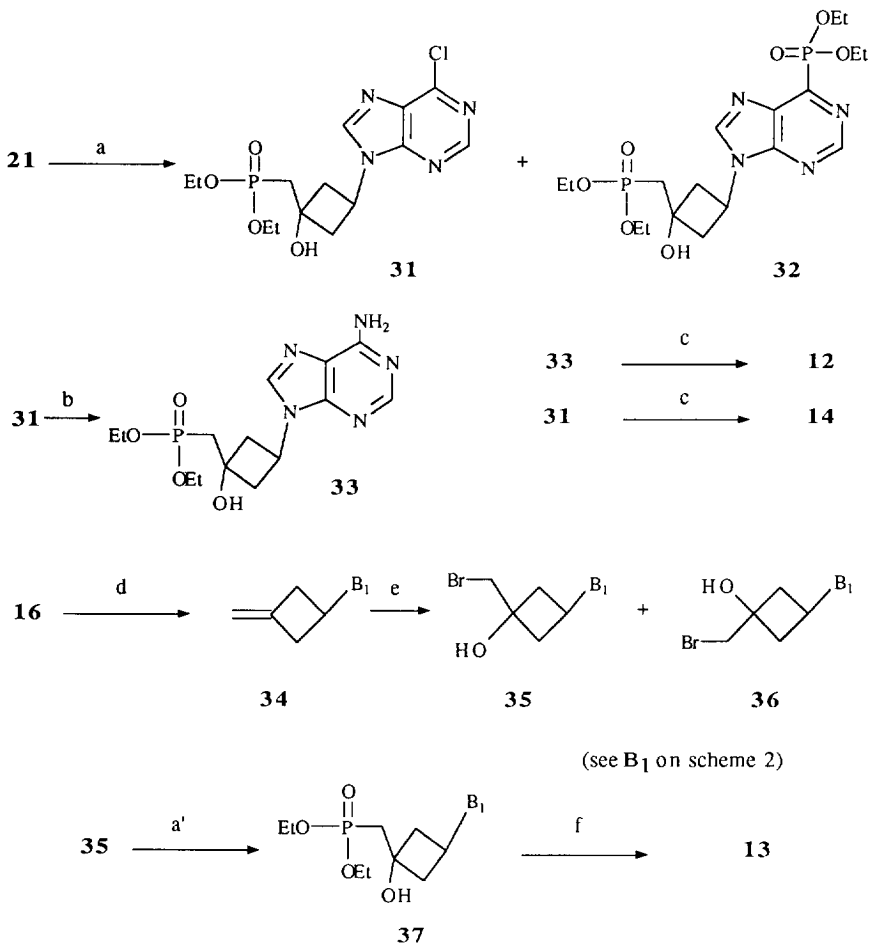
[a]H-1 signals in the ^1H NMR spectra of compounds **21-36** in DMSO-d_6. q= quintet; m= multiplet; dq= doublet of quintet. δ : chemical shifts in ppm; J : coupling constants in Herz.

Furthermore assignment of the stereochemistry of the *trans* (**35**) and *cis* (**36**) bromohydrins is suggested by the comparison of their ^1H NMR spectra in DMSO-d_6. Thus the hydroxyl group in **36** is oriented towards the

purine and therefore is subjected to a ring current with δ_{OH} of 5.77 ppm to be compared with δ_{OH} of 5.53 ppm in **35**. The chemical shift of H-1 is also influenced by the proximity of OH in the *trans* isomer (**35**): δ= 5.01 ppm to be compared to a δ of 4.55 ppm in the *cis* isomer **36**.

The Michaelis-Arbuzof reaction of bromohydrins **21** and **35**, with triethylphosphite yielded the desired diethyl phosphonic acid ester derivatives **31** and **37**, respectively. In the case of 6-chloropurine derivative **21**, the reaction with triethylphosphite was performed at 100° C to avoid the displacement of the 6 chlorine atom of the purine by triethylphosphite (SN_{Ar} reaction). The byproduct **32** was formed only in low yield (<10%) in these conditions, and in higher yield (>25%) above 120°C. Monoethylester **12-14**, obtained by treatment with potassium or sodium hydroxide in aqueous dioxane, were purified by reversed phase HPLC (scheme 5).

Scheme 5



reagents and conditions: a: $(EtO)_3P$; 100°C; 24 h; 85% of **31** and 8% of **32**, or $(EtO)_3P$; reflux, 40% of **31**, 25% of **32**. a': $(EtO)_3P$; reflux; 24 h; 43% of **37**; b: liq. NH_3; EtOH; 40°C; 24 h; 67%. c: NaOH (4 eq.); H_2O/dioxane; 65°C, 24 h. d: Na (4 eq.); MeOH; reflux; 90 min.; 93%. e : NBS (1.2 eq.); AcOEt/H_2O; 30 min.; 61%; f: KOH(4 eq.); H2O/dioxane; 65°C, 24h.

These monoethylesters were synthesized as potential prodrugs, capable of being hydrolyzed in cells[21] to the corresponding free phosphonic acids. These phosphonate derivatives (**12-14**) were considered as analogues of the expected monophosphate metabolites of **5a** and of its guanine analogue. Antiviral activities were measured in primary peripheral blood mononuclear cells (PBMC) infected with HIV-1 (III B strain) or HIV-2 (D194 strain).[24] On these viruses, the most active compound **9** had respectively an IC_{50} of 3.9μM and 1.5μM, and compound **10** 95μM and 46μM, whereas 30% inhibition of HIV-1 replication was observed with **11** at 100μM and 50% inhibition of HIV-2 at 45μM. No cytotoxicity was detected with compounds **9-11** up to 100μM (MTT assay). Phosphonate derivatives **12, 13** and **14** were found inactive on HIV-1 replication but slightly inhibited cell metabolism (10-20% at the highest concentration tested: 10-100μM).

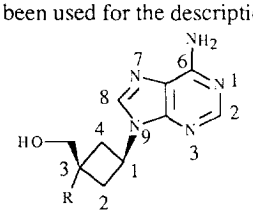
CONCLUSION

This paper describes synthetic approaches toward 3'-fluorocyclobutyl nucleoside analogues.[20] The best general method for introducing a fluorine atom in the presence of an amino-purine (adenine or guanine) turned out to be the direct fluoro-iodination of an olefinic precursor by iodine fluoride generated *in situ* from silver fluoride and iodine, leading to a good yield of separable isomers. Contrary to the generally observed instability of 4'-fluoro-ribonucleosides [19] and as expected for carbocyclic nucleosides, the presence of a fluorine atom in the cyclobutane portion did not lead to the release of the purine under acidic conditions. This was shown, for example, by the high yield of guanine derivative **10** obtained from precursor **28** under acidic conditions. The nucleophilic substitution of iodine and bromine in the presence of an α fluoro group proved easy in the cyclobutyl derivatives studied.

To the best of our knowledge, we report in this article the first example of a Michaelis-Arbuzof reaction of a 6-chloropurine bromohydrin derivative with triethylphosphite.

EXPERIMENTAL

The melting points were taken on a Kofler hot stage apparatus and were uncorrected. Elemental analyses were performed by the "Service de Microanalyse", CNRS, ICSN, 91198 Gir sur Yvette, France. Fast atom bombardment (FAB) and chemical ionization (CI) mass spectra (MS) were obtained from the "Laboratoire de Spectrometrie de Masse", CNRS, ICSN, 91198 Gif sur Yvette, France. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 200 MHz on a Bruker AC200 spectrometer. Chemical shifts (δ) are reported in ppm units with tetramethylsilane as an internal standard and coupling constants (J) are given in hertz (Hz). For the sake of clarity, the same numbering has been used for the description of all NMR spectra, as follows:



Preparative HPLC of phosphonate monoester derivatives were performed on a Gilson equipment (305 pump with UV detection UV 115). A reverse phase C18 Dynamax (21.4mm x 25cm) colomn was used with ethanol-water 9:1 as eluent.

1-Bromomethyl-3-(6-Chloro-9H-purin-9-yl)-cyclobutanol 21 and 22. A solution of **15**[9] (1 g, 4.53 mmol) in AcOEt (20ml) was added to an aqueous solution (25ml) of KOH (380 mg, 6.8 mmol) and NBS

(1.05 g, 5.90mmol) and stirred vigorously for 15 min. The organic layer was dried over Na_2SO_4 and the volatile removed under reduced pressure to give a mixture of *cis* and *trans* alcohol isomers which were separated by colomn chromatography on silica gel (CH_2Cl_2-MeOH 95:5). *Cis* isomer **22** (768 mg, 53%): mp 134°C (amorphous solid). ^1H NMR ($CDCl_3$) δ : 8.7 (s, 1H, H-2), 8.2 (s, 1H, H-8), 4.84 (m, 1H, H-1), 3.85 (s, 2H, CH_2Br), 3.1 (m, 2H, cyclobutane), 2.85 (m, 2H, cyclobutane). M.S. (FAB): 317-319-321 $(MH)^+$, 237-239 $(MH-Br)^+$, 155-157 (6-chloropurine)$^+$, 131. *Anal.* Calcd for $C_{10}H_{10}BrClN_4O$: C, 37.79; H, 3.15; N, 17.64; O, 5.04. Found: C, 38.05; H, 3.13; N, 17.48; O, 5.06. *Trans* isomer **21** (628 mg, 44%): mp 128°C (amorphous solid). ^1H NMR ($CDCl_3$) δ : 8.7 (s, 1H, H-2), 8.05 (s, 1H, H-8), 5.25 (q, 1H, J=8.5 Hz, H-1), 3.65 (s, 2H, CH_2Br), 3.1 (m, 2H, cyclobutane), 2.8 (m, 2H, cyclobutane). M.S. (CI, isobutane): 317-319 $(MH)^+$, 237-239 $(MH-Br)^+$, 181-183 $(MH-BrCH_2COCH_3)^+$, 155-157 (6-chloropurine)$^+$. *Anal.* Calcd for $C_{10}H_{10}BrClN_4O$: C, 37.79; H, 3.15; N, 17.64; O, 5.04. Found: C, 38.04; H, 3.23; N, 17.73; O, 5.09.

6-Chloro-9H-9-(*cis*-3-bromomethyl-*trans*-3-fluoro-cyclobutyl) purine 23. To a stirred solution of **22** (1.483 g, 4.47 mmol) in cooled CH_2Cl_2 (50 ml, 0°C) was slowly added DAST (0.74 ml, 5.6 mmol). After 15 min, the reaction was quenched by pouring into a saturated and cooled aqueous solution of K_2CO_3 (50 ml). The organic layer was dried over Na_2SO_4 and the volatile removed under reduced pressure to give a residual oil which was purified by chromatography on silica gel column (CH_2Cl_2-MeOH 95:5). *Trans*-fluoro isomer **23** was eluted first and was always contaminated with a small amount of the elimination product **24**.This mixture was used without further purification in the next step. (yield 79%); mp 107°C. ^1H NMR ($CDCl_3$) δ : 8.75 (s, 1H, H-2), 8.15 (s, 1H, H-8), 5.25 (q, 1H, J=8.5Hz, H-1), 3.85 (d, 2H, J=21.5 Hz, $\underline{CH_2}Br$), 3.25 (m, 2H, cyclobutane), 3 (m, 2H, cyclobutane). M.S. (CI, isobutane): 319-321 $(MH)^+$, 299-301 $(MH-HF)^+$, 181-183 (MH-BrCH2COCH3)$^+$, 155-157 (6-chloropurine)$^+$. A second compound (**24**) was eluted as an oil after evaporation and crystallized from cyclohexane: (65 mg,6%); mp 112-114°C. ^1H NMR ($CDCl_3$) δ : 8.77 (s, 1H, H-2), 8.24 (s, 1H, H-8), 6.15 (q, 1H, J=3Hz, vinylic H), 5.20 (q, 1H, J=8.5Hz, H-1), 3.44 (m, 2H, cyclobutane), 3.40 (m, 2H, cyclobutane). M.S. (CI, isobutane): 299-301 $(MH)^+$, 255-257, 221-223, 155-157 (6-chloropurine)$^+$. *Anal.* Calcd for $C_{10}H_8BrClN_4$: C, 40.10; H, 2.69; N, 18.70. Found: C, 39.94; H, 3.03; N, 18.73.

Acetic acid-*cis*-3-(6-Chloropurin-9-yl)-*trans*-1-fluoro-cyclobutyl methylester 25. A stirred solution of **23** (450 mg, 1.4 mmol) in DMF (20 ml) was treated with dry KOAc (548 mg, 5.6 mmol) and catalytic 18-crown-6 (10 mg). After total consumption of the substrat (4 hours), the reaction was quenched by pouring into iced water (50 ml) and the solution was extracted with CH_2Cl_2 (2x50 ml). The organic layer was dried over Na_2SO_4 and the volatile removed under reduced pressure to give a residual oil which was purified by chromatography on silica gel column (AcOEt-heptane 2:1). *Trans* fluoro isomer **25** (400 mg, 95%) was obtained as a colourless oil. ^1H NMR ($CDCl_3$) δ : 8.7 (s, 1H, H-2), 8.1 (s, 1H, H-8), 5.3 (q, 1H, J=8.5Hz, H-1), 4.4 (d, 2H, J=21.5Hz, $\underline{CH_2}OAc$) 2.8-3.4 (m, 4H, cyclobutane), 2.1 (s, 3H, CH_3). M.S. (CI, isobutane): 299-301 $(MH)^+$, 155-157 (6-chloropurine)$^+$. *Anal.* Calcd for $C_{12}H_{12}ClFN_4O_2$: C, 48.24; H, 4.02; N, 18.76. Found: C, 48.38; H, 4.15; N, 18.64.

***trans*-1-fluoro-*cis*-3-(adenin-9-yl)-cyclobutyl methanol 9.** A 150 ml stainless steel autoclave was charged with a solution of **25** (192 mg, 0.64 mmol) in 50 ml ethanol/liquid ammonia (3/1) and heated at 40°C for 24 hours. After cooling to room temperature and removal of the solvent, the residual oil was purified by colomn chromatography on silica gel (CH_2Cl_2-EtOH 9:1). *trans* -fluoro isomer **9** was obtained in 66% yield as an amorphous solid: mp 168°C. ^1H NMR (DMSO d_6) δ : 8.3 (s, 1H, H-2), 8.17 (s, 1H, H-8), 7.27 (s, 2H, NH_2), 5.25 (q, 1H, J=8.5Hz, H-1), 5.2 (t, 1H, J'=4.5Hz, OH), 3.7 (dd, 2H, J=21.5Hz and J'=4.5Hz,

$\underline{CH_2}OH$), 2.65-3.1 (m, 4H, cyclobutane). M.S. (EI): 238 $(MH)^+$, 237 $(M)^+$, 162 $(MH\text{-}HOCH_2CF{=}CH_2)^+$, 135 (adenine)$^+$. *Anal.* Calcd for $C_{10}H_{12}FN_5O$: C, 50.63; H, 5.1; N, 29.52. Found: C, 50.6; H, 5.19; N, 29.63.

***Cis*-9-(*trans*-3-fluoro-*cis*-3-hydroxymethyl-cyclobutyl) hypoxanthine 11.** A solution of **25** (367 g, 1.22 mmol) in aqueous 1N HCl (10 ml) was refluxed for 2 hours. After cooling to room temperature, the solution was evaporated under reduced pressure to give a residual oil which was purified by colomn chromatography on alumina (type T) (AcOEt-EtOH 8:2). *trans* -fluoro isomer **11** was obtained in 91% yield: mp 245°C (amorphous solid). ^1H NMR (DMSO d_6) δ : 12.35 (broad s, 1H, NH), 8.3 (s, 1H, H-2), 8.1 (s, 1H, H-8), 5.25 (m, 1H, H-1), 3.65 (dxd, 2H, J=21.5Hz and J'=4.5Hz, $\underline{CH_2}OH$), 2.6-3.05 (m, 4H,, cyclobutane). M.S. (EI): 238 $(M)^+$, 162 $(MH\text{-}HOCH_2CF{=}CH_2)^+$, 137 (hypoxanthine+H)$^+$, 136 (hypoxanthine)$^+$. *Anal.* Calcd for $C_{10}H_{11}FN_4O_2$, 1/2 H_2O: C, 48.58; H, 4.85; N, 22.67. Found: C, 48.7; H, 4.96; N, 22.59.

6-Chloro-9-(3-fluoro-3-iodomethyl-cyclobutyl)-9H-purin-2-yl amine 26 and 27. A solution of olefin **16**[9](500 mg, 2.12 mmol) in dichloromethane was treated with AgF and iodine as described[19] to afford a mixture of *cis* and *trans* isomers which were separated by column chromatography (silica gel ; 2x 95 cm) eluting with ethyle acetate-heptane 2:1. *trans* Isomer **26** was eluted first (fluorine atom being in *trans* with respect to the base) 347 mg ; mp : 200-202°C (ethanol) : MS (CI, isobutane) : 382. ^1H NMR (DMSO-d_6) δ : 8.26 (s, 1H, H-8), 6.90 (s, 2H, NH_2), 5.09 (q, 1H, J=8.32 Hz, H-1), 3.83 (d, 2H, $I\underline{CH_2}$, $^3J_{H\text{-}F}$= 24.23 Hz), 3.10-2.68 (m, 4H, cyclobutane). *Anal.* Calcd for $C_{10}H_{10}N_5OClFI$: C, 31.48 ; H, 2.64 ; N, 18.35 ; F, 4.98. Found : C, 31.70 ; H, 2.68 ; N, 18.38 ; F,5.29. A second product was then obtained which corresponded to the *cis* isomer **27** : 172 mg (total yield : 65.3 %) ; mp : 202-204°C (ethanol) ; MS (CI, isobutane) : 382 ; ^1H NMR (DMSO-d_6) δ : 8.25 (s,1H, H-8), 6.82 (s, 2H, NH_2), 4.62 (dq, 1H, H-1, ^3J=8.25 Hz;$^4J_{H\text{-}F}$= 3Hz), 3.78 (d, 2H, $I\underline{CH_2}$, $^3J_{H\text{-}F}$= 24.26 Hz), 3.32-2.80 (m, 4H, cyclobutane). *Anal.* Calcd for $C_{10}H_{10}N_5OClFI$: C, 31.48 ; H, 2.64 ; N, 18.35 ; F, 4.98. Found : C, 31.77 ; H, 2.72 ; N, 18.07 ; F, 4.79.

Acetic acid-3-(2-amino-6-chloro-purin-9-yl)-*trans*-1-fluoro-cyclobutyl methylester 28. A solution of *trans* **26** (313.3 mg, 1 mmol) in dry DMF (100 ml) was treated with KOAc (804 mg, 8.2 mmol) at 100°C for 15 h with stirring. The mixture was then cooled, evaporated to dryness (oil pump) and the residue was partionned between dichloromethane (200 ml) and water (50 ml). The organic phase was washed twice with water (20 ml), dried ($MgSO_4$), filtered and evaporated to dryness. Purification was then carried out by column chromatography (2 x 95 cm) on silica gel prepared in AcOEt-heptane 1:1. The column was eluted successively with 1 L of AcOEt-heptane 1:1 and 1 L of AcOEt-heptane 2:1 to afford **28** as an oil which crystallized on standing. Yield : 79% ; mp : 170-172°C (AcOEt). ^1H NMR ($CDCl_3$) δ : 7.73 (s, 1H, H-8), 5.43 (s, 2H, NH_2), 5.12 (q, 1H, J=8.38 Hz, H-1), 4.64 (d, 2H, $Ac\underline{OCH_2}$, $^3J_{CH2\text{-}F}$ = 22.94 Hz), 3.27-2.80 (m, 4H, cyclobutane), 2.15 (s, 3H, CH_3). *Anal.* Calcd for $C_{12}H_{13}N_5O_2ClF$: C, 45.94 ; H, 4.18 ; N, 22.32 ; Cl, 11.48. Found : C, 45.95 ; H, 4.12 ; N, 22.42 ; Cl, 11.48.

2-Amino-9-(*trans*-3-fluoro-*cis*-3-hydroxymethyl-cyclobutyl)-1,9-dihydropurin-6-one 10. A solution of acetoxy derivative **28** (100 mg, 0.318 mmol) in 1N HCl (100 ml) was heated at 100°C for 6 h, cooled and evaporated to dryness. The solid residue was dissolved in 2 ml of water and neutralized with 6N NaOH. A precipitate was obtained which was filtered and washed with cooled water. Yield : 96% ; mp : > 260°C ; ^1H NMR (DMSO-d_6) δ : 10.59 (s, 1H, NH), 8.03 (s, 1H, H-8), 6.42 (s, 2H, NH_2), 5.12-4.98 (m, 2H, OH, H-1), 3.64 (dd, 2H, $\underline{CH_2}OH$, $^3J_{H\text{-}OH}$ = 4.75 Hz, $^3J_{H\text{-}F}$ = 20.81 Hz), 2.97-2.62 (m, 4H, cyclobutane). *Anal.* Calcd for $C_{10}H_{12}N_5O_2F/1/3H_2O$: C, 46.33 ; H, 4.92 ; N, 27.01 ; Found : C, 46.58 ; H, 4.95 ; N, 27.21.

6-Methoxy-9-(3-methylencyclobutyl)-9H-purin-2-yl amine 34. A solution of 6-chloro-9-(3-methylenecyclobutyl)-9H-purin-2-yl amine **16**[9] (4.5 g ; 19.1 mmol) and sodium (1.2 g ; 52 mmol) in methanol

(400 ml) was heated under reflux for 90 min. After evaporation to dryness, the residue was dissolved on CH_2Cl_2 (200 ml) and washed with water (4 x 50 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated to give an oil which gave crystals on trituration with ether (4.1 g ; 93 %). mp = 123-124°C. ^1H NMR (DMSO-d_6) δ 8.10 (s, 1H, H-8), 6.45 (s, 2H, NH_2), 4.98 (m, 2H, CH_2=) ; 4.93 (q, 1H, J=8Hz, H-1), 3.99 (s, 3H, OCH_3), 3.39 (m, 2H, cyclobutane), 3.15 (m, 2H, cyclobutane). *Anal.* Calcd for $C_{11}H_{13}N_5O$: C, 57.29 ; H, 5.68 ; N, 30.38. Found : C, 57.14 ; H, 5.62 ; N, 30.30.

1-Bromomethyl-3-(2-amino-6-methoxy-9H-purin-9-yl) cyclobutanol 35 and 36. A solution of **34** (1.7 g ; 7.35 mmol) in AcOEt (225 ml) was stirred vigorously with H_2O (375 ml) and NBS (1.56 g ; 8.83 mmol) at room temperature for 30 min. The organic phase was separated while the aqueous phase was extracted 3 times with AcOEt (50 ml). The combined organic phases were washed twice with 5 % aqueous $NaHSO_3$ (30 ml portions) and twice with water (30 ml portions), dried ($MgSO_4$), filtered and evaporated to dryness. The oily residue was adsorbed on silica gel and subjected to column chromatography (50 x 2.5 cm), eluting with CH_2Cl_2-EtOH 95:5. A first compound was eluted (**36**) (308 mg) mp = 170-172°C (CH_2Cl_2) ; Rf = 0.33. ^1H NMR DMSOd_6 δ : 8.03 (s, 1H, H-8), 6.38 (s, 2H, NH_2), 5.77 (s, 1H, OH), 4.55 (m, 1H, H-1), 3.95 (s, 3H, O<u>C</u>H$_3$), 3.74 (s, 2H, <u>C</u>H$_2$ Br), 2.80-2.50 (m, 4H, 2 x CH_2). *Anal.* Calcd for $C_{11}H_{14}N_5O_2$ Br C, 40,26 ; H, 4.30 ; N, 21.34. Found : C, 40.13 ; H, 4.29 ; N, 21.15. A second compound (**35**) was eluted (1153 mg) Rf = 0.24 ; mp = 198-202°C (CH_2Cl_2) (decomposition) ^1H NMR DMSO-d_6 δ : 8.05 (s, 1H, H-8), 6.40 (s, 2H, NH_2), 5.53 (s, 1H, OH), 5.01 (q, 1H, J=8.42 Hz, H-1), 3.95 (s,3H, CH_3), 3.77 (s, 2H, <u>C</u>H$_2$ Br), 2.68 (m, 2H, cyclobutane), 2.42 (m, 2H, cyclobutane). *Anal.* Calcd for $C_{11}H_{14}N_5O_2Br$: C, 40.26 ; H, 4.30 ; N, 21.34. Found : C, 40.44 ; H, 4.30 ; N, 21.09.

***trans*-1-Diethoxyphosphonomethyl-*trans*-3-(2-amino-6-methoxy-9H-purin-9-yl)-cyclobutanol 37.** A solution of bromo derivative **35** (753 mg; 2.29 mmol) and freshly distilled triethyl phosphite (250 ml) was heated under N_2 at 120°C for 24 h.Excess of triethylphosphite was evaporated *in vacuo* (oil pump) and the residue was purified by column chromatography on silica gel prepared in CH_2Cl_2. Elution was carried out successively with CH_2Cl_2, CH_2Cl_2-EtOH 99:1 and 98:2 to eliminate some impurities. Compound **37** was then eluted with CH_2Cl_2-EtOH 97:3 to give a solid which was washed with ether. Yield: 43.5% (385 mg); mp 165°C. ^1H NMR (CD_3OD) δ: 8.24 (s, 1H, H-8), 5.62 (s, broad, 3H, NH_2, OH), 5.25 (q, 1H, H-1, J=8.4Hz), 4.14 (m, 7H, OCH_3,2x<u>CH</u>$_2$OP), 3.01-2.75 (m, 4H, 2xCH_2), 2.47 (d, 2H, CH_2-P, J=17.10 Hz), 1.35 (t, 6H, 2xCH_3). *Anal.* Calcd for $C_{15}H_{24}N_5O_5$ P: C, 46.75 ; H, 6.28 ; N, 18.17. Found : C, 46.93 ; H, 6.24 ; N, 17.92.

***trans*-1-Diethoxyphosphonomethyl-*trans*-3-(6-chloro-9H-purin-9-yl)-cyclobutanol 31.** A solution of **21** (600 mg, 1.89 mmol) in triethylphophite (5 ml) was heated at 100°C for 24 h. The solution was then evaporated under reduced pressure to give a residual oil which was purified by colomn chromatography on silica gel (CH_2Cl_2-MeOH 92:8). *Cis* phosphonate **31** was obtained as an amorphous solid (601 mg, 85%); mp 96°C ; ^1H NMR ($CDCl_3$) δ : 8.65 (s, 1H, H-2), 8.1 (s, 1H, H-8), 5.25 (q, 1H, J=8.5Hz, H-1), 4.1 (m, 4H, CH_3<u>CH</u>$_2$), 3.1 (m, 2H, cyclobutane), 2.8 (m, 2H, cyclobutane), 2.4 (d, 2H, CH_2P, J=27.5Hz), 1.3 (t, 6H, <u>CH</u>$_3$$CH_2$, J=8.5Hz). M.S. (CI, isobutane): 375-377 $(MH)^+$, 155-157 (6-chloropurine)$^+$. *Anal.* Calcd for $C_{14}H_{20}ClN_4O_4P$, 2/3 H_2O: C, 43.49; H, 5.56; N, 14.49. Found: C, 43.81; H, 5.31; N, 14.11. A second compound (**32**) was obtained as an oil in 8% yield: ^1H NMR ($CDCl_3$) δ : 9.1 (s, 1H, H-2), 8.2 (s, 1H, H-8), 5.3 (q, 1H, J=8.5Hz, H-1), 4.35 (m, 4H, 2x<u>CH</u>$_2$$CH_3$), 4.15 (q, 4H, J=8.5Hz, 2x<u>CH</u>$_2$$CH_3$), 3.1 (m, 2H, cyclobutane), 2.75 (m, 2H, cyclobutane), 2.4 (d, 2H, J=27.5Hz, CH_2P), 1.4 (t, 6H, J=8.5Hz, CH_2<u>CH</u>$_3$), 1.3 (t, 6H, J=8.5Hz, CH_2<u>CH</u>$_3$). M.S. (FAB): 499 $(M+Na)^+$, 477 $(MH)^+$, 257 $(Et_2O_3P$-purine$)^+$, 201, 123.

***trans*-1-Diethoxyphosphonomethyl-*trans*-3-(6-amino-9H-purin-9-yl)-cyclobutanol 33.** A 150 ml stainless steel autoclave was charged with a solution of **31** (300 mg, 0.8 mmol) in 50 ml of ethanol-liquid ammonia (3:1) and heated at 40°C for 24 hours. After cooling to room temperature and removal of the solvent, the residual oil was purified by chromatography on silica gel column (CH_2Cl_2-EtOH 8:2) to give **33** as an oil (191 mg, 67%); ^1H NMR (CD_3OD) δ : 8.25 (s, 1H, H-2), 8.15 (s, 1H, H-8), 5.25 (m, 1H, H-1), 4.6 (broad s, 3H, OH and NH_2), 4.15 (m, 4H, 2x$\underline{CH_2}CH_3$), 3.05 (m, 2H, cyclobutane), 2.75 (m, 2H, cyclobutane), 2.47 (d, 2H, J=27.5Hz, $\underline{CH_2}P$), 1.3 (t, 6H, J=8.5Hz, 2xCH_3). M.S. (CI, isobutane): 356 $(MH)^+$, 136 $(adenine)^+$. *Anal.* Calcd for $C_{14}H_{20}ClN_4O_4P, H_2O$: C, 45.04; H, 6.48; N, 18.76. Found: C, 44.93; H, 6.31; N, 18.31.

General procedure for the synthesis of phosphonate potassium (or sodium) salt monoethylesters. A solution of phosphonate diethylester **31**, **33** or **37** (0.3 mmol) in distilled dioxane (10 ml) and 4N aqueous KOH or NaOH (10 ml) was stirred at 75° C for 6h. The mixture was cooled, neutralized with concentrated aqueous HCl and evaporated to dryness. The residue was extracted with absolute EtOH and subjected twice to reverse phase chromatography eluting with ethanol-water 9:1.

2-Amino-9-(*cis*-3-ethoxyphosphonomethyl-*trans*-3-hydroxycyclobutyl)-1,9-dihydro-purin-6-one potassium salt 13. Following the general procedure from **37** in 4N aqueous KOH, **13** was obtained as a hygroscopic solid in 42% yield; mp 202-204 °C. ^1H NMR (CD_3OD) δ: 7.88 (s, 1H, H-8), 5.05 (q, 1H, J=8.5 Hz, H-1), 4.89 (broad s, OH, NH_2, NH), 3.95 (m,2H, O$\underline{CH_2}CH3$), 2.92 (m, 2H, cyclobutane), 2.63 (m, 2H, cyclobutane), 2.15 (d, 2H, $\underline{CH_2}$-P, ^{2}J=16.6Hz), 1.25 (t, 3H, J=7.0 Hz, $\underline{CH_3}CH_2$). *Anal.* Calcd for $C_{12}H_{17}N_5O_5PK$, 3 H_2O: C, 33.10; H, 5.32; N, 16.08. Found: C, 33.03; H, 5.39; N, 15.98.

***trans*-1-Ethoxyphosphonomethyl-*trans*-3-(6-amino-9H-purin-9-yl)-cyclobutanol sodium salt 12.** Following the general procedure from **33** in 4N aqueous NaOH, **12** was obtained as a solid in 70% yield; mp 196-202°C ; ^1H NMR (CD_3OD) δ: 8.33 (s, 1H, H-2), 8.19 (s, 1H, H-8), 5.23 (q, 1H, H-1, J=8.5 Hz), 3.94 (q, 2H,J= 7 Hz, $\underline{CH_2}CH_3$), 2.97 (m, 2H, H-3,H-4), 2.70 (m, 2H, H-3, H-4), 2.12 (d, 2H, J=16.7 Hz, CH_2-P), 1.25 (t, 3H, $CH_2\underline{CH_3}$, J=7.0 Hz). *Anal.* Calcd for $C_{12}H_{17}N_5O_4PNa$,2 H_2O : C, 39.78; H, 5.84; N, 19.33. Found: C, 39.34; H, 5.51; N, 19.61.

9-(*cis*-3-Ethoxyphosphonomethyl-*trans*-3-hydroxycyclobutyl)-1,9-dihydro-purin-6-one sodium salt 14. Following the general procedure from **31** in 4N aqueous NaOH, **14** was obtained as an oil in 38% yield.^1H NMR (CD_3OD) δ: 8.55 (s,1H,H-2), 8.19 (s, 1H, NH), 8.03 (s,1H,H-8),5.26(q, 1H,H-1, J=8.4 Hz), 3.94 (m, 2H, $\underline{CH_2}CH_3$), 2.90 (m, 2H, H-2, H-4), 2.60 (m, 2H, H-2, H-4), 1.25 (t,3H, $CH_2\underline{CH_3}$, J=4.2Hz). *Anal.* Calcd for $C_{12}H_{16}N_4O_5PNa$, 2 H_2O: C, 39.67; H, 5.55; N, 15.42; Found: C, 40.01; H, 5.42; N, 15.28.

X-Ray structure determination of compound 22. The main crystal data are summarized as follows: $C_{10}H_{10}BrClN_4O$, M = 317.6. Crystal dimensions 0.6 x 0.4 x 0.3 mm^3. Automatic, graphite monochromated (λ = 1.5418 Å) 4-circle Nonius diffractometer. Monoclinic, $P2_1/n$, Z = 4. **a** = 7.047 (3), **b** = 8.983 (7), **c** = 19.295 (5) Å and β = 91.86 (2)°. V = 1221 (1) $Å^3$, d_x = 1.71, μ = 6.6 cm^{-1}. ω/2θ scan mode (2θ < 120°), |h| < 7, k < 10, l < 21 gave 2039 reflexions in which 1674 were independent and > 3σ (I). Lorentz-polarization, no absorption corrections. Direct methods[22] and full-matrix least squares[23] : C, N, O, Br, Cl anisotropic, H isotropic refinement to R = 5.4 %. Weighting scheme w = $[\sigma^2(F) + 0.0002\ F^2]^{-1}$, σ from counting statistics. Supplementary material is available on request.

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