Synthesis, Anti-HBV, and Anti-HIV Activities of 3'-Halogenated Bis(hydroxymethyl)-cyclopentenyladenines

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Supporting Information

ABSTRACT: Synthesis of 3'-halogeno analogues (**5a–d**) of 9-[c-4,*t*-5-bis(hydroxymethyl)-cyclopent-2-en-*r*-1-yl]-9*H*-adenine (BCA, **3**) was accomplished by means of dual utilization of the vinyl sulfone functional moieties in both **10** and **16** utilizing a S_N2' conjugate-addition reaction and a sulfur-extrusive stannylation, respectively. Evaluation of the antiviral activities of **5a–d** revealed that introduction of a halogeno-substituent into the 3'-position of (–)-BCA diminished its anti-HIV-1 activity but increased the inhibitory activity for the reverse transcriptase of HBV in that the 3'-fluorinated BCA **5d** exhibited the highest activity without significant cytotoxicity.

KEYWORDS: Carbocyclic nucleosides, halogeno-substituent, anti-HBV

Since the discovery of carbovir (**1**)^{1,2} and its prodrug abacavir (**2**),³ anti-HIV agents, carbocyclic nucleosides have been recognized as an important class of antiviral agents (Figure 1). In 1992, a novel anti-HIV active carbocyclic nucleoside, (±)-9-[c-4,*t*-5-bis(hydroxymethyl)-cyclopent-2-en-*r*-1-yl]-9*H*-adenine (BCA) (**3**)^{4–9} emerged as a hybrid derivative of **1** and carbocyclic oxetanocin (COXT, **4**)^{10–12}

Figure 1. Structure of **1–5**.

Asymmetric synthetic studies of BCA revealed that the depicted (–)-enantiomer of **3** is the active stereoisomer.^{8,9} Although **3** shows promising anti-HIV activity, only one study concerning structure–activity relationships has been reported. Thus, 4'-branched derivatives have been synthesized on the basis of intramolecular S_H2' cyclization.¹³ With a view to expanding the medicinal chemistry of BCA, we have extended the studies toward the preparation of 3'-halogenated BCA analogues (**5**). We were particularly intrigued by the possibility of exploiting the mildness and wide scope of vinyl stannanes to elaborate a wide range of alkenes. In this Letter we describe the development of synthetic methods for the novel BCA derivatives **5** by utilizing vinyl stannane chemistry. In this study, we have found that **5a–d** exhibited selective inhibitory activity against the reverse transcriptase (RT) of HBV.

The retrosynthetic analysis for the target **5** is illustrated in Scheme 1. The vinylstannane **A** was selected as a key precursor for the synthesis of **5** because of its versatility as a synthon for synthesizing a variety of substituted alkenes. The key precursor

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Scheme 1. Retrosynthetic Analysis

A would be prepared from the vinyl sulfone B through radical-mediated sulfur-extrusive stannylation reaction^{14–20} and introduction of adenine base by an $\text{S}_{\text{N}}2$ manner. For preparing B, we selected vinyl sulfone C as substrate. $\text{S}_{\text{N}}2'$ -addition elimination reaction of C with hydroxymethyl synthon $\text{Pg}^2\text{OCH}_2\text{Li}$ would proceed efficiently, assisted by the electron withdrawing PhSO_2 group, to give B via resonance-stabilized carbanion D in which the β' -dioxolanyl structure acts as a good leaving group to release its ring strain.

Initially, preparation of cyclopentenyl phenylsulfone 10 was examined (Scheme 2). Cyclopentenone 6, prepared from D-

Scheme 2. Preparation of Vinyl Phenylsulfone 10

ribose according to the literature procedure,²¹ was converted to mesylate 7 by the following three step sequence: (1) hydrogenation of the double bond using 10% Pd/C, (2) NaBH_4 reduction of the resulting ketone, and (3) mesylation of the formed secondary alcohol. Treatment of 7 with sodium thiophenolate (NaSPh) in refluxing MeCN gave sulfide 8 in 95% isolated yield. The sulfide 8 was oxidized to the corresponding sulfoxide with $m\text{-CPBA}$ and subsequent Pummerer-type dehydrogenation of the sulfoxide by treatment with $(\text{F}_3\text{CCO})_2\text{O}$ /pyridine gave vinyl sulfide 9. Finally, the sulfide 9 was converted to the desired 10 in 99% yield.

We next examined PhSO_2 -assisted $\text{S}_{\text{N}}2'$ β -addition–elimination reaction^{22–28} of 10 with organolithium species as carbon nucleophiles for introducing the 4'- β -hydroxymethyl unit of the target molecule 5, and the results are shown in Table 1. Initially, reaction with methoxymethyl-protected hydroxymethyl lithium (MOMOCH_2Li) was examined

Table 1. Reaction of Vinylsulfone 10 with Organolithium Reagents

entry	R (equiv)	yield [%] of 11	yield [%] of 11
1	$\text{CH}_2\text{OCH}_2\text{OCH}_3$ (1.2)	18	23
2	$\text{CH}_2\text{OCH}_2\text{OCH}_3$ (2.4)	18	36
3	$\text{CH}_2\text{OCH}_2\text{OCH}_3$ (3.0)	27	43
4	CH_2OBn (3.0)	10	17
5	$\text{CH}_2\text{O}t\text{-Bu}$ (3.0)	13	66
6	$(E)\text{-CH=CHPh}$ (3.0)	72	
7	CH=CH_2 (3.0)	81	

(entry 1). When 10 was treated with MOMOCH_2Li prepared *in situ* from $\text{MOMOCH}_2\text{SnBu}_3$ and $n\text{-BuLi}$ at -80°C in THF,^{29–31} the main pathway of the reaction was an unexpected substitution of the PhSO_2 group via an α -addition–elimination mechanism to give 12a (23% isolated yield). The desired $\text{S}_{\text{N}}2'$ product 11a was obtained in 18% yield as a single stereoisomer (entry 1). The β -configuration of the introduced carbon substituent in 11a was confirmed by NOE experiments (see Supporting Information). The stereochemical outcome is rationalized by a steric repulsion exerted by the sterically encumbered TBDPSOCH_2 group at the neighboring γ -position. Similar results were observed when the reaction was carried out by increasing the amount of MOMOCH_2Li (entries 2 and 3). To improve the isolated yield of 11, benzyl- and *tert*-butyl-protected hydroxymethyl lithium, BnOCH_2Li ^{29–31} (entry 4) and $t\text{-BuOCH}_2\text{Li}$ ³¹ (entry 5), were reacted with 10. However, these reactions also gave the undesired 12b or 12c as major products in 17% and 66% isolated yields, respectively, along with 11b (10%) and 11c (13%). In contrast to the above results, when styryllithium (PhCH=CHLi , generated *in situ* from PhCH=CHSnBu_3 and BuLi)³² was utilized, the desired substitution product 11d could be obtained in 72% isolated yield as a sole product (entry 6). Similarly, vinyl lithium ($\text{H}_2\text{C=CHLi}$, prepared *in situ* from $\text{H}_2\text{C=CHSnBu}_3$ and BuLi)^{33,34} gave 11e in 81% isolated yield (entry 7). On the basis of the isolated yields of 11, the vinyl group-substituted 11e was found to be a suitable substrate for the synthesis of the target molecules, and we envisioned transforming the vinyl-substituent into a hydroxymethyl group at later stage.^{35,36}

It has been reported that α -oxyalkyl lithium derived from phenyloxetane reacted with cyclopropylmethyl bromide to give the ring-opened linear butenyl-substituted oxetane through an SET process.³⁷ This fact suggested to us that the mechanism of the α -substitution of the phenylsulfanyl group of 10 observed in the reaction of alkoxyethyl lithium could be via radical coupling of alkoxyethyl radical with the vinyl radical. To confirm the possibility of the radical mechanism, 10 was treated with $t\text{-BuOCH}_2\text{Li}$ in the presence of an excess amount of radical scavenger galvinoxyl (3.0 equiv). However, the α -

Scheme 3. Radical-Mediated Sulfur-Extrusive Stannylation of Sulfones 11e, 14, and 16

Scheme 4. Synthesis of 3'-Halogeno-BCA 5

substitution product **12c** was obtained in 63% yield, and the SET mechanism was ruled out. Another possible mechanism is addition–elimination initiated by α -attack of the carbon nucleophile at the vinyl sulfone; indeed, a similar reaction pathway has been proposed in C-ethynylation utilizing arylsulfonylacetylene.^{38,39} At the present time, the latter mechanism is thought to be via the α -substitution pathway.

With the precursor **11e** for the carbohydrate moiety of **5** in hand, the radical-mediated sulfur-extrusive stannylation was examined (Scheme 3). When **11e** was treated with Bu_3SnH and AIBN in the presence of $i\text{-Pr}_2\text{NEt}$ in refluxing benzene for 4 h according to our previously reported procedure,¹⁹ the desired vinylstannane **13** was obtained in 36% yield along with unreacted **11e**. An improved result was obtained in the stannylation of benzoyl-protected vinyl sulfone **14**²⁰ to furnish **15** in 52% yield. This result led us to examine the reaction of nucleoside derivative **16**. Nucleoside **16** was prepared in 86% yield by reacting **11e** with N^6 -bis(Boc)adenine (**17**)^{40,41} in the presence of DIAD and Ph_3P in THF.⁴² The stannylation reaction of **16** was carried out under the above reaction conditions, and the desired tributylstannane **18** could be obtained in better yield (54%) with the recovery of unchanged **16** (40%).

Next, halogenation of the tributylstannane **18** was examined (Scheme 4), and the results are shown in Table 2. Treatment of **18** with iodine gave the corresponding iodide **19a** in quantitative yield (entry 1). Bromination of **18** with N -bromosuccinimide (NBS) gave **19b** in 74% yield (entry 2).

Table 2. Halogenation of Vinylstannane **18**

entry	condition	product	X	yield [%]
1	I_2/CCl_4 , 0 °C	19a	I	98
2	NBS/THF, rt	19b	Br	74
3	NCS/THF, reflux	19c	Cl	33
4	CuCl_2/THF , rt	19c	Cl	51
5	XeF_2 , AgOTf, DTBMP/ CH_2Cl_2 , rt	19d	F	61

Likewise, when chlorination of **18** using N -chlorosuccinimide (NCS) was carried out, the chloride **19c** was obtained in only 33% yield. The isolated yield could be improved to 51% yield by reacting with CuCl_2 ⁴³ (entry 4). The fluoro derivative **19d** was obtained in 61% yield by treatment of **18** with XeF_2 in the presence of AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP)⁴⁴ (entry 5).

Oxidative cleavage of the terminal olefin of the 3'-halogenated **19a–d** was conducted under Lemieux–Johnson conditions in the presence of 2,6-lutidine,⁴⁵ and subsequent NaBH_4 reduction of the resulted aldehyde gave **20a–d** (Scheme 4). It is noteworthy that in this transformation the internal trisubstituted alkene moiety of the substrate was stable to the oxidative cleavage and that the protected target molecules **20a–d** were formed in moderate yields. Finally, removal of the Boc- and TBDPS-protecting groups of **20a–d** was performed by the treatment with 3 M HCl at 50 °C to yield the target 3'-halogeno-BCA derivatives **5a–d** in 79–99% isolated yields. For the comparison of the antiviral activities,

Table 3. Anti-HIV and Anti-HBV Activities of Compounds 5a–d and 3

entry	compd	R	HIV-1 _{IIIb}		HBV _{WT} ^D	
			EC ₅₀ (μM)	CC ₅₀ (μM) (MT4)	EC ₅₀ (μM)	CC ₅₀ (μM) (HepG2)
1	5a	I	>1	>100 ^b	0.436 ± 0.000	ND ^c
2	5b	Br	>1	>100 ^b	0.029 ± 0.017	>100
3	5c	Cl	>1	>100 ^b	0.146 ± 0.000	ND ^c
4	5d	F	>1	>100 ^b	0.019 ± 0.003	>100
5	3 (BCA)	H	0.77 ^a	153	0.0457 ± 0.0002	>100
6	entecavir				0.0038	52.9

^aData taken from ref 4. ^bMT2 cell. ^cNot determined.

the parent compound (–)-BCA (3) was prepared from 5a through radical reduction conditions. The ¹H and ¹³C NMR spectra of the synthesized 3 were consistent with the reported data.⁸ This result supported the depicted structures of 5 synthesized in this study.

Finally, anti-HIV-1 activities of 5a–d were evaluated, and the results are summarized in Table 3. The reported anti-HIV-1 data of BCA was also listed in entry 5.⁴ Unfortunately, none of the compounds (5a–d) synthesized in this study showed significant anti-HIV-1 activity (>100 μM). This result suggests that the introduction of the halogeno-substituent at the 3'-position of BCA has adverse effects on the inhibition of reverse transcriptase of HIV-1. However, 5a–d were found to exhibit potent anti-HBV activities presumably due to inhibition of HBV reverse transcriptase. Furthermore, this study has shown that BCA itself possesses anti-HBV activity (entry 5). As can be seen with entry 4, 3'-fluoro-BCA (5d) was the most potent inhibitor in this study (EC₅₀ = 0.019 μM). A striking feature of these novel compounds is that none show cytotoxicity to HepG2 cell up to 100 μM. Although the potency of the fluorinated BCA 5d is 5 times less than that of positive control entecavir (entry 6), entecavir was found to be more toxic than that of 3'-fluoro-BCA. This result could pave the way for developing novel nontoxic and potent anti-HBV agents.

Of note, HBV's reverse transcriptase (RT) is extremely insoluble, and to date, no research has succeeded in preparing HBV-RT solution. Thus, it has been impossible for one to conduct reverse transcriptase assay with HBV-RT; no crystallographic analyses have been successful; and no detailed structure of HBV-RT's active site is known. However, it is quite plausible that the nucleoside analogs discovered in the present study act against HBV-RT due to the fact that all the new compounds reported in the present work have the 2',3'-dideoxynucleoside configuration.^{50,51} Indeed, in order to circumvent the notoriously high insolubility of HBV-RT, we have most recently generated "hybrid" reverse transcriptase species of HIV-1-RT and HBV-RT and have demonstrated that HIV-1-RT containing a Q151M substitution (151-Met is an HBV-RT's critical active site amino acid) at the nucleotide-binding site (N-site) of HIV-1-RT serves as a tool for examining the interactions of anti-HBV nucleosides with HBV-RT.^{46–48,51}

It is commonly seen that certain nucleoside analogs are highly active against HIV-1, but not against HBV.⁴⁹ For example, azidothymidine (zidovudine) is potent against HIV-1, but basically inert against HBV,⁴⁹ while entecavir, an FDA-approved anti-HBV therapeutic, is potent against HBV but not against HIV-1.⁴⁹ Since 2'-fluoro-BCA (5d) exerted potent activity against HBV (Table 3), it is assumed that the compound was intracellularly well triphosphorylated and incorporated into the growing DNA chain of HBV genome

being mediated by HBV-RT without exerting significant cytotoxicity (CC₅₀ > 100 μM). Also, it should be noted that MT-2 cell line is of a human lymphocyte origin, while HepG2 is of a human hepatocytic tumor origin and their susceptibility to the cytotoxicity of certain agents could very often vary. Nevertheless, the CC₅₀ of 5d with MT-2 cells was 100 μM and that with HepG2 was >100 μM, strongly suggesting that 5d's toxicity is insignificant. Of note, the specificity index of 5d (CC₅₀/EC₅₀) is 5263.16, indicating that, categorically, 5d has no significant cytotoxicity. Since the amounts of compounds newly synthesized are often low and scarce and the concentrations of such novel compounds usually are not tested at >100 μM. Further testing of the anti-HBV activity against other HBV species and safety profiles of 5d are future topics.

In conclusion, a synthetic method for the novel 3'-halogeno-BCA derivatives has been developed. The method includes two key steps: (1) S_N2' reaction of β'-dioxolanylcyclopentenylphenylsulfone 10 with vinyl lithium and (2) tin-radical-mediated sulfur-extrusive stannylation of 3'-phenylsulfonylated BCA derivative 16 to lead to the formation of key precursor vinyl stannane 18 for the target molecules. The former S_N2' reaction has proceeded with high-β-face selectively due to the sterically encumbered TBDPS-oxylmethyl group substituted at the γ-position of 10. Evaluation of antiviral activities revealed that introduction of halogeno-substituents into the 3'-position diminished the anti-HIV-1 activity of BCA. Interestingly, 3'-substitution of BCA with a halogen atom gave rise to an increase in the potency of inhibition of reverse-transcriptase of HBV. In general, halogenation of small molecular-weight compounds increases metabolic stability, delays inactivation of the compounds, and elongates their dosage periods because, chemically, carbon-and-halogen bonds are highly stable as compared to carbon-and-hydrogen bonds. Halogenation also increases lipophilicity due to its greater hydrophobicity, often increasing cell membrane penetration and oral bioavailability. It is not evident at this time whether the halogenation of the two compounds enhanced their cellular penetration, whether the triphosphorylated compounds intracellularly longer persisted and accumulated due to their possibly increased chemical stability, or whether halogenation strengthened their binding to the reverse transcriptase of HBV. The elucidation of the actual mechanism of the strengthened antiviral activity of the halogenated compounds against HBV is a topic of future studies.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.8b00374.

Experimental procedures and full characterization for compounds **5**, **7**–**20** (PDF)

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Notes

The authors declare no competing financial interest.

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