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Facile Access to 2'-*O*-Acyl Prodrugs of 1-(β-D-Arabinofuranosyl)-5(*E*)-(2-Bromovinyl)uracil (BVAraU) via Regioselective Esterase-Catalyzed Hydrolysis of 2',3',5'-Triesters[1]

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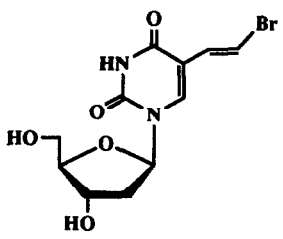
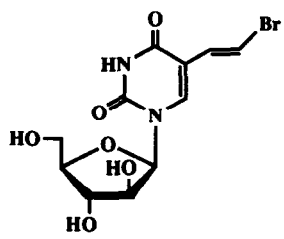
Key Words: 2'-*O*-Acyl, BVAraU, Pig liver esterase, Pyridinium bromide perbromide.

Abstract: Treatment of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-[2-(trimethylsilyl)-vinyl]uracil (**3**) with pyridinium bromide perbromide and deacetylation gave BVAraU (**2**). Pig liver esterase (EC 3.1.1.1) catalyzed the regioselective hydrolysis of 1-(2,3,5-tri-*O*-acyl-β-D-arabinofuranosyl)uracil derivatives to their 2'-*O*-acyl monoesters.

5(*E*)-(2-Bromovinyl)-2'-deoxyuridine (BVDU) (**1**) is a potent inhibitor of herpes simplex virus type 1 (HSV-1) and varicella zoster virus (VZV), and is clinically effective.[2] Unfortunately, therapeutic applications of this agent are limited by the enzymatic cleavage of the glycosyl bond. The arabinofuranosyl analogue (BVAraU) (**2**) undergoes very little glycosyl cleavage and exhibits potent and selective anti-HSV activity after analogous metabolic activation via 5'-phosphorylation by viral-encoded thymidine kinases in infected cells.[3] However, BVAraU is absorbed poorly from the gastrointestinal tract. Prolonged enhancement of serum drug levels has been noted with 5'-*O*-alkoxycarbonyl prodrugs of BVDU.[4] We now report further studies on the conversion of 5-[2-(trimethylsilyl)vinyl]uracil nucleosides into 5-(2-bromovinyl) products[5,6] and synthetic applications of pig liver esterase[7] (PLE) to provide a mild new synthesis of BVAraU and selected 2',3',5'-tri-*O*-acyl and 2'-*O*-acyl prodrugs.

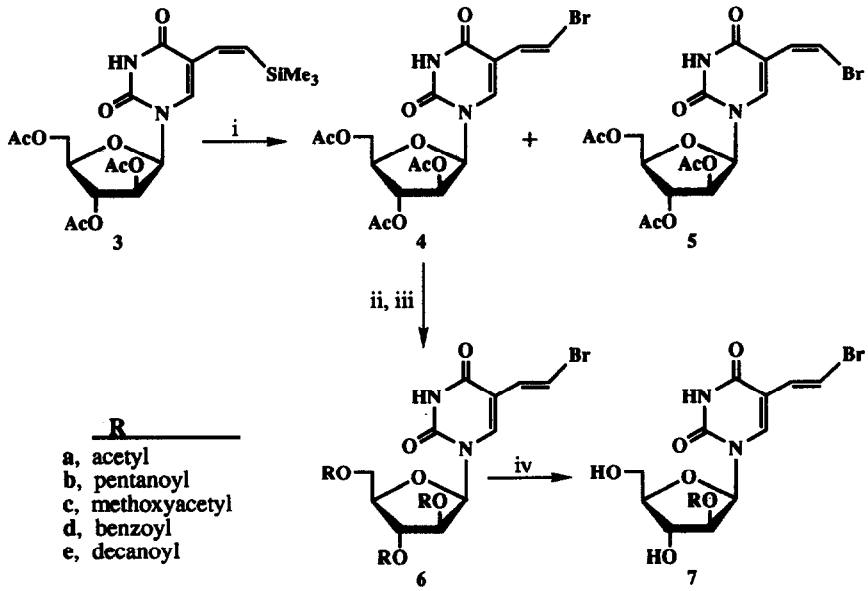


BVDU (1)



BVAraU (2)

Preparations of *E*- and *Z*-vinylsilanes and their stereospecific bromination have been noted. Treatment of 2-(trimethylsilyl)styrenes with bromine was reported to give bromostyrenes with retained stereochemistry in non-polar solvents.[8,9] Our electrophilic halogenations of 5-[2-(trimethylsilyl)vinyl]uracil nucleosides with metal halides and an oxidant preferentially gave the more thermodynamically stable *E* isomer in non-polar solvents. The *E/Z* ratios of our product vinyl halides were sensitive to the polarity of the reaction medium and the specific halogen rather than the stereochemistry of the precursor vinylsilane.[5,6] We now describe a mild new preparation of BVAraU with the convenient brominating system pyridinium bromide perbromide in dichloromethane. Higher *E/Z* ratios were obtained than in benzene, in which an unusual *Z* to *E* isomerization of *Z*-vinylsilane **3** occurred,[5,6] and *E/Z* product ratios ranged from 6:3 to 2:7 in acetonitrile, methanol, and methanol/water. Treatment of **3**[5,6] with pyridinium bromide perbromide/dichloromethane/0° C gave 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5(*E*)-(2-bromovinyl)uracil (**4**, 78%) plus *Z*-isomer **5** (12%).[10] Compound **4** was deacetylated with NH_3/MeOH to give BVAraU (**2**). Treatment of **2** with acyl chlorides in pyridine gave good yields of the 2',3',5-tri-*O*-acyl derivatives (**4**, **6b-e**).



(i) $C_5H_5N{\cdot}HBr_3$. (ii) NH_3/MeOH. (iii) R'COCl/C_5H_5N. (iv) Pig liver esterase/pH 7.4.

PLE is a convenient model for release of ester prodrugs by non-specific esterases.[11] Regioselective hydrolysis of the 2',3',5'-tri-*O*-acyl compounds **4**, **6b-e** occurred upon their exposure to commercial PLE[12] to

give the 2'-esters **7a-e** in high yields within 30-240 min (reaction times and yields were determined by HPLC: gradient, MeOH/H_2O). Similar results had been noted with 9-(2,3,5-tri-*O*-acyl-β-D-arabinofuranosyl)adenine esters and a cell-paste of *Bacillus subtilis*.[13]

The structures of the 2'-*O*-acyl derivatives **7a-e** were supported by ^1H NMR spectroscopy. Irradiation at the H1' resonances simplified the pseudo-triplets for H2' centered at δ ~5.3, whereas peaks in the region of δ 3.5-5.0 (H3',4',5',5") remained unchanged. Compound **7b** was synthesized independently by acylation of 3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxan-1,3-diyl)-BVAraU at O2' with pentanoyl chloride. Removal of the disiloxanyl group with ammonium fluoride in methanol[14] (NH_4F/MeOH) provided authentic **7b**.

Analogous regioselective hydrolyses of the 2',3',5'-tri-*O*-acetyl and 2',3',5'-tri-*O*-(*p*-toluyl) esters of AraU and the 2',3',5'-tri-*O*-acetyl esters of AraA and AraC were effected with PLE. In contrast, the 2',3',5'-tri-*O*-acetyl and 2',3',5'-tri-*O*-benzoyl esters of the ribonucleoside uridine underwent complete hydrolysis to uridine within 120 min. The markedly retarded rates of hydrolysis of the 2'-*O*-acyl esters of the arabinonucleosides suggest that they might function as slow-release lipophilic prodrugs with long serum lifetimes. The major initial metabolites of the 2',3',5'-tri-*O*-acyl esters **4**, **6b-e** would expected to be **7a-e**. Thus, selective esterase cleavage of **4**, **6b-e** should provide the secondary prodrugs **7a-e** which would have greater aqueous solubility than the triesters and more stable pharmacokinetic properties than the fully deprotected arabinonucleosides.

In summary, the preparation of BVAraU (**2**) from vinylsilane precursor **3** and pyridinium bromide perbromide proceeds readily in good yield. The facile preparation of a new class of 2'-*O*-acyl prodrugs (**7a-e**) of BVAraU via selective esterase-catalyzed hydrolysis of their triester precursors (**4**, **6b-e**) has been demonstrated. The commercial availability of pig liver esterase also makes this regioselective hydrolysis of arabinonucleoside triesters a synthetically attractive route to their 2'-*O*-acyl derivatives. Experimental details and biological studies will be reported elsewhere.

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References and Notes

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1. Presented in part at the "X° Convegno Nazionale della Divisione di Chimica Farmaceutica della S.C.I." *Poster Comm.*, Abstract p. 3. Siena. September 1991.
2. De Clercq, E.; Walker, R. T. *Pharmacol. Ther.* **1984**, *26*, 1-44.
3. Ayisi, N. K.; Wall, R. A.; Wanklin, R. J.; Machida, H.; De Clercq, E.; Sacks, S. L. *Mol. Pharmacol.*, **1987**, *31*, 422-429.
4. Boyd, M. R.; Cole, M.; Harnden, M. R.; Luk, K.; Rush, M. A.; Sutton, D.; Vere Hodge, R. A. *J. Antimicrob. Chemother.* **1986**, *18*, Suppl. B, 207-213.

5. Robins, M. J. and Manfredini, S. *Tetrahedron Lett.* **1990**, *31*, 5633-5636.

6. Robins, M. J.; Manfredini, S.; Wood, S. G.; Wanklin, R. J.; Rennie, B. A.; Sacks, S. L. *J. Med. Chem.* **1991**, *34*, 2275-2280.

7. Baraldi, P. G.; Manfredini, S.; Pollini, G. P.; Romagnoli, R.; Simoni, D.; Zanirato, V. *Tetrahedron Lett.* **1992**, *33*, 2871-2874.

8. a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin. 1983; pp. 82-83. b) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths Monographs in Chemistry and Chemical Engineering: London. 1981; pp. 62-76.

9. Koenig, K. E.; Weber, W. P. *Tetrahedron Lett.* **1973**, 2533-2536.

10. Pyridinium bromide perbromide (0.068 g, 0.21 mmol) was added to a stirred solution of **3** (0.10 g, 0.21 mmol) in dichloromethane (40 mL) at 0 °C and the mixture was allowed to warm to ambient temperature. After 15 min, TLC (silica plates predeveloped with triethylamine[6]) indicated the absence of starting **3**. The solution was washed (2% $NaHSO_3/H_2O$; H_2O), evaporated, and the residue was purified (preparative HPLC) to give **4** (78%) plus the *Z*-isomer[5] (**5**, 12%): ^1H NMR (200 MHz, $CDCl_3$) δ 6.69 & 7.41 (d, J = 13.5 Hz, 1 & 1 H, *E*-vinyl), 6.40 & 7.03 (d, J = 8.2 Hz, 1 & 1 H, *Z*-vinyl).

11. Kawaguchi, T.; Suzuki, Y.; Nambu, N.; Nagai T. *Chem. Pharm. Bull.* **1985**, *33*, 2956-2961.

12. Typical experimental conditions: compound **6b** (10 mg, 0.0166 mmol) was dissolved in EtOH (10 mL) and added with vigorous stirring to 500 mL of 0.1 M phosphate buffer (pH 7.4) solution at 37 °C. After 5 min, 200 units of pig liver esterase (PLE, Fluka, EC 3.1.1.1) were added and the reaction was monitored by HPLC (gradient, $MeOH/H_2O$). Selective hydrolysis was complete in 30 min [after 24 h, BVAraU (**2**) also was present (5-10%)]. The mixture was cooled at -78 °C, allowed to warm to room temperature, and filtered through a membrane filter (Millipore, 0.45 μm). Concentration in vacuo gave a residue that was purfied by semipreparative HPLC (gradient, $MeOH/H_2O$) to give **7b** (7 mg, 98%).
6b (oil): ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (m, 9 H), 1.2-1.7 (m, 12 H), 2.2-2.5 (m, J = 5.0 Hz, 6 H), 4.20 (m, 1 H, H4'), 4.32 (m, 1 H, H5'), 4.60 (dd, $J_{5''\text{-}4'}$ = 7 Hz, $J_{5''\text{-}5'}$ 12 Hz, 1 H, H5''), 5.05 (dd, $J_{2'\text{-}3'}$ = 1.6 Hz, $J_{3'\text{-}4'}$ = 5 Hz, 1 H, H3'), 5.43 (dd, $J_{1'\text{-}2'}$ = 3.6 Hz, 1 H, H2'), 6.29 (d, 1 H, H1'), 6.75 (d, J = 13.6 Hz, 1 H, vinyl), 7.46 (d, 1 H, vinyl), 7.60 (s, 1 H, H6), 10.00 (br s, 1 H, NH).
7b: mp 149-151 °C ($MeOH/Et_2O$); UV ($MeOH/H_2O$) max 250, 296 nm (ε 13 500, 9700), min 215, 271 nm (ε 3000, 5400); ^1H NMR (200 MHz, Me_2SO-d_6) δ 0.93 (t, J = 7 Hz, 3 H), 1.2-1.5 (m, 4 H), 2.25 (q, 2 H), 3.5-4.0 (m, 4 H, H3',4',5'), 5.00 (t, J = 2.2 Hz, 1 H, OH5'); 5.30 (pseudo-t, 1 H, H2'), 5.53 (d, J = 6 Hz, 1 H, OH3'), 6.26 (d, J = 5 Hz, 1 H, H1'), 6.67 (d, J = 13.6 Hz, 1 H, vinyl), 7.39 (d, 1 H, vinyl), 7.66 (s, 1 H, H6), 9.00 (br s, 1 H, NH). Anal. Calcd for $C_{16}H_{21}BrN_2O_7$: C, 44.36; H, 4.89; N, 6.47. Found: C, 44.38; H, 4.90; N, 6.47.

13. a) Baker, D. C.; Haskell, T. H.; Putt, S. R.; Sloan, B. J. *J. Med. Chem.* **1979**, *22*, 273-279; b) Baker, D. C.; Kumar, S. D.; Waites, W. J.; Arnett, G.; Shannon, W. M.; Higuchi, W. I.; Lambert, W. J. *J. Med. Chem.*, **1984**, *27*, 270-274.

14. Zhang, W. and Robins, M. J. *Tetrahedron Lett.*, **1992**, *33*, 1177-1180.

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