Synthesis, separation, and absolute configuration of the two 5-(2,2-dibromocyclopropyl) and four 5-(2-bromocyclopropyl) diastereomers of 2′-deoxyuridine

MANJU TANDON, LEONARD I. WIEBE, AND EDWARD E. KNAUS[1]

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta., Canada T6G 2N8

Received March 9, 1989

MANJU TANDON, LEONARD I. WIEBE, and EDWARD E. KNAUS. Can. J. Chem. **67**, 1484 (1989).

The reaction of 3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxy-5-vinyluridine (**2**) with dibromocarbene, generated from $PhHgCBr_3$ under thermal neutral conditions, yielded a mixture of the 5-[(1*S*)-2,2-dibromocyclopropyl]- (**3***a*) and 5-[(1*R*)-2,2-dibromocyclopropyl]-3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxy-5-vinyluridine (**4***a*) diastereomers, which were separated (1:1 ratio). Treatment of **3***a* and **4***a* with methanolic ammonia afforded the respective 5-[(1*S*)-2,2-dibromocyclopropyl]- (**3***b*) and 5-[(1*R*)-2,2-dibromocyclopropyl]-2′-deoxyuridines (**4***b*). The absolute configuration of **3***b* has been established by X-ray crystal structure determination. Monodebromination of **3***b*, using zinc dust in HOAc at 50°C, gave a mixture of the 5-[(1*S*,2*S*)-2-bromocyclopropyl]- (**5**) and 5-[(1*S*,2*R*)-2-bromocyclopropyl]- (**6**) diastereomers, which were separated and their respective configuration assigned by ^1H nuclear magnetic resonance. A similar monodebromination of **4***b* yielded the 5-[(1*R*,2*R*)-2-bromocyclopropyl]- (**7**) and 5-[(1*R*,2*S*)-2-bromocyclopropyl]-2′-deoxyuridine (**8**) diastereomers. Relationships between physicochemical properties, such as melting point and tlc R_f value, and the configuration of the chiral cyclopropyl carbon(s) were observed. The chemical shifts for the ^{13}C nuclear magnetic resonances are also of diagnostic value for determination of the respective configuration of the cyclopropyl carbons of the 5-(2-bromocyclopropyl) isomers **5–8**.

Key words: bromocyclopropanes, 2′-deoxyuridines, absolute configuration, antiviral activity.

MANJU TANDON, LEONARD I. WIEBE et EDWARD E. KNAUS. Can. J. Chem. **67**, 1484 (1989).

La réaction de la 3-*N*-3′,5′-di-*O*-tribenzoyl-2′-déoxy-5-vinyluridine (**2**) avec le dibromocarbène, préparé à partir du $PhHgCBr_3$ dans des conditions neutres et thermiques, conduit à un mélange des 5-[(1*S*)-2,2-dibromocyclopropyl]- (**3***a*) et 5-[(1*R*)-2,2-dibromocyclopropyl]-3-N-3′,5′-di-*O*-tribenzoyl-2′-déoxy-5-vinyluridines (**4***a*) diastéréomères qui ont été séparées (rapport 1:1). Les réactions des composés **3***a* et **4***a* avec de l'ammoniac en milieu méthanolique conduisent aux 5-[(1*S*)-2,2-dibromocyclopropyl]- (**3***b*) et 5-[(1*R*)-2,2-dibromocyclopropyl]-2′-déoxyuridines (**4***b*) respectives. On a déterminé la configuration absolue du composé **3***b* en procédant à une détermination de structure par diffraction des rayons-X. La monodébromation du produit **3***b*, réalisée à l'aide de poudre de zinc dans HOAc à 50°C, fournit un mélange des diastéréomères 5-[(1*S*,2*S*)-2-bromocyclopropyl]- (**5**) et 5-[(1*S*,2*R*)-2-bromocyclopropyl]- (**6**) que l'on a séparé et dont les configurations respectives ont été déterminées par résonance magnétique nucléaire du ^1H. Une monodébromation semblable réalisée sur le composé **4***b* fournit les 5-[(1*R*,2*R*)-2-bromocyclopropyl]- (**7**) et 5-[(1*R*,2*S*)-2-bromocyclopropyl]- 2′-déoxyuridines (**8**) diastéréomères. On a observé une corrélation entre les propriétés physicochimiques, comme les points de fusion et les valeurs des R_f des ccm, et les configurations des carbones chiraux des cyclopropyles. Les déplacements chimiques en résonance magnétique nucléaire du ^{13}C peuvent aussi être utilisés pour déterminer les configurations respectives des carbones du cyclopropyle des 5-(2-bromocyclopropyles) isomères **5–8**.

Mots clés : bromocyclopropanes, 2′-deoxyuridines, configuration absolue, activité antivirale.

[Traduit par la revue]

Introduction

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU) is a potent and selective antiviral agent against herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (1). BVDU is selectively phosphorylated by HSV-1 encoded thymidine kinase and metabolically trapped within infected cells, but not in uninfected host cells (2, 3). Structure–activity correlations for olefinic 5-substituted-2′-deoxyuridines indicated optimum inhibition of HSV-1 occurred when the C-5 substituent was unsaturated and conjugated with the pyrimidine ring, was not longer than four carbon atoms in length, had the *E* stereochemistry, and included a hydrophobic electronegative atom (4). It was anticipated that 2′-deoxyuridine possessing a 5-(2,2-dibromocyclopropyl) or 5-(2-bromocyclopropyl) substituent could serve as a biological isostere of the (*E*)-5-(2-bromovinyl) substituent present in BVDU. The hybridization of the cyclopropane bonds is considered to result in a higher electron density for the C—C bonds. Furthermore, the cyclopropyl moiety interacts with neighboring π-electron systems and *p*-electron centers similar to a vinyl group (5, 6).

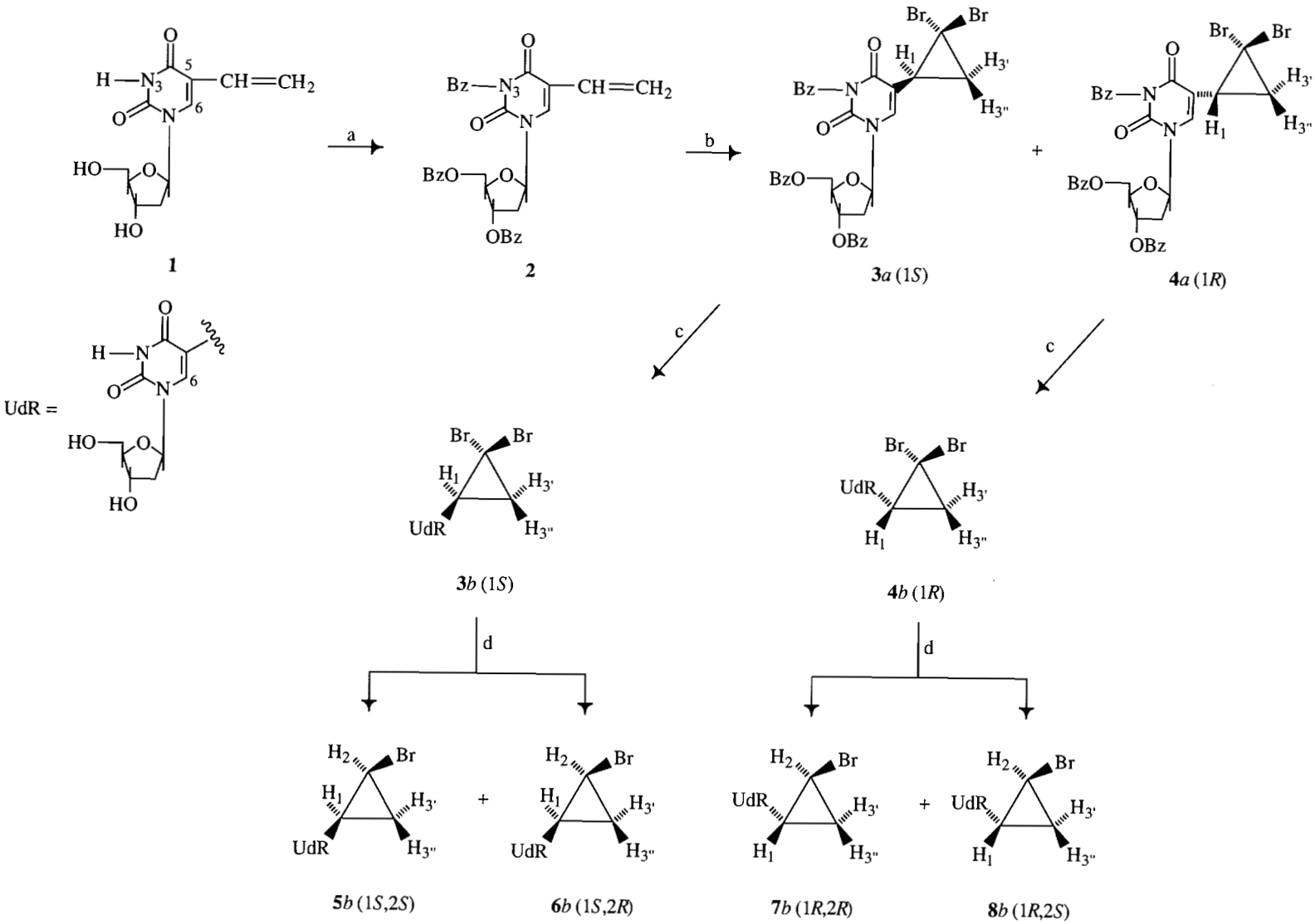
Acquisition of all dibromocyclopropyl and bromocyclopropyl diastereomers is required to determine the effect of cyclopropyl substituent stereochemistry upon antiviral activity. We now describe the synthesis, separation, and assignment of the absolute configuration for the 5-(2,2-dibromocyclopropyl) **3***b*–**4***b* and 5-(2-bromocyclopropyl) **5–8** derivatives of 2′-deoxyuridine.

Results and discussion

The 5-vinyl substituent of 5-vinyl-2′-deoxyuridine (**1**) is expected to be a poor substrate for dibromocarbene addition since it is conjugated with the 5,6-olefinic bond of the uracil ring. In an earlier study we reported that the reaction of (*E*)-5-(2-ethoxycarbonylvinyl)-3-methyl-2′-deoxyuridine with diazomethane yielded (*E*)-5-(2-ethoxycarbonylvinyl)-3-methyl-2′-deoxyuridine (7). Therefore, **1** was elaborated to 3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxy-5-vinyluridine (**2**) as illustrated in Scheme 1 (78% yield). Reaction of **2** with dichlorocarbene, generated from chloroform and sodium hydroxide in the presence of the phase transfer catalyst benzyltriethylammonium bromide, afforded 3-*N*-dichloromethyl-3′,5′-di-*O*-benzoyl-2′-deoxy-5-vinyluridine.[2] The latter result indicates that dibromocarbene must be generated under neutral conditions to preserve the integrity of the 3-*N*-benzoyl substituent. Thus, reaction of

[1]Author to whom correspondence may be addressed.

[2]E. E. Knaus, L. I. Wiebe, and M. Tandon. Unpublished results.



(a) PhCOCl, pyridine, $(i\text{-Pr})_2CHCH_2NH_2$; (b) $PhHgCBr_3$, dry benzene, 80 °C; (c) NH_3, MeOH, 25 °C; (d) Zn dust, HOAc, 50 °C

SCHEME 1

the Seyferth reagent (8) phenyl(tribromomethyl)mercury ($PhHgCBr_3$) with **2** in dry benzene at 80°C yielded a mixture of two diastereomers (**3***a* and **4***a*), which were separated by silica gel column chromatography (1:1 ratio, 63% total isolated yield). Removal of the protective benzoyl substituents from **3***a* and **4***a*, by treatment with methanolic ammonia, yielded 5-[(1*S*)-2,2-dibromocyclopropyl]-2′-deoxyuridine (**3***b*) and 5-[(1*R*)-2,2-dibromocyclopropyl]-2′-deoxyuridine (**4***b*) in 71 and 74% isolated yields, respectively.

The X-ray crystal structure of **3***b* indicated that the absolute configuration of the C-5 substituent was [(1*S*)-2,2-dibromocyclopropyl] (9). The bond lengths and angles for **3***b* are similar to those of 2′-deoxyuridine (10) and the 1,1-dibromocyclopropyl moiety (11, 12) in other compounds. The pyrimidine ring of **3***b* is *anti* with respect to the deoxyribose ring, and the latter ring system is in the 2′-*endo* conformation. Compound **4***b*, which is a diastereomer of **3***b*, must therefore have a 5-[(1*R*)-2,2-dibromocyclopropyl] substituent.

Monodebromination of the 5-[(1*S*)-2,2-dibromocyclopropyl] diastereomer (**3***b*), using zinc dust in glacial acetic acid, yielded a mixture of two diastereomers, which were separated by silica gel column chromatography. In this reaction a new chiral center is introduced at the C-2 position of the 5-(2-bromocyclopropyl) substituent. An ^1H nmr difference nOe spectrum was acquired for the more polar diastereomer (R_f 0.15, solvent system C). Irradiation of the cyclopropyl H-1 proton at δ 1.98 produced a 10.8% enhancement for the cyclopropyl H-2 proton at δ 3.34 and a 7.7% enhancement for the cyclopropyl H-3′ proton at δ 1.42. Therefore, the cyclopropyl H-1 and H-2, as well as H-1 and H-3′ protons, must be *cis* to each other. Since the configuration of this product at the cyclopropyl C-1 position must be *S*, it is therefore the 5-[(1*S*,2*S*)-2-bromocyclopropyl] diastereomer (**5**). A large number of spectra of substituted cyclopropane derivatives have been recorded. The magnitude of the vicinal coupling constant for J_{cis} is always larger than J_{trans} for any given pair of cyclopropyl stereoisomers (13). The vicinal coupling constants for the diastereomer **5** are in agreement with the assigned 1*S*,2*S* configuration where $J_{1,2}$ = 8.5 (*cis*), $J_{1,3''}$ = 6.8 (*trans*), $J_{1,3'}$ = 9.2 (*cis*), $J_{2,3''}$ = 4.4 (*trans*), and $J_{2,3'}$ = 8.5 Hz (*cis*). A long-range allylic coupling $J_{1,6}$ = 1.2 Hz was also observed. The configuration of the other diastereomer **6** (R_f 0.29, solvent system C) obtained in this reaction, which also must have the 1*S* configuration, was assigned on the magnitude of the vicinal coupling constants in the ^1H nmr spectrum that can be correlated with the geometrical arrangement of the cyclopropyl substituents. Diastereomer **6** has a 5-[(1*S*,2*R*)-2-bromocyclopropyl] substituent since it exhibited vicinal coupling constants $J_{1,2}$ = 4.3 (*trans*), $J_{1,3'}$ = 10.1 (*cis*), $J_{1,3''}$ = 6.8 (*trans*), $J_{2,3'}$ = 4.3 (*trans*), and $J_{2,3''}$ = 7.5 Hz (*cis*).

A similar monodebromination of the 5-[(1*R*)-2,2-dibromocyclopropyl] diastereomer **4***b* afforded a mixture of two diastereomers, which were separated by multiple development preparative tlc and then silica gel column chromatography of the enriched tlc fractions. The more polar diastereomer (R_f 0.27, solvent system C) possesses a 5-[(1*R*,2*R*)-2-bromocyclopropyl] substituent (**7**) since the ^1H nmr spectrum exhibited vicinal coupling constants $J_{1,2}$ = 7.1 (*cis*), $J_{1,3'}$ = 7.1 (*trans*), $J_{1,3''}$ = 9.1 (*cis*), $J_{2,3'}$ = 4.3 (*trans*), and $J_{2,3''}$ = 7.1 Hz (*cis*). The less polar diastereomer (R_f 0.32, solvent system C) has a 5-[(1*R*,2*S*)-2-bromocyclopropyl] substituent (**8**) since the ^1H nmr spectrum displayed vicinal coupling constants $J_{1,2}$ = 4.3 (*trans*), $J_{1,3'}$ = 6.8 (*trans*), $J_{1,3''}$ = 9.8 (*cis*), $J_{2,3'}$ = 7.5 (*cis*), and $J_{2,3''}$ = 4.3 (*trans*).

A number of relationships or correlations between physicochemical properties and nmr spectral data for the cyclopropyl hydrogens and carbons were observed, which, in conjunction with the magnitude of the vicinal coupling constants described previously, will be of value in assigning the configuration of the cyclopropyl chiral carbons(s) of **3***b*–**4***b* and **5**–**8** (see Table 1). Compounds having the 1*S* configuration exhibit higher melting points since 1*S* (**3***b*) > 1*R* (**4***b*); 1*S*,2*S* (**5**) > 1*R*,2*R* (**7**); and 1*S*,2*R* (**6**) > 1*R*,2*S* (**8**). Diastereomers having the same configuration at the C-1 and C-2 positions possess higher melting points since 1*S*,2*S* (**5**) > 1*S*,2*R* (**6**) and 1*R*,2*R* (**7**) > 1*R*,2*S* (**8**). Compounds having the 1*S* configuration are more polar as indicated by their relative R_f values since 1*S* (**3***b*) < 1*R* (**4***b*); 1*S*,2*S* (**5**) < 1*R*,2*R* (**7**); and 1*S*, 2*R* (**6**) < 1*R*,2*S* (**8**). Diastereomers having the same configuration at C-1 and C-2 are more polar as the R_f values of 1*S*,2*S* (**5**) < 1*S*,2*R* (**6**) and 1*R*,2*R* (**7**) < 1*R*,2*S* (**8**). Although the rotations are equal, but of opposite sign, **3***b* and **4***b*, **5** and **6**, and **7** and **8**, respectively, are not enantiomers. Since each set of these diastereomers differs in configuration at only one chiral center, each set of diastereomers can also be called epimers. Examination of the ^1H nmr spectral data for the cyclopropyl chemical shifts (Table 1) indicates that the bromine substituent shields the adjacent *cis* H-3 proton relative to the *trans* H-3 proton (**5**–**8**) and the H-2 proton is shielded by a *cis*-2′-deoxyuridine substituent (**6**, **8**) relative to the *trans* H-2 proton (**5**, **7**). These correlations are consistent with the fact that all substituents, including bromine, generally shield *cis* vicinal protons in a cyclopropyl ring system (13). The chemical shifts of the cyclopropyl carbons for the *cis* 1*S*,2*S* (**5**) and 1*R*,2*R* (**7**), as well as these for the *trans* 1*S*,2*R* (**6**) and 1*R*,2*S* (**8**), are very similar. In compounds **5** and **7**, where the 2′-deoxyuridine and bromo substituents are *cis*, C-1 is deshielded δ 3.4–4.3, C-2 is shielded δ 4.4–5.0, and C-3 is shielded δ 3.3–3.6 relative to the corresponding carbon atoms in the *trans* compounds **6** and **8**. These differences in ^{13}C chemical shifts provide a rapid method to distinguish the *cis* (1*S*,2*S*, 1*R*,2*R*) from the *trans* (1*S*,2*R*, 1*R*,2*S*) stereoisomers.

Biological and biochemical studies for **3***b*–**4***b* and **5**–**8** are now in progress and will be reported elsewhere.

Experimental

Melting points were determined on a Büchi capillary apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AM-300 spectrometer. Chemical shifts are given in ppm downfield from tetramethylsilane as internal standard. The ^1H nmr assignments were confirmed by double irradiation experiments. The ^{13}C nmr resonances were assigned by use of the *J* modulation technique to determine the number of attached hydrogens. Specific rotations were measured on an Optical Activity Ltd. digital polarimeter. Thin-layer chromatography (tlc) was performed using Whatman MK6F silica gel microslides (250 μm thickness). Preparative tlc was carried out using Whatman PLK5F plates (1 mm thickness). The tlc solvent systems employed were A: toluene:ethyl acetate (4:1 v/v), B: chloroform:methanol (9:1 v/v), C: ethyl acetate:*n*-propanol:water (41:10:20 v/v/v). This last solvent mixture was mixed thoroughly, allowed to separate, and the upper layer was used in all instances where solvent C is indicated. Column chromatography was carried out using Merck 7734 silica gel (100–200 μm particle size). Pyridine and benzene were distilled from CaH_2, and methanol was distilled from Mg / I_2, prior to use. $PhHgCBr_3$ (8) and 5-vinyl-2′-deoxyuridine (14) (Lit. (15) mp 230°C; found mp 228°C) were prepared according to the literature procedures. Abbreviation: cp = cyclopropyl.

3-N-3′,5′-Di-O′-tribenzoyl-2′-deoxy-5-vinyluridine (**2**)

Benzoyl chloride (0.65 g, 4.64 mmol) was added to a solution of **1**

TABLE 1. Some physical and nmr spectral data[a] for the cyclopropyl hydrogens and carbons

Compound	Configuration	Melting point (°C)	R_f	$[\alpha]_D^{23}$	δ (ppm)						
					H-1	H-2	H-3′	H-3″	C-1	C-2	C-3
3*b*	1*S*	180–185	0.40[b]	−80.8°	2.58	—	1.90	1.93	29.92	29.29	26.66
4*b*	1*R*	145–150	0.50[b]	+80.8°	2.67	—	2.02	1.98	29.83	29.95	26.48
5	1*S*, 2*S*	171–172	0.15[c]	+65.0°	1.98	3.34	1.42	1.14	23.89	15.90	13.36
6	1*S*, 2*R*	116–118	0.29[c]	−62.5°	2.14	3.10	1.24	1.44	20.33[d]	20.48[d]	16.68
7	1*R*, 2*R*	126–128	0.27[c]	−65.0°	2.00	3.40	1.10	1.44	24.65	15.82	13.18
8	1*R*, 2*S*	113–115	0.32[c]	+62.5°	2.14	3.10	1.46	1.24	20.36[d]	20.81[d]	16.77

[a]Chemical shifts are in parts per million with respect to $S_{TMS} = 0$.
[b]Solvent system B.
[c]Solvent system C.
[d]The chemical shifts of C-1 and C-2 may be interchanged.

(0.56 g, 2.2 mmol) in dry pyridine (25 mL) at 0–5°C with stirring. The reaction mixture was allowed to warm to 25°C and then maintained at this temperature for 2 h. The reaction mixture was cooled to 0–5°C and then diisopropylethylamine (0.43 g, 3.3 mmol) and benzoyl chloride (0.33 g, 2.32 mmol) were added. The reaction mixture was warmed to 25°C and the mixture was stirred for 12 h. Ice-water (25 mL) was added and the solvent was removed *in vacuo*. Two consecutive extractions of the residue with a chloroform:water mixtue (3:1 v / v, 40 mL), washing the chloroform extract in succession with cold 5% aqueous HCl (10 mL), 5% aqueous $NaHCO_3$ (10 mL), cold water (2 × 15 mL), drying the chloroform extract (Na_2SO_4), filtration, and removal of the solvent *in vacuo* yielded impure **2**. Purification on a silica gel column using toluene:ethyl acetate (19:1 v / v) as eluant gave **2**: 0.973 g, 77.6%; mp 245°C; R_f 0.58 (solvent system A); ^{1}H nmr ($CDCl_3$) δ: 2.44 (ddd, J_{gem} = 13.7, $J_{1',2'}$ = 8.7, $J_{2',3'}$ = 6.6 Hz, 1H, H-2′), 2.88 (ddd, J_{gem} = 13.7, $J_{1',2'}$ = 5.0, $J_{2',3'}$ = 1.5 Hz, 1H, H-2′), 4.68 (m, 1H, H-4′), 4.76–4.98 (m, 2H, H-5′), 5.18 (dd, J = 11.1, 1.7 Hz, 1H, —CH=C*H*H), 5.74 (m, 1H, H-3′), 5.92 (dd, J = 17.2, 1.7 Hz, 1H, —CH=CH*H*), 6.16 (dd, J = 17.2, J = 11.1 Hz, 1H, —*CH*=CHH), 6.54 (dd, $J_{1',2'}$ = 8.7, J = 5.0 Hz, 1H, H-1′), 7.52–8.20 (m, 16H, phenyl hydrogens, H-6).

*5-[(1S)-2,2-Dibromocyclopropyl]-3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxyuridine* (**3***a*) *and 5-[(1R)-2,2-dibromocyclopropyl]-3-*N*-3′,5′-di-*O*-tribenzoyl-2′-deoxyuridine* (**4***a*)

Phenyl(tribromomethyl)mercury (1.96 g, 3.7 mmol) was added to a solution of **2** (2.1 g, 3.7 mmol) in dry benzene (50 mL) under a nitrogen atmosphere with stirring and the reaction mixture was heated at reflux for 2 h. Additional aliquots of $PhHgCBr_3$ (1.96 g, 3.7 mmol) were added to the reaction mixture at 2, 4, and 6 h respectively, after initiation of the reaction, which was allowed to proceed for 9 h in total reaction time. The reaction mixture was cooled to 25°C and the PhHgBr, which precipitated during the reaction, was removed by filtration. Removal of the solvent *in vacuo* gave a mixture of **3***a* and **4***a*, which were separated by silica gel column chromatography using a solvent gradient starting with toluene and ending with toluene:ethyl acetate (19:1 v / v). The two diastereomers **3***a* and **4***a* were obtained in a ratio of 1:1 (0.86 g each, 62.8% combined chemical yield) as foams: **3***a*, R_f 0.54 (solvent system A); mp 220°C; ^{1}H nmr ($CDCl_3$) δ: 1.56 (dd, $J_{3',3''}$ = 11.0, $J_{1,3'}$ = 9.1 Hz, 1H, cp H-3′), 1.61 (dd, $J_{3',3''}$ = 11.0, $J_{1,3''}$ = 8.1 Hz, 1H, cp H-3″), 2.28 (ddd, J_{gem} = 13.5, $J_{1',2'}$ = 8.6, $J_{2',3'}$ = 6.6 Hz, 1H, H-2′), 2.44 (ddd, $J_{1,3'}$ = 9.1, $J_{1,3''}$ = 8.1, $J_{1,6}$ = 1.34 Hz, 1H, cp H-1), 2.78 (dd, J_{gem} = 13.5, $J_{1',2'}$ = 5.0 Hz, 1H, H-2′), 4.52 (m, 1H, H-4′), 4.64–4.8 (m, 2H, H-5′), 5.56 (d, $J_{2',3'}$ = 6.6 Hz, 1H, H-3′), 6.34 (dd, $J_{1',2'}$ = 8.6 and 5.0 Hz, 1H, H-1′), 7.32–8.04 (m, 16H, phenyl hydrogens, H-6).

4*a*: R_f 0.63 (solvent system A); mp 228°C; ^{1}H nmr ($CDCl_3$) δ: 1.46 (t, $J_{3',3''}$ = 8.1, $J_{1,3'}$ = 8.1 Hz, 1H, cp H-3′), 1.73 (dd, $J_{1,3''}$ = 10.1, $J_{3',3''}$ = 8.1 Hz, 1H, cp H-3″), 2.22 (ddd, J_{gem} = 13.5, $J_{1',2'}$ = 8.6, $J_{2',3'}$ = 6.6 Hz, 1H, H-2′), 2.52 (dd, $J_{1,3''}$ = 10.1, $J_{1,3'}$ = 8.1 Hz, 1H, cp H-1), 2.74 (dd, J_{gem} = 13.5, $J_{1',2'}$ = 4.8 Hz, 1H, H-2′), 4.48 (m, 1H, H-4′), 4.58–4.78 (m, 2H, H-5′), 5.56 (d, $J_{2',3'}$ = 6.6 Hz, 1H, H-3′), 6.34 (dd, $J_{1',2'}$ = 8.6, $J_{1',2'}$ = 4.8 Hz, 1H, H-1′), 7.3–8.06 (m, 16H, phenyl hydrogens, H-6).

5[(1S)-2,2-Dibromocyclopropyl]-2′-deoxyuridine (**3***b*)

A solution of **3***a* (0.50 g, 0.68 mmol) in a saturated solution of ammonia in methanol (15 mL) was stirred at 25°C for 15 h. Removal of the solvent *in vacuo* yielded a residue, which was purified by silica gel column chromatography using $CHCl_3$:MeOH (19:1 v / v) as eluant to afford **3***b*: 0.205 g, 71%; R_f 0.40 (solvent system B); mp 180–185°C (dec.) after recrystallization from chloroform:methanol; $[\alpha]_D^{23}$ −80.8° (*c* 0.74, MeOH); ^{1}H nmr (CD_3OD) δ: 1.90 (dd, $J_{3',3''}$ = 15.5, $J_{1,3'}$ = 10.0 Hz, 1H, cp H-3′), 1.93 (dd, $J_{3',3''}$ = 15.5, $J_{1,3''}$ = 8.5 Hz, 1H, cp H-3″), 2.18 (m, 2H, H-2′), 2.58 (ddd, $J_{1,3'}$ = 10.0, $J_{1,3''}$ = 8.5, $J_{1,6}$ = 1.33 Hz, 1H, cp H-1), 3.70 (m, 2H, H-5′), 3.86 (m, 1H, H-4′), 4.34 (m, 1H, H-3′), 6.22 (t, $J_{1',2'}$ = 6.1 Hz, 1H, H-1′), 7.96 (d, $J_{1,6}$ = 1.33 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 26.7 (cp C-3), 29.3 (cp C-2), 29.9 (cp C-1), 41.7 (C-2′), 62.6 (C-5′), 72.2 (C-3′), 86.8 (C-1′), 89.1 (C-4′), 112.9 (C-5), 140.8 (C-6), 152.8 (C-2), 165.5 (C-4). *Anal.* calcd. for $C_{12}H_{14}Br_2N_2O_5$: C 33.82, H 3.31, N 6.57; found: C 33.61, H 3.37, N 6.41.

5-[(1R)-2,2-Dibromocyclopropyl]-2′-deoxyuridine (**4***b*)

Treatment of **3***b* with a saturated solution of ammonia in methanol, as described for **3***a* above, gave **4***b*: 0.215 g, 74.5%; R_f 0.50 (solvent system B); mp 145–150°C (dec.) after recrystallization from chloroform:methanol; $[\alpha]_D^{23}$ +80.8° (*c* 0.74, MeOH); ^{1}H nmr (CD_3OD) δ: 1.98 (dd, $J_{1,3''}$ = 10.5, $J_{3',3''}$ = 10.0 Hz, 1H, cp H-3″), 2.02 (dd, $J_{3',3''}$ = 10.0, $J_{1,3'}$ = 8.6 Hz, 1H, cp H-3′), 2.13 (ddd, J_{gem} = 12.7, $J_{1',2'}$ = 6.35, $J_{2',3'}$ = 5.5 Hz, 1H, H-2′), 2.28 (ddd, J_{gem} = 12.7, $J_{1',2'}$ = 6.35, $J_{2',3'}$ = 3.9 Hz, 1H, H-2′), 2.67 (ddd, $J_{1,3''}$ = 10.5, $J_{1,3'}$ = 8.6, $J_{1,6}$ = 1.34, 1H, cp H-1), 3.75 (dd, J_{gem} = 12.4, $J_{4',5'}$ = 3.3 Hz, 1H, H-5′), 3.84 (dd, J_{gem} = 12.4, $J_{4',5'}$ = 3.3 Hz, 1H, H-5′), 3.93 (m, 1H, H-4′), 4.37 (m, 1H, H-3′), 6.28 (t, $J_{1',2'}$ = 6.35 Hz, 1H, H-1′), 8.05 (d, $J_{1,6}$ = 1.34 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 26.48 (cp C-3), 29.83 (cp C-1), 29.95 (cp C-2), 42.22 (C-2′), 62.38 (C-5′), 71.73 (C-3′), 86.77 (C-1′), 89.13 (C-4′), 112.82 (C-5), 140.35 (C-6), 151.79 (C-2), 163.20 (C-4). *Anal.* calcd. for $C_{12}H_{14}Br_2N_2O_5$: C 33.82, H 3.31, N 6.57; found: C 34.17, H 3.19, N 6.67.

5-[(1S,2S)-2-Bromocyclopropyl]-2′-deoxyuridine (**5**) *and 5-[(1S,2R)-2-bromocyclopropyl]-2′-deoxyuridine* (**6**)

Zinc dust (0.46 g, 7.0 mmol) was added in aliquots over a 5 h period to a stirred solution of **3***b* (0.2 g, 0.47 mmol) in glacial acetic acid (5 mL) at 50°C. The reaction, which was monitored by tlc, was complete in 5 h. The reaction mixture was cooled to 25°C, filtered, and the filtercake was washed with glacial acetic acid (3 mL). Removal of the solvent from the combined filtrates *in vacuo* gave a residue that was purified on a silica gel column using ethyl acetate:*n*-propanol:water (700:1:2 v / v / v, upper layer) as eluant. This separation provided enriched fractions containing predominantly **5** and **6**, respectively. Each enriched fraction **5** and **6** was individually separated on a silica gel

column using chloroform:methanol (95:5 v/v) as eluant to yield the two separate diastereomers **5** and **6**: yield **5**, 53 mg, 32.5%; R_f 0.15 (solvent system C, upper layer); mp 171–172°C; $[\alpha]_D^{23}$ +65.0° (*c* 0.61, MeOH); ^{1}H nmr (CD_3OD) δ: 1.14 (dt, $J_{1,3''}$ = 6.8, $J_{3',3''}$ = 6.8, $J_{2,3''}$ = 4.4 Hz, $W_{\frac{1}{2}}$ = 21.7 Hz, 1H, cp H-3″), 1.42 (dt, $J_{1,3'}$ = 9.2, $J_{2,3'}$ = 8.5, $J_{3',3''}$ = 6.8 Hz, $W_{\frac{1}{2}}$ = 24.5 Hz, 1H, cp H-3′), 1.98 (dq, $J_{1,3'}$ = 9.2, $J_{1,2}$ = 8.5, $J_{1,3''}$ = 6.8, $J_{1,6}$ = 1.2 Hz, $W_{\frac{1}{2}}$ = 24.4 Hz, 1H, cp H-1), 2.24 (m, 1H, H-2′), 3.34 (dt, $J_{1,2}$ = 8.5, $J_{2,3'}$ = 8.5, $J_{2,3''}$ = 4.4 Hz, 1H, cp H-2, partially overlapped with CD_3OD), 3.74 (dd, *J* = 12.4, 3.5 Hz, 1H, H-5′), 3.80 (dd, *J* = 12.4, 3.1 Hz, 1H, H-5′), 3.96 (m, 1H, H-4′), 4.4 (m, 1H, H-3′), 6.3 (t, $J_{1',2'}$ = 6.7 Hz, 1H, H-1′), 8.0 (d, $J_{1,6}$ = 1.2 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 13.36 (cp C-3), 15.90 (cp C-2), 23.89 (cp C-1), 41.57 (C-2′), 62.76 (C-5′), 72.30 (C-3′), 86.68 (C-1′), 89.04 (C-4′), 113.16 (C-5), 140.41 (C-6), 152.03 (C-2), 166.17 (C-4). *Anal.* calcd. for $C_{12}H_{15}BrN_2O_5$: C 41.51, H 4.35, N 8.07; found: C 41.72, H 4.62, N 8.09.

Diastereomer **6**: yield 47 mg, 28.8%; R_f 0.29 (solvent system C, upper layer); mp 116–118°C; $[\alpha]_D^{23}$ −62.5° (*c* 0.4, MeOH); ^{1}H nmr (CD_3OD) δ: 1.24 (octet, $J_{1,3'}$ = 10.1, $J_{3',3''}$ = 6.8, $J_{2,3'}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 18.5 Hz, 1H, cp H-3′), 1.44 (q, $J_{2,3''}$ = 7.5, $J_{3',3''}$ = 6.8, $J_{1,3''}$ = 6.8 Hz, $W_{\frac{1}{2}}$ = 21.8 Hz, 1H, cp H-3″), 2.14 (septet, $J_{1,3'}$ = 10.1, $J_{1,3''}$ = 6.8, $J_{1,2}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 22.5 Hz, 1H, cp H-1), 2.24 (m, 2H, H-2′), 3.1 (quintet, $J_{2,3''}$ = 7.5, $J_{2,3'}$ = 4.3, $J_{1,2}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 17.7 Hz, 1H, cp H-2), 3.78 (m, 2H, H-5′), 3.92 (m, 1H, H-4′), 4.4 (m, 1H, H-3′), 6.26 (t, $J_{1',2'}$ = 6.5 Hz, 1H, H-1′), 7.84 (d, $J_{1,6}$ = 1.14 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 16.68 (cp C-3), 20.33 and 20.84 (cp C-1 and cp C-2), 41.54 (C-2′), 62.45 (C-5′), 71.85 (C-3′), 86.59 (C-1′), 88.93 (C-4′), 114.30 (C-5), 137.57 (C-6), 151.83 (C-2), 165.39 (C-4). *Anal.* calcd. for $C_{12}H_{15}BrN_2O_5$: C 41.51, H 4.35, N 8.07; found: C 41.72, H 4.62, N 8.09.

5-[(1R,2R)-2-Bromocyclopropyl]-2′-deoxyuridine (7) and 5-(1R,2S)-2-bromocyclopropyl]-2′-deoxyuridine (8)

Reaction of **4***b* (0.2 g, 0.47 mmol) with zinc dust, using the same procedure described for the monodebromination of **3***b* above, gave a mixture of diastereomers **7** and **8**. This mixture was subjected to multiple development preparative tlc on Whatman PLK5F plates, 1.0 mm in thickness, using solvent system C (upper layer) as the development solvent. This separation provided enriched fractions containing predominantly **7** and **8**, respectively. Each one of these enriched fractions was enriched further by silica gel column chromatography using ethyl acetate:*n*-propanol:water (700:1:2 v/v/v, upper layer) as eluant. Further separation on a silica gel column using chloroform: methanol (19:1 v/v) as eluant yielded the two diastereomers **7** and **8**, respectively: yield **7**, 54 mg, 33.1%; R_f 0.27 (solvent system C, upper layer); mp 126–128°C (dec.); $[\alpha]_D^{23}$ −65.0° (*c* 0.61, MeOH); ^{1}H nmr (D_2O, solvent suppression) δ: 1.1 (dt, $J_{1,3'}$ = 7.1, $J_{3',3''}$ = 6.8, $J_{2,3'}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 21.0 Hz, 1H, cp H-3′), 1.44 (dt, $J_{1,3''}$ = 9.1, $J_{2,3''}$ = 7.1, $J_{3',3''}$ = 6.8 Hz, $W_{\frac{1}{2}}$ = 23.2 Hz, 1H, cp H-3″), 2.0 (dq, $J_{1,3''}$ = 9.1, $J_{1,2}$ = 7.1, $J_{1,3'}$ = 7.1, $J_{1,6}$ = 1.3 Hz, $W_{\frac{1}{2}}$ = 26.4 Hz, 1H, cp H-1), 2.38 (m, 2H, H-2′), 3.40 (dt, $J_{1,2}$ = 7.1, $J_{2,3''}$ = 7.1, $J_{2,3'}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 19.6 Hz, 1H, cp H-2), 3.74 (m, 2H, H-5′), 4.06 (m, 1H, H-4′), 4.45 (m, 1H, H-3′), 6.31 (t, $J_{1',2'}$ = 6.3 Hz, 1H, H-1′), 7.85 (d, $J_{1,6}$ = 1.3 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 13.18 (cp C-3), 15.82 (cp C-2), 24.65 (cp C-1), 41.99 (C-2′), 62.45 (C-5′), 71.94 (C-3′), 86.61 (C-1′), 89.11 (C-4′), 113.16 (C-5), 139.72 (C-6), 151.98 (C-2), 166.14 (C-4). *Anal.* calcd. for $C_{12}H_{15}BrN_2O_5$: C 41.51, H 4.35, N 8.07; found: C 41.68, H 4.64, N 7.95.

Diastereomer **8**: yield 60 mg, 36.8%; R_f 0.32 (solvent system C, upper layer); mp 113–115°C (dec.); $[\alpha]_D^{23}$ +62.5° (*c* 0.4, MeOH); ^{1}H nmr (CD_3OD) δ: 1.24 (octet, $J_{1,3''}$ = 9.8, $J_{3',3'}$ = 6.8, $J_{2,3''}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 22.6 Hz, 1H, cp H-3″), 1.46 (q, $J_{2,3'}$ = 7.5, $J_{1,3'}$ = 6.8, $J_{3',3''}$ = 6.8 Hz, $W_{\frac{1}{2}}$ = 21.7 Hz, 1H, cp H-3′), 2.14 (septet, $J_{1,3''}$ = 9.8, $J_{1,3'}$ = 6.8, $J_{1,2}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 22.8 Hz, 1H, cp H-1), 2.24 (m, 2H, H-2′), 3.1 (quintet, $J_{2,3'}$ = 7.5, $J_{2,3''}$ = 4.3, $J_{1,2}$ = 4.3 Hz, $W_{\frac{1}{2}}$ = 17.5 Hz, 1H, cp H-2), 3.75 (m, 2H, H-5′), 3.92 (m, 1H, H-4′), 4.4 (m, 1H, H-3′), 6.26 (t, *J* = 6.4 Hz, 1H, H-1′), 7.88 (d, $J_{1,6}$ = 1.1 Hz, 1H, H-6); ^{13}C nmr (CD_3OD) δ: 16.77 (cp C-3), 20.36 and 20.81 (cp C-1 and cp C-2), 41.64 (C-2′), 62.51 (C-5′), 71.88 (C-3′), 86.68 (C-1′), 89.01 (C-4′), 114.11 (C-5), 137.56 (C-6), 151.85 (C-2), 165.42 (C-4). *Anal.* calcd. for $C_{12}H_{15}BrN_2O_5$: C 41.51, H 4.35, N 8.07; found: C 41.50, H 4.18, N 7.68.

Acknowledgements

We are grateful to the Medical Research Council of Canada (Grant No. MT-5965) for financial support of this research and to the Alberta Heritage Foundation for Medical Research for a Fellowship to one of us (M.T.).

1. A. S. Jones, J. R. Sayers, R. T. Walker, and E. De Clercq. J. Med. Chem. **31**, 268 (1988).
2. Y. C. Cheng, G. Dutschman, J. J. Fox, K. A. Watanabe, and H. Machida. Antimicrob. Agents Chemother. **20**, 420 (1981).
3. E. De Clercq, J. Descamps, P. De Somer, P. J. Barr, A. S. Jones, and R. T. Walker. Proc. Natl. Acad. Sci (USA), **76**, 2947 (1979).
4. J. Goodchild, R. A. Porter, R. H. Raper, I. S. Sim, R. M. Upton, J. Viney, and H. J. Wadsworth. J. Med. Chem. **26**, 1252 (1983).
5. A. De Meijere. Angew. Chem. Int. Ed. Engl. **18**, 809 (1979).
6. P. G. Gassman. Chem. Commun. 793 (1967).
7. M. Tandon, T. Iwashina, L. Xu, E. Knaus, L. Wiebe, D. Tovell, and D. Tyrrell. Biochem. Arch. **4**, 131 (1988).
8. D. Seyferth and R. L. Lambert. J. Organometal. Chem. **16**, 21 (1969).
9. S. A. Moore, B. D. Santarsiero, T. Lin, M. N. G. James, M. Tandon, L. I. Wiebe, and E. E. Knaus. Acta Crystallogr. Sect. C: Cryst. Struct. Commun. **45**, 647 (1989).
10. E. A. Green, R. D. Rosenstein, R. Shiono, D. J. Abraham, B. L. Trus, and R. E. Marsh. Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem. **B31**, 102 (1975).
11. J. W. Lauher and J. A. Ibers. J. Am. Chem. Soc. **97**, 561 (1975).
12. M. E. Jason and J. A. Ibers. J. Am. Chem. Soc. **99**, 6012 (1977).
13. L. M. Jackman and S. Sternhell. Applications of nuclear magnetic resonance spectrometry in organic chemistry. 2nd ed. Pergamon Press, Toronto. 1969. pp. 228–229 and 286.
14. S. G. Rahim, M. J. H. Duggan, R. T. Walker, A. S. Jones, R. L. Dyer, J. Balzarini, and E. De Clercq. Nucleic Acids Res. **10**, 5285 (1982).
15. R. A. Sharma and M. Bobek. J. Org. Chem. **40**, 2377 (1975).