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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

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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 phenylsulfanyethynyl 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

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ASSOCIATED CONTENT

Supporting Information

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

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benzoyl-protected **17** underwent the stannylation in the manner of retention of configuration. Following XeF₂-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.

Graphical Abstract

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 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 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 stannylation⁶ 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 **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.

The starting material was acetylene derivative **7** that was prepared from D-ribose by a literature procedure.⁸ Compound **7** was reacted with Ph₃P=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 Bu₄NF 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** $\rightarrow$ **I** $\rightarrow$ **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 TrOCH₂–groups because *syn*-isomer **13** has a lower diastereomeric ratio (*Z/E* = 1.4/1) than that of *anti*-**12**.

When the reaction of **6** was carried out at ambient temperature using Et₃B 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 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 Bu₃SnH and AIBN in the presence of *i*-Pr₂NEt 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 Bu₃Sn- and TrOCH₂-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 NH₃/MeOH.

Next, the transformation of **16** and **18** to fluorinated carbocyclic ribonucleosides (*Z*)- and (*E*)-**23** was examined (Scheme 7). Thus, (*E*)-**16** was reacted with Boc-protected 2-amino-6-chloropurine (**20**)^{11a,b} under Mitsunobu conditions¹² [bis(2-methoxyethyl)azodicarboxylate (DMEAD),¹³ Ph₃P] in toluene under reflux conditions to give **21** in moderate yield. When the vinylstanne **21** was reacted with XeF₂, AgOTf, and 2,6-*di-tert*-butyl-4-methylpyridine (**22**)^{14a,b} in CH₂Cl₂, 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 Bu₃Sn 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 carried out by treatment with aqueous TFA or HCO₂H 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-tetraisopropylidisiloxane 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 unsatisfactory 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 exhibited a better SI value ($>23 \times 10^3$) than that (21×10^3) of **1** (Table 4). These results indicated that 6''-fluorinated 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 F₂₅₄. 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 $\text{Ph}_3\text{PCH}_2\text{OCH}_3\text{Cl}$ (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 $-30\text{ }^\circ\text{C}$. 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 $-30\text{ }^\circ\text{C}$. 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: $[\alpha]_{\text{D}}^{18} - 84.5$ ($c = 1.30$, 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 ($\text{M}^+ - \text{H}$). HRMS (FAB+): calcd for $\text{C}_{11}\text{H}_{15}\text{O}_4$ 211.0970, Found 211.0996 [$\text{M}^+ - \text{H}$].

***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 CH₂Cl₂ (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 NaHCO₃ and CH₂Cl₂. 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, CHCl₃); ¹H NMR (400 MHz, C₆D₆) 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); ¹³C NMR (125 MHz, C₆D₆) 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, 102.9, 108.2, 108.4, 149.5, 151.6; FAB-MS *m/z* 325 (*M*⁺ - H). HRMS (FAB+): calcd for C₁₇H₂₉O₄Si 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 NaHCO₃ and AcOEt. The organic layer was dried by Na₂SO₄; 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 Na₂SO₄ 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₄O₄SeSi 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*-Pr₂NEt (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 NaHCO₃ and CH₂Cl₂. 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, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR for major isomer **11** (125 MHz, CDCl₃) 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; ¹³C NMR for minor isomer **11** (125 MHz, CDCl₃) 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 C₄₁H₄₈O₄SeSi 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 PhSSO₂Ph (6.04 g, 24.1 mmol) via cannula. After 50 min stirring at the same temperature, the mixture was partitioned between aq. saturated NH₄Cl 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 Et₂O/hexane: mp 126–128 °C. $[\alpha]_D^{18} - 0.6$ (*c* = 1.61, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₄₇H₅₂O₄SSeSi: 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 μ L, 0.74 mmol) was added freshly opened Et₃B (1.0 mol/L in THF, 740 μ L, 0.74 mmol) at -70 °C under a positive pressure of dry Ar (including trace amount of O₂). The resulting mixture was stirred for 96 h at the same temperature. During this reaction, further Et₃B (740 μ L) 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 ^1H 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:** $[\alpha]_{\text{D}}^{18} + 148.1$ (c = 0.35, CHCl_3); ^1H 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 $\text{C}_{35}\text{H}_{34}\text{O}_4\text{S}$: C, 76.33; H, 6.22, Found: C, 76.54; H, 6.32. **Physical data for (E)-anti-12:** $[\alpha]_{\text{D}}^{18} - 258.5$ (c = 0.47, CHCl_3); ^1H 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 $\text{C}_{35}\text{H}_{34}\text{O}_4\text{S} \cdot 1/2 \text{H}_2\text{O}$: C, 75.09; H, 6.30, Found: C, 75.07; H, 6.12. **Physical data for (Z)-syn-13:** $[\alpha]_{\text{D}}^{18} - 48.2$ (c = 0.46, CHCl_3); ^1H 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 $\text{C}_{35}\text{H}_{34}\text{O}_4\text{S} \cdot 1/4 \text{H}_2\text{O}$: C, 75.72; H, 6.26, Found: C, 75.58; H, 6.15. **Physical data for (E)-syn-13:** $[\alpha]_{\text{D}}^{18} + 4.1$ (c = 0.51, CHCl_3); ^1H 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 m/z 550 (M^+). Anal. Calcd for $\text{C}_{35}\text{H}_{34}\text{O}_4\text{S}$: C, 76.33; H, 6.22, Found: C, 76.34; H, 6.28.

(1S)-1-((4S,5S)-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 Bu₄NF (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: $[\alpha]_D^{18} - 15.3$ ($c = 0.35$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₄₁H₃₈O₄SSe·H₂O: C, 68.04; H, 5.57, Found: C, 67.84; H, 5.24.

(((1S)-1-((4R,5S)-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 CH₂Cl₂ (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 NaHCO₃ and CH₂Cl₂. Column chromatography on silica gel (hexane/Et₂O = 20/1) of the organic layer gave **15** (2.98 g, 97%) as an oil: $[\alpha]_D^{18} - 6.1$ ($c = 0.80$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₅₀H₅₈O₄SSeSi: 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), Bu₃SnH (1.82 mL, 6.75 mmol), AIBN (186 mg, 1.13 mmol), and *i*-Pr₂NEt (589 μ L, 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/Et₂O = 15/1, 1.24 g, 75% as an oil) and (E)-**16** (hexane/Et₂O = 5/1, 172 mg, 10% as an oil), respectively. **Physical data for (Z)-16:** $[\alpha]_D^{20} - 5.9$ ($c = 0.71$, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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:** $[\alpha]_D^{16} - 111.8$ ($c = 0.35$, $CHCl_3$); 1H 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.

(3aR,4S,6R,6aR,Z)-2,2-Dimethyl-5-((phenylthio)methylene)-6-((trityloxy)methyl)tetrahydro-4H-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*-Pr₂NEt (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: $[\alpha]_D^{19} - 312.6$ ($c = 0.67$, $CHCl_3$); 1H 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: $[\alpha]_D^{19} - 109.1$ ($c = 0.52$, $CHCl_3$); 1H 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/Et₂O = 15/1 to 5/1) gave (*Z*)-16 (62 mg, 23%) and (*E*)-16 (136 mg, 51%), respectively.

(3aR,4S,6R,6aR,E)-2,2-Dimethyl-5-((phenylthio)methylene)-6-((trityloxy)methyl)tetrahydro-4H-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: $[\alpha]_D^{18} - 258.1$ ($c = 0.51$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₄₂H₃₈O₅S·H₂O: 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), Bu₃SnH (460 μ L, 1.71 mmol), AIBN (47 mg, 0.29 mmol), and *i*-Pr₂NEt (149 μ L, 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/Et₂O = 7/1, 340 mg, 71% as an oil) and unchanged (*E*)-**17** (hexane/Et₂O = 5/1, 32 mg, 9%), respectively: $[\alpha]_D^{16} - 123.6$ ($c = 0.67$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₄₈H₆₀O₅Sn: 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*-Pr₂NEt (1.58 mL, 9.09 mmol) in CH₂Cl₂ (30 mL) was added TMSCl (577 μ L, 4.55 mmol) at 0 °C. After 20 min stirring at this temperature, this was stirred for a further 40 min at rt. The resulting mixture was partitioned between aq. saturated NaHCO₃ and CH₂Cl₂. 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*-Pr₂NEt (793 μ L, 4.55 mmol), Bu₃SnH (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, NH₃/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/Et₂O = 4/1, 1.6 g, 72%, as an oil) and (*E*)-*anti*-**12** (hexane/Et₂O = 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 Ph₃P (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: $[\alpha]_D^{16} - 86.4$ ($c = 1.33$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₅₆H₇₅ClN₅O₇Sn 1084.4377, Found 1084.4355 [$M^+ + H$].

Fluorination of 21; Formation of Fluoride (*E*)-23.

To a CH₂Cl₂ (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 XeF₂ (1.14 g, 6.72 mmol) 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 NaHCO₃ and CH₂Cl₂. Column chromatography on neutral silica gel of the organic layer gave (*E*)-**23** (3.02 g, 78%) as a foam: $[\alpha]_D^{16} - 44.6$ ($c = 0.42$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; ¹⁹F NMR (470 MHz, CDCl₃) δ -120.60 (d, $J_{H,F} = 73.4$ Hz). FAB-MS m/z 812 ($M^+ + H$). HRMS (FAB+): calcd for C₄₄H₄₈ClFN₅O₇ 812.3226, Found 812.3256 [$M^+ + H$].

Fluorination of (*Z*)-18; Formation of Fluoride 24.

To a CH₂Cl₂ (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 XeF₂ (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 NaHCO₃ and CH₂Cl₂. 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 NH₄Cl and CHCl₃. Column chromatography on silica gel (hexane/AcOEt = 5/1) of the organic layer gave **24** (681 mg, 74%) as a foam: $[\alpha]_D^{16} - 63.6$ ($c = 0.33$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 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, $J_{\text{H,F}} = 82.8$ 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, $J_{\text{C,F}} = 6.0$ Hz), 65.9, 70.8, 77.2, 82.4, 87.2, 111.6, 126.1 (d, $J_{\text{C,F}} = 2.4$ Hz), 127.2, 127.9, 128.6, 143.5, 147.0 (d, $J_{\text{C,F}} = 261.0$ Hz); ^{19}F NMR (470 MHz, CDCl_3) δ -132.88 (d, $J_{\text{H,F}} = 73.8$ Hz). FAB-MS m/z 499 ($\text{M}^+ + \text{K}$). Anal. Calcd for $\text{C}_{29}\text{H}_{29}\text{FO}_4 \cdot 4/5 \text{H}_2\text{O}$: 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: $[\alpha]_{\text{D}}^{16} + 1.4$ ($c = 0.95$, CHCl_3); ^1H 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, $J_{\text{H,F}} = 81.6$ 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, $J_{\text{C,F}} = 2.4$ Hz), 60.9, 64.1, 82.2, 83.5, 85.2, 87.6, 111.9, 120.9 (d, $J_{\text{C,F}} = 4.8$ Hz), 127.3, 128.0, 128.4, 130.1, 143.3, 144.7, 149.4 (d, $J_{\text{C,F}} = 273.5$ Hz), 150.4, 150.9, 151.7, 152.0; ^{19}F NMR (470 MHz, CDCl_3) δ -119.86 (d, $J_{\text{H,F}} = 88.8$ Hz). FAB-MS m/z 812 (M^+), 850 ($\text{M}^+ + \text{K}$). Anal. Calcd for $\text{C}_{44}\text{H}_{47}\text{ClFN}_5\text{O}_7$: 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-tetraisopropylidisiloxane (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 $> 250^\circ\text{C}$; $[\alpha]_{\text{D}}^{13} - 54.8$ ($c = 0.12$, MeOH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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, $J_{\text{H,F}} = 82.8$ Hz, 1H), 7.59 (s, 1H), 10.59 (br-s, 1H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) 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, $J_{\text{C,F}} = 9.6$ Hz), 60.5, 72.2, 74.3, 116.9, 118.7 (d, $J_{\text{C,F}} = 7.2$ Hz), 135.3, 149.9 (d, $J_{\text{C,F}} = 259.1$ Hz), 151.3, 153.7, 157.0; ^{19}F NMR (470 MHz, $\text{DMSO}-d_6$) δ -127.15 (d,

$J_{\text{H,F}} = 74.3 \text{ Hz}$). FAB-MS m/z 554 ($\text{M}^+ + \text{H}$). HRMS (FAB+): calcd for $\text{C}_{24}\text{H}_{41}\text{FN}_5\text{O}_5\text{Si}_2$ 554.2630, Found 554.2635 [$\text{M}^+ + \text{H}$].

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 ($\text{AcOEt}/\text{MeOH} = 50/1$ containing 0.25% of H_2O) gave (Z)-25 (992 mg, 64%) as a solid. mp > 250 (dec) $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} + 1.3$ ($c = 0.67$, MeOH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.88–1.07 (m, 27H), 2.85–2.86 (m, 1H), 3.16 (d, $J = 5.2 \text{ Hz}$, 1H), 3.88 (t, $J = 3.6 \text{ Hz}$, 1H), 4.18–4.22 (m, 2H), 5.00 (s, 1H), 5.45 (d, $J = 4.4 \text{ Hz}$, 1H), 6.51 (br-s, 2H), 7.18 (d, $J_{\text{H,F}} = 81.6 \text{ Hz}$, 1H), 7.42 (s, 1H), 10.60 (br-s, 1H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) 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, $J_{\text{C,F}} = 6.0 \text{ Hz}$), 134.3, 149.0 (d, $J_{\text{C,F}} = 257.9 \text{ Hz}$), 150.9, 153.7, 156.7; ^{19}F NMR (470 MHz, $\text{DMSO}-d_6$) δ -127.48 (d, $J_{\text{H,F}} = 88.8 \text{ Hz}$). FAB-MS m/z 554 ($\text{M}^+ + \text{H}$). Anal. Calcd for $\text{C}_{24}\text{H}_{40}\text{FN}_5\text{O}_5\text{Si}_2 \cdot 1/2 \text{H}_2\text{O}$: 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*-Pr₂NEt (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 ($\text{AcOEt}/i\text{-PrOH} = 7/1$). 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 ($\text{AcOEt}/80\%\text{MeOH} = 50/1$). This gave (E)-26 (148 mg, 67%) as a solid. mp > 240 (dec) $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} - 8.0$ ($c = 0.67$, MeOH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) 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, $J_{\text{H,F}} = 83.6 \text{ Hz}$, 1H), 7.57 (s, 1H), 10.60 (br-s, 1H); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) 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, $J_{\text{C,F}} = 10.7 \text{ Hz}$), 61.7 (d, $J_{\text{C,F}} = 4.7 \text{ Hz}$), 72.7, 117.1, 121.1 (d, $J_{\text{C,F}} = 7.2 \text{ Hz}$), 135.1, 149.8 (d, $J_{\text{C,F}} = 258.7 \text{ Hz}$), 151.1, 153.7, 157.0; ^{19}F NMR (470 MHz, $\text{DMSO}-d_6$) δ -127.48 (d, $J_{\text{H,F}} = 88.8 \text{ Hz}$). FAB-MS m/z 538 ($\text{M}^+ + \text{H}$). HRMS (FAB+): calcd for $\text{C}_{24}\text{H}_{41}\text{-FN}_5\text{O}_4\text{Si}_2$ 538.2681, Found 538.2701 [$\text{M}^+ + \text{H}$].

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*-Pr₂NEt (140 μ L, 0.8 mmol) was added PhOC(S)Cl (110 μ L, 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 NaHCO₃ and CH₂Cl₂. 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 TTMS (247 μ L, 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: $[\alpha]_D^{25} + 18.1$ (*c* = 0.08, MeOH); ¹H 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); ¹³C 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; ¹⁹F 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 C₂₄H₄₁FN₅O₄Si₂ 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 NH₃/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 H₂O 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; $[\alpha]_D^{25} - 1.6$ (*c* = 0.67, MeOH); ¹H 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); ¹³C 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; ¹⁹F 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 C₁₂H₁₅FN₅O₃ 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 H₂O 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); ^1H 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, $J_{\text{H,F}} = 83.2$ Hz, 1H), 7.67 (s, 1H); ^{13}C NMR (125 MHz, DMSO- d_6) δ 40.9, 50.8 (d, $J_{\text{C,F}} = 3.6$ Hz), 51.4, 62.2, 71.0, 116.2, 123.1 (d, $J_{\text{C,F}} = 3.6$ Hz), 135.8, 147.1 (d, $J_{\text{C,F}} = 257.9$ Hz), 150.9, 153.4, 156.8; ^{19}F NMR (470 MHz, DMSO- d_6) δ –127.12 (d, $J_{\text{H,F}} = 87.2$ Hz). FAB-MS m/z 296 ($\text{M}^+ + \text{H}$). HRMS (FAB+): calcd for $\text{C}_{12}\text{H}_{15}\text{FN}_5\text{O}_3$ 296.1159, Found 296.1163 [$\text{M}^+ + \text{H}$].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

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

Scheme 1.
Retrosynthetic Analysis for **3**

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

Scheme 3.
Preparation of Radical Precursor 6

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

Scheme 5.

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

Scheme 6.

Sulfur-Extrusive Stannylation of Sulfides 12, 17, and 19

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

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

Table 1.

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

entry	precursor	temp. [°C]	time [h] ^a	yield [%] of <i>anti</i> -12 (Z/E) ^b	yield [%] of <i>syn</i> -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

^aThe reaction times were determined by complete consumption of the corresponding precursors monitoring by TLC.^bThe ratio of *Z/E* isomer was determined by integration from ¹H NMR spectra.^cA catalytic amount of AIBN was used as an initiator instead of Et₃B.^dUncyclized **14** was recovered in 26% after desilylation.

Table 2.

Sulfur-Extrusive Stannylation of the Sulfides 12 and 17

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

^{*a*}The stannane (*E*)-**16** was obtained after desilylation of intermediate by NH₃/MeOH.

^{*b*}(*E*)-**12** was recovered in 22% as the unchanged sulfide.

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

compd.	EC ₅₀ (μM)	CC ₅₀ (μM) (HepG2)	SI
(<i>E</i>)-3	0.0003 ± 0.00001	34.9 ± 1.2	116 × 10 ³
1	0.0005 ± 0.0003	13.8 ± 8.3	28 × 10 ³

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

compd.	EC ₅₀ (μ M)	CC ₅₀ (μ M) (HepG2)	SI
(<i>Z</i>)-3	0.0044 $\pm$ 0.0003	>100	>23 $\times$ 10 ³
1	0.0025 $\pm$ 0.0002	52.9	21 $\times$ 10 ³