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Diastereoselective Synthesis of 6″-(*Z*)- and 6″-(*E*)-Fluoro Analogues of Anti-hepatitis B Virus Agent Entecavir and Its Evaluation of the Activity and Toxicity Profile of the Diastereomers

Hiroki Kumamoto,[*,†] Misato Fukano,[†] Tomohiko Nakano,[†] Keito Iwagami,[†] Chiaki Takeyama,[†] Satoru Kohgo,[§] Shuhei Imoto,[∥] Masayuki Amano,[⊥] Nobuyo Kuwata-Higashi,[⊥] Manabu Aoki,[#] Hiroshi Abe,[▽] Hiroaki Mitsuya,[○] Kiyoshi Fukuhara,[†] and Kazuhiro Haraguchi[‡]

[†]School of Pharmacy, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

[‡]Nihon Pharmaceutical University, 10281 Komuro, Inamachi, Kita-adachi-gun, Saitama 362-0806, Japan

[§]Center for Clinical Sciences, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan

[∥]Faculty of Pharmaceutical Sciences, Sojo University, 4-22-1 Ikeda, Kumamoto 860-0082, Japan

[⊥]Department of Infectious Diseases and Hematology, Kumamoto University School of Medicine, Kumamoto 860-8556, Japan

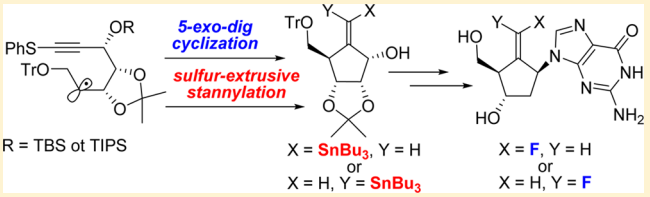
[#]Department of Medical Technology, Kumamoto Heath Science University, 325 Izumimachi, Kumamoto 861-5598, Japan

[▽]Department of Chemistry, Graduate School of Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602, Japan

[○]Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

Supporting Information

ABSTRACT: A method for the diastereoselective synthesis of 6″-(*Z*)- and 6″-(*E*)-fluorinated analogues of the anti-HBV agent entecavir has been developed. Construction of the methylenecyclopentane skeleton of the target molecules has been accomplished by radical-mediated 5-*exo*-*dig* cyclization of the selenides **6** and **15** having the phenylsulfanylethynyl structure as a radical accepting moiety. In the radical reaction of the TBS-protected precursor **6**, (*Z*)-*anti*-**12** was formed as a major product. On the other hand, TIPS-protected **15** gave (*E*)-*anti*-**12**. The sulfur-extrusive stannylation of *anti*-**12** furnished a mixture of geometric isomers of the respective vinylstannane, whereas benzoyl-protected **17** underwent the stannylation in the manner of retention of configuration. Following XeF_2-mediated fluorination, introduction of the purine base and deoxygenation of the resulting carbocyclic guanosine gave the target (*E*)- and (*Z*)-**3** after deprotection. Evaluation of the anti-HBV activity of **3** revealed that fluorine-substitution at the 6″-position of entecavir gave rise to a reduction in the cytotoxicity in HepG2 cells with retention of the antiviral activity.



INTRODUCTION

Hepatitis B is one of the most imperious viral diseases in the world. It has been known to be a major cause of chronic disease, which in turn leads to cirrhosis/hepatocellular carcinoma.[1] As one of the best choices for the treatment of this disease,[2] entecavir (Baraclude, **1**, Figure 1)[3a,b] has been used for chronic patients due to its lack of significant adverse effects.[4] Entecavir is a structurally carbocyclic analogue of deoxyguanosine (dG) and inhibits HBV reverse transcriptase, which in turn leads to chain termination of the positive strand of HBV DNA. The exomethylene functionality at the 6′-position of **1** is an essential pharmacophore for the significant antiviral activity. In fact, the potency of carbocyclic dG **2**, which is an analogue lacking the exomethylene functionality, is 10 times less than that of **1**.[3a] To combat the emergence of resistant virus, the development of a more potent and less toxic novel anti-HBV agent is critical. To study the structure−activity relationship of **1**, we have designed the 6″-fluorinated analogues **3**, which feature polarized exomethylene moieties without alteration of the molecular shape of **1**, due to fluorine's high

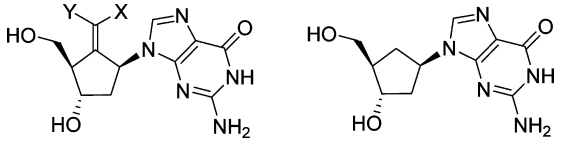


Figure 1. Structures of entecavir (**1**), carbocyclic dG (**2**), and target molecules (**3**).

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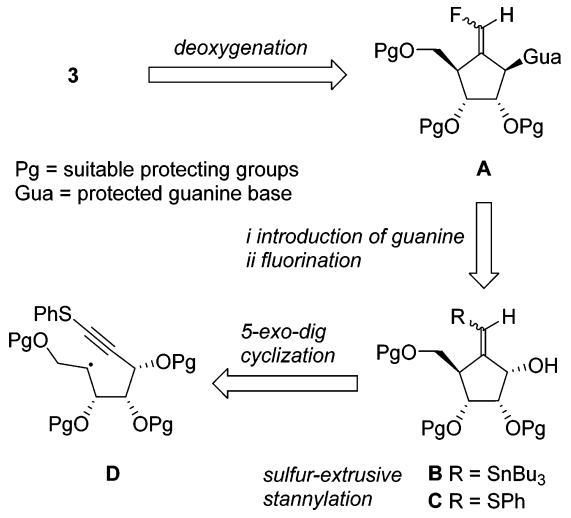
electronegativity and small van der Waals radius.[5a,b] Herein, we wish to report the diastereoselective synthesis of (*Z*)- and (*E*)-**3** based on the 5-*exo*-*dig* mode cyclization reaction of 5-hexynyl carbon-radicals having the phenylsulfanylethynyl moiety as a radical accepting group, and the following sulfur-extrusive stannylation of the resulting vinyl sulfide as key steps. Evaluation of their anti-HBV activity and toxicity profiles is also described.

RESULTS AND DISCUSSION

Retrosynthetic analysis for **3** is depicted in Scheme 1. The target molecule **3** would be synthesized by deoxygenation of

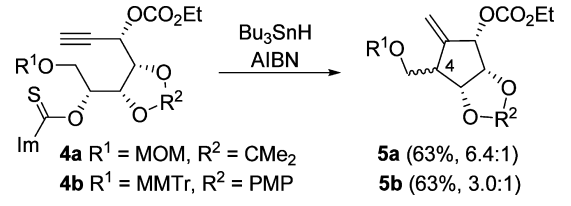
Scheme 1. Retrosynthetic Analysis for 3



the 2′-hydroxyl group and subsequent deprotection of the carbocyclic guanosine derivative **A**. The key intermediate **A** could be constructed from phenylsulfanyl derivative **C** by radical-mediated sulfur-extrusive stannylation[6] and subsequent electrophilic fluorination of the resulting vinyl stannane **B**. We have envisioned that the intermediate **C** can be synthesized by 5-*exo*-*dig* mode radical cyclization of a hexynyl radical, utilizing a phenylsulfanylethynyl radical accepting moiety **D**.

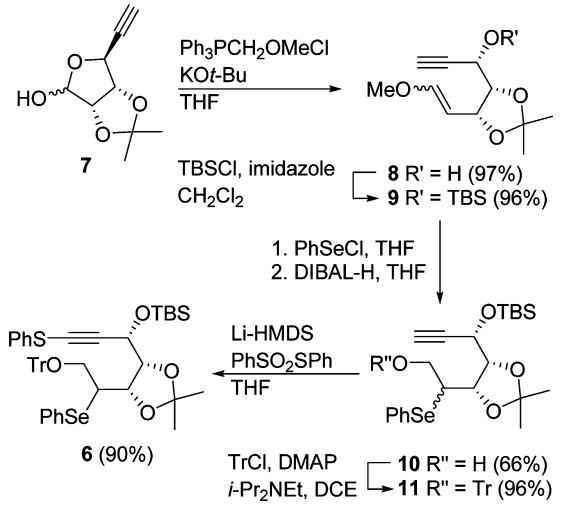
Carbon-centered radical-mediated intramolecular cyclization has been demonstrated to be a powerful method for constructing the cyclopentane structure of carbocyclic nucleosides. As shown in Scheme 2, when thiocarbamates **4a**[7a] and

Scheme 2. Precedent Radical-Mediated 5-*exo*-*dig* Cyclization Using Thiocarbamates as Precursors



4b[7b] were reacted with tributyltin hydride/AIBN in benzene under reflux conditions, 5-*exo*-*dig* cyclization proceeded to give methylenecyclopentanes **5a** and **5b**. In this reaction, *anti*- and *syn*-isomers were formed in ratios of 3.0:1 to 6.4:1. One would anticipate that, when the radical cyclization reaction is carried out under milder conditions, the chemical yields and diastereoselectivity of *anti*- and *syn*-isomers can be improved. Therefore, we have selected the selenide **6** as a radical precursor for **D**, which enables us to perform the radical reaction at room temperature due to the lower bond energy of the C−Se bond. The synthetic scheme for **6** is illustrated in Scheme 3.

Scheme 3. Preparation of Radical Precursor 6



The starting material was acetylene derivative **7** that was prepared from D-ribose by a literature procedure.[8] Compound **7** was reacted with $Ph_3P{=}CHOMe$ to give the enol ether **8** (97% yield), and then the resulting propargyl alcohol was protected with the TBS group to provide **9** (96% yield). Electrophilic phenylselenenylation of the enol ether of **9** by reacting with PhSeCl, followed by DIBAL-H reduction of the resulting aldehyde, gave phenylseleno alcohol **10** as a mixture of diastereomers (*ca.* 10:1) in moderate yield. Tritylation of the primary alcohol of **10** and subsequent introduction of a phenylthio group at the terminal acetylene of **11** furnished the desired radical precursor **6** in excellent yield.

With the carbon-radical precursor **6** in hand, carbon-centered radical-mediated cyclization of **6** was examined (Scheme 4 and Table 1). When the selenide **6** was treated with tris(trimethylsilyl)silane (TTMSS)[9a,b] in the presence of AIBN in refluxing toluene, the four isomeric cyclized products (*Z*)-*anti*-**12**, (*E*)-*anti*-**12**, (*Z*)-*syn*-**13**, and (*E*)-*syn*-**13** were obtained after the removal of the TBS group by treating the reaction mixture with Bu_4NF in the presence of AcOH (entry 1). The stereochemistry of the four isomers was determined on the basis of NOE experiments as depicted in Figure 2. The major isomer *anti*-**12** could be isolated in 47% yield (*Z*/*E* = 3.8/1) along with the minor *syn*-isomer (14%, *Z*/*E* = 1.4/1). This radical reaction is thought to proceed via a chair form-like transition state **I** and **II** (5-*exo*-*dig* manner) with the resulting α-phenylsulfanylvinyl radical **III**−**VI** abstracting a hydrogen atom from TTMSS to give **12** and **13**. Transition state **II** is energetically unfavorable due to steric repulsion between the trityloxymethyl and isopropylidene groups. Therefore, the major reaction pathway appears to follow **6** → **I** → **12**, leading to the predominant formation of *anti*-isomer (*anti*-**12**/*syn*-**13** = 3.36/1). This is a similar result to that observed in the formation of **5b** from **4b**.[7b] Moreover, the predominant formation of the (*Z*)-isomers most likely reflects a steric interaction between PhS− and $TrOCH_2$− groups because *syn*-isomer **13** has a lower diastereomeric ratio (*Z*/*E* = 1.4/1) than that of *anti*-**12**.

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Scheme 4. Radical-Mediated 5-*exo-dig* Cyclization of the Precursors 6, 14, and 15

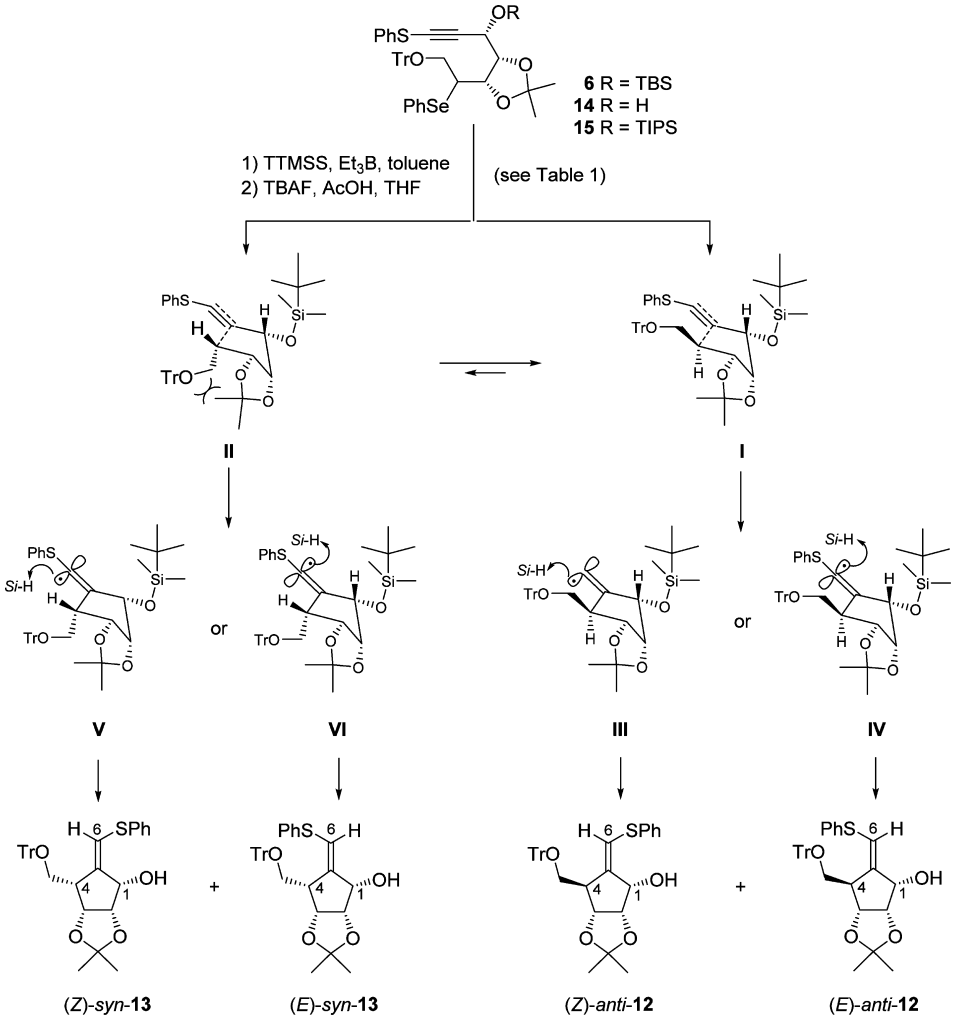

Table 1. Radical-Mediated 5-*exo-dig* Cyclization of Precursors 6, 14, and 15

entry	precursor	temp. [°C]	time [h][a]	yield [%] of *anti*-**12** (*Z*/*E*)[b]	yield [%] of *syn*-**13** (*Z*/*E*)[b]	ratio of **12**/**13**
1	**6**	110[c]	20	47 (3.8/1)	14 (1.4/1)	3.36/1
2	**6**	rt	9	63 (11.1/1)	17 (2.9/1)	3.71/1
3	**6**	−30	20	70 (25.0/1)	17 (5.6/1)	4.12/1
4	**6**	−70	20[d]	56 (20.0/1)	3 (1/0)	17.5/1
5	**6**	−70	96	73 (50.0/1)	14 (9.1/1)	5.21/1
6	**14**	−70	96	62 (1.0/1)	31 (1.4/1)	2.00/1
7	**15**	−50	120	69 (1/7.1)	13 (0/1)	5.31/1

[a]The reaction times were determined by complete comsumption of the corresponding precursors monitoring by TLC. [b]The ratio of *Z*/*E* isomer was determined by integration from ^{1}H NMR spectra. [c]A catalytic amount of AIBN was used as an initiator instead of Et_3B. [d]Uncyclized **14** was recovered in 26% after desilylation.

When the reaction of **6** was carried out at ambient temperature using Et_3B as a radical initiator, diastereoselectivities of *anti*-**12**/*syn*-**13** and (*Z*)-/(*E*)-isomer were slightly improved (entry 2). As can be seen in entries 3 and 4, decreasing the reaction temperature further improved the diastereoselectivity of both the *anti*-/*syn*-isomers and (*Z*)/(*E*)-isomers. The best result was obtained at −70 °C, in which *trans*-**12** could be obtained in 73% isolated yield (*Z*/*E* = 50/1) along with *cis*-**13** (14%, *Z*/*E* = 9.1/1) (entry 5). As can be seen in the reaction of **14**, the protection of the secondary alcohol at the 1-position was essential for good diastereoselectivity (entry 6).

Interestingly, the (*E*)-*anti*-**12** was found to be formed as a major product from triisopropylsilyl (TIPS) group-protected **15** under reaction conditions as illustrated in entry 7. In this reaction, the incipient α-phenylsulfanylvinyl radical **VII** is thought to undergo a 1,6-transfer reaction of a hydrogen atom from the isopropyl group on the silyl protector to the vinyl radical to give a seemingly stable tertiary α-silylalkyl radical **VIII**, which gave rise to (*E*)-*anti*-**12** (Scheme 5).[10] To validate this assumption, the energy levels of both intermediates **VII** and **VIII** were calculated using UB3LYP/6-31G(d,p). As anticipated, the energy level of intermediate **VIII** is 15.66 kcal/mol lower than that of the vinyl radical **VII** (see the

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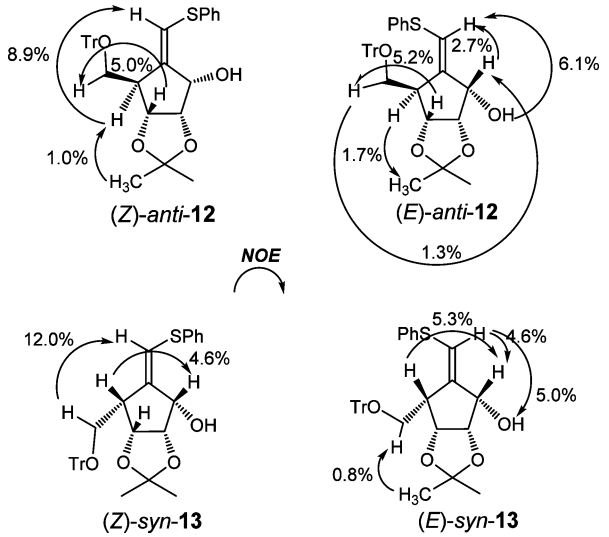
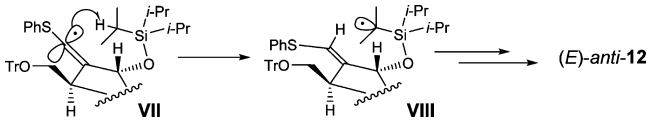


Figure 2. NOE Experiments of Compounds **12** and **13**.

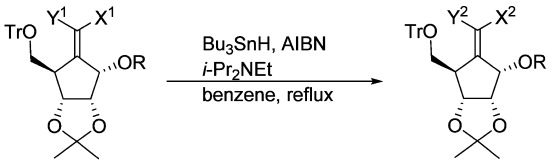
Scheme 5. 1,6-Transfer of Hydrogen Atom To Lead to the Predominant Formation of (*E*)-*anti*-12



Supporting Information). However, the possibility of the similar 1,6-hydrogen transfer from the TBS group included in **6** also cannot be ruled out; the actual factor for this opposite stereoselectivity is not clear.

Radical-mediated sulfur-extrusive stannylation was examined next (Scheme 6 and Table 2). When (*Z*)-*anti*-**12** was treated with Bu_3SnH and AIBN in the presence of *i*-Pr_2NEt in refluxing benzene,[6f] the expected vinyl stannane (*Z*)-**16** was obtained in 75% yield along with its isomer (*E*)-**16** (10%) (entry 1).[6e,g] The stereochemistry was assigned on the basis of NOE experiments as described in Figure 3. In the case of the benzoate (*Z*)-**17**, desired (*Z*)-**18** could be obtained as a sole isomer in 78% yield (entry 2). The isomerization in the sulfur-extrusive stannylation was also observed in the case of (*E*)-*anti*-**12** to give a mixture of (*E*)-**16** (51%) and (*Z*)-**16** (23%). The remarkable formation of isomerized (*Z*)-**16** could be due to the steric repulsion between the Bu_3Sn- and $TrOCH_2$-moieties. To see if this assumption is true, benzoyl group protected (*E*)-**17** was subjected to the radical stannylation, and expectedly, (*E*)-**18** could be obtained in 71% isolated yield as a sole product (entry 4). As shown in entry 5, TMS-protected (*E*)-**19** gave (*E*)-**16** in 72% yield along with the unreacted (*E*)-**12** (22% yield) after desilylation by treatment with NH_3/MeOH.

Scheme 6. Sulfur-Extrusive Stannylation of Sulfides 12, 17, and 19



(*Z*)-**12** R = H, X^1 = SPh, Y^1 = H
(*Z*)-**17** R = Bz, X^1 = SPh, Y^1 = H
(*E*)-**12** R = H, X^1 = H, Y^1 = SPh
(*E*)-**17** R = Bz, X^1 = H, Y^1 = SPh
(*E*)-**19** R = TMS, X^1 = H, Y^1 = SPh

(*Z*)-**16** R = H, X^2 = $SnBu_3$, Y^2 = H
(*Z*)-**18** R = Bz, X^2 = $SnBu_3$, Y^2 = H
(*E*)-**16** R = H, X^2 = H, Y^2 = $SnBu_3$
(*E*)-**18** R = Bz, X^2 = H, Y^2 = $SnBu_3$

Table 2. Sulfur-Extrusive Stannylation of the Sulfides 12 and 17

entry	precursor	yield [%] of stannanes	*E*/*Z* ratio
1	(*Z*)-**12**	75 [(*Z*)-**16**], 10 [(*E*)-**16**]	1/7.5
2	(*Z*)-**17**	78 [(*Z*)-**18**]	only *Z*
3	(*E*)-**12**	51 [(*E*)-**16**], 23 [(*Z*)-**16**]	2.22/1
4	(*E*)-**17**	71 [(*E*)-**18**]	only *E*
5	(*E*)-**19**	72 [(*E*)-**16**][a,b]	only *E*

[a]The stannane (*E*)-**16** was obtained after desilylation of intermediate by NH_3/MeOH. [b](*E*)-**12** was recovered in 22% as the unchanged sulfide.

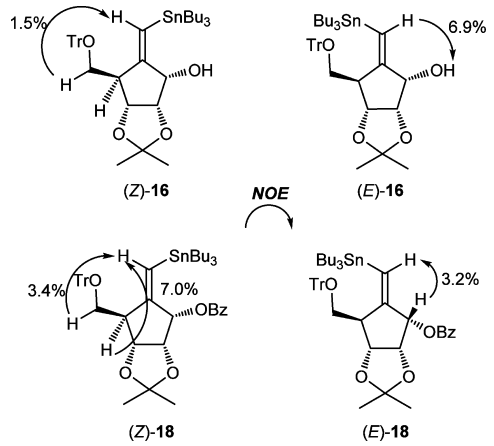
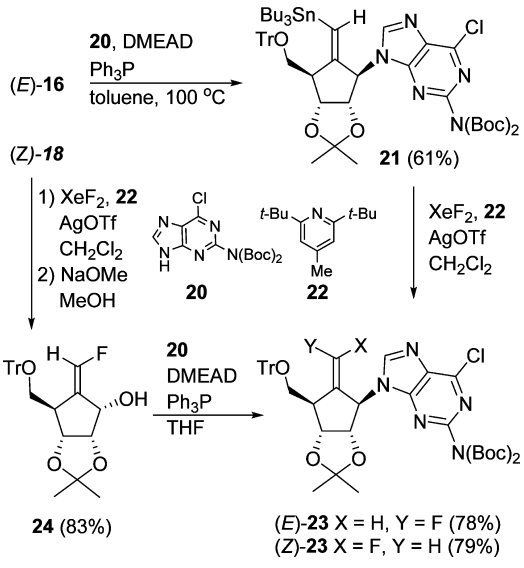


Figure 3. NOE Experiments of compounds **12** and **13**.

Scheme 7. Conversion to (*Z*)- and (*E*)-23



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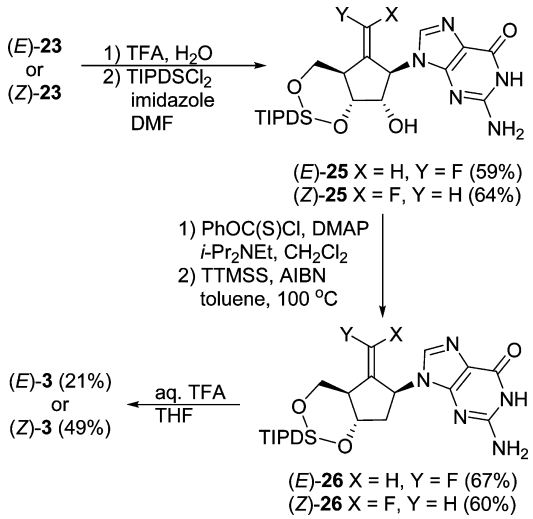
toluene under reflux conditions to give **21** in moderate yield. When the vinylstanne **21** was reacted with XeF_2, AgOTf, and 2,6-di-*tert*-butyl-4-methylpyridine (**22**)[14a,b] in CH_2Cl_2, the target 6″-(*E*)-fluoronucleoside (*E*)-**23** could be obtained in 78% yield. Mitsunobu reaction of (*Z*)-**16**, on the other hand, was found to be sluggish even in refluxing xylene, which may be due to the steric repulsion exerted by the bulky Bu_3Sn group. This result prompted us to carry out the fluorination of the benzoylated (*Z*)-**18** initially to give the fluoride **24** in 83% yield. Next, Mitsunobu-type substitution reaction between **24** and **20** readily proceeded at room temperature to provide (*Z*)-**23** in good yield.

Finally, deoxygenation of the 2′-position of **23** was examined (Scheme 8). Global deprotection of (*E*)- and (*Z*)-**23** was

Scheme 8. Transformation to (*Z*)- and (*E*)-3



carried out by treatment with aqueous TFA or HCO_2H to yield the corresponding triols. Silylation of both the 3′- and 5′-hydroxyl groups of the resulting triols using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane gave (*E*)- and (*Z*)-**25**, respectively. Compound **25** was transformed into the corresponding 2′-*O*-thiocarbonate and subsequent radical deoxygenation of the thiocarbonate using TTMSS and AIBN provided (*E*)- and (*Z*)-**26** in moderate yields, respectively. Target (*E*)- and (*Z*)-**3** were obtained after desilylation of **26** with aqueous TFA. These unsatisfied yields of **3** might be derived from the isolation step by HPLC (the conditions were not optimized), albeit the complete consumption of both of **26** were observed on TLC.

Evaluation of the anti-HBV activity of these synthetic compounds was conducted with HepG2 2.2.15 cells transfected with the HBV genome. As shown in Table 3, (*E*)-**3** possessed a better SI value (116×10^3) than that (28×10^3) of entecavir (**1**), but significant toxicity to the host cells was observed. In the case of (*Z*)-**3**, the potency of its anti-HBV activity is also similar to that of **1**. However, it was found that (*Z*)-**3** does not show cytotoxicity against HepG2 cells up to 100 μM and

Table 3. Anti-HBV Activity and Cytotoxicity of (*E*)-3 and Entecavir (1)

compd.	EC_{50} (μM)	CC_{50} (μM) (HepG2)	SI
(*E*)-**3**	0.0003 ± 0.00001	34.9 ± 1.2	116×10^3
1	0.0005 ± 0.0003	13.8 ± 8.3	28×10^3

exhibited a better SI value ($>23 \times 10^3$) than that (21×10^3) of **1** (Table 4). These results indicated that 6″-fluorinated

Table 4. Anti-HBV Activity and Cytotoxicity of (*Z*)-3 and Entecavir (1)

compd.	EC_{50} (μM)	CC_{50} (μM) (HepG2)	SI
(*Z*)-**3**	0.0044 ± 0.0003	>100	$>23 \times 10^3$
1	0.0025 ± 0.0002	52.9	21×10^3

derivatives of entecavir are less toxic analogues with retention of its potent anti-HBV activity. Further studies on the structure−activity relationships of 6″-substituted derivatives of entecavir are underway.

EXPERIMENTAL SECTION

General. NMR (^1H, ^{13}C, and ^{19}F) spectra were recorded with ^1H, 400 or 500 MHz, ^{13}C, 125 MHz, and ^{19}F, 470 MHz, respectively. Chemical shifts were reported relative to Me_4Si, except for fluorine-containing compounds where $CFCl_3$ was used as an internal standard. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. HRMS were obtained by the FAB technique with a double sector mass spectrometer. Column chromatography was carried out on silica gel. Thin-layer chromatography (TLC) was performed on a precoated silica gel plate F_{254}. THF was distilled from benzophenone ketyl.

***(S)*-1-((4*S*,5*R*)-5-(2-Methoxyvinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (8).** To a stirred suspension of $Ph_3PCH_2OCH_3Cl$ (19.9 g, 58.1 mmol) in anhydrous THF (90 mL) was dropwise added *t*-BuOK (1.0 mol/L in THF, 43.5 mL, 43.5 mmol) at −30 °C. The resulting orange mixture was stirred at rt for 2 h. To the mixture was added a THF (25 mL) solution of **7** (2.67 g, 14.5 mmol) at −30 °C. The mixture was stirred for a further 2.5 h at rt. The resulting mixture was partitioned between Et_2O and H_2O. Column chromatography on neutral silica gel (hexane/Et_2O = 1/1) of the organic layer gave **8** (2.98 g, 97%, *E*/*Z* = *ca.* 3:1) as an oil: $[\alpha]_D^{18}$ −84.5 (*c* = 1.30, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 1.28 (s, 1H), 1.29 (s, 3H), 1.56 (s, 1H), 1.59 (s, 1H), 2.20 (d, *J* = 2.0 Hz, 1H), 2.21 (d, *J* = 2.0 Hz, 0.33H), 2.81 (d, *J* = 7.2 Hz, 1H), 2.92 (d, *J* = 7.6 Hz, 0.33H), 2.95 (s, 1H), 3.18 (s, 3H), 4.07 (dd, *J* = 6.8 and 5.2 Hz, 1H), 4.32 (dd, *J* = 6.8 and 4.8 Hz, 0.33H), 4.34−4.37 (m, 1H), 4.40−4.43 (m, 0.33H), 4.45 (dd, *J* = 8.8 and 6.4 Hz, 1H), 4.83 (dd, *J* = 8.4 and 6.4 Hz, 0.33H), 5.08 (dd, *J* = 12.4 and 9.2 Hz, 1H), 5.38 (ddd, *J* = 9.6, 6.8, and 1.2 Hz, 0.33H), 5.55 (dd, *J* = 6.4 and 1.2 Hz, 0.33H), 4.42 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 0. 25.3, 25.3, 27.4, 27.5, 55.6, 59.4, 62.8, 63.3, 71.5, 74.5, 74.9, 76.3, 80.7, 80.8, 83.5, 83.6, 98.2, 102.5, 108.6, 108.9, 149.2, 151.9. FAB-MS *m*/*z* 211 (M^+ − H). HRMS (FAB+): calcd for $C_{11}H_{15}O_4$ 211.0970, Found 211.0996 [M^+ − H].

***tert*-Butyl(((*S*)-1-((4*R*,5*R*)-5-(2-methoxyvinyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-yl}oxy)dimethylsilane (9).** To a CH_2Cl_2 (40 mL) solution of **8** (2.74 g, 12.9 mmol) and imidazole (2.63 38.7 mmol) was added TBSCl (2.53 g, 16.8 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 h. The mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. Column chromatography on neutral silica gel (hexane/AcOEt = 5/1) of the organic layer gave **9** (4.04 g, 96%, *E*/*Z* = *ca.* 3:1) as an oil: $[\alpha]_D^{18}$ +23.0 (*c* = 0.90, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 0.12 (s, 3H), 0.16 (s, 1H), 0.24 (s, 3H), 0.27 (s, 1H), 0.97 (s, 9H), 0.99 (s, 3H), 1.28 (s, 4H), 1.52 (s, 3H), 1.56 (s, 1H), 2.09 (d, *J* = 2.4 Hz, 1H), 2.11 (d, *J* = 2.4 Hz, 0.33H), 3.01 (s, 1H), 3.18 (s, 3H), 4.15 (t, *J* = 6.4 Hz, 1H), 4.30 (t, *J* = 6.0 Hz, 0.33H), 4.49 (dd, *J* = 8.8 and 6.0 Hz, 1H), 4.55 (dd, *J* = 6.0 and 2.4 Hz, 1H), 4.59 (dd, *J* = 5.6 and 2.4 Hz, 0.33H), 4.82 (dd, *J* = 9.2 and 6.4 Hz, 0.33H), 5.05 (dd, *J* = 12.8 and 8.8 Hz, 1H), 5.46 (ddd, *J* = 9.2, 6.4, and 0.8 Hz, 0.33H), 5.63 (dd, *J* = 6.4 and 0.8 Hz, 0.33H), 6.42 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ −4.7, −4.5, −3.9, −3.8, 18.3, 18.4, 25.5, 26.0, 27.9, 28.0, 55.6, 59.3, 63.3, 63.8, 71.4, 74.7, 75.0, 76.8, 80.8, 80.9, 83.6, 83.9, 99.5,

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102.9, 108.2, 108.4, 149.5, 151.6; FAB-MS m/z 325 ($M^+ - H$). HRMS (FAB+): calcd for $C_{17}H_{29}O_4Si$ 325.1835, Found 325.1855 [$M^+ - H$].

2-((4*S*,5*R*)-5-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)prop-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(phenylselanyl)ethan-1-ol (10). To a wet THF (150 mL) solution of **9** (9.73 g, 29.8 mmol) was dropwise added a THF (50 mL) solution of PhSeCl (5.99 g, 31.3 mmol) at −80 °C. After 1 h stirring of the resulting mixture, this was stirred at rt for a further 15 min. The mixture was partitioned between aq. saturated $NaHCO_3$ and AcOEt. The organic layer was dried by Na_2SO_4; then evaporated all of the volatiles without heating. The residue was dissolved in dry THF (150 mL) and then treated with DIBAL-H (1.02 mol/L in toluene, 58.4 mL, 59.6 mmol) at −80 °C. After 1 h stirring at the same temperature, this was partitioned between 0.5 N HCl and AcOEt. The organic layer was dried by Na_2SO_4 and filtrated through a Celite pad. After evaporation of the filtrate, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 7/1). This gave **10** (9.25 g, 66%, *ca.* 10:1 of diastereomixture) as an oil: $[\alpha]_D^{15}$ +7.8 (c = 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.14 (s, 0.3H), 0.17 (s, 0.3H), 0.20 (s, 3H), 0.90 (s, 9H), 0.92 (s, 0.9H), 1.35 (s, 0.3H), 1.39 (s, 3H), 1.57 (s, 3H), 1.59 (s, 0.3H), 2.42−2.45 (m, 1H), 2.48 (d, J = 2.0 Hz, 0.1H), 2.55 (d, J = 2.0 Hz, 1H), 2.82−2.86 (m, 0.1H), 3.64−3.86 (m, 3.3H), 4.24 (dd, J = 8.8 and 6.0 Hz, 1H), 4.33 (dd, J = 6.4 and 3.6 Hz, 0.1H), 4.36 (dd, J = 8.8 and 6.4 Hz, 0.1H), 4.43 (t, J = 6.0 Hz, 1H), 4.90−4.94 (m, 1.1H), 7.24−7.34 (m, 3.3H), 7.57−7.63 (m, 2.2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.4, −4.3, −3.7, 18.1, 18.4, 24.8, 25.1, 25.8, 25.9, 26.8, 26.9, 45.9, 46.0, 62.3, 63.0, 63.6, 63.7, 75.2, 75.5, 76.9, 78.8, 79.4, 80.8, 83.1, 108.4, 109.4, 126.2, 127.4, 128.0, 128.4, 129.1, 129.3, 135.0, 135.3; FAB-MS m/z 470 (M^+ + H). HRMS (FAB+): calcd for $C_{22}H_{34}O_4SeSi$ 470.1392, Found 470.1405 [M^+].

***tert*-Butyl(((1*S*)-1-((4*R*,5*S*)-2,2-dimethyl-5-(1-(phenylselanyl)-2-(trityloxy)ethyl)-1,3-dioxolan-4-yl)prop-2-yn-1-yl)oxy)-dimethylsilane (11).** A mixture of **10** (1.75 g, 3.73 mmol), DMAP (503 mg, 4.10 mmol), *i*-Pr_2NEt (1.95 mL, 11.2 mmol), and TrCl (1.56 g, 5.60 mmol) in 1,2-dichloroethane (37 mL) was heated at 70 °C for 40 h. The resulting mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. Column chromatography on silica gel (hexane/AcOEt = 11/1) of the organic layer gave **11** (2.54 g, 96%, *ca.* 10:1 of diastereomeric mixture) as a foam: $[\alpha]_D^{18}$ +100.4 (c = 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H), 0.11 (s, 0.3H), 0.13 (s, 0.3H), 0.18 (s, 3H), 0.82 (s, 9H), 0.89 (s, 0.9H), 1.32 (s, 0.3H), 1.39 (s, 3H), 1.43 (s, 0.3H), 1.51 (s, 3H), 2.42 (d, J = 2.0 Hz, 0.1H), 2.55 (d, J = 2.0 Hz, 1H), 3.42 (dd, J = 9.2 and 4.0 Hz, 1H), 3.52 (t, J = 9.2 Hz, 1H), 3.60−3.61 (m, 0.2H), 3.64−3.67 (m, 0.1H), 3.74−3.77 (m, 1H), 4.21 (dd, J = 8.8 and 7.2 Hz, 1H), 4.29 (dd, J = 6.4 and 4.4 Hz, 0.1H), 4.50 (dd, J = 9.2 and 6.4 Hz, 0.1H), 4.76−4.77 (m, 0.1H), 4.90 (dd, J = 6.8 and 1.6 Hz, 1H), 5.24 (dd, J = 9.2 and 1.6 Hz, 1H), 7.12−7.82 (m, 22H); ^{13}C NMR for major isomer **11** (125 MHz, $CDCl_3$) δ −4.6, −3.3, 18.1, 24.3, 25.8, 26.0, 44.6, 61.8, 65.2, 75.1, 75.7, 79.5, 83.6, 86.7, 108.6, 126.9, 127.1, 127.7, 128.7, 128.9, 129.8, 133.4, 143.9; ^{13}C NMR for minor isomer **11** (125 MHz, $CDCl_3$) δ −4.5, −4.2, 18.3, 25.0, 25.9, 26.6, 43.2, 62.9, 63.4, 75.0, 76.5, 80.8, 83.4, 86.6, 108.8, 126.9, 127.6, 128.0, 128.6, 128.9, 129.0, 134.6, 144.4; FAB-MS m/z 712 (M^+ + H). HRMS (FAB+): calcd for $C_{41}H_{48}O_4SeSi$ 712.2487, Found 712.2453 [M^+ + H].

***tert*-Butyl(((1*S*)-1-((4*R*,5*S*)-2,2-dimethyl-5-(1-(phenylselanyl)-2-(trityloxy)ethyl)-1,3-dioxolan-4-yl)-3-(phenylthio)prop-2-yn-1-yl)oxy)dimethylsilane (6).** To a THF (160 mL) solution of **11** (*ca.* 10:1, 13.2 g, 18.6 mmol) was dropwise added Li-HMDS (1.3 mol/L in THF, 17.8 mL, 23.2 mmol) at −78 °C; then the mixture was stirred for 15 min at the same temperature. To the resulting solution was dropwise added a THF (40 mL) solution of $PhSSO_2Ph$ (6.04 g, 24.1 mmol) via cannula. After 50 min stirring at the same temperature, the mixture was partitioned between aq. saturated NH_4Cl and AcOEt. Column chromatography on silica gel of the organic layer gave **6** (hexane/AcOEt = 17/1, 13.76 g, 90%, single isomer) as a foam. This was recrystallized from Et_2O/hexane: mp 126−128 °C. $[\alpha]_D^{18}$ −0.6 (c = 1.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.15 (s, 3H), 0.83 (s, 9H), 1.40 (s, 3H), 1.52 (s, 3H), 3.43 (dd, J = 9.6 and 4.2 Hz, 1H), 3.53 (t, J = 9.6 Hz, 1H), 3.79−3.83 (m, 1H), 4.31 (dd, J = 8.8 and 7.2 Hz, 1H), 4.93 (dd, J = 7.2 and 2.0 Hz, 1H), 5.46 (d, J = 8.8 Hz, 1H), 7.12−7.15 (m, 2H), 7.18−7.27 (m, 11H), 7.30−7.34 (m, 2H), 7.35−7.40 (m, 8H), 7.46−7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −3.4, 18.1, 24.4, 25.9, 26.1, 44.7, 63.0, 65.3, 73.5, 75.7, 79.7, 86.7, 99.0, 108.5, 126.3, 126.4, 126.9, 127.0, 128.7, 128.9, 129.1, 129.8, 132.6, 133.3, 143.9; FAB-MS m/z 820 (M^+). Anal. Calcd for $C_{47}H_{52}O_4SSeSi$: C, 68.84; H, 6.39, Found: C, 68.84; H, 6.40.

Radical-Mediated 5-*exo*-*dig* Cyclization (Table 1, entry 4). To a toluene (7.4 mL) solution of **6** (300 mg, 0.37 mmol) and tris(trimethylsilyl)silane (TTMSS) (228 μL, 0.74 mmol) was added freshly opened Et_3B (1.0 mol/L in THF, 740 μL, 0.74 mmol) at −70 °C under a positive pressure of dry Ar (including trace amount of O_2). The resulting mixture was stirred for 96 h at the same temperature. During this reaction, further Et_3B (740 μL) was added every 24 h. The mixture was partitioned between aq. saturated $NaHCO_3$ and AcOEt. Column chromatography on silica gel (hexane/Et_2O = 17/1) of the organic layer gave crude cyclized product (228 mg, foam). The mixture was used for the next reaction without further purification. The residue was dissolved in THF (3.7 mL). Then, this was sequentially treated with AcOH (21 μL, 0.37 mmol) and Bu_4NF (1.0 mol/L in THF, 1.85 mL, 1.85 mmol). The resulting mixture was heated at 60 °C for 48 h. After disappearance of the silyl ether on TLC (hexane/AcOEt = 3/1), the mixture was partitioned between aq. saturated $NaHCO_3$ and AcOEt. The organic layer was purified by preparative TLC (hexane/AcOEt = 4/1 including 0.5% of Et_3N, twice evolution). This gave **12** (148 mg, 73%, Z/E = 50.0:1, as a foam calculated by integration of ^{1}H NMR) and **13** (28 mg, 14%, Z/E = 9.1:1, as a foam), respectively. Analytical samples were prepared by HPLC separation [hexane/AcOEt = 4/1, (*Z*)-*anti*-**12** (t_R = 12.0 min), (*E*)-*anti*-**12** (t_R = 13.8 min), (*Z*)-*syn*-**13** (t_R = 15.8 min), and (*E*)-*syn*-**13** (t_R = 19.3 min)]. When compound **6** (10.0 g, 12.19 mmol) was performed in the same manner, an analytically pure (*Z*)-*anti*-**12** (4.88 g, 73% as a foam) was obtained after careful purification by column chromatography on silica gel (hexane/Et_2O = 10/1 to 4/1). **Physical data for (*Z*)-*anti*-12**: $[\alpha]_D^{18}$ α148.1 (c = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.50 (s, 3H), 2.84−2.86 (m, 1H), 2.93 (d, J = 8.0 Hz, 1H), 3.14 (dd, J = 9.2 and 4.8 Hz, 1H), 3.25 (dd, J = 9.2 and 4.4 Hz, 1H), 4.46 (dd, J = 6.0 and 1.2 Hz, 1H), 4.74 (t, J = 6.0 Hz, 1H), 4.93 (ddt, J = 8.0, 6.4, and 2.0 Hz, 1H), 6.39 (t, J = 1.6 Hz, 1H), 7.19−7.30 (m, 12H), 7.35−7.40 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 26.5, 49.9, 66.1, 73.0, 79.6, 82.5, 87.2, 111.3, 123.1, 126.5, 127.1, 127.9, 128.6, 129.0, 129.3, 137.0, 142.8, 143.6; FAB-MS m/z 550 (M^+). Anal. Calcd for $C_{35}H_{34}O_4S$: C, 76.33; H, 6.22, Found: C, 76.54; H,6.32. **Physical data for (*E*)-*anti*-12**: $[\alpha]_D^{18}$ −258.5 (c = 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.41 (s, 3H), 2.48 (d, J = 10.8 Hz, 1H), 3.06−3.08 (m, 1H), 3.13 (dd, J = 8.8 and 4.0 Hz, 1H), 3.31 (dd, J = 8.8 and 4.0 Hz, 1H), 4.52 (d, J = 5.6 Hz, 1H), 4.69 (t, J = 5.6 Hz, 1H), 4.83 (ddt, J = 10.8, 6.0, and 2.0 Hz, 1H), 6.57 (t, J = 1.6 Hz, 1H), 7.19−7.25 (m, 5H), 7.27−7.33 (m, 9H), 7.37−7.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 26.7, 47.8, 64.3, 74.9, 79.0, 81.8, 87.2, 110.7, 118.8, 126.3, 127.1, 127.9, 128.6, 128.6, 129.0, 136.2, 143.6, 147.2; FAB-MS m/z 550 (M^+). Anal. Calcd for $C_{35}H_{34}O_4S\cdot 1/2\ H_2O$: C, 75.09; H, 6.30, Found: C, 75.07; H, 6.12. **Physical data for (*Z*)-*syn*-13**: $[\alpha]_D^{18}$ −48.2 (c = 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 6H), 2.66−2.70 (m, 1H), 2.84 (d,, J = 8.4 Hz, 1H), 3.24 (dd, J = 9.2 and 7.2 Hz, 1H), 3.61 (dd, J = 9.2 and 6.0 Hz, 1H), 4.50−4.58 (m, 2H), 4.72 (t, J = 5.2 Hz, 1H), 6.26 (t, J = 2.0 Hz, 1H), 7.18−7.30 (m, 14H), 7.43−7.46 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 26.0, 44.6, 61.5, 73.3, 78.0, 79.4, 86.8, 111.1, 120.5, 126.2, 126.9, 127.7, 128.6, 128.9, 129.0, 137.3, 140.6, 143.9; FAB-MS m/z 550 (M^+). Anal. Calcd for $C_{35}H_{34}O_4S\cdot 1/4\ H_2O$: C, 75.72; H, 6.26, Found: C, 75.58; H, 6.15. **Physical data for (*E*)-*syn*-13**: $[\alpha]_D^{18}$ +4.1 (c = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.42 (s, 3H), 2.52 (d, J = 8.4 Hz, 1H), 2.85−2.90 (m, 1H), 3.66 (t, J = 8.8 Hz, 1H), 3.69 (dd, J = 8.8 and 5.4 Hz, 1H), 4.13−4.16 (m, 1H), 4.54 (t, J = 6.0 Hz, 1H), 4.97 (t, J = 6.0 Hz, 1H), 6.37 (t, J = 1.6 Hz, 1H), 7.17−7.30 (m, 14H), 7.51−7.53 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 26.0, 44.9, 60.7, 73.6, 77.8, 86.9, 111.6, 120.4, 126.5, 126.8, 127.6, 129.0, 129.1, 136.3, 141.5, 144.2; FAB-MS

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m/*z* 550 (M^+). Anal. Calcd for $C_{35}H_{34}O_4S$: C, 76.33; H, 6.22, Found: C, 76.34; H, 6.28.

(1*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-(1-(phenylselanyl)-2-(trityloxy)ethyl)-1,3-dioxolan-4-yl)-3-(phenylthio)prop-2-yn-1-ol (14). To a mixture of **6** (3.17 g, 3.87 mmol) and AcOH (0.22 mL, 3.87 mmol) in THF (30 mL) was added Bu_4NF (1.0 mol/L in THF, 8.5 mL, 8.50 mmol) at 0 °C. The mixture was stirred at rt for 7 h. After evaporation of all of volatiles of the resulting mixture, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5/1). This gave **14** (2.44 g, 89%) as a foam: $[\alpha]_D^{18}$ −15.3 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.51 (s, 3H), 2.54 (d, *J* = 7.6 Hz, 1H), 3.41 (d, *J* = 10.0 and 4.4 Hz, 1H), 3.48 (t, *J* = 10.0 Hz, 1H), 3.93−3.98 (m, 1H), 4.18 (t, *J* = 2.8 Hz, 1H), 4.64 (t, *J* = 2.0 Hz, 1H), 5.05 (t, *J* = 2.8 Hz, 1H), 7.11−7.15 (m, 2H), 7.18−7.27 (m, 11H), 7.29−7.36 (m, 8H), 7.41−7.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9, 26.7, 42.9, 62.8, 65.6, 73.4, 76.6, 79.4, 87.2, 97.7, 108.6, 126.4, 126.6, 127.0, 127.4, 127.8, 128.6, 129.0, 129.2, 132.2, 134.1, 143.7; FAB-MS *m*/*z* 707 (M^+ + H). Anal. Calcd for $C_{41}H_{38}O_4SSe{\cdot}H_2O$: C, 68.04; H, 5.57, Found: C, 67.84; H, 5.24.

(((1*S*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-(1-(phenylselanyl)-2-(trityloxy)ethyl)-1,3-dioxolan-4-yl)-3-(phenylthio)prop-2-yn-1-yl)oxy)triisopropylsilane (15). To a mixture of **14** (2.44 g, 3.46 mmol) and 2,6-lutidine (1.53 mL, 13.84 mmol) in CH_2Cl_2 (35 mL) was dropwise added TIPSOTf (1.9 mL, 6.92 mmol) at 0 °C. The resulting mixture was stirred at rt for 13.5 h. After addition of 0.3 mL of MeOH, the mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. Column chromatography on silica gel (hexane/Et_2O = 20/1) of the organic layer gave **15** (2.98 g, 97%) as an oil: $[\alpha]_D^{18}$ −6.1 (*c* = 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95−1.01 (m, 18H), 1.04−1.11 (m, 3H), 1.42 (s, 3H), 1.52 (s, 3H), 3.44 (dd, *J* = 10.0 and 4.0 Hz, 1H), 3.55 (t, *J* = 10.0 Hz, 1H), 3.88−3.91 (m, 1H), 4.33 (dd, *J* = 9.0 and, 7.5 Hz, 1H), 4.97 (dd, *J* = 7.5 and 2.5 Hz, 1H), 5.42 (d, *J* = 9.0 Hz, 1H), 7.00−7.12 (m, 2H), 7.15−7.16 (m, 2H), 7.18−7.27 (m, 9H), 7.29−7.33 (m, 4H), 7.38−7.41 (m, 6H), 7.46−7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 18.3, 24.4, 26.1, 44.3, 63.3, 65.2, 73.4, 75.8, 79.8, 86.7, 98.9, 108.4, 126.5, 126.5, 126.8, 126.9, 127.7, 128.6, 128.8, 129.0, 129.9, 132.4, 132.7, 143.9; FAB-MS *m*/*z* 901 (M^+ + K). Anal. Calcd for $C_{50}H_{58}O_4SSeSi$: C, 69.66; H, 6.78, Found: C, 69.46; H, 6.76.

Sulfur-Extrusive Stannylation of (*Z*)-*anti*-12. A mixture of (*Z*)-*anti*-**12** (1.24 g, 2.25 mmol), Bu_3SnH (1.82 mL, 6.75 mmol), AIBN (186 mg, 1.13 mmol), and *i*-Pr_2NEt (589 μL, 3.38 mmol) in benzene (22.5 mL) was refluxed for 6 h. After evaporation of all of volatiles, the resulting residue was purified by column chromatography on neutral silica gel. This gave (*Z*)-**16** (hexane/Et_2O = 15/1, 1.24 g, 75% as an oil) and (*E*)-**16** (hexane/Et_2O = 5/1, 172 mg, 10% as an oil), respectively. **Physical data for (*Z*)-16**: $[\alpha]_D^{20}$ −5.9 (*c* = 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−0.89 (m, 9H), 0.91−0.98 (m, 6H), 1.27−1.35 (m, 6H), 1.32 (s, 3H), 1.48−1.54 (m, 6H), 1.56 (s, 3H), 2.33−2.37 (m, 1H), 2.66−2.67 (m, 1H), 3.08 (dd, *J* = 8.5 and 4.5 Hz, 1H), 3.21 (dd, *J* = 8.5 and 4.5 Hz, 1H), 4.40 (d, *J* = 5.0 Hz, 1H), 4.64−4.68 (m, 2H), 5.98−6.11 (m, 1H), 7.21−7.25 (m, 3H), 7.27−7.30 (m, 6H), 7.37−7.39 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 13.7, 24.9, 26.5, 27.4, 29.4, 52.9, 66.2, 74.2, 79.3, 81.0, 87.0, 110.4, 125.9, 127.0, 127.8, 128.6, 143.8, 160.1; FAB-MS *m*/*z* 732 (M^+ + H). Anal. Calcd for $C_{41}H_{56}O_4Sn$: C, 67.31; H, 7.72, Found: C, 67.33; H, 7.72. **Physical data for (*E*)-16**: $[\alpha]_D^{16}$ −111.8 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77−0.90 (m, 15H), 1.19−1.28 (m, 6H), 1.32 (s, 3H), 1.36 (s, 1H), 1.38−1.46 (m, 6H), 2.21−2.25 (m, 1H), 2.50−2.52 (m, 1H), 3.07 (dd, *J* = 8.8 and 5.6 Hz, 1H), 3.17 (dd, *J* = 8.8 and 4.0 Hz, 1H), 4.50−4.52 (m, 1H), 4.60−4.66 (m, 2H), 6.13−6.28 (m, 1H), 7.20−7.25 (m, 3H), 7.29−7.30 (m, 6H), 7.35−7.38 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1, 13.6, 24.7, 26.4, 27.3, 29.0, 51.2, 60.0, 74.9, 78.9, 80.4, 87.2, 110.1, 122.3, 127.1, 127.8, 128.7, 143.6, 161.2; FAB-MS *m*/*z* 732 (M^+ + H). Anal. Calcd for $C_{41}H_{56}O_4Sn$: C, 67.31; H, 7.72, Found: C, 67.40; H, 7.71.

(3a*R*,4*S*,6*R*,6a*R*,*Z*)-2,2-Dimethyl-5-((phenylthio)methylene)-6-((trityloxy)methyl)tetrahydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-yl benzoate (*Z*)-17. To a mixture of (*Z*)-*anti*-**12** (4.86 g, 8.83 mmol), DMAP (1.30 g, 10.6 mmol), and *i*-Pr_2NEt (3.08 mL, 17.7 mmol) in CH_2Cl_2 (60 mL) was added BzCl (1.55 mL, 13.3 mmol) at 0 °C. The resulting mixture was stirred at rt for 18 h. This was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. Column chromatography on silica gel (hexane/AcOEt = 5/1) of the organic layer gave (*Z*)-**17** (5.77 g, quant.) as a foam: $[\alpha]_D^{19}$ −312.6 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.29 (s, 3H), 3.07−3.09 (m, 1H), 3.20 (dd, *J* = 9.2 and 4.8 Hz, 1H), 3.34 (dd, *J* = 9.2 and 4.0 Hz, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 5.04 (t, *J* = 5.6 Hz, 1H), 5.63−5.95 (m, 1H), 6.53 (t, *J* = 1.6 Hz, 1H), 7.21−7.32 (m, 14H), 7.41−7.47 (m, 8H), 7.54−7.58 (m, 1H), 8.19−8.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 26.3, 48.9, 65.8, 74.2, 79.3, 83.4, 87.3, 111.5, 125.0, 126.7, 127.2, 128.0, 128.3, 128.6, 129.0, 129.5, 130.0, 130.1, 132.8, 136.2, 139.5, 143.6, 165.7; FAB-MS *m*/*z* 693 (M^+ + K). Anal. Calcd for $C_{42}H_{38}O_5S{\cdot}1/2\ H_2O$: C, 75.99; H, 5.92, Found: C, 76.08; H, 5.76.

Sulfur-Extrusive Stannylation of (*Z*)-17. (*Z*)-**17** (9170 mg, 1.4 mmol) was treated in the same manner as that described for (*Z*)-*anti*-**12**. Column chromatography on silica gel (hexane/AcOEt = 11/1) gave (*Z*)-**18** (910 mg, 78%) as an oil: $[\alpha]_D^{19}$ −109.1 (*c* = 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74−0.93 (m, 15H), 1.15−1.24 (m, 6H), 1.26 (s, 3H), 1.31 (s, 3H), 1.35−1.44 (m,6H), 2.98−3.00 (m, 1H), 3.22 (dd, *J* = 8.8 and 4.4 Hz, 1H), 3.35 (dd, *J* = 8.8 and 4.8 Hz, 1H), 4.44 (dd, *J* = 6.0 and 1.2 Hz, 1H), 4.94 (t, *J* = 6.0 Hz, 1H), 5.70−5.73 (m, 1H), 6.11−6.24 (m, 1H), 7.22−7.26 (m, 4H), 7.29−7.33 (m, 5H), 7.42−7.45 (m, 8H), 7.54−7.58 (m, 1H), 8.09−8.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.2, 13.6, 25.3, 26.5, 27.2, 29.1, 51.7, 65.8, 76.4, 79.0, 82.7, 87.0, 111.3, 127.0, 127.8, 128.2, 128.7, 128.8, 219.9, 130.4, 132.8, 143.8, 157.0, 166.4; FAB-MS *m*/*z* 836 (M^+ + H). Anal. Calcd for $C_{48}H_{60}O_5Sn$: C, 68.99; H, 7.24, Found: C, 68.96; H, 7.25.

Sulfur-Extrusive Stannylation of (*E*)-*anti*-12. Compound (*E*)-*anti*-**12** (201 mg, 0.365 mmol) was treated in the same manner as that described for (*Z*)-*anti*-**12**. Column chromatography on silica gel (hexane/Et_2O = 15/1 to 5/1) gave (*Z*)-**16** (62 mg, 23%) and (*E*)-**16** (136 mg, 51%), respectively.

(3a*R*,4*S*,6*R*,6a*R*,*E*)-2,2-Dimethyl-5-((phenylthio)methylene)-6-((trityloxy)methyl)tetrahydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-yl Benzoate (*E*)-17. (*E*)-*anti*-**12** (800 mg, 1.45 mmol) was treated in the same manner as that described for (*Z*)-**17**. Column chromatography on silica gel (hexane/AcOEt = 7/1) gave (*E*)-**17** (892 mg, 84%) as a foam: $[\alpha]_D^{18}$ −258.1 (*c* = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.38 (s, 3H), 3.19 (dd, *J* = 9.2 and 4.0 Hz, 1H), 3.24−3.26 (m, 1H), 3.41 (dd, *J* = 9.2 and 4.4 Hz, 1H), 4.55 (d, *J* = 5.2 Hz, 1H), 5.04 (t, *J* = 1.6 Hz, 1H), 5.90−5.91 (m, 1H), 6.56 (s, 1H), 7.22−7.26 (m, 4H), 7.30−7.37 (m, 10H), 7.43−7.47 (m, 8H), 7.55−7.59 (m, 1H), 8.13−8.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0. 25.5, 26.8, 47.4, 64.0, 76.1, 78.3, 82.6, 87.3, 111.2, 119.5, 126.4, 127.1, 127.9, 128.4, 128.6, 129.1, 129.8, 129.9, 133.1, 136.1, 143.0, 143.6, 165.8; FAB-MS *m*/*z* 693 (M^+ + K). Anal. Calcd for $C_{42}H_{38}O_5S{\cdot}H_2O$: C, 74.98; H, 5.99, Found: C, 74.71; H, 5.66.

Sulfur-Extrusive Stannylation of (*E*)-17. A mixture of (*E*)-**17** (373 mg, 0.57 mmol), Bu_3SnH (460 μL, 1.71 mmol), AIBN (47 mg, 0.29 mmol), and *i*-Pr_2NEt (149 μL, 0.86 mmol) in benzene (5.7 mL) was refluxed. After 12 h refluxing, AIBN (47 mg, 0.29 mmol) was added. The resulting mixture was refluxed for a further 12 h. Column chromatography on silica gel of the mixture gave (*E*)-**18** (hexane/Et_2O = 7/1, 340 mg, 71% as an oil) and unchanged (*E*)-**17** (hexane/Et_2O = 5/1, 32 mg, 9%), respectively: $[\alpha]_D^{16}$ −123.6 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76−0.92 (m, 15H), 1.21−1.31 (m, 6H), 1.30 (s, 3H), 1.35 (s, 3H), 1.39−1.52 (m, 6H), 2.68−2.69 (m, 1H), 3.15 (dd, *J* = 8.8 and 5.6 Hz, 1H), 3.19 (dd, *J* = 8.8 and 4.0 Hz, 1H), 4.56 (d, *J* = 5.6 Hz, 1H), 4.95−4.98 (m, 1H), 5.75−5.76 (m, 1H), 6.11−6.25 (m, 1H), 7.22−7.26 (m, 4H), 7.29−7.32 (m, 5H), 7.42−7.47 (m, 8H), 7.55−7.59 (m, 1H), 8.13−8.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.2, 13.7, 25.4, 26.7, 27.3, 29.0, 50.9, 65.9, 76.1, 78.3, 81.6, 87.3, 110.7, 123.7, 127.1, 127.9, 128.3, 128.7, 129.8, 130.3, 132.9, 143.6, 156.1, 166.0; FAB-MS *m*/*z* 837 (M^+ + H). Anal. Calcd for $C_{48}H_{60}O_5Sn$: C, 68.99; H, 7.24, Found: C, 69.19; H, 7.26.

Sulfur-Extrusive Stannylation of (*E*)-19. To a mixture of (*E*)-**12** (1.67 g, 3.03 mmol), imidazole (413 mg, 6.06 mmol), and *i*-Pr_2NEt 1.58 mL, 9.09 mmol) in CH_2Cl_2 (30 mL) was added TMSCl (577 μL,

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4.55 mmol) at 0 °C. After 20 nim stirring at this temperature, this was stirred for a further 40 min at rt. The resulting mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was evaporated. The crude TMS ether (*E*)-**19** was used for the next reaction without further purification. To a benzene solution of the above residue were added *i*-Pr_2NEt (793 μL, 4.55 mmol), Bu_3SnH (2.45 mL, 9.09 mmol), and AIBN (250 mg, 1.52 mmol). The resulting mixture was refluxed for 12 h. To the mixture was added AIBN (250 mg, 1.52 mmol); then the mixture was refluxed for a further 12 h. After evaporation of all of volatiles, NH_3/MeOH (saturated at 0 °C, 40 mL) was added, and the mixture was stirred for 40 h at rt. After evaporation of all of volatiles, the residue was purified by column chromatography on neutral silica gel. This gave (*E*)-**16** (hexane/Et_2O = 4/1, 1.6 g, 72%, as an oil) and (*E*)-*anti*-**12** (hexane/Et_2O = 1/1, 375 mg, 22% as a foam), respectively.

Mitsunobu Reaction of (*E*)-16; Formation of Nucleoside 21. To a mixture of (*E*)-**16** (5.93 g, 8.1 mmol), Boc-protected 2-amino-6-chloripurine **20** (5.99 g, 16.2 mmol), and Ph_3P (4.25 g, 16.2 mmol) in toluene (80 mL) was added DMEAD (3.79 g, 16.2 mmol) at 0 °C. The resulting mixture was stirred for 45 min at the same temperature and then stirred for a further 45 min at rt. The resulting yellow solution was heated at 100 °C for 10 min. The mixture was partitioned between AcOEt and brine. Column chromatography on neutral silica gel of the organic layer (hexane/AcOEt = 5/1) gave **21** (5.38 g, 61%) as a foam: $[\alpha]_D^{16}$ −86.4 (*c* = 1.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77−0.94 (m, 15H), 1.21−1.28 (m, 6H), 1.30 (s, 3H), 1.34−1.43 (m, 6H), 1.45 (s, 18H), 1.56 (s, 3H), 2.88 (t, *J* = 9.0 Hz, 1H), 3.11−3.14 (m, 1H), 3.51 (dd, *J* = 9.0 and 4.4 Hz, 1H), 4.63−4.71 (m, 1H), 5.18−5.19 (m, 1H), 6.06−6.17 (m, 1H), 7.18−7.25 (m, 9H), 7.34−7.36 (m, 6H), 7.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.3, 13.7, 25.3, 27.2, 27.5, 27.9, 29.0, 51.7, 65.5, 68.2, 82.4, 83.4, 84.9, 87.6, 111.3, 127.3, 127.9, 128.5, 130.3, 135.4, 143.1, 144.6, 150.6, 150.7, 151.8, 153.0, 154.5; ; FAB-MS *m*/*z* 1084 (M^+ + H). HRMS (FAB+): calcd for $C_{56}H_{75}ClN_5O_7Sn$ 1084.4377, Found 1084.4355 [M^+ + H].

Fluorination of 21; Formation of Fluoride (*E*)-23. To a CH_2Cl_2 (100 mL) solution of **21** (5.20 g, 4.8 mmol), 2,6,-di-*tert*-butyl-4-methylpyridine (DTBMP, 2.96 g, 14.4 mmol), and XeF_2 (1.14 g, 6.72 mmo) was added AgOTf (1.73 g, 6.72 mmol) at 0 °C. The resulting mixture was stirred at rt for 15 min. The mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. Column chromatography on neutral silica gel of the organic layer gave (*E*)-**23** (3.02 g, 78%) as a foam: $[\alpha]_D^{16}$ −44.6 (*c* = 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.45 (s, 18H), 1.54 (s, 3H), 3.18 (dd, *J* = 9.2 and 6.4 Hz, 1H), 3.40 (dd, *J* = 9.2 and 6.4 Hz, 1H), 3.57−3.60 (m, 1H), 4.53 (d, *J* = 5.2 Hz, 1H), 4.89−4.90 (m, 1H), 5.40 (s, 1H), 6.75 (d, $J_{H,F}$ = 80.0 Hz, 1H), 7.22−7.25 (m, 3H), 7.28−7.31 (m, 6H), 7.41−7.45 (m, 6H), 8.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 27.4, 27.8, 29.7, 46.0, 62.3 (d, $J_{C,F}$ = 8.0 Hz), 63.0, 82.6, 83.6, 85.0, 87.7, 111.8, 121.4 (d, $J_{C,F}$ = 10.8 Hz), 127.4, 128.0, 128.5, 128.6, 130.2, 143.2, 144.0, 150.2 (d, $J_{C,F}$ = 266.3 Hz), 150.6, 151.2, 151.9, 152.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.60 (d, $J_{H,F}$ = 73.4 Hz). FAB-MS *m*/*z* 812 (M^+ + H). HRMS (FAB+): calcd for $C_{44}H_{48}ClFN_5O_7$ 812.3226, Found 812.3256 [M^+ + H].

Fluorination of (*Z*)-18; Formation of Fluoride 24. To a CH_2Cl_2 (40 mL) suspension of (*Z*)-**18** (1.54 g, 1.84 mmol), DTBMP (1.13 g, 5.52 mmol), and AgOTf (760 mg, 2.94 mmol) was added XeF_2 (840 mg, 0.97 mmol) in one portion at 0 °C. The resulting mixture was stirred at rt for 20 min. The mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. The organic layer was filtrated through a Celite pad. The filtrate was evaporated. The resulting residue was treated with NaOMe (990 mg, 18.4 mmol) and MeOH (40 mL). The mixture was stirred at rt for overnight. The mixture was partitioned between aq. saturated NH_4Cl and $CHCl_3$. Column chromatography on silica gel (hexane/AcOEt = 5/1) of the organic layer gave **24** (681 mg, 74%) as a foam: $[\alpha]_D^{16}$ −63.6 (*c* = 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.50 (s, 3H), 2.76−2.79 (m, 1H), 2.83 (d, *J* = 7.2 Hz, 1H), 3.11 (dd, *J* = 9.2 and 5.2 Hz, 1H), 3.16 (dd, *J* = 9.2 and 4.8 Hz, 1H), 4.38 (dt, *J* = 6.0 and 2.0 Hz, 1H), 4.61 (t, *J* = 6.0 Hz, 1H), 4.90−4.93 (m, 1H), 6.59 (dt, $J_{H,F}$ = 82.8 Hz, *J* = 2.0 Hz, 1H), 7.22−7.26 (m, 3H), 7.29−7.32 (m, 6H), 7.37−7.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 26.4, 29.7, 44.5 (d, $J_{C,F}$ = 6.0 Hz), 65.9, 70.8, 77.2, 82.4, 87.2, 111.6, 126.1 (d, $J_{C,F}$ = 2.4 Hz), 127.2, 127.9, 128.6, 143.5, 147.0 (d, $J_{C,F}$ = 261.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −132.88 (d, $J_{H,F}$ = 73.8 Hz). FAB-MS *m*/*z* 499 (M^+ + K). Anal. Calcd for $C_{29}H_{29}FO_4 \cdot 4/5\ H_2O$: C, 73.34; H, 6.49, Found: C, 73.02; H,6.28.

Mitsunobu Reaction of 24: Formation of (*Z*)-23. To a THF (50 mL) solution of **24** (1.69 g, 3.67 mmol), Boc-protected 2-amino-6-chloripurine **20** (2.71 g, 7.34 mmol), and Ph_3P (1.93 g, 7.34 mmol) was added di(methoxyethyl)azodicarboxylate (DMEAD) (1.72 g, 7.34 mmol) at 0 °C. After 2 h stirring of the resulting mixture, this was stirred for a further 18 h at rt. The mixture was partitioned between H_2O and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 4/1) of the organic layer gave (*Z*)-**23** (2.35 g, 79%) as a foam: $[\alpha]_D^{16}$ +1.4 (*c* = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.44 (s, 18H), 1.53 (s, 3H), 3.10−3.13 (m, 1H), 3.16 (t, *J* = 8.8 Hz, 1H), 3.42 (dd, *J* = 8.8 and 4.8 Hz, 1H), 4.63−4.64 (m, 1H), 4.88 (d, *J* = 2.0 Hz, 1H), 6.76 (d, $J_{H,F}$ = 81.6 Hz, 1H), 7.20−7.29 (m, 9H), 7.37−7.39 (m, 6H), 7.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0, 27.3, 27.8, 46.8 (d, $J_{C,F}$ = 2.4 Hz), 60.9, 64.1, 82.2, 83.5, 85.2, 87.6, 111.9, 120.9 (d, $J_{C,F}$ = 4.8 Hz), 127.3, 128.0, 128.4, 130.1, 143.3, 144.7, 149.4 (d, $J_{C,F}$ = 273.5 Hz), 150.4, 150.9, 151.7, 152.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.86 (d, $J_{H,F}$ = 88.8 Hz). FAB-MS *m*/*z* 812 (M^+), 850 (M^+ + K). Anal. Calcd for $C_{44}H_{47}ClFN_5O_7$: C, 65.06; H, 5.83; N, 8.62, Found: C, 65.14; H, 5.82; N, 8.62.

Deprotection and Subsequent Silylation of (*E*)-23; Formation of (*E*)-25. To a mixture of (*E*)-**23** (550 mg, 0.68 mmol) in H_2O (6 mL) was added TFA (6 nL). The resulting yellow suspension was stirred at rt for 48 h. To the mixture was added EtOH (10 mL), then evaporated all of volatiles. This azeotropic evaporation was repeated three times. The residue was treated with NH_3/MeOH (0 °C saturated, 30 mL). The resulting mixture was stirred for 15 min at rt. The mixture was evaporated until most of the MeOH was eliminated. To the residue was added DMF (5 mL), then evaporated under azeotropic conditions using toluene. The resulting solid was dried for 48 h under vacuum condition. To a DMF (13.5 mL) solution of the above residue and imidazole (138 mg, 2.03 mmol) was dropwise added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$, 213 μL, 0.68 mmol) at 0 °C. The resulting mixture was stirred for a further 1 h at the same temperature. To this was added H_2O (30 mL), and then it was extracted by AcOEt. After evaporation of all of the volatiles of the organic layer, the residue was purified by column chromatography on silica gel (AcOEt/80%MeOH = 30/1). This gave (*E*)-**25** (220 mg, 59%) as a solid: mp > 250 °C; $[\alpha]_D^{13}$ −54.8 (*c* = 0.12, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91−1.06 (m, 1H), 2.96−2.99 (m, 1H), 4.13−4.27 (m, 4H), 4.92 (d, *J* = 3.6 Hz, 1H), 5.36 (d, *J* = 5.2 Hz, 1H), 6.47 (br-s, 2H), 6.84 (d, $J_{H,F}$ = 82.8 Hz, 1H), 7.59 (s, 1H), 10.59 (br-s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.1, 12.8, 13.0, 13.1, 17.0, 17.0, 17.0, 17.1, 17.4, 17.4, 17.5, 17.7, 47.4, 58.0 (d, $J_{C,F}$ = 9.6 Hz), 60.5, 72.2, 74.3, 116.9, 118.7 (d, $J_{C,F}$ = 7.2 Hz), 135.3, 149.9 (d, $J_{C,F}$ = 259.1 Hz), 151.3, 153.7, 157.0; ^{19}F NMR (470 MHz, DMSO-d_6) δ −127.15 (d, $J_{H,F}$ = 74.3 Hz). FAB-MS *m*/*z* 554 (M^+ + H). HRMS (FAB+): calcd for $C_{24}H_{41}FN_5O_5Si_2$ 554.2630, Found 554.2635 [M^+ + H].

Deprotection and Subsequent Silylation of (*Z*)-23; Formation of (*Z*)-25. Compound (*Z*)-**23** (2.29 g, 2.82 mmol) was dissolved in THF (8 mL) and 80% HCO_2H (30 mL). The resulting mixture was heated at 60 °C for 4 h. After evaporation of all of the volatiles, the residue was coevaporated with EtOH (*ca.* 30 mL). This was treated with NH_3/MeOH (0 °C saturated, *ca.* 30 mL). The residue was evaporated, then coevaporated with toluene (*ca.* 30 mL) for three times. The resulting residue was dissolved in pyridine (50 mL). To the suspension was added $TIPDSCl_2$ (933 μL, 2.96 mmol) at 0 °C. The resulting suspension was stirred for 20 h at the same temperature. The mixture was treated with crushed ice. After 20 min stirring, the mixture was adsorbed with silica gel. Column chromatography on silica gel (AcOEt/MeOH = 50/1 containing 0.25% of H_2O) gave (*Z*)-**25** (992 mg, 64%) as a solid. mp > 250 (dec) °C; $[\alpha]_D^{14}$ +1.3 (*c* = 0.67, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ

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0.88−1.07 (m, 27H), 2.85−2.86 (m, 1H), 3.16 (d, J = 5.2 Hz, 1H), 3.88 (t, J = 3.6 Hz, 1H), 4.18−4.22 (m, 2H), 5.00 (s, 1H), 5.45 (d, J = 4.4 Hz,1 H), 6.51 (br-s, 2H), 7.18 (d, $J_{H,F}$ = 81.6 Hz, 1H), 7.42 (s, 1H), 10.60 (br-s, 1H) ; ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.0, 12.6, 12.6, 12.7, 16.8, 16.9, 16.9, 17.0, 17.2, 17.2, 17.3, 17.5, 43.6, 56.4, 59.3, 71.8, 74.8, 116.5, 118.5 (d, $J_{C,F}$ = 6.0 Hz), 134.3, 149.0 (d, $J_{C,F}$ = 257.9 Hz), 150.9, 153.7, 156.7; ^{19}F NMR (470 MHz, DMSO-d_6) δ −127.48 (d, $J_{H,F}$ = 88.8 Hz). FAB-MS m/z 554 (M^+ + H). Anal. Calcd for $C_{24}H_{40}FN_5O_5Si_2 \cdot 1/2\ H_2O$: C, 51.22; H, 7.34; N, 12.44, Found: C, 51.09; H, 7.25; N, 12.23.

Radical Deoxygenation of (*E*)-25; Formation of (*E*)-26. To a mixture of (*E*)-**25** (226 mg, 0.41 mmol), DMAP (55 mg, 0.45 mmol), and *i*-Pr_2NEt (178 μL, 1.02 mmol) in CH_2Cl_2 (8 mL) was added PhOC(S)Cl (141 μL, 1.02 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. The mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. The inorganic layer was further washed with AcOEt. The combined organic layer was evaporated. The residue was roughly purified by column chromatography on silica gel (AcOEt/*i*-PrOH = 7/1). This gave a crude thiocarbonate. This was used for next reaction without further purification. A mixture of the thiocarbonate, TTMSS (315 μL, 1.02 mmol), and AIBN (34 mg, 0.21 mmol) in toluene (8 mL) was heated at 100 °C for 0.5 h. The mixture was purified by column chromatography on silica gel (AcOEt/80%MeOH = 50/1). This gave (*E*)-**26** (148 mg, 67%) as a solid. mp > 240 (dec) °C; $[\alpha]_D^{14}$ −8.0 (c = 0.67, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.91−1.05 (m, 28H), 2.10−2.17 (m, 1H), 2.45−2.47 (m, 1H), 2.83−2.87 (m, 1H), 3.99 (dd, J = 11.6 and 7.2 Hz, 1H), 4.16 (dd, J = 11.6 and 4.4 Hz, 1H), 4.50−4.52 (m, 1H), 5.21−5.24 (m, 1H), 6.47 (br-s, 2H), 7.00 (d, $J_{H,F}$ = 83.6 Hz, 1H), 7.57 (s, 1H), 10.60 (br-s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.1, 12.6, 13.0, 13.0, 17.0, 17.1, 17.4, 17.4, 17.5, 17.7, 39.9, 51.4, 52.0 (d, $J_{C,F}$ = 10.7 Hz), 61.7 (d, $J_{C,F}$ = 4.7 Hz), 72.7, 117.1, 121.1 (d, $J_{C,F}$ = 7.2 Hz), 135.1, 149.8 (d, $J_{C,F}$ = 258.7 Hz), 151.1, 153.7, 157.0; ^{19}F NMR (470 MHz, DMSO-d_6) δ −127.48 (d, $J_{H,F}$ = 88.8 Hz). FAB-MS m/z 538 (M^+ + H). HRMS (FAB+): calcd for $C_{24}H_{41}FN_5O_4Si_2$ 538.2681, Found 538.2701 [M^+ + H].

Radical Deoxygenation of (*Z*)-25; Formation of (*Z*)-26. To a mixture of (*Z*)-**25** (177 mg, 0.32 mmol), DMAP (43 mg, 0.35 mmol), and *i*-Pr_2NEt (140 μL, 0.8 mmol) was added PhOC(S)Cl (110 μL, 0.8 mmol) at 0 °C. The resulting solution was stirred at the same temperature for 1 h. The mixture was partitioned between aq. saturated $NaHCO_3$ and CH_2Cl_2. The inorganic layer was further extracted by AcOEt. After evaporation of all of the volatiles of the combined organic layer, the residue was roughly purified by column chromatography on silica gel (AcOEt/*i*-PrOH = 7/1). This gave a crude thiocarbonate. This was used for the next step without further purification. The crude thiocarbonate was dissolved in degassed toluene; to this were sequentially added TTMSS (247 μL, 0.8 mmol) and AIBN (26 mg, 0.16 mmol). The resulting mixture was heated at 100 °C for 0.5 h. Column chromatography on silica gel (AcOEt/80% MeOH = 50/1) of the resulting mixture gave (*Z*)-**26** (103 mg, 60%) as a foam: $[\alpha]_D^{14}$ +18.1 (c = 0.08, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90−1.05 (m, 28H), 2.00 (dd, J = 12.8 and 6.0 Hz, 1H), 2.12−2.20 (m, 1H), 2.59−2.61 (m, 1H), 4.01 (dd, J = 12.0 and 3.6 Hz, 1H), 4.14 (dd, J = 12.0 and 3.6 Hz, 1H), 4.38−4.44 (m, 1H), 5.35 (d, J = 7.6 Hz, 1H), 6.50 (br-s, 2H), 7.10 (d, $J_{H,F}$ = 81.2 Hz, 1H), 7.43 (s, 1H), 10.61 (br-s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 12.0, 12.4, 12.6, 12.6, 16.9, 16.9, 17.0, 17.2, 17.2, 17.3, 17.4, 39.7, 48.7 (d, $J_{C,F}$ = 2.4 Hz), 49.1 (d, $J_{C,F}$ = 3.6 Hz), 59.7, 71.1, 116.4, 120.1 (d, $J_{C,F}$ = 7.2 Hz), 134.5, 148.0 (d, $J_{C,F}$ = 257.9 Hz), 150.7, 153.6, 156.7; ^{19}F NMR (470 MHz, DMSO-d_6) δ −126.91 (d, $J_{H,F}$ = 88.8 Hz). FAB-MS m/z 538 (M^+ + H). HRMS (FAB+): calcd for $C_{24}H_{41}FN_5O_4Si_2$ 538.2681, Found 538.2685 [M^+ + H].

2-Amino-9-((1*S*,3*R*,4*S*,*E*)-2-(fluoromethylene)-4-hydroxy-3-(hydroxymethyl)cyclopentyl)-1,9-dihydro-6*H*-purin-6-one (*E*)-3. To a THF (2 mL) solution of (*E*)-**26** (145 mg, 0.27 mmol) was added 80% TFA (5 mL). The mixture was stirred at rt for 24 h. After evaporation of all of the volatiles, the residue was treated with NH_3/MeOH (0 °C saturated, 5 mL) at rt for 15 min. The resulting mixture was evaporated. The residue was purified by reverse phase HPLC (7% MeCN in H_2O containing 0.1% of AcOH, 20 mL/min, t_R = 7.9 min). This gave (*E*)-**3** (17 mg, 21%) as a solid: mp 228−230 °C; $[\alpha]_D^{14}$ −1.6 (c = 0.67, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.01−2.06 (m, 1H), 2.24−2.30 (m, 1H), 2.78 (br-s, 1H), 3.55−3.66 (m, 2H), 4.27 (br-s, 1H), 4.92 (d, J = 2.8 Hz, 1H), 4.96 (t, J = 1.6 Hz, 1H), 5.41−5.43 (m, 1H), 6.42 (s, 2H), 6.62 (d, $J_{H,F}$ = 82.8 Hz, 1H), 7.77 (s, 1H), 10.55 (br-s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 40.1, 52.1, 52.2, 60.6, 71.2, 116.6, 124.9 (d, $J_{C,F}$ = 8.4 Hz), 135.9, 148.2 (d, $J_{C,F}$ = 254.3 Hz), 151.3, 153.7, 157.0; ^{19}F NMR (470 MHz, DMSO-d_6) δ −131.23 (d, $J_{H,F}$ = 88.8 Hz). FAB-MS m/z 296 (M^+ + H). HRMS (FAB+): calcd for $C_{12}H_{15}FN_5O_3$ 296.1159, Found 296.1161 [M^+ + H].

2-Amino-9-((1*S*,3*R*,4*S*,*Z*)-2-(fluoromethylene)-4-hydroxy-3-(hydroxymethyl)cyclopentyl)-1,9-dihydro-6*H*-purin-6-one (*Z*)-3. Compound (*Z*)-**26** (157 mg, 0.29 mmol) was treated with the same procedure as that described for (*E*)-**26**. The mixture was purified by reverse phase HPLC (7% MeCN in H_2O containing 0.1% of TFA, 20 mL/min, t_R = 3.4−6.2 min). After evaporation of all of the volatiles, the residue was triturated with MeCN. The precipitate was collected and dried in vacuo. This gave (*Z*)-**3** (42 mg, 49%) as a solid: mp > 210 (dec) °C; $[\alpha]_D^{16}$ +35.3 (c = 0.11, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.04−2.08 (m, 2H), 2.50−2.52 (m, 1H), 3.50−3.56 (m, 1H), 3.63−3.67 (m, 1H), 4.17 (br-s, 1H), 4.96−4.97 (m, 2H), 5.48−5.50 (m, 1H), 6.41 (br-s, 2H), 6.88 (d, $J_{H,F}$ = 83.2 Hz, 1H), 7.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 40.9, 50.8 (d, $J_{C,F}$ = 3.6 Hz), 51.4, 62.2, 71.0, 116.2, 123.1 (d, $J_{C,F}$ = 3.6 Hz), 135.8, 147.1 (d, $J_{C,F}$ = 257.9 Hz), 150.9, 153.4, 156.8; ^{19}F NMR (470 MHz, DMSO-d_6) δ −127.12 (d, $J_{H,F}$ = 87.2 Hz). FAB-MS m/z 296 (M^+ + H). HRMS (FAB+): calcd for $C_{12}H_{15}FN_5O_3$ 296.1159, Found 296.1163 [M^+ + H].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00105.

^{1}H and ^{13}C NMR spectra for all new compounds and calculated structures of intermediates **VII** and **VIII** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kumamoto@pharm.showa-u.ac.jp.

Notes

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■ REFERENCES

(1) White, D. O.; Fenner, F. J. *Medical Virology*, 4th ed.; Academic: New York, 1994; Chapter 22.

(2) Dienstag, J. L. *N. Engl. J. Med.* **2008**, *359*, 1486−1500.

(3) (a) Innaimo, S. F.; Seifer, M.; Bisacchi, G. S.; Stabdring, D. N.; Zahler, R.; Colonno, R. J. *Antimicrob. Agents Chemother.* **1997**, *41*, 1444−1448. (b) Yamanaka, G.; Wilson, T.; Innaimo, S.; Bisacchi, G. S.; Egli, P.; Rinehart, J. K.; Zahler, R.; Colonno, R. J. *Antimicrob. Agents Chemother.* **1999**, *43*, 190−193.

DOI: 10.1021/acs.joc.6b00105
J. Org. Chem. 2016, 81, 2827−2836

(4) (a) Will, H.; Reiser, W.; Weimer, T.; Pfaff, E.; Büscher, M.; Sprengel, R.; Cattaneo, R.; Schaller, H. *J. Virol.* **1987**, *61*, 904−911. (b) Scott, L. J.; Keating, G. M. *Drugs* **2009**, *69*, 1003−1033.
(5) As selected reviews, see: (a) Wang, J.; Sánchez-Roselló, M.; Aceña, L.; del Pozo, C.; Sorochinsky, A. L.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506. (b) Qiu, X.-L.; Xu, X.-H.; Qing, F.-L. *Tetrahedron* **2010**, *66*, 789−843.
(6) (a) Watanabe, Y.; Ueno, Y.; Araki, T.; Endo, T.; Okawara, M. *Tetrahedron Lett.* **1986**, *27*, 215−218. (b) Dubois, E.; Beau, J.-M. *Tetrahedron Lett.* **1990**, *31*, 5165−5168. (c) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7440. (d) Wnuk, S. F.; Robins, M. J. *Can. J. Chem.* **1993**, *71*, 192−198. (e) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, F. M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45−58. (f) Onuma, S.; Kumamoto, H.; Kawato, K.; Tanaka, H. *Tetrahedron* **2002**, *58*, 2497−2503. (g) Kumamoto, H.; Onuma, S.; Tanaka, H. *J. Org. Chem.* **2004**, *69*, 72−78. (h) Kumamoto, H.; Deguchi, K.; Wagata, T.; Furuya, Y.; Odanaka, Y.; Kitade, Y.; Tanaka, H. *Tetrahedron* **2009**, *65*, 8007−8013.
(7) (a) Gaudino, J. J.; Wilcox, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 4374−4380. (b) Takagi, C.; Sukeda, M.; Kim, H.-S.; Wataya, Y.; Yabe, S.; Kitade, Y.; Matsuda, A.; Shuto, S. *Org. Biomol. Chem.* **2005**, *3*, 1245−1251.
(8) Marco-Contelles, J.; Destabel, C.; Gallego, P.; Chiara, J. L.; Bernabé, M. *J. Org. Chem.* **1996**, *61*, 1354−1362.
(9) (a) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641−3642. (b) As a review, see: Chatgilialoglu, C. *Chem.—Eur. J.* **2008**, *14*, 2310−2320.
(10) Examples of 1,6 hydrogen transfer on the α-silyl radicals; see: (a) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037−5038. (b) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, *64*, 819−825.
(11) (a) Dey, S.; Garner, P. *J. Org. Chem.* **2000**, *65*, 7697−7699. (b) Fletcher, S.; Shahani, V. M.; Lough, A. J.; Gunning, P. T. *Tetrahedron* **2010**, *66*, 4621−4632.
(12) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1−28.
(13) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566−567.
(14) (a) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461−1471. (b) As a review, see: Tius, M. A. *Tetrahedron* **1995**, *51*, 6605−6634.

DOI: 10.1021/acs.joc.6b00105
J. Org. Chem. 2016, 81, 2827−2836