Bioorganic & Medicinal Chemistry Letters, Vol.3, No.6, pp. 1215-1218, 1993
Printed in Great Britain

0960-894X/93 \$6.00 + .00

OPTICALLY ACTIVE FLUORINATED CYCLOBUTANE NUCLEOSIDE ANALOGS WITH POTENT ANTI-HERPES ACTIVITY

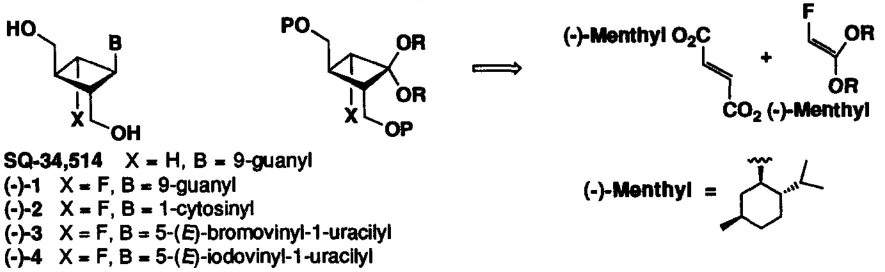
Saleem Ahmad,* Gregory S. Bisacchi, A. Kirk Field,[1] Glenn A. Jacobs, A. Vickie Tuomari,
Bridget McGeever-Rubin, Gregory D. Vite and Robert Zahler
The Bristol Myers Squibb Pharmaceutical Research Institute
P. O. Box 4000, Princeton, NJ 08543-4000

(*Received in USA* 16 *February* 1993)

Summary: The synthesis and antiherpes activity of several optically active 4'-fluoro-2',3'-dihydroxymethylcyclobutyl nucleoside analogs are described. A key synthetic step is the diastereoselective [2+2] cycloaddition of a novel fluoroketene acetal with (-)-dimenthyl fumarate.

In the preceding paper we reported the synthesis and antiherpes activity of a novel fluorocyclobutyl nucleoside analog (±)-**1**.[2] In order to ascertain the antiviral activities of the individual enantiomers composing (±)-**1**, we wished to prepare the two antipodes, (-)-**1** and (+)-**1**. Initially we prepared (-)-**1** using the methodology described in the preceding paper, i. e. via fluorination of (2S,3S)-trans-2,3-bis(benzyloxymethyl)cyclobutanone.[3] However, we felt that a more convergent approach to this class of 4'-fluorocyclobutane nucleoside analogs would involve an asymmetric [2+2] cycloaddition reaction of a fluoroketene acetal with (-)-dimenthyl fumarate (see Figure 1). We had previously used a similar [2+2] approach to synthesize the enantiomerically pure non-fluorinated analog **SQ-34,514**.[3] In this communication we report extension of this approach to the preparation of the 4'-fluoro-2',3'-dihydroxymethylcyclobutyl nucleoside analog (-)-**1** and its "unnatural" enantiomer (+)-**1**, as well as several nucleobase analogs of (-)-**1**.

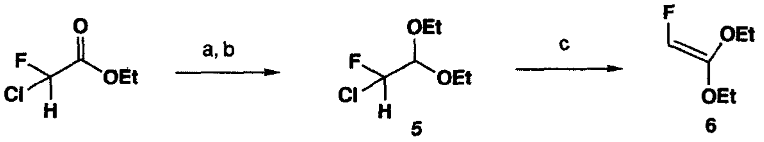
Figure 1



SQ-34,514 X = H, B = 9-guanyl
(-)-**1** X = F, B = 9-guanyl
(-)-**2** X = F, B = 1-cytosinyl
(-)-**3** X = F, B = 5-(*E*)-bromovinyl-1-uracilyl
(-)-**4** X = F, B = 5-(*E*)-iodovinyl-1-uracilyl

Synthesis: Although several preparations of difluoro- and monochloroketene acetals have been reported in the literature,[4] there are no reports on the synthesis and isolation of monofluoroketene dialkyl acetals.[5] We report here the first synthesis of fluoroketene diethyl acetal (**6**).[2,7] DIBAL reduction of commercially available ethyl chlorofluoroacetate, followed by quenching the reaction mixture with dry HCl in ethanol, afforded a 45% yield of chlorofluoroacetaldehyde diethyl acetal **5**. The fluoroketene acetal **6** was obtained in a 68% yield by dehydrochlorination of **5** using potassium t-butoxide in THF.

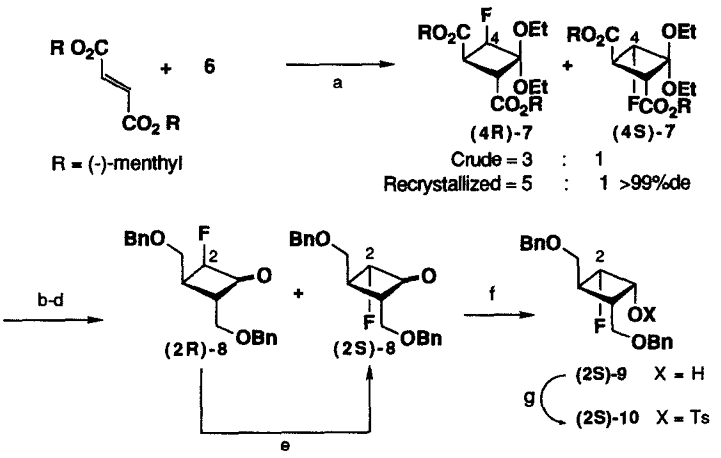
Scheme 1



a) DIBAL/toluene; b) HCl/EtOH; c) potassium t-butoxide/THF

Lewis acid catalyzed, low temperature [2+2] cycloaddition[3] of the fluoroketene acetal **6** with (-)-dimenthyl fumarate afforded a crude mixture containing the α- and β-fluoro cyclobutanes **(4R)**- and **(4S)-7**, respectively, in a 3:1 ratio (along with 40-50% unreacted dimenthyl fumarate). A single recrystallization from hexane afforded a 37% isolated yield of a 5:1 mixture of **(4R)**- and **(4S)-7**, with no detectable (NMR and HPLC) diastereomer resulting from addition to the opposite face of dimenthyl fumarate.

Scheme 2

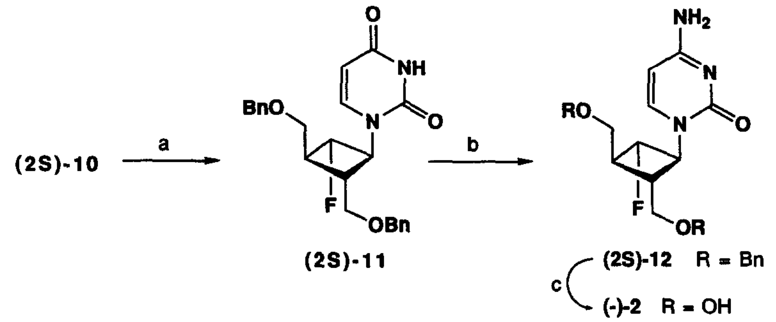


a) Et_2AlCl/toluene-hexane, -78°C, 37%; b) LAH/THF, 95%; c) BnBr/NaH/DMF, 98%; d) aq. H_2SO_4/ acetonitrile, 100% crude; e) DBU/acetonitrile, 100% crude; f) LS-Selectride, 60%; g) TsCl/Py, 93%

Reduction, benzylation, and acid catalyzed hydrolysis of the mixture containing **(4S)**- and **(4R)-7** afforded fluorocyclobutanones **(2R)**- and **(2S)-8**. This was subjected to equilibration by treatment with DBU in acetonitrile to afford predominantly the thermodynamically more stable **(2S)-8**.[9] Stereoselective reduction of the crude ketone **(2S)-9** using LS-Selectride afforded a 60% yield of the cyclobutyl alcohol **(2S)-9** after flash chromatography (identical by proton NMR to the corresponding racemic compound described in the preceding paper). This methodology was subsequently extended to the synthesis of the "unnatural" enantiomer (+)-**1** via a [2+2] reaction of **6** with (+)-dimenthyl fumarate.

Synthesis of the cytosine analog (-)-**2** was carried out as outlined in Scheme 3. Treatment of the tosylate **(2S)-10** with freshly generated anhydrous tetrabutylammonium uracil (prepared by reaction of uracil with tetrabutylammonium hydroxide in a 1:1 ratio) afforded **(2S)-11** in a 67% yield. Sequential treatment of this compound with p-chlorophenyl dichlorophosphate, 1,2,4-triazole and ammonium hydroxide afforded the cytosine derivative **(2S)-12** in a 61% yield.[10] The target nucleoside (-)-**2** was prepared in a 74% yield via removal of the benzyl protecting groups of **(2S)-12** by transfer hydrogenolysis.

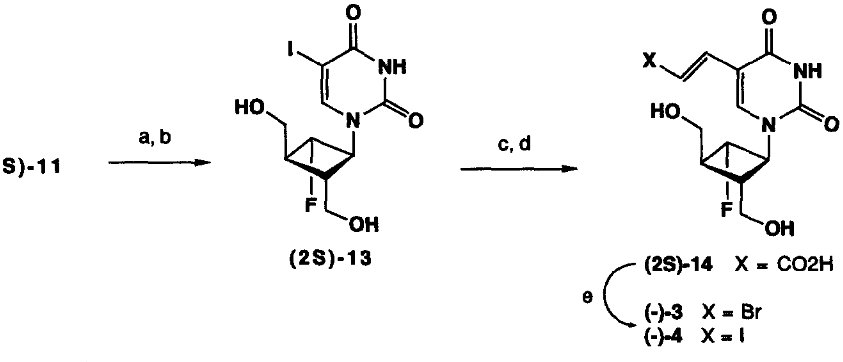
Scheme 3



a) Tetrabutylammonium uracil/DMF, 67%; b) i. p-chlorophenyl dichlorophosphate/Py; ii. 1,2,4-triazole; iii. ammonium hydroxide, 61%; c) $Pd(OH)_2$/cyclohexene/ethanol, 74%

Preparation of the bromo- and iodovinyluracil analogs ((-)-3 and (-)-4, respectively) was carried out as described in Scheme 4. Deprotection of the uracil derivative **(2S)-11** under transfer hydrogenolysis conditions afforded the corresponding dihydroxymethyl cyclobutane derivative, which was treated with iodine and dilute nitric acid to afford **(2S)-13**. Palladium catalyzed coupling of **(2S)-13** with methyl acrylate, followed by saponification of the resulting ester, gave the corresponding α,β-unsaturated carboxylic acid **(2S)-14**.[11a] The bromo- and iodovinyluracil nucleoside analogs, (-)-**3** and (-)-**4**, respectively, could conveniently be prepared by treatment of the acid **(2S)-14** with N-bromo or N- iodosuccinimide (see Scheme 4).

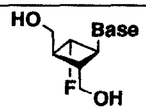
Scheme 4



a) $Pd(OH)_2$/cyclohexene/ethanol, 77%; b) I_2/0.8 N HNO_3/dioxane, 99%; c) $Pd(OAc)_2$/ Ph_3P/methylacrylate/dioxane, 90%; d) i. 2N KOH, ii. 10% HCl, 62%; e) NBS/$KHCO_3$/ DMF, 60%; or NIS/KOAc/DMF, 68%

Biology: The optically pure compound (-)-**1** showed similar antiviral activity when compared to the racemate (±)-**1** against a broad spectrum of herpes viruses in viral plaque reduction assays.[11b] The "unnatural" enantiomer (+)-**1** did not show significant activity. The cytosine analog (-)-**2** and the bromo- and iodovinyluracil analogs ((-)-**3** and (-)-**4**) respectively, were significantly less active in cell culture than the guanine derivative (-)-**1**. Although (-)-**1** is equipotent to acyclovir, the leading treatment for HSV-1, HSV-2, and VZV (Zoster) infections, the high cellular toxicity for (-)-**1** (Vero cell growth inhibition, 600 µm for acyclovir *vs* 6.25-25 µm for (-)-**1**) discouraged further work in this series.

Table

					
		ED$_{50}$ mM			
Compound	Base	HSV-1 (Schooler)	HSV-2 (186)	VZV (Ellen)	HCMV (AD169)
(±)-**1**	9-Guanyl	0.7-1.8	0.7	1.8-3.5	3.5-35
(-)-**1**	9-Guanyl	0.7-1.7	0.3-0.7	0.7-1.7	18-35
(+)-**1**	9-Guanyl	88	88-176	88-177	>353
(-)-**2**	1-Cytosinyl	>411	≥411	>411	>411
(-)-**3**	5-(*E*)-Bromovinyl-1-uracilyl	>286	>286	286	>286
(-)-**4**	5-(*E*)-Iodovinyl-1-uracilyl	>252	>252	25-63	>252
Acyclovir	-	0.2-0.4	0.4-0.8	2-4	20-40

References and Notes:

1. Current address: Hybridon Incorporated, Worcester, Massachusetts.
2. Zahler, R.; Vite, G. D.; Goodfellow, V. S.; Ahmad, S. Eur. Pat. Appl. EP 458363.
3. Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997-7000.
4. Selman, S.; Squire, E. N.; U. S. Patents # US 3480603; US 3502732; US 3480603; US 3502732; Leonard, N. J.; Cruickshank, K. A. *J. Org. Chem.* **1985**, *50*, 2480-2488.
5. Attempts to purify and isolate the previously reported fluoroketene ethyl trimethylsilyl acetal,[6] generated via TMSCl trapping of the lithium enolate of ethyl fluoroacetate were unsuccessful.
6. Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720-4721.
7. Preparation of Chlorofluoroacetaldehyde Diethyl Acetal (**5**): A solution of DIBAL (1M in toluene, 780 mL, 780 mmol) was added at -78° to -75°C dropwise under argon to a stirred solution of ethyl chlorofluoroacetate (100 g, 709 mmol, PCR Incorporated) in 550 mL of dry toluene. The reaction mixture was stirred at that temperature for 30 minutes, then transferred via a cannula to a stirred solution of anhydrous HCl (230 g, 6.3 moles) in absolute ethanol (1000 mL) at -78°C. The mixture was allowed to warm to room temperature and subjected to fractional distillation using a vigreux column until ca. 1800 mL distillate had been collected. The remaining material was flash distilled (slowly increasing the vacuum from 150 mm to 0.1 mm until no more liquid remained in the pot) and collected separately. The flash distillate, containing **5** along with the corresponding hemiacetal, was combined with 25 mL ethanol and subjected to fractional distillation under atmospheric pressure affording the title compound (55 g, 45% yield) as a colorless liquid (boiling point 152-154°C). ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.94 (dd, J = 5.3, 50.4 Hz, 1H, H-CF), 4.59 (t, J = 5.28 Hz, 1H, H-C$(OEt)_2$), 3.73 (m, 4H), 1.26 (t, J = 7.04, 6H).

   Preparation of Fluoroketene Diethyl Acetal (**6**):[8] A solution of **5** (55.0 g, 321.6 mmol) in 50 mL dry THF was added dropwise at 0°C under argon to a stirred suspension of potassium t-butoxide (50.0 g, 445.6 mmol) in 250 mL THF. The reaction mixture was stirred at 35°C for 12 h, refluxed for 1 h (monitored by ^{1}H NMR), followed by fractional distillation using a vigreux column until 250 mL solvent had been collected. The remaining material was flash distilled (as above) and collected separately. The flash distillate was subjected to fractional distillation at atmospheric pressure affording the title compound (29.5 g, 68% yield) as a colorless liquid (boiling point 123-126°C). ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.35 (d, J = 77.4 Hz, 1H, H-CF=), 4.01 (q, J = 7.04 Hz, 2H), 3.73 (q, J = 7.04 Hz, 2H), 1.30 (t, J = 7.04 Hz, 3H), 1.26 (t, J = 7.04 Hz, 3H). ^{13}C NMR (270 MHz, $CDCl_3$) δ 151.77 (d, $J_{C\text{-}F}$ = 21.5 Hz, =C$(OEt)_2$), 124.54 (d, $J_{C\text{-}F}$ = 230.9 Hz, =CHF), 65.50, 65.02, 14.80, 14.34.
8. Hydrolysis of **6** affords ethyl fluoroacetate which is highly toxic (see The Merck Index for toxicity of fluoroacetic acid). It is recommended that this compound be handled with extreme care in a fume hood.
9. The (2R)-**8**:(2S)-**8** = 1:7 after treatment with DBU. The reaction was performed at low concentrations (6-10 mmol/1000 mL solvent) to avoid intermolecular condensation reactions.
10. a) Sung, W. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1089. b) Sung, W. L. *J. Org. Chem.* **1982**, *47*, 3623-3628.
11. a) Slusarchyk, W. A.; Bisacchi, G. S.; Field, A. K.; Hockstein, H. R.; Jacobs, G. A.; McGeever-Rubin, B.; Tino, J. T.; Tuomari, A. V.; Yamanaka, G. A.; Young, M. G.; Zahler, R. *J. Med. Chem* **1992**, *35*, 1799-1806. b) Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415-1421.