



Cite this: *RSC Adv.*, 2023, 13, 15999

# Synthesis of novel entecavir analogues having 4'-cyano-6''-fluoromethylenecyclopentene skeletons as an aglycone moiety as highly potent and long-acting anti-hepatitis B virus agent†

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Encouraged by our recent findings that 4'-cyano-deoxyguanosine (2), entecavir analogues 4 and 5 are highly potent anti-hepatitis B virus (HBV) agents, we designed and synthesized 6 having a hybridized structure of 4 and 5. The chiral quaternary carbon portion at the 4'-position, which is substituted by cyano- and 5'-hydroxymethyl groups, was stereospecifically constructed by radical-mediated 5-*exo-dig* mode cyclization of 10. The introduction of the fluorine atom into the 6''-position was achieved by radical-mediated stannylation of sulfide (*E*)-11 and subsequent electrophilic fluorination of (*E*)-12. The desired (*E*)-6 was obtained after the introduction of the guanine base into (*E*)-18 under Mitsunobu conditions and following global deprotection. The stereoisomer (*Z*)-6 was also prepared by the same procedure using (*Z*)-12. Compound (*E*)-6 showed highly potent anti-HBV activity ( $EC_{50} = 1.2$  nM) with favorable cytotoxicity ( $CC_{50} = 93$   $\mu$ M).

Received 17th March 2023

Accepted 9th May 2023

DOI: 10.1039/d3ra01750h

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## 1. Introduction

The infection of hepatitis B virus (HBV)<sup>1,2</sup> causes a serious hepatopathy, which develops chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (HCC).<sup>3</sup> HBV possesses a double-strand circular DNA as a genome, which is regenerated from pre-genomic RNA catalyzed by its own reverse transcriptase (RT) for efficient replication.<sup>4,5</sup> Lately, the anti-HBV chemotherapy by typically employing nucleoside analogue RT inhibitors (NRTIs),<sup>6,7</sup> such as entecavir (1, Fig. 1),<sup>8–10</sup> has improved the morbidity and mortality of CHB, cirrhosis, and HCC. Despite this effective treatment, the longtime continuous

use of NRTIs is necessary, which in turn leads to the emergence of drug-resistant HBV variants, which pose serious challenges.<sup>11</sup>

We have previously reported that purine nucleosides having a cyano group at the 4'-position on the deoxyribosyl moiety, such as 2 and 3, exert potent anti-HBV activity compared to 1 not only against wild type but also against entecavir-resistant HBV.<sup>12</sup> Molecular models of HBV-reverse transcriptase (RT) with corresponding triphosphate of 2 and 3 indicate that, 2 or 3-triphosphate is well accommodated in HBV-RT due to an excellent interaction between hydrophobic pockets of HBV-RT and 4'-cyano group.<sup>13</sup> Unfortunately, these purine nucleosides proved to be overly cytotoxic. One of our recent studies towards the development of nucleoside anti-HBV agents has revealed that the entecavir analogue (4) possessing a fluorine atom at the

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ra01750h>

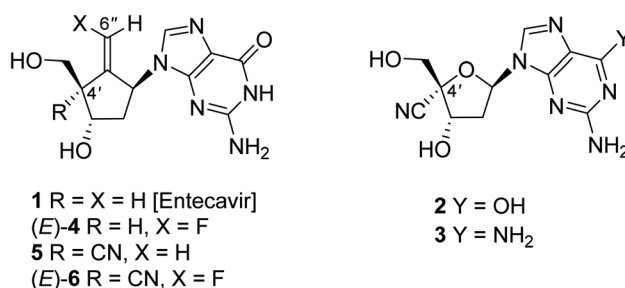


Fig. 1 Structures of compounds 1–6.



olefin terminal is more potent against wild-type HBV than the parent compound **1** and less cytotoxic albeit the actual roles of the fluorine atom located at the olefin terminal have been unclear.<sup>13</sup> Recently, we found that compound **5**, which is a 4'-cyano-derivative of entecavir (**1**), possesses potent activity against an entecavir-resistant HBV variant without causing significant cytotoxicity.<sup>14</sup> Based on these findings, we designed, synthesized, and identified a novel nucleoside analogue (*E*)-**6** that possesses a hybridized structure between (*E*)-**4** and **5**,<sup>15</sup> which exerts a long-acting and highly potent anti-HBV activity without significant cytotoxicity. In this study, we wish to report the details of the synthesis of (*E*)-**6** and its stereoisomer (*Z*)-**6** and their biological and structural features.

## 2. Results and discussion

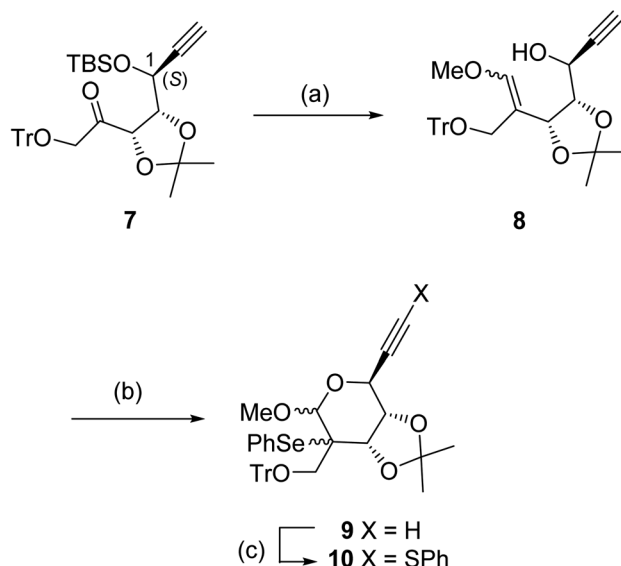
### 2.1. Chemistry

We have established a diastereoselective synthetic route for (*E*)-**4** through a radical-mediated 5-*exo-dig* mode cyclization of the selenide through the construction of the methylenecyclopentene unit.<sup>13</sup> The highly stereochemical outcome at the 4-position might be derived from the steric repulsion between the trityloxymethyl function and the cyclic acetonide. One would anticipate that if this radical technique was applied for the preparation of title molecule **6**, then the stereoselectivity for the newly generated quaternary carbon center would decrease, due to the steric repulsion between the cyclic acetonide and the cyano group (or its masked form). Accordingly, we planned the novel synthetic route for **6** as depicted in Scheme 1 as a retrosynthetic analysis.

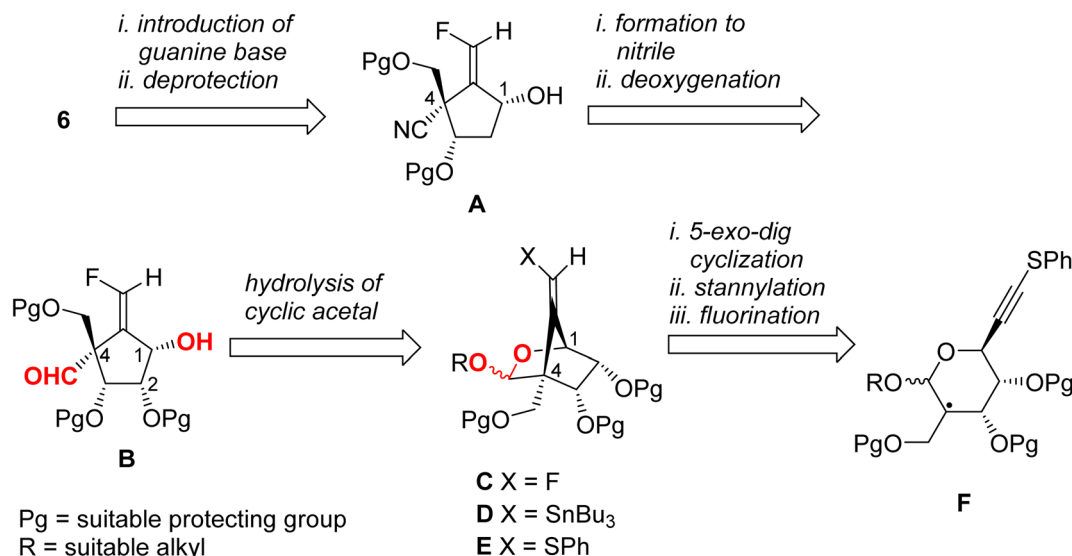
Target molecule **6** was prepared from alcohol **A** by the introduction of a guanine base under S<sub>N</sub>2 manner and deprotection. Cyanide **A** was prepared from **B** by deoxygenation of the 2-hydroxyl group and nitrile formation of the 4-formyl group. Aldehyde **B** was derived from cyclic acetal **C** by hydrolysis. The relative configuration of the 1-hydroxyl group

and the 4-formyl group must be fixed at this stage. Fluoride **C** was prepared from stannane **D** by electrophilic fluorination. The stannane **D** was converted from sulfide **E** employing the radical-mediated stannylation.<sup>13</sup> The bicyclo[2.2.1] system of **E** may be stereospecifically constructed by a radical-mediated 5-*exo-dig* cyclization of carbon-centered radical **F**. Therefore, we started to prepare the corresponding radical precursor for **F**.

The ketone **7** having a 1-*(S)* configuration was stereoselectively protected from D-ribose by a reported method (Scheme 2).<sup>16</sup> Treatment of **7** with the ylide (Ph<sub>3</sub>P=CHOMe) prepared from Ph<sub>3</sub>PCH<sub>2</sub>OMeCl and BuLi gave the enol ether **8** in 77% yield as a diastereomeric mixture (*ca.* 7:3, the

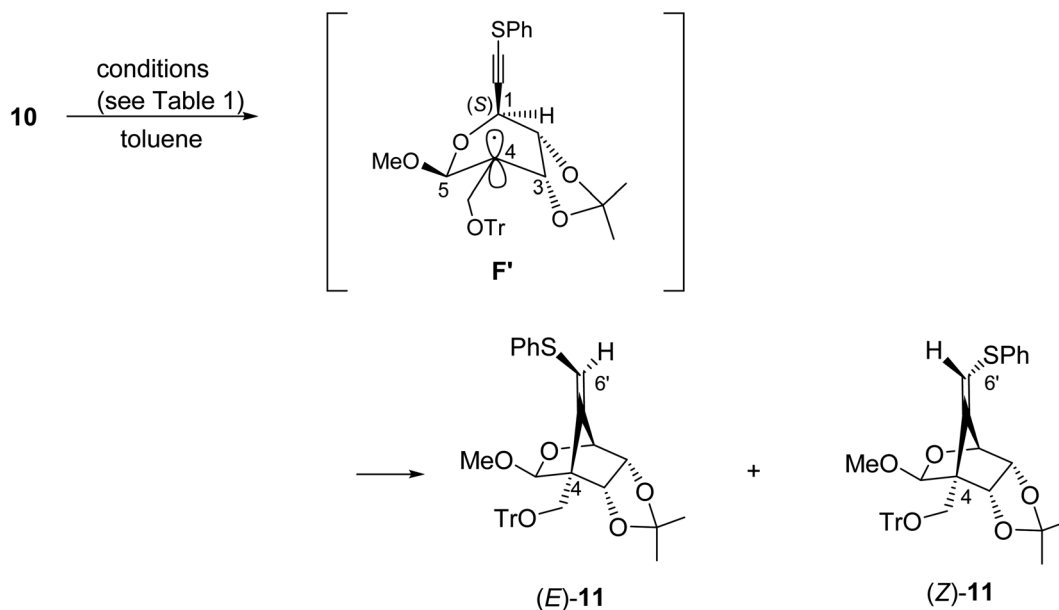


**Scheme 2** Conditions: (a) (i) Ph<sub>3</sub>PCH<sub>2</sub>OMeCl, BuLi, THF, 0 °C, (ii) Bu<sub>4</sub>NF, THF (77% for two steps); (b) PhSeCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, -80 °C to RT (84%); (c) PhSO<sub>2</sub>SPh, LDA, THF, -80 °C (79%).



**Scheme 1** Retrosynthetic analysis for **6**.



Table 1 Radical-mediated 5-*exo-dig* cyclization of **10**

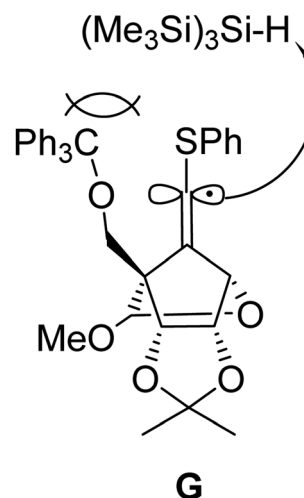
Entry	Reductant	Initiator	Temp. (°C)	Time (h)	Yield of (E)-11/(Z)-11 (%)	Ratio of (E)-11/(Z)-11
1	$[(\text{Me}_3\text{Si})_3\text{SiH}]$	AIBN	100	1.5	80/10	8.0
2	$[(\text{Me}_3\text{Si})_3\text{SiH}]$	$\text{Et}_3\text{B}$	Rt	0.5	82/7	11.7
3	$\text{Bu}_3\text{SnH}$	$\text{Et}_3\text{B}$	Rt	0.5	71/10	7.1
4	$[(\text{Me}_3\text{Si})_3\text{SiH}]$	$\text{Et}_3\text{B}$	−50	8	90/5	18
5	$[(\text{Me}_3\text{Si})_3\text{SiH}]$	$\text{Et}_3\text{B}$	−85	23.5 <sup>a</sup>	89/4 <sup>a</sup>	22.3

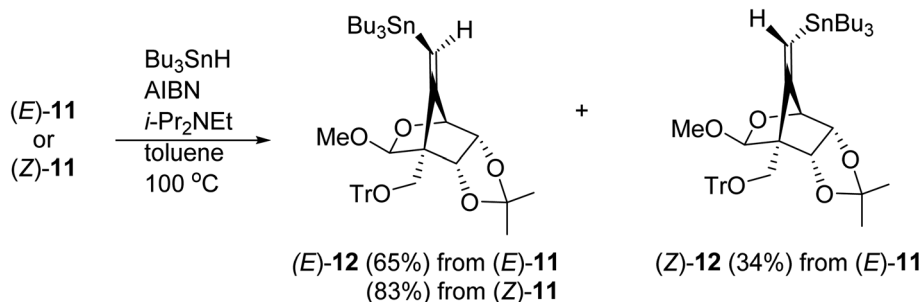
<sup>a</sup> A trace amount of **10** was observed on TLC.

stereochemistries of the isomers were not determined) after desilylation using  $\text{Bu}_4\text{NF}$ . When the enol ether **8** was reacted with  $\text{PhSeCl}$  in the presence of a stoichiometric amount of pyridine at  $-80^\circ\text{C}$ , the required intramolecular selenoetherification readily proceeded to form seleno methyl glycoside **9** as a mixture of three diastereomers (*ca.* 20:12:1, the actual stereochemistries of the diastereomers were not determined at this stage). The desired radical precursor **10** was obtained in moderate yield after the introduction of the PhS group at the terminal alkyne moiety of **9** *via* lithium acetylide (generated by LDA).

We next examined the radical-mediated cyclization of the precursor **10** (Table 1). When the selenide **10** was reacted with tris(trimethylsilyl)silane  $[(\text{Me}_3\text{Si})_3\text{SiH}]$  in the presence of a catalytic amount of AIBN as an initiator in hot toluene, the desired 5-*exo-dig* mode cyclization readily proceeded to afford the desired cyclic products having a methylenecyclopentane skeleton (*Z*)- and (*E*)-**11** [the ratio of the (*E*)-/(*Z*)-configuration of 6'-position was 8.0 : 1, entry 1]. The stereochemistry of both isomers was confirmed by NOE experiments as illustrated in Table 1 (see the Experimental section). The stereochemistries of the 4-position of both (*Z*)- and (*E*)-**11** were completely controlled as (*S*)-configuration, as we expected before. The free rotation of both 3,4- and 4,5-carbon-carbon bonds of the radical intermediate **F'** are certainly forbidden, due to the

presence of the oxo(methoxy)methano bridge between 1- and 4-position. Therefore, the radical cyclization stereospecifically proceeded to give only (4*S*)-products, since the stereochemistry of the 1-position possessing a radical acceptor moiety of **F'** is (*S*)-configuration.

Fig. 2 Reduction of radical intermediate **G** by  $(\text{Me}_3\text{Si})_3\text{SiH}$ .



Scheme 3 Radical-mediated sulfur-extrusive stannylation of 11.

The ratio of the  $(E)$ -/ $(Z)$ -configuration of the 6'-position was increased to 11.7 : 1 when the reaction was carried out at room temperature using  $\text{Et}_3\text{B}$  as an initiator (entry 2). The use of  $\text{Bu}_3\text{SnH}$  instead of  $(\text{Me}_3\text{Si})_3\text{SiH}$ , on the other hand, lowered the ratio to 7.1 : 1 (entry 3). Further increase of the stereoselectivity was observed along with the decrease of the reaction temperature (entries 4 and 5). The high  $(E)$ -stereoselectivity of the 6'-position might be derived from the steric repulsion between the bulky reductant  $(\text{Me}_3\text{Si})_3\text{SiH}$  and triethoxymethyl ( $\text{TrOCH}_2$ -) groups of the generated vinyl radical intermediate **G**, which may prevent an approach from the same face of the  $\text{TrOCH}_2$ - group (Fig. 2).

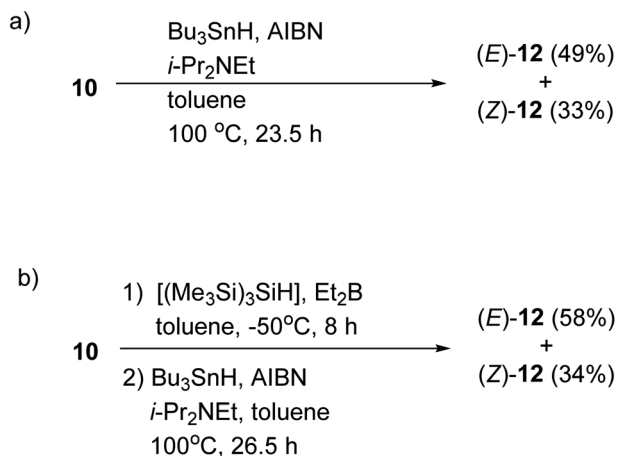
The radical-mediated sulfur extrusive stannylation of **11** was next carried out (Scheme 3). When the sulfide  $(E)\text{-}11$  was treated with  $\text{Bu}_3\text{SnH}$  and AIBN in the presence of  $i\text{-Pr}_2\text{NEt}$  in hot toluene, the vinylstannanes  $(E)\text{-}12$  (65%) and  $(Z)\text{-}12$  (34%) were obtained, respectively. Stereochemical analysis of **12** was also confirmed by NOE experiments as depicted in Scheme 3 (see Experimental section). In the case of radical-stannylation for  $(Z)\text{-}11$ , on the other hand,  $(Z)\text{-}12$  (83%) was the sole product. Similar results for these stereoselectivities were previously observed.<sup>13</sup>

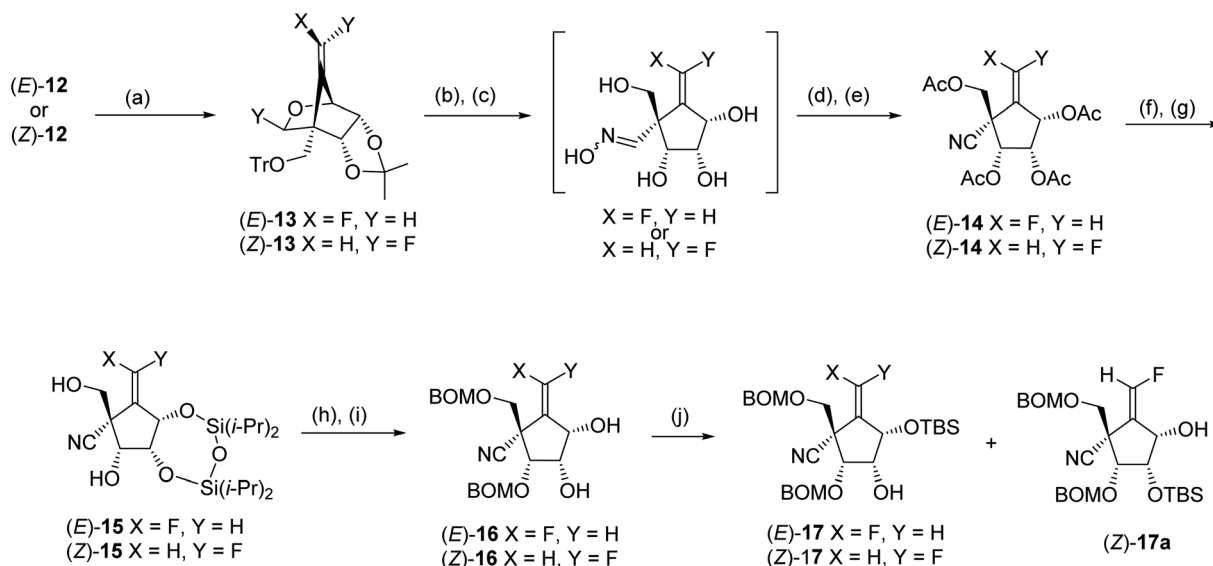
We also confirmed the possibility of the direct one-pot conversion of sulfide **10** into stannane **12** (Scheme 4). When the sulfide **10** was reacted with  $\text{Bu}_3\text{SnH}$  and AIBN in the

presence of  $i\text{-Pr}_2\text{NEt}$  in heating toluene, the stannanes  $(E)\text{-}12$  (49%) and  $(Z)\text{-}12$  (33%) were obtained, respectively, and the ratio of  $(E)\text{-}12$  :  $(Z)\text{-}12$  was 1.48 : 1, Scheme 4a. As illustrated in Scheme 4b on the other hand, the yield of **12** was slightly increased when the residue containing  $(E)$ - and  $(Z)\text{-}11$ , which was prepared in a described manner in Table 1; entry 4, was reacted with  $\text{Bu}_3\text{SnH}$  and AIBN. The ratio of  $(E)\text{-}12$  :  $(Z)\text{-}12$  was consistent with the results of Table 1 and Scheme 3. Therefore, the one-pot conversion without purification described in Scheme 4b should be comparable to the sequential manner.

Electrophilic fluorination of vinylstannanes **12** readily proceeded by treatment with  $\text{XeF}_2$  and  $\text{AgOTf}$  in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).<sup>17,18</sup> This gave the corresponding vinyl fluorides  $(E)\text{-}13$  and  $(Z)\text{-}13$ , respectively (Scheme 5). The vinyl fluorides  $(E)\text{-}13$  and  $(Z)\text{-}13$  were converted to the cyanides  $(E)\text{-}14$  and  $(Z)\text{-}14$ , respectively, by the following four-step sequence: (1) acidic hydrolysis of all of the acid labile protecting groups including the cyclic acetal function; (2) transformation of the generated formyl group into the corresponding oxime; (3) acetylation of all of the hydroxy groups include the oxime hydroxyl group and (4)  $\beta$ -elimination of the oxime acetate by the treatment with heating  $\text{AcOH}$  in the presence of a catalytic amount of  $\text{NaOAc}$ . In order to discriminate between the four hydroxyl groups of **14**, we selected a cyclic protection technique, which has been frequently employed, especially for the selective protection of 3' and 5' hydroxyl groups of nucleosides. After deacetylation of  $(E)\text{-}14$  by treatment with  $\text{NH}_3/\text{MeOH}$ , the resulting tetraol was reacted with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane ( $\text{TIPDSCl}_2$ ) in cold pyridine. Unexpectedly, the sole product was silyl ether  $(E)\text{-}15$  in which the primary alcohol remained and the two secondary alcohols were protected instead. A similar result was observed in the case of  $(Z)\text{-}14$ ; this might be due to the steric hindrance around the primary alcohol derived from  $(E)$ - and  $(Z)\text{-}14$ . Protection of these free hydroxyl groups in  $(E)\text{-}15$  and  $(Z)\text{-}15$  was carried out by the reaction with  $\text{BOMCl}$ . *cis*-Diols  $(E)\text{-}16$  and  $(Z)\text{-}16$  were prepared, respectively, after desilylation in moderate yields. The secondary alcohol of  $(E)\text{-}16$  was selectively protected again into  $(E)\text{-}17$  using bulky  $\text{TBSCl}$ . However, in the case of  $(Z)\text{-}16$ , mono silyl ether  $(Z)\text{-}17$  was obtained as an inseparable mixture with  $(Z)\text{-}17\text{a}$  (ca. 3 : 2 of diastereomeric mixture).

In order to reduce the free 2-hydroxyl group,  $(E)$ - and  $(Z)\text{-}17$  were treated with triflic anhydride into the corresponding triflate (Scheme 6); the reaction of the triflate with lithium iodide

Scheme 4 One-pot conversion of sulfide **10** into stannane **12**. (a) The reaction was carried out at 100 °C. (b) The reaction was carried out under the condition described in entry 4 (Table 1) before a treatment with  $\text{Bu}_3\text{SnH}$  and AIBN.



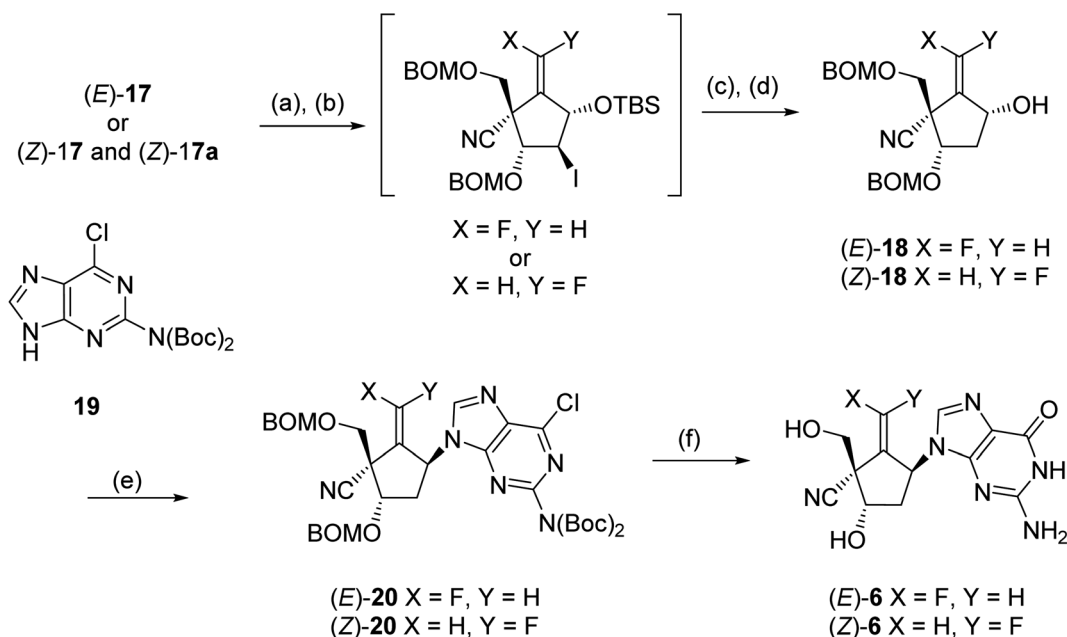
**Scheme 5** Conditions: (a) XeF<sub>2</sub>, AgOTf, DTBMP, CH<sub>2</sub>Cl<sub>2</sub>; (b) 80% AcOH, THF, 80 °C; (c) H<sub>2</sub>N–OH·HCl, pyridine; (d) Ac<sub>2</sub>O, pyridine; (e) NaOAc, AcOH, 80 °C; (f) NH<sub>3</sub>/MeOH, 4 °C; (g) TIPDSCl<sub>2</sub>, pyridine, –30 °C; (h) BOMCl, *i*-Pr<sub>2</sub>NEt, Bu<sub>4</sub>NI, toluene, 80 °C; (i) Bu<sub>4</sub>NF, THF; (j) TBSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>.

gave iodides, respectively. The desired carbocyclic units (*E*)- and (*Z*)-18 were prepared by radical-mediated deiodination using (Me<sub>3</sub>Si)<sub>3</sub>SiH and subsequent desilylation by treatment with Bu<sub>4</sub>NF [the pure (*Z*)-18 was isolated at this stage]. The introduction of guanine base for (*E*)- and (*Z*)-18 was carried out under Mitsunobu<sup>19</sup> condition employing the Boc-protected 2-amino-6-chloropurine (**19**)<sup>20,21</sup> and bis(methoxyethyl)azodicarboxylate (DMEAD),<sup>22</sup> the carbocyclic nucleosides (*E*)-20 (53%) and (*Z*)-20 (92%) were gained, respectively. Finally, the global deprotection

of (*E*)- and (*Z*)-20 was conducted by treatment with 80% TFA, and the synthesis of title molecules (*E*)-6 and (*Z*)-6 was achieved after HPLC purification.

## 2.2. Biological evaluation

The anti-HBV activity and cytotoxicity of compounds were determined using the HBV-producing HepG2 2.2.15 human hepatoblastoma cell line.<sup>12,14,15</sup> The anti-HBV activity and



**Scheme 6** Conditions: (a) Tf<sub>2</sub>O, pyridine; (b) LiI, DMF; (c) (Me<sub>3</sub>Si)<sub>3</sub>SiH, Et<sub>3</sub>B, toluene; (d) Bu<sub>4</sub>NF, THF; (e) **19**, DMEAD, Ph<sub>3</sub>P, toluene; (f) 80% TFA, HPLC purification.





Table 2 Antiviral activity and cytotoxicity of compounds 1–6

Compound	EC <sub>50</sub> (nM) against HBV	CC <sub>50</sub> (μM) in HepG2.2.15
1	2.3 ± 0.6	63
2	0.3 ± 0.1	3.0 ± 0.2
3	0.5 ± 0.2	3.6 ± 0.2
( <i>E</i> )-4	0.9 ± 0.3	83 ± 14
5	3.5 ± 23	>100
( <i>E</i> )-6	1.2 ± 0.7	93
( <i>Z</i> )-6	585 ± 358	>100

cytotoxicity of compounds 1–6 are summarized in Table 2. Entecavir served as a control. In the present study, compound (*E*)-6 showed significant anti-HBV activity (EC<sub>50</sub> = 1.2 nM) with favorable cytotoxicity (CC<sub>50</sub> = 93 μM). By contrast, compound (*Z*)-6 displayed ~500 times lower anti-HBV activity compared to compound (*E*)-6 and showed no cytotoxicity up to 100 μM. These results indicate that *E*-positioned fluorine in the cyclopentyl moiety contributes to compound (*E*)-6's potent anti-HBV activity.

### 2.3. Structural models of the interactions of (*E*)-6-TP with HBV<sub>WT</sub>-RT

Using sequence alignment and homology between HBV-RT and HIV-RT, we built a structure of an HBV<sub>WT</sub>-RT primer/template (p/t) complex.<sup>12,14</sup> Coordinates of the complex of ETV with HBV<sub>WT</sub>-RT (p/t) were used to generate a model of the interactions of (*E*)-6-triphosphate (TP) with HBV<sub>WT</sub>-RT (p/t) (Fig. 3). The aminopurine group of (*E*)-6-TP formed hydrogen bond interactions with Met-171. The magnesium ion coordinated with the triphosphate

group, and has polar interactions with Asp83, Val84, and Asp205. The triphosphate moiety has hydrogen bond interactions with the side chain atoms of Ser85. The 4'-cyano substituent had a hydrogen bond interaction with the backbone NH of Phe-88. The fluorine of (*E*)-6-TP forms polar interactions with Met-204. This favorable interaction is not possible for (*Z*)-6-TP and may account for the difference in activities between these stereoisomers. (*E*)-6-TP also has many favorable van der Waals interactions with HBV<sub>WT</sub>-RT (p/t) as shown in Fig. 3.

The figure shows a ribbon representation of HBV<sub>WT</sub>-RT (purple) with active site residues in stick mode (a and b). The (*E*)-6-TP forms multiple interactions inside the active site. Hydrogen bonds are shown as black dashed lines, while fluorine contacts are shown as cyan dashed lines. While the aminopurine forms a hydrogen bond with the backbone carbonyl oxygen of M-171, the cyano group forms an additional hydrogen bond with the backbone amino group of F88. The side chain atoms of Ser85 form bifurcate hydrogen bond interactions with the triphosphate group. Magnesium ion (Mg<sup>2+</sup>) at the active-site periphery is shown in green and metal coordinations (under 3 Å) are highlighted in green color. The magnesium ion coordinated between the triphosphate group and the side chain carboxyl groups of D-83, D-205, and the main chain carbonyl oxygen of V-84. Fluorine atoms engage in interactions such as hydrogen bonds with the side chain of M-204. Surface representation of HBV<sub>WT</sub>-RT with the hydrophobicity scale (c and d). The center part of (*E*)-6-TP sandwiched between F-88 and Y-89 and aminopurine moiety was further stretched along the hydrophobic residue M171. On the opposite side, the cyan color indicates negatively-charged residues around the phosphate group coordinated with Mg<sup>2+</sup>.

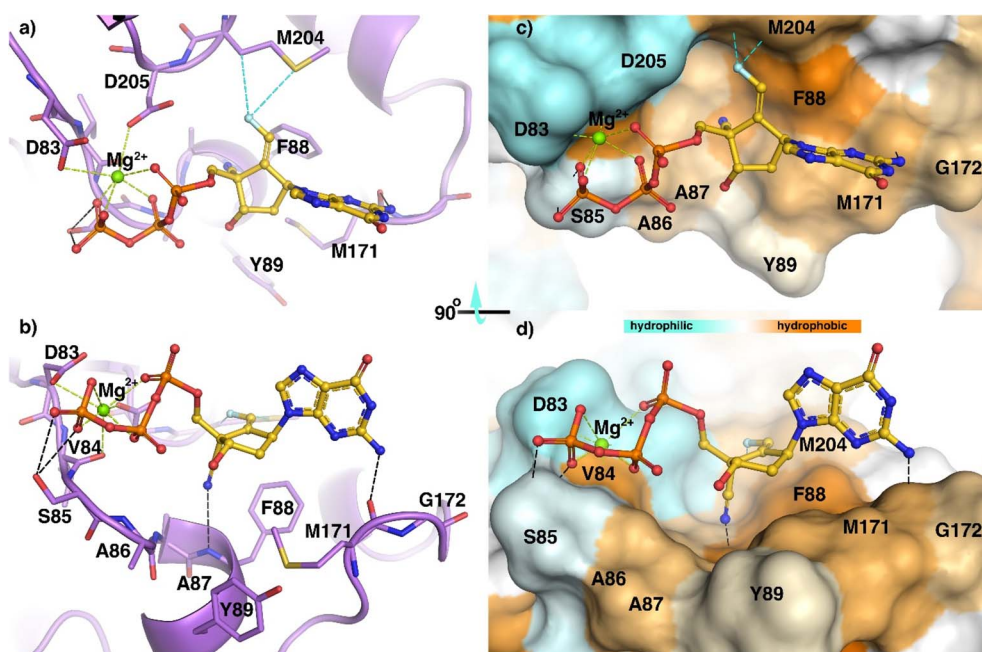


Fig. 3 Model of structural interactions of (*E*)-6-TP inside the active site of HBV<sub>WT</sub>-RT in stick mode (a and b) and as a surface representation of HBV<sub>WT</sub>-RT with the hydrophobicity scale (c and d).



### 3. Conclusion

Our previous findings that nucleosides **2**, **3**, (*E*)-**4**, and **5** are strong candidates for anti-HBV agents encouraged us to carry out this study. Synthesis of the entecavir analogues **6** possessing a cyano group and fluorine atom at 4'- and 6''-position was accomplished based on radical-mediated stereospecific 5-*exo dig* mode cyclization of **10**, sulfur-extrusive stannylation of **11** and subsequent electrophilic fluorination into **13**, and construction of the cyano group employing the formyl group generated by hydrolysis of **13**, which was located at the chiral quaternary carbon, as representative steps. Both diastereomers (*E*)- and (*Z*)-**6** were synthesized after deoxygenation, the introduction of guanine base, and global deprotection. Of the two diastereomers **6** synthesized in this study, (*E*)-**6** showed higher anti-HBV activity than (*Z*)-**6** and parent compound **1** with lower cytotoxicity than that of **1**. Molecular models suggested that both the cyano group and fluorine atoms of (*E*)-**6** have strong interactions with HBV<sub>WT</sub>-RT and must be partly responsible for its high anti-HBV activity.

### 4. Experimental section

#### 4.1. Chemistry

**General.** NMR (<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F) spectra were recorded with a JEOL JNMAL-400 or JEOL JNM ECA-500 instrument (<sup>1</sup>H, 500 or 400 MHz, <sup>13</sup>C, 125 MHz, <sup>19</sup>F, 470 MHz). Chemical shifts are reported relative to Me<sub>4</sub>Si, except for fluorine-containing compounds where CFCl<sub>3</sub> was used as an internal standard. Mass spectra (MS) were taken in FAB mode with *m*-nitrobenzyl alcohol as a matrix. Column chromatography was carried out on silica gel (Micro Bead Silica Gel PSQ 100B, Fuji Silysia Chemical Ltd.) or neutral silica gel (Silica Gel 60N, Kanto Chemical Co., Inc.). Thin-layer chromatography (TLC) was performed on pre-coated silica gel plate F<sub>254</sub>. THF was distilled from benzophenone ketyl.

(*S*)-1-((4*S*,5*R*)-5-(1-Methoxy-3-(trityloxy)prop-1-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-ol (**8**). To an anhydrous THF (200 mL) suspension of Ph<sub>3</sub>PCH<sub>2</sub>OMeCl (47.4 g, 138.4 mmol), BuLi (2.66 mol L<sup>-1</sup> in hexane, 49.5 mL, 131.6 mmol) was added dropwise at -80 °C under a positive pressure of dry Ar. The resulting suspension was stirred for 2 h at rt. To this was dropwise added a THF (150 mL) solution of **7** (15.8 g, 27.7 mmol) at 0 °C. The resulting mixture was further stirred at rt for 22 h. The resulting dark brown mixture was partitioned between aqueous saturated NH<sub>4</sub>Cl and AcOEt. After evaporation of all the volatiles in the organic layer, the residue was dissolved in THF (100 mL). To this was added Bu<sub>4</sub>NF (1.0 mol L<sup>-1</sup> in THF, 30.5 mL, 30.5 mmol), then stirred at rt for 5 h. The resulting mixture was partitioned between aqueous saturated NH<sub>4</sub>Cl and AcOEt. After evaporation of all the volatiles of the organic layer, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5/1). This gave **8** (10.34 g, 77%, *ca.* 7 : 3 of diastereomeric mixture) as a foam. [ $\alpha$ ]<sub>D</sub><sup>26</sup> -26.5 (*c* 0.68, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  1.31 (s, 2.1H), 1.325 (s, 0.9H), 1.330 (s, 0.9H), 1.34 (s, 2.1H), 2.31 (d, *J* = 2.3 Hz, 0.3H), 2.43 (d, *J* = 2.3 Hz, 0.7H), 3.24 (d, *J* = 5.8 Hz, 0.3H), 3.53 (d, *J* = 5.2 Hz,

0.7H), 3.68 (s, 0.9H), 3.71 (d, *J* = 10.0 Hz, 0.7H), 3.73 (s, 2.1H), 3.94 (d, *J* = 10.0 Hz, 0.7H), 4.01 (dd, *J* = 8.0 and 6.3 Hz, 0.7H), 4.17-4.18 (m, 0.7H), 4.24 (dd, *J* = 7.5 and 6.9 Hz, 0.3H), 4.51 (d, *J* = 5.2 Hz, 0.7H), 5.10 (dd, *J* = 5.2 and 2.3 Hz, 0.3H), 6.21 (d, *J* = 1.1 Hz, 0.3H), 6.46 (s, 0.7H), 7.11-7.25 (m, 3H), 7.29-7.32 (m, 6H), 7.44-7.49 (m, 6H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  24.9, 25.2, 26.7, 27.3, 58.7, 60.4, 60.5, 61.5, 61.9, 62.5, 73.2, 73.4, 73.5, 79.9, 80.1, 82.8, 83.2, 87.7, 88.0, 107.1, 107.8, 108.5, 110.7, 127.1, 127.9, 128.8, 143.4, 143.8, 148.5, 150.8. ESI-MS (*m/z*): 507 [M<sup>+</sup> + Na]. HRMS (ESI<sup>+</sup>): calcd for C<sub>31</sub>H<sub>32</sub>O<sub>5</sub>Na 507.2142, found 507.2155 [M<sup>+</sup> + Na].

(3*aS*,4*S*,7*aS*)-4-Ethynyl-6-methoxy-2,2-dimethyl-7-(phenylselanyl)-7-((trityloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-*c*]pyran (**9**). To a CH<sub>2</sub>Cl<sub>2</sub> (200 mL) solution of **8** (14.6 g, 30.12 mmol) and pyridine (24.4 mL, 301.2 mmol) was added PhSeCl (6.07 g, 31.6 mmol) in one portion at -80 °C. The resulting mixture was stirred at the same temperature for 5 h, and then stirred further for 20 h at rt. The mixture was partitioned between aqueous saturated NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub>. After evaporation of all the volatiles in the organic layer, the residue was purified by column chromatography on silica gel (toluene). This gave **9** (16.24 g, 84%, *ca.* 20 : 12 : 1 of inseparable diastereomeric mixture) as a foam. [ $\alpha$ ]<sub>D</sub><sup>26</sup> +38.1 (*c* 1.08, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) of the two major diastereomers  $\delta$  1.19 (s, 1.89H), 1.22 (s, 1.11H), 1.48 (s, 1.11H), 1.51 (s, 1.89H), 2.53 (d, *J* = 1.7 Hz, 0.37H), 2.54 (s, *J* = 2.3 Hz, 0.63H), 3.33 (d, *J* = 9.8 Hz, 0.37H), 3.34 (d, *J* = 10.3 Hz, 0.63H), 3.47 (s, 1.11H), 3.50 (s, 1.89H), 3.54-3.58 (m, 0.93H), 3.80 (d, *J* = 10.3 Hz, 1H), 4.01 (d, *J* = 5.2 Hz, 0.63H), 4.19-4.21 (m, 1H), 4.40 (d, *J* = 4.0 Hz, 0.37H), 7.11-7.33 (m, 12H), 7.40-7.46 (m, 6H), 7.59-7.60 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) of the two major diastereomers  $\delta$  25.55, 25.58, 28.3, 28.4, 51.8, 52.7, 57.26, 57.34, 62.8, 66.3, 67.0, 67.1, 73.7, 74.0, 74.4, 74.8, 75.9, 77.1, 77.2, 78.4, 80.7, 80.8, 87.0, 87.5, 102.2, 104.0, 108.9, 109.7, 125.4, 125.5, 126.88, 126.92, 127.5, 127.6, 127.8, 127.9, 128.3, 128.56, 128.61, 128.7, 128.8, 128.9, 129.0, 129.2, 138.4, 138.7, 143.6, 143.7. ESI-MS (*m/z*): 663 [M<sup>+</sup> + Na]. HRMS (ESI<sup>+</sup>): calcd for C<sub>37</sub>H<sub>36</sub>O<sub>5</sub>NaSe 663.1624, found 663.1635 [M<sup>+</sup> + Na].

(3*aS*,4*S*,7*aS*)-6-Methoxy-2,2-dimethyl-7-(phenylselanyl)-4-((phenylthio)ethynyl)-7-((trityloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-*c*]pyran (**10**). To an anhydrous THF (60 mL) solution of **9** (4.05 g, 5.87 mmol) was dropwise added LDA (1.5 mol L<sup>-1</sup> in THF, 7.83 mL, 11.75 mmol) at -80 °C under positive pressure of dry Ar. After 10 min stirring of the mixture, this was stirred for 10 min at rt. To this was added a THF (25 mL) solution of PhSO<sub>2</sub>SPh (2.94 g, 11.75 mmol) at -80 °C, then the mixture was stirred further for 30 min at the same temperature. After the addition of further LDA (3.92 mL, 5.87 mmol), the mixture was partitioned between aqueous saturated NH<sub>4</sub>Cl and AcOEt. After evaporation of all the volatiles in the organic layer, the residue was purified by column chromatography on silica gel (toluene). This gave **10** (3.46 g, 79%, *ca.* 100 : 33 : 7 of inseparable diastereomeric mixture) as a foam. [ $\alpha$ ]<sub>D</sub><sup>26</sup> +18.8 (*c* 0.49, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) of the two major diastereomers  $\delta$  1.21 (s, 2.25H), 1.23 (s, 0.75H), 1.48 (s, 0.75H), 1.52 (s, 2.25H), 3.35 (d, *J* = 9.5 Hz, 0.25H), 3.39 (d, *J* = 10.9 Hz, 0.75H), 3.48 (s, 0.75H), 3.50 (dd, *J* = 9.5 and 4.6 Hz, 0.75H), 3.51 (s, 2.25H), 3.58 (d, *J* =

9.5 Hz, 0.25H), 3.80 (d,  $J = 10.9$  Hz, 0.75H), 4.06 (d,  $J = 4.6$  Hz, 0.75H), 4.20 (dd,  $J = 9.2$  and  $4.6$  Hz, 0.25H), 4.39 (d,  $J = 9.5$  Hz, 0.75H), 4.41 (d,  $J = 9.2$  Hz, 0.25H), 4.44 (d,  $J = 4.6$  Hz, 0.25H), 4.74 (s, 0.75H), 4.80 (s, 0.25H), 7.15–7.22 (m, 3H), 7.23–7.25 (m, 8H), 7.29–7.36 (m, 3H), 7.39–7.41 (m, 6H), 7.43–7.45 (m, 3H), 7.62–7.64 (m, 2H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz) of the two major diastereomers  $\delta$  25.6, 26.1, 28.3, 28.4, 52.0, 52.9, 57.3, 57.4, 62.6, 66.2, 68.17, 68.24, 73.2, 73.5, 74.3, 74.8, 77.2, 78.5, 87.0, 87.5, 95.5, 95.6, 102.1, 104.0, 108.9, 109.6, 126.57, 126.62, 126.7, 126.9, 127.0, 127.1, 127.5, 127.8, 128.3, 128.6, 128.7, 128.8, 128.9, 129.0, 129.2, 129.4, 138.4, 138.7. ESI-MS ( $m/z$ ): 749 [ $\text{M}^+ + \text{H}$ ], HRMS (ESI+): calcd for  $\text{C}_{43}\text{H}_{41}\text{O}_5\text{SSe}$  749.1840, found 749.1875 [ $\text{M}^+ + \text{H}$ ].

### Radical-mediated 5-exo-dig mode cyclization of selenide **10**; formation to **11** (Table 1)

**Entry 1.** A toluene (7 mL) solution of **10** (500 mg, 0.67 mmol),  $(\text{Me}_3\text{Si})_3\text{SiH}$  (413  $\mu\text{L}$ , 1.34 mmol) and AIBN (21 mg, 0.13 mmol) was heated at 100  $^\circ\text{C}$  for 1.5 h. After evaporation of all the volatile components, the residue was purified by column chromatography on the silica gel. This gave (*Z*)-**11** (hexane/AcOEt = 8 : 1, 41 mg, 10% as a foam) and (*E*)-**11** (hexane/AcOEt = 6 : 1, 317 mg, 80% as a foam), respectively.

**Entry 2.** To a toluene (7 mL) solution of **10** (500 mg, 0.67 mmol) and  $(\text{Me}_3\text{Si})_3\text{SiH}$  (413  $\mu\text{L}$ , 1.34 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 13.4 mL, 1.34 mmol) in one portion at RT. The resulting mixture was stirred further for 30 min at the same temperature. After evaporation of all of the volatile components, the residue was purified by column chromatography on silica gel. This gave (*Z*)-**11** (hexane/AcOEt = 8 : 1, 26 mg, 7%) and (*E*)-**11** (hexane/AcOEt = 6 : 1, 327 mg, 82%) respectively.

**Entry 3.** To a toluene (7 mL) solution of **10** (500 mg, 0.67 mmol) and  $\text{Bu}_3\text{SnH}$  (360  $\mu\text{L}$ , 1.34 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 13.4 mL, 1.34 mmol) in one portion at rt. The resulting mixture was stirred further for 30 min at the same temperature. After evaporation of the volatile components, the residue was purified by column chromatography on silica gel. This gave (*Z*)-**11** (hexane/AcOEt = 8 : 1, 41 mg, 10%) and (*E*)-**11** (hexane/AcOEt = 6 : 1, 282 mg, 71%).

**Entry 4.** To a toluene (7 mL) solution of **10** (500 mg, 0.67 mmol) and  $(\text{Me}_3\text{Si})_3\text{SiH}$  (413  $\mu\text{L}$ , 1.34 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 13.4 mL, 1.34 mmol) in one portion at  $-50$   $^\circ\text{C}$ . The resulting mixture was stirred for a further 8 h at the same temperature. The mixture was treated in the same manner as described in Entry 2. This gave (*Z*)-**11** (20 mg, 5%) and (*E*)-**11** (358 mg, 90%) respectively.

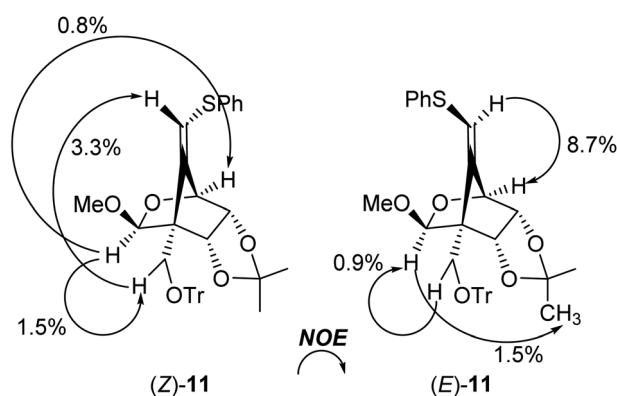
**Entry 5.** To a toluene (7 mL) solution of **10** (500 mg, 0.67 mmol) and  $(\text{Me}_3\text{Si})_3\text{SiH}$  (413  $\mu\text{L}$ , 1.34 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 13.4 mL, 1.34 mmol) in one portion at  $-80$   $^\circ\text{C}$ . The resulting mixture was stirred further for 23.5 h at the same temperature. The mixture was treated in the same manner as described in Entry 2. This gave (*Z*)-**11** (14 mg, 4%) and (*E*)-**11** (353 mg, 89%) respectively.

**Physical data for (*Z*)-**11**.**  $[\alpha]_{\text{D}}^{27} +90.3$  ( $c$  1.26,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.41 (s, 3H), 1.63 (s, 3H), 3.318 (d,  $J = 9.6$  Hz, 1H), 3.321 (s, 3H), 3.64 (d,  $J = 9.6$  Hz, 1H), 4.36 (dd,  $J = 8.0$  and  $2.0$  Hz, 1H), 4.69 (d,  $J = 2.0$  Hz, 1H), 4.76 (d,  $J = 8.0$  Hz, 1H), 5.07 (s, 1H), 5.86 (s, 1H), 7.23–7.29 (m, 14H), 7.44–7.46 (m, 6H).  $^{13}\text{C}$

NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  25.6, 25.7, 55.3, 57.4, 58.6, 74.9, 78.0, 78.3, 76.6, 86.6, 101.8, 114.6, 115.4, 126.5, 127.1, 127.5, 127.8, 128.8, 129.0, 135.3, 143.5, 143.7. ESI-MS ( $m/z$ ): 615 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{37}\text{H}_{36}\text{O}_5\text{NaS}$  615.2176, found 615.2190 [ $\text{M}^+ + \text{Na}$ ].

**Physical data for (*E*)-**11**.**  $[\alpha]_{\text{D}}^{26} +70.0$  ( $c$  0.66,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.40 (s, 3H), 1.70 (s, 3H), 3.42 (s, 3H), 3.64 (d,  $J = 9.2$  Hz, 1H), 3.81 (d,  $J = 9.2$  Hz, 1H), 4.31 (dd,  $J = 10.3$  and  $2.3$  Hz, 1H), 4.32 (s, 1H), 4.58 (d,  $J = 10.3$  Hz, 1H), 5.31 (s, 1H), 6.25 (s, 1H), 7.19–7.25 (m, 1H), 7.28–7.31 (m, 5H), 7.52–7.53 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  25.5, 25.8, 55.7, 58.1, 61.0, 78.6, 79.0, 79.6, 86.5, 102.5, 115.3, 118.4, 126.9, 127.4, 127.6, 129.0, 129.6, 135.2, 139.5, 163.9. ESI-MS ( $m/z$ ): 593 [ $\text{M}^+ + \text{H}$ ], HRMS (ESI+): calcd for  $\text{C}_{37}\text{H}_{37}\text{O}_5\text{S}$  593.2381, found 593.2388 [ $\text{M}^+ + \text{H}$ ].

### NOE experiments of (*Z*)- and (*E*)-**11**.



**Radical-mediated sulfur-extrusive stannylation of (*E*)-**11**; formation to (*E*)- and (*Z*)-**12**.** A toluene (200 mL) solution of (*E*)-**11** (23.3 g, 39.4 mmol),  $\text{Bu}_3\text{SnH}$  (42.3 mL, 157.4 mmol),  $i\text{-Pr}_2\text{NEt}$  (27.4 mL, 157.4 mmol), and AIBN (6.46 g, 39.4 mmol) was stirred at 100  $^\circ\text{C}$  for 25 h. After evaporation of all the volatile components in the resulting mixture, the residue was purified by column chromatography on the silica gel. This gave (*Z*)-**12** (hexane/AcOEt = 20 : 1, 10.3 g, 34% as an oil) and (*E*)-**12** (hexane/AcOEt = 15 : 1, 19.8 g, 65% as an oil).

**Physical data for (*Z*)-**12**.**  $[\alpha]_{\text{D}}^{27} +60.8$  ( $c$  1.69,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.82–0.94 (m, 15H), 1.23–1.30 (m, 6H), 1.40 (s, 3H), 1.41–1.45 (m, 6H), 1.63 (s, 3H), 3.24 (d,  $J = 9.2$  Hz, 1H), 3.33 (s, 3H), 3.52 (d,  $J = 9.2$  Hz, 1H), 4.09 (d,  $J = 2.0$  Hz, 1H), 4.26 (dd,  $J = 8.0$  and  $2.0$  Hz, 1H), 4.29 (d,  $J = 8.0$  Hz, 1H), 5.14–5.15 (m, 1H), 5.45–5.56 (m, 1H), 7.22–7.25 (m, 3H), 7.28–7.31 (m, 6H), 7.48–7.49 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  10.4, 13.6, 25.5, 25.8, 27.2, 28.9, 54.9, 57.3, 59.5, 78.2, 78.6, 78.9, 86.3, 101.8, 114.7, 119.1, 126.9, 127.7, 128.9, 144.0, 156.3, 78.7, 80.8, 81.1, 86.1, 102.8, 114.6, 119.6, 126.8, 127.7, 128.8, 144.2, 156.2. ESI-MS ( $m/z$ ): 797 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{43}\text{H}_{58}\text{O}_5\text{-NaSn}$  797.3208, found 797.3218 [ $\text{M}^+ + \text{Na}$ ].

**Physical data for (*E*)-**12**.**  $[\alpha]_{\text{D}}^{26} +56.6$  ( $c$  0.71,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.53–0.62 (m, 6H), 0.78–0.81 (m, 9H), 1.09–1.16 (m, 6H), 1.24–1.28 (m, 6H), 1.40 (s, 3H), 1.68 (s, 3H), 3.29 (d,  $J = 8.1$  Hz, 1H), 3.38 (s, 3H), 3.63 (d,  $J = 8.1$  Hz, 1H), 4.13 (d,  $J = 1.7$  Hz, 1H), 4.27 (dd,  $J = 8.1$  and  $1.7$  Hz, 1H), 4.36 (d,  $J = 8.1$  Hz, 1H), 5.34 (s, 1H), 5.66–5.74 (m, 1H), 7.21–7.24 (m, 3H), 7.28–7.31

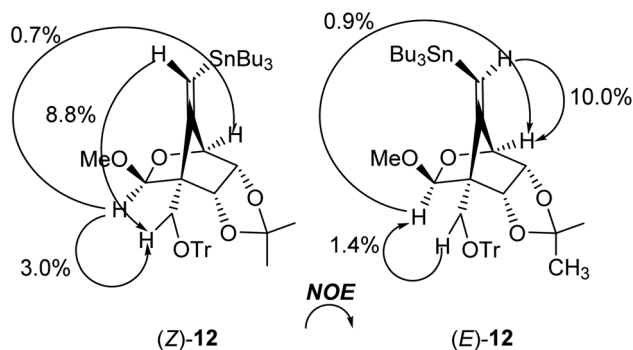




(m, 6H), 7.53–7.54 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  11.0, 13.7, 25.4, 25.8, 27.1, 28.9, 55.7, 57.1, 60.6, 78.7, 80.7, 81.1, 86.1, 102.8, 114.6, 119.6, 126.8, 127.7, 128.8, 144.2, 156.2. ESI-MS ( $m/z$ ): 797 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{43}\text{H}_{58}\text{O}_5\text{NaSn}$  797.3208, found 797.3214 [ $\text{M}^+ + \text{Na}$ ].

**Radical-mediated sulfur-extrusive stannylation of (Z)-11; formation to (Z)-12.** Compound (Z)-11 (1.13 g, 1.91 mmol) was treated with the same procedure described for (E)-17. This exclusively gave (Z)-12 (1.22 g, 83%) as an oil.

**NOE experiments of (Z)- and (E)-12.**



**Direct one-pot conversion of 10 into 12 (Scheme 4b).** To a toluene (7 mL) solution of **10** (500 mg, 0.67 mmol) and  $(\text{Me}_3\text{Si})_3\text{SiH}$  (413  $\mu\text{L}$ , 1.34 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 13.4 mL, 1.34 mmol) in one portion at  $-50^\circ\text{C}$ . The resulting mixture was stirred for a further 8 h at the same temperature. After the evaporation of all the volatile components, the residue was used for the next step without further purification. A mixture of the residue,  $\text{Bu}_3\text{SnH}$  (900  $\mu\text{L}$ , 3.35 mmol),  $i\text{-Pr}_2\text{NEt}$  (584  $\mu\text{L}$ , 3.35 mmol), and AIBN (110 mg, 0.67 mmol) in toluene (7 mL) was stirred at  $100^\circ\text{C}$  for 23.5 h. After evaporation of all the volatile components in the resulting mixture, the residue was purified by column chromatography on the silica gel. This gave (Z)-12 (hexane/AcOEt = 20:1, 185 mg, 34%) and (E)-12 (hexane/AcOEt = 15:1, 301 mg, 58%).

(3*aS*,4*S*,6*S*,7*S*,7*aR*,*E*)-8-(Fluoromethylene)-6-methoxy-2,2-dimethyl-7-((trityloxy)methyl)tetrahydro-4*H*-4,7-methano[1,3]dioxolo[4,5-*c*]pyran [(E)-13]. To a mixture of (E)-12 (19.8 g, 25.6 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (11.8 g, 57.6 mmol) and  $\text{XeF}_2$  (4.56 g, 26.9 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (200 mL) was added  $\text{AgOTf}$  (1.64 g, 6.4 mmol). The resulting mixture was stirred for 100 min at room temperature. The mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  and aqueous-saturated  $\text{NaHCO}_3$ . After evaporation of the volatiles in the organic layer, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1). This gave (E)-13 (11.26 g, 88%) as a solid. Mp  $228\text{--}231^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{26} +91.2$  ( $c$  1.05,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.39 (s, 3H), 1.66 (s, 3H), 3.40 (s, 3H), 3.51 (d,  $J$  = 9.5 Hz, 1H), 3.75 (d,  $J$  = 9.5 Hz, 1H), 4.29 (dd,  $J$  = 8.0, and 2.0 Hz, 1H), 4.39 (t,  $J_{\text{H,F}}$  = 2.0 Hz and  $J$  = 2.0 Hz, 1H), 4.54 (d,  $J$  = 8.0 Hz, 1H), 5.25 (s, 1H), 6.60 (d,  $J_{\text{H,F}}$  = 82.5 Hz, 1H), 7.23–7.26 (m, 3H), 7.29–7.32 (m, 6H), 7.50–7.51 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  25.5, 25.7, 55.7, 57.5, 60.3 (d,  $J_{\text{C,F}}$  = 2.4 Hz), 74.8 (d,  $J_{\text{C,F}}$  = 10.8 Hz), 79.7, 79.9 (d,  $J_{\text{C,F}}$  = 3.5 Hz), 86.4, 102.1, 115.9, 122.4 (d,  $J_{\text{C,F}}$  = 7.2 Hz), 126.9, 127.6, 128.9, 141.9 (d,  $J_{\text{C,F}}$  = 262.3 Hz), 143.9.

$^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$   $-136.2$  (d,  $J_{\text{H,F}}$  = 73.3 Hz). ESI-MS ( $m/z$ ): 525 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{31}\text{H}_{31}\text{FNaO}_5$  525.2048, found 525.2048 [ $\text{M}^+ + \text{Na}$ ].

(3*aS*,4*S*,6*S*,7*S*,7*aR*,*Z*)-8-(Fluoromethylene)-6-methoxy-2,2-dimethyl-7-((trityloxy)methyl)tetrahydro-4*H*-4,7-methano[1,3]dioxolo[4,5-*c*]pyran [(Z)-13]. Compound (Z)-17 (10.8 g, 14.0 mmol) was treated with the same procedure described for (E)-13. This gave (Z)-13 (3.27 g, 47%) as a foam.  $[\alpha]_{\text{D}}^{26} +77.5$  ( $c$  0.23,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.40 (s, 3H), 1.61 (s, 3H), 3.24 (d,  $J$  = 9.8 Hz, 1H), 3.32 (s, 3H), 3.58 (d,  $J$  = 9.8 Hz, 1H), 4.39 (dd,  $J$  = 8.0 and 2.0 Hz, 1H), 4.77 (d,  $J$  = 8.0 Hz, 1H), 4.83 (d,  $J$  = 2.0 Hz, 1H), 5.03 (d,  $J_{\text{H,F}}$  = 4.0 Hz, 1H), 6.17 (d,  $J_{\text{H,F}}$  = 83.8 Hz, 1H), 7.24–7.26 (m, 3H), 7.30–7.33 (m, 6H), 7.44–7.47 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  25.5, 25.7, 55.3 (d,  $J_{\text{C,F}}$  = 3.8 Hz), 55.4, 58.3, 72.9, 77.3, 78.3 (d,  $J_{\text{C,F}}$  = 3.6 Hz), 79.2, 86.6, 101.8, 116.0, 123.7 (d,  $J_{\text{C,F}}$  = 11.9 Hz), 127.1, 127.9, 128.7, 140.3 (d,  $J_{\text{C,F}}$  = 258.7 Hz), 143.6.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$   $-132.5$  (d,  $J_{\text{H,F}}$  = 73.4 Hz). ESI-MS ( $m/z$ ): 525 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{31}\text{H}_{31}\text{FNaO}_5$  525.2048, found 525.2061 [ $\text{M}^+ + \text{Na}$ ].

(1*S*,2*R*,3*R*,4*S*,*E*)-4-(Acetoxymethyl)-4-cyano-5-(fluoromethylene)cyclopentane-1,2,3-triyl triacetate [(E)-14]. To a THF (20 mL) solution of (E)-13 (11.0 g, 22.0 mmol) was added 80% AcOH (100 mL). The resulting suspension was stirred at  $80^\circ\text{C}$  for 5 h. After evaporation of all of the volatiles of the mixture, the residue was dissolved in pyridine (100 mL). To this was added  $\text{HO-NH}_2 \cdot \text{HCl}$  (3.1 g, 43.1 mmol) at  $0^\circ\text{C}$ , then, the mixture was stirred for 30 h at room temperature. After monitoring the disappearance of an intermediate aldehyde and generation of oxime by TLC ( $\text{CHCl}_3/\text{MeOH}$  = 3:1), to this was added  $\text{Ac}_2\text{O}$  (31.1 mL, 329.3 mmol) at  $0^\circ\text{C}$ . The resulting mixture was stirred at room temperature for 40 h. After the addition of MeOH (50 mL), the mixture was partitioned between aqueous saturated  $\text{NaHCO}_3$  and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 1:1) of the organic layer gave crude pentaacetate (7.02 g) as an oil. To an AcOH (100 mL) solution of the oil was added NaOAc (100 mg). The mixture was stirred at  $80^\circ\text{C}$  for 96 h. After evaporation of all the volatile components, the residue was partitioned between aqueous-saturated  $\text{NaHCO}_3$  and AcOEt. Column chromatography on silica gel (hexane/AcOEt = 1:1) of the organic layer gave (E)-14 (5.01 g, 64% for four steps) as an oil.  $[\alpha]_{\text{D}}^{26} +9.5$  ( $c$  0.43,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.119 (s, 3H), 2.122 (s, 3H), 2.16 (s, 3H), 2.18 (s, 3H), 4.41 (d,  $J$  = 11.5 Hz, 1H), 4.44 (d,  $J$  = 11.5 Hz, 1H), 5.38 (d,  $J$  = 3.5 Hz, 1H), 5.46–5.47 (m, 1H), 5.64–5.66 (m, 1H), 6.92 (dd,  $J_{\text{H,F}}$  = 77.9 Hz and  $J$  = 2.3 Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.47, 20.51, 20.6, 45.0, 63.1 (d,  $J_{\text{C,F}}$  = 2.4 Hz), 68.9 (d,  $J_{\text{C,F}}$  = 8.3 Hz), 70.5, 71.1, 114.8, 116.6 (d,  $J_{\text{C,F}}$  = 7.2 Hz), 151.6 (d,  $J_{\text{C,F}}$  = 271.8 Hz), 169.3, 169.6, 169.7, 169.8.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$   $-118.9$  (d,  $J_{\text{H,F}}$  = 73.4 Hz). ESI-MS ( $m/z$ ): 372 [ $\text{M}^+ + \text{H}$ ], HRMS (ESI+): calcd for  $\text{C}_{16}\text{H}_{19}\text{FNO}_8$  372.1095, found 372.1079 [ $\text{M}^+ + \text{H}$ ].

(1*S*,2*R*,3*R*,4*S*,*Z*)-4-(Acetoxymethyl)-4-cyano-5-(fluoromethylene)cyclopentane-1,2,3-triyl triacetate [(Z)-14]. Compound (Z)-13 (3.3 g, 6.6 mmol) was treated with the same procedure described for (E)-14. This gave (Z)-14 (1.01 g, 42% for four steps) as a solid. Mp  $157\text{--}158^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{26} -7.0$  ( $c$  0.33,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.12 (s, 3H), 2.14 (s, 3H), 2.16 (s, 3H), 2.18 (s, 3H), 4.16 (d,  $J$  = 11.5 Hz, 1H), 4.35 (d,  $J$  = 11.5 Hz, 1H), 5.29 (d,  $J$  = 4.0 Hz,



1H), 5.45 (dd,  $J = 5.2$  and  $4.0$  Hz, 1H), 6.02–6.04 (m, 1H), 7.03 (dd,  $J_{\text{H,F}} = 76.8$  Hz and  $J = 2.3$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.38, 20.42, 20.46, 20.53, 45.1 (d,  $J_{\text{C,F}} = 6.0$  Hz), 65.1, 67.4, 70.0, 71.6, 116.4, 118.0 (d,  $J_{\text{C,F}} = 10.8$  Hz), 152.1 (d,  $J_{\text{C,F}} = 273.5$  Hz), 169.3, 169.46, 169.52, 169.6.  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  –118.3 (d,  $J = 73.4$  Hz). MS (ESI<sup>+</sup>)  $m/z$   $\text{C}_{16}\text{H}_{18}\text{FNNaO}_8$ , 394 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{16}\text{H}_{18}\text{FNNaO}_8$  394.0909, found 394.0900 [ $\text{M}^+ + \text{Na}$ ].

(5*S*,7*S*,8*R*,8*aR*,*E*)-6-(Fluoromethylene)-8-hydroxy-7-(hydroxymethyl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-cyclopenta[[1,3,5,2,4]trioxadisilepine-7-carbonitrile [(*E*)-15]. To a THF (10 mL) solution of (*E*)-14 (5.0 g, 13.5 mmol) was added  $\text{NH}_3/\text{MeOH}$  (saturated at 0 °C, 70 mL). The resulting solution was kept at 4 °C for 80 h. After evaporation of all the volatile components, the crude residue was azeotropic and dried with toluene. The residue was dissolved in anhydrous pyridine (60 mL). To this was dropwise added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (4.68 mL, 14.8 mmol) at –50 °C. The mixture was stirred further for 45 h at –30 °C. After the addition of MeOH (100 mL) and evaporation of all volatiles, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 7 : 5). This gave (*E*)-15 (3.07 g, 51%) as a solid. Mp 84–86 °C;  $[\alpha]_{\text{D}}^{26} -6.1$  ( $c$  0.88,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.04–1.10 (m, 28H), 2.06 (dd,  $J = 7.5$  and  $5.5$  Hz, 1H), 3.09 (d,  $J = 12.4$  Hz, 1H), 3.99 (dd,  $J = 10.9$  and  $7.5$  Hz, 1H), 4.04 (dd,  $J = 10.9$  and  $5.5$  Hz, 1H), 4.28 (d,  $J = 12.4$  and  $3.2$  Hz, 1H), 4.42 (dd,  $J = 6.3$  and  $3.2$  Hz, 1H), 4.67–4.69 (m, 1H), 6.89 (dd,  $J_{\text{H,F}} = 80.8$  Hz and  $J = 2.9$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  12.86, 12.91, 13.0, 14.2, 16.7, 16.9, 17.20, 17.29, 17.35, 17.41, 17.5, 48.3, 63.4, 71.7, 73.7 (d,  $J_{\text{C,F}} = 7.2$  Hz), 75.5, 116.4, 121.6 (d,  $J_{\text{C,F}} = 6.0$  Hz), 149.3 (d,  $J_{\text{C,F}} = 261.5$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  –130.5 (d,  $J = 88.0$  Hz). ESI-MS ( $m/z$ ): 446 [ $\text{M}^+ + \text{H}$ ], HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{20}\text{H}_{37}\text{FNO}_5\text{Si}_2$  446.2194, found 446.2199 [ $\text{M}^+ + \text{H}$ ].

(5*S*,7*S*,8*R*,8*aR*,*Z*)-6-(Fluoromethylene)-8-hydroxy-7-(hydroxymethyl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-cyclopenta[[1,3,5,2,4]trioxadisilepine-7-carbonitrile [(*Z*)-15]. Compound (*Z*)-14 (1.01 g, 2.72 mmol) was treated with the same procedure described for (*E*)-15. This gave (*Z*)-15 (877 mg, 72%) as a solid. Mp 100–103 °C;  $[\alpha]_{\text{D}}^{27} +1.8$  ( $c$  0.46,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.05–1.12 (m, 28H), 2.24 (dd,  $J = 8.0$  and  $5.4$  Hz, 1H), 3.21 (d,  $J = 10.9$  Hz, 1H), 3.73 (dd,  $J = 10.9$  and  $8.0$  Hz, 1H), 3.87 (dd,  $J = 10.9$  and  $5.4$  Hz, 1H), 4.02 (dd,  $J = 10.9$  and  $4.0$  Hz, 1H), 4.33 (t,  $J = 4.0$  Hz, 1H), 5.007–5.011 (m, 1H), 7.03 (dd,  $J_{\text{H,F}} = 79.0$  Hz and  $J = 2.3$  Hz, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  12.9, 13.2, 13.5, 16.9, 16.95, 17.0, 17.1, 17.25, 17.32, 17.4, 17.5, 49.4 (d,  $J_{\text{C,F}} = 6.0$  Hz), 66.4, 72.6, 73.7, 74.9, 118.4, 121.9 (d,  $J_{\text{C,F}} = 8.4$  Hz), 151.2 (d,  $J_{\text{C,F}} = 271.1$  Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  –122.7 (d,  $J_{\text{H,F}} = 73.4$  Hz). ESI-MS ( $m/z$ ): 446 [ $\text{M}^+ + \text{H}$ ], HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{20}\text{H}_{37}\text{FNO}_5\text{Si}_2$  446.2194, found 446.2202 [ $\text{M}^+ + \text{H}$ ].

(1*S*,2*R*,3*S*,4*S*,*E*)-2-((Benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-5-(fluoromethylene)-3,4-dihydroxycyclopentane-1-carbonitrile [(*E*)-16]. To a mixture of (*E*)-15 (3.07 g, 6.89 mmol),  $i\text{-Pr}_2\text{NEt}$  (14.4 mL, 82.7 mmol) and  $\text{Bu}_4\text{NI}$  (15.3 g, 41.3 mmol) in anhydrous toluene (60 mL) was added BOMCl (6.35 mL, 58.1 mmol). The resulting mixture was stirred at 80 °C for 6 days. After the addition of MeOH (10 mL), the mixture was partitioned between aqueous saturated  $\text{NaHCO}_3$  and AcOEt, and the

organic layer was further washed with brine. After the evaporation of all of the volatiles in the organic layer, the residue was used for the next step without further purification. To a THF (100 mL) solution of the residue was added  $\text{Bu}_4\text{NF}$  (1.0 mol  $\text{L}^{-1}$  in THF, 17.2 mL, 17.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 22 h. After the addition of AcOH (900  $\mu\text{L}$ ) and evaporation of all the volatiles of the mixture, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 7 : 5). This gave (*E*)-16 (2.81 g, 92% for two steps) as an oil.  $[\alpha]_{\text{D}}^{26} -34.8$  ( $c$  0.27,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.58 (d,  $J = 10.9$  Hz, 1H), 2.89 (d,  $J = 3.5$  Hz, 1H), 3.83 (d,  $J = 9.7$  Hz, 1H), 3.92 (d,  $J = 9.7$  Hz, 1H), 4.06–4.10 (m, 1H), 4.25 (d,  $J = 3.4$  Hz, 1H), 4.40–4.43 (m, 1H), 4.56 (d,  $J = 12.1$  Hz, 1H), 4.58 (d,  $J = 12.1$  Hz, 1H), 4.72 (d,  $J = 12.3$  Hz, 1H), 4.74 (t,  $J = 6.3$  Hz, 2H), 4.75 (d,  $J = 12.3$  Hz, 1H), 4.97 (t,  $J = 7.2$  Hz, 2H), 6.90 (dd,  $J_{\text{H,F}} = 79.0$  Hz and  $J = 2.3$  Hz, 1H), 7.28–7.37 (m, 10H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  46.4, 67.6, 70.1, 70.9, 71.0 (d,  $J_{\text{C,F}} = 3.6$  Hz), 72.3, 78.2, 94.8, 95.1, 116.8, 122.6 (d,  $J_{\text{C,F}} = 2.4$  Hz), 127.9, 127.95, 128.03, 128.2, 128.5, 128.6, 136.9, 137.2, 150.4 (d,  $J_{\text{C,F}} = 266.3$  Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  –125.7 (d,  $J_{\text{H,F}} = 73.4$  Hz). ESI-MS ( $m/z$ ): 444. [ $\text{M}^+ + \text{H}$ ], HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{24}\text{H}_{27}\text{FNO}_6$  444.1822, found 444.1834 [ $\text{M}^+ + \text{H}$ ].

(1*S*,2*R*,3*S*,4*S*,*Z*)-2-((Benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-5-(fluoromethylene)-3,4-dihydroxycyclopentane-1-carbonitrile [(*Z*)-16]. Compound (*Z*)-15 (825 mg, 1.85 mmol) was treated with the same procedure described for (*E*)-16. This gave (*Z*)-16 (752 mg, 92%) as an oil.  $[\alpha]_{\text{D}}^{27} +9.2$  ( $c$  0.27,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.60 (d,  $J = 9.2$  Hz, 1H), 3.13 (d,  $J = 6.9$  Hz, 1H), 3.57 (d,  $J = 9.8$  Hz, 1H), 3.60 (d,  $J = 9.8$  Hz, 1H), 4.05–4.06 (m, 1H), 4.18 (d,  $J = 2.9$  Hz, 1H), 4.62 (t,  $J = 12.3$  Hz, 2H), 4.68–4.71 (m, 1H), 4.75 (t,  $J = 12.0$  Hz, 2H), 4.79 (t,  $J = 7.7$  Hz, 2H), 4.95 (d,  $J = 7.2$  Hz, 1H), 5.02 (d,  $J = 7.2$  Hz, 1H), 7.04 (dd,  $J_{\text{H,F}} = 79.0$  Hz and  $J = 1.7$  Hz, 1H), 7.29–7.38 (m, 10H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  46.9 (d,  $J_{\text{C,F}} = 6.0$  Hz), 69.3, 70.3, 70.4, 70.9, 71.6, 79.5, 94.8, 95.3, 118.7, 123.1 (d,  $J_{\text{C,F}} = 10.8$  Hz), 127.9, 128.0, 128.1, 128.6, 137.0, 137.2, 152.3 (d,  $J_{\text{C,F}} = 268.7$  Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  –120.4 (d,  $J = 73.3$  Hz). ESI-MS ( $m/z$ ): 466 [ $\text{M}^+ + \text{Na}$ ], HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{24}\text{H}_{26}\text{FNNaO}_6$  466.1636, found 466.1629 [ $\text{M}^+ + \text{Na}$ ].

(1*S*,2*R*,3*R*,4*S*,*E*)-2-((Benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-4-((tert-butyl dimethylsilyl)oxy)-5-(fluoromethylene)-3-hydroxycyclopentane-1-carbonitrile [(*E*)-17]. To a mixture of (*E*)-16 (204 mg, 0.46 mmol) and imidazole (94 mg, 1.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added TBSCl (167 mg, 1.1 mmol) at 0 °C. The resulting mixture was stirred at rt for 4.5 h. After the addition of MeOH (1 mL), the mixture was partitioned between aqueous saturated  $\text{NaHCO}_3$  and  $\text{CH}_2\text{Cl}_2$ . Column chromatography on silica gel (hexane/AcOEt = 3 : 1) of the organic layer gave (*E*)-17 (205 mg, 80%) as an oil.  $[\alpha]_{\text{D}}^{27} -20.0$  ( $c$  0.37,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.12 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 2.67 (d,  $J = 2.3$  Hz, 1H), 3.92 (d,  $J = 10.9$  Hz, 1H), 3.94 (d,  $J = 10.9$  Hz, 1H), 4.04–4.05 (m, 1H), 4.20 (d,  $J = 3.4$  Hz, 1H), 4.45–4.47 (m, 1H), 4.56 (s, 2H), 4.73 (d,  $J = 12.0$  Hz, 1H), 4.74 (s, 2H), 4.78 (d,  $J = 12.0$  Hz, 1H), 4.96 (t,  $J = 7.4$  Hz, 2H), 6.68 (dd,  $J_{\text{H,F}} = 79.6$  Hz and  $J = 2.3$  Hz, 1H), 7.29–7.37 (m, 10H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  –4.9, –4.8, 18.1, 25.7, 46.0, 67.7, 69.9, 70.4, 71.6 (d,  $J_{\text{C,F}} = 7.2$  Hz), 72.6, 77.4, 94.8, 94.9,



116.6, 122.1 (d,  $J_{C,F}$  = 4.8 Hz), 127.8, 127.9, 128.0, 128.1, 128.5, 137.2, 137.3, 149.3 (d,  $J_{C,F}$  = 263.9 Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -127.6 (d,  $J_{H,F}$  = 73.3 Hz). MS (ESI+)  $m/z$   $\text{C}_{30}\text{H}_{40}\text{FNNaO}_6\text{Si}$ , 580 [ $\text{M}^+$  + Na]. HRMS (ESI+): calcd for  $\text{C}_{30}\text{H}_{40}\text{FNNaO}_6\text{Si}$  580.2501, found 580.2512 [ $\text{M}^+$  + Na].

**Silylation of Z-21; formation to (1S,2R,3R,4S,Z)-2-((benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-4-((tert-butyltrimethylsilyl)oxy)-5-(fluoromethylene)-3-hydroxycyclopentane-1-carbonitrile [(Z)-17] and its regioisomer [(Z)-17a].** Compound (Z)-16 (646 mg, 1.46 mmol) was treated with the same procedure described for (E)-17. This gave an inseparable mixture of (Z)-17 and (Z)-17a (721 mg, ca. 3 : 2 of mixture, 89%) as an oil. The residue was used for the next step without further separation.  $^1\text{H}$  NMR of the mixture of (Z)-17 and (Z)-17a ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.14 (s, 1.2H), 0.16 (s, 3.6H), 0.17 (s, 1.2H), 0.93 (s, 5.4H), 0.95 (s, 3.6H), 2.80 (d,  $J$  = 10.5 Hz, 0.4H), 3.02 (d,  $J$  = 8.2 Hz, 0.6H), 3.61 (d,  $J$  = 9.7 Hz, 0.4H), 3.62 (d,  $J$  = 9.8 Hz, 0.6H), 3.67–3.69 (m, 1H), 3.97–4.02 (m, 1.2H), 4.10 (dd,  $J$  = 5.2 and 3.5 Hz, 0.4H), 4.16 (d,  $J$  = 3.5 Hz, 0.4H), 4.60–4.63 (m, 3H), 4.70–4.78 (m, 4H), 4.88–4.98 (m, 4H), 6.96 (dd,  $J_{H,F}$  = 80.2 Hz and  $J$  = 2.3 Hz, 0.6H), 7.03 (dd,  $J_{H,F}$  = 79.0 Hz and  $J$  = 1.7 Hz, 0.4H), 7.30–7.35 (m, 10H).  $^{13}\text{C}$  NMR of the mixture of (Z)-22 and (Z)-22a ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  -5.24, -5.17, -5.15, -4.8, -4.7, 18.2, 18.3, 25.7, 25.8, 46.4 (d,  $J_{C,F}$  = 7.2 Hz), 46.7 (d,  $J_{C,F}$  = 6.0 Hz), 69.7, 70.0, 70.1, 70.2, 70.3, 70.4, 70.46, 70.53, 71.8, 73.3, 78.3, 78.6, 94.7, 94.81, 94.84, 118.7, 118.8, 122.7 (d,  $J_{C,F}$  = 10.8 Hz), 123.6 (d,  $J_{C,F}$  = 10.8 Hz), 127.91, 127.93, 128.2, 128.5, 137.1, 137.2, 137.4, 150.8 (d,  $J_{C,F}$  = 268.7 Hz), 151.9 (d,  $J_{C,F}$  = 268.7 Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -123.1 (d,  $J_{H,F}$  = 73.4 Hz) and -121.8 (d,  $J_{H,F}$  = 73.3 Hz). MS (ESI+)  $m/z$   $\text{C}_{30}\text{H}_{40}\text{FNNaO}_6\text{Si}$ , 580 [ $\text{M}^+$  + Na]. HRMS (ESI+): calcd for  $\text{C}_{30}\text{H}_{40}\text{FNNaO}_6\text{Si}$  580.2501, found 580.2519 [ $\text{M}^+$  + Na].

**(1S,3R,5S,E)-5-((Benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-2-(fluoromethylene)-3-hydroxycyclopentane-1-carbonitrile [(E)-18].** To a  $\text{CH}_2\text{Cl}_2$  (35 mL) solution of (E)-17 (2.5 g, 4.48 mmol) and pyridine (1.45 mL, 17.9 mmol) was dropwise added trifluoromethanesulfonic anhydride (1.51 mL, 8.96 mmol) at -30 °C. The resulting mixture was stirred for 40 min at the same temperature, then this was stirred further for 2 h at RT. The mixture was partitioned between aqueous saturated  $\text{NaHCO}_3$  and  $\text{CH}_2\text{Cl}_2$ . After the evaporation of all of the volatiles in the organic layer, the residue was used for the next step without further purification. To a DMF (50 mL) solution of the residue was added LiI (6.0 g, 44.8 mmol) at rt. The resulting solution was stirred at rt for 60 h in the dark. The resulting brown solution was partitioned between brine and AcOEt. After evaporation of all the volatiles of the organic layer gave a crude iodide. To a toluene (40 mL) solution of the iodide and  $(\text{Me}_3\text{Si})_3\text{SiH}$  (2.75 mL, 8.96 mmol) was added  $\text{Et}_3\text{B}$  (1.0 mol  $\text{L}^{-1}$  in THF, 4.48 mL, 4.48 mmol) in one portion. The resulting mixture was stirred for 20 min at rt in an open air. After evaporation of all volatiles, the residue was roughly purified by column chromatography on silica gel (hexane/AcOEt = 4 : 1). This gave a crude silyl ether (ca. 2.3 g) as an oil. This was used for the next step without further purification. To a THF (20 mL) solution of the crude product was dropwise added  $\text{Bu}_4\text{NF}$  (1.0 mol  $\text{L}^{-1}$  in THF, 5.38 mL, 5.38 mmol) at rt. The resulting mixture was stirred for

a further 1.5 h at the same temperature. After the addition of AcOH (300  $\mu\text{L}$ ) and evaporation of all the volatile components, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1 : 1). This gave (E)-18 (1.18 g, 62% for four steps) as an oil.  $[\alpha]_{\text{D}}^{26}$  -15.6 (c 1.53,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.01 (ddd,  $J$  = 14.9, 5.2 and 4.6 Hz, 1H), 2.08 (ddd,  $J$  = 14.9, 5.2 and 2.3 Hz, 1H), 2.74 (d,  $J$  = 11.5 Hz, 1H), 3.37 (d,  $J$  = 9.8 Hz, 1H), 3.94 (d,  $J$  = 9.8 Hz, 1H), 4.53–4.56 (m, 2H), 4.57 (d,  $J$  = 12.0 Hz, 1H), 4.65 (d,  $J$  = 12.0 Hz, 1H), 4.68 (d,  $J$  = 11.5 Hz, 1H), 4.75 (d,  $J$  = 11.5 Hz, 1H), 4.77 (d,  $J$  = 6.9 Hz, 1H), 4.81 (d,  $J$  = 6.9 Hz, 1H), 4.91 (d,  $J$  = 7.4 Hz, 1H), 4.95 (d,  $J$  = 7.4 Hz, 1H), 7.03 (d,  $J_{H,F}$  = 79.6 Hz, 1H), 7.29–7.40 (m, 10H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  39.2, 50.3, 67.3, 70.2, 71.2, 71.3, 79.3, 93.7, 94.8, 117.8, 124.3, 127.9, 128.0, 128.1, 128.5, 137.2, 137.3, 151.4 (d,  $J_{C,F}$  = 271.1 Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -121.3 (d,  $J_{H,F}$  = 88.0 Hz). ESI-MS ( $m/z$ ): 428 [ $\text{M}^+$  + H], HRMS (ESI+): calcd for  $\text{C}_{24}\text{H}_{27}\text{FNO}_5$  428.1873, found 428.1878 [ $\text{M}^+$  + H].

**(1S,3R,5S,Z)-5-((Benzyloxy)methoxy)-1-(((benzyloxy)methoxy)methyl)-2-(fluoromethylene)-3-hydroxycyclopentane-1-carbonitrile [(Z)-17].** A mixture of compounds (Z)-17 and (Z)-17a (636 mg, 1.14 mmol, ca. 3 : 2 of the mixture) was treated with the same procedure described for (E)-18. This gave (Z)-18 (227 mg, 47%, for four steps) as an oil.  $[\alpha]_{\text{D}}^{26}$  +2.0 (c 0.3,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.05 (ddd,  $J$  = 14.9, 6.3 and 4.0 Hz, 1H), 2.11 (dt,  $J$  = 14.9 and 2.3 Hz, 1H), 2.58 (d,  $J$  = 8.6 Hz, 1H), 3.47 (d,  $J$  = 10.0 Hz, 1H), 3.50 (d,  $J$  = 10.0 Hz, 1H), 4.39–4.40 (m, 1H), 4.60 (d,  $J$  = 11.5 Hz, 1H), 4.64 (d,  $J$  = 11.5 Hz, 1H), 4.68 (d,  $J$  = 12.1 Hz, 1H), 4.74 (d,  $J$  = 12.1 Hz, 1H), 4.78 (d,  $J$  = 9.8 Hz, 1H), 4.80 (d,  $J$  = 9.8 Hz, 1H), 4.88–4.91 (m, 1H), 4.90 (d,  $J$  = 10.3 Hz, 1H), 4.92 (d,  $J$  = 10.3 Hz, 1H), 6.97 (dd,  $J_{H,F}$  = 79.6 Hz and  $J$  = 1.2 Hz, 1H), 7.29–7.39 (m, 10H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  38.4, 50.1 (d,  $J_{C,F}$  = 6.0 Hz) 0.69.2, 70.0 (d,  $J_{C,F}$  = 2.4 Hz), 70.2, 70.3, 79.1, 93.6, 94.8, 119.0, 126.2 (d,  $J_{C,F}$  = 6.6 Hz), 127.97, 127.99, 128.1, 128.5, 128.6, 137.1, 137.2, 150.5 (d,  $J_{C,F}$  = 266.3 Hz).  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -121.5 (d,  $J$  = 73.3 Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -121.5 (d,  $J_{H,F}$  = 73.3 Hz). ESI-MS ( $m/z$ ): 428 [ $\text{M}^+$  + H], HRMS (ESI+): calcd for  $\text{C}_{24}\text{H}_{27}\text{FNO}_5$  428.1873, found 428.1878 [ $\text{M}^+$  + H].

**Mitsunobu reaction of (E)-18; formation to (E)-20.** To a toluene (8 mL) solution of (E)-18 (272 mg, 0.64 mmol), protected 2-amino-6-chloropurine (19) (473 mg, 1.28 mmol) and  $\text{Ph}_3\text{P}$  (336 mg, 1.28 mmol), a toluene (4 mL) solution of DMEAD (300 mg, 1.28 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The mixture was partitioned between brine and AcOEt. After evaporation of all volatiles of the organic layer, the residue was roughly purified by column chromatography on silica gel (hexane/AcOEt = 1 : 1). The obtained crude product was further purified by HPLC (hexane/AcOEt = 1 : 1, 20 mL  $\text{min}^{-1}$ ,  $R_t$  = 7.6 min). This gave (E)-20 (265 mg, 53%) as a foam.  $[\alpha]_{\text{D}}^{26}$  +33.8 (c 0.3,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.47 (s, 18H), 2.46 (ddd,  $J$  = 1.29, 6.9 and 5.2 Hz, 1H), 2.58 (ddd,  $J$  = 12.9, 8.0 and 4.6 Hz, 1H), 4.07 (d,  $J$  = 9.8 Hz, 1H), 4.10 (d,  $J$  = 9.8 Hz, 1H), 4.57 (d,  $J$  = 12.0 Hz, 1H), 4.57–4.59 (m, 1H), 4.64 (d,  $J$  = 12.0 Hz, 1H), 4.66 (d,  $J$  = 12.0 Hz, 1H), 4.77 (d,  $J$  = 12.0 Hz, 1H), 4.83 (t,  $J$  = 6.9 Hz, 2H), 4.88 (d,  $J$  = 7.2 Hz, 1H), 4.92 (d,  $J$  = 7.2 Hz, 1H), 5.75–5.76 (m, 1H), 6.67 (dd,  $J_{H,F}$  = 77.3 Hz and  $J$  = 1.8 Hz, 1H), 7.32–7.36 (m, 10H), 8.20 (s,





1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  27.9, 36.5, 50.2 (d,  $J_{\text{C,F}} = 7.2$  Hz), 67.2, 70.5 (d,  $J_{\text{C,F}} = 9.6$  Hz), 84.0, 94.2, 95.0, 116.5, 119.6 (d,  $J_{\text{C,F}} = 6.0$  Hz), 127.9, 128.0, 128.1, 128.6, 130.4, 137.1, 137.2, 144.3, 150.6, 151.4 (d,  $J_{\text{C,F}} = 271.2$  Hz), 151.8, 152.0, 152.1.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -119.5 (d,  $J_{\text{H,F}} = 73.4$  Hz). ESI-MS ( $m/z$ ): 801 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{39}\text{H}_{44}\text{ClFN}_6\text{NaO}_8$  801.2785, found 801.2799 [ $\text{M}^+ + \text{Na}$ ].

**Mitsunobu reaction of (Z)-18; formation to (Z)-20.** Compound (Z)-18 (74 mg, 0.173 mmol) was treated with same procedure described for (E)-20. This gave (Z)-20 (124 mg, 92%) as a foam.  $[\alpha]_{\text{D}}^{26} +54.6$  (c 0.44,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.45 (s, 18H), 2.54–2.57 (m, 2H), 3.95 (d,  $J = 10.0$  Hz, 1H), 4.13 (d,  $J = 10.0$  Hz, 1H), 4.64–4.69 (m, 4H), 4.76 (d,  $J = 12.1$  Hz, 1H), 4.83 (s, 2H), 4.90 (d,  $J = 7.5$  Hz, 1H), 4.93 (d,  $J = 7.5$  Hz, 1H), 5.79–5.82 (m, 1H), 7.01 (dd,  $J_{\text{H,F}} = 77.9$  Hz and  $J = 2.3$  Hz, 1H), 7.31–7.36 (m, 10H), 8.10 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  27.9, 36.4, 50.3 (d,  $J_{\text{C,F}} = 4.8$  Hz), 53.3, 69.5, 70.4 (d,  $J_{\text{C,F}} = 6.0$  Hz), 78.0, 83.9, 94.2, 94.9, 118.4, 120.1 (d,  $J_{\text{C,F}} = 9.6$  Hz), 127.9, 128.1, 128.5, 128.6, 130.5, 137.1, 137.3, 145.3, 151.5, 151.57, 151.58 (d,  $J_{\text{C,F}} = 271.1$  Hz), 151.7.  $^{19}\text{F}$  NMR (470 MHz,  $\text{CDCl}_3$ )  $\delta$  -119.0 (d,  $J = 73.3$  Hz).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 470 MHz)  $\delta$  -119.0 (d,  $J_{\text{H,F}} = 73.3$  Hz). ESI-MS ( $m/z$ ): 801 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{39}\text{H}_{44}\text{ClFN}_6\text{NaO}_8$  801.2785, found 801.2801 [ $\text{M}^+ + \text{Na}$ ].

**(1S,3S,5S,E)-3-(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-(fluoromethylene)-5-hydroxy-1-(hydroxymethyl)cyclopentane-1-carbonitrile (E)-6.** To a THF (1 mL) solution of (E)-20 (84 mg, 0.11 mmol) was added 80% TFA (4 mL). The resulting mixture was stirred for 72 h at rt. After evaporation of all volatile components of the mixture, the residue was treated with  $\text{NH}_3/\text{MeOH}$  (saturated at 0 °C, 4 mL). This was kept at 4 °C for 14 h, then volatiles were evaporated. The residue was purified by RP-HPLC (30% MeOH, 10 mL  $\text{min}^{-1}$ ,  $R_t = 8.72$  min). This gave (E)-6 (28 mg, 81%) as a solid. Mp > 200 °C decomp.;  $[\alpha]_{\text{D}}^{24} + 55.7$  (c 0.11, MeOH);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  2.11–2.13 (m, 1H), 2.49–2.50 (m, 1H), 3.77 (dd,  $J = 11.5$  and 6.3 Hz, 1H), 3.82 (dd,  $J = 11.5$  and 5.7 Hz, 1H), 4.42 (br-s, 1H), 5.52–5.56 (m, 1H), 5.87 (t,  $J = 6.3$  Hz, 1H), 6.08 (d,  $J = 4.6$  Hz, 1H), 6.44 (br-s, 2H), 6.75 (dd,  $J_{\text{H,F}} = 79.1$  Hz and  $J = 2.3$  Hz, 1H), 7.80 (s, 1H), 10.40 (br-s, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 125 MHz)  $\delta$  37.5, 51.5 (d,  $J_{\text{C,F}} = 6.0$  Hz), 53.6, 61.9, 70.7, 116.7, 118.9, 121.4 (d,  $J_{\text{C,F}} = 4.8$  Hz), 135.9, 150.4 (d,  $J_{\text{C,F}} = 262.7$  Hz), 150.9, 153.5, 156.8.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 470 MHz)  $\delta$  -126.7 (d,  $J_{\text{H,F}} = 73.3$  Hz). ESI-MS ( $m/z$ ): 321 [ $\text{M}^+ + \text{H}$ ], 343 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{13}\text{H}_{14}\text{FN}_6\text{O}_3$  321.1106, found 321.1112 [ $\text{M}^+ + \text{H}$ ].

**(1S,3S,5S,Z)-3-(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-(fluoromethylene)-5-hydroxy-1-(hydroxymethyl)cyclopentane-1-carbonitrile (Z)-6.** Compound (Z)-20 (264 mg, 0.34 mmol) was treated with the same procedure described for (E)-6. This gave (Z)-6 (47 mg, 43%,  $R_t = 9.92$  min) as a solid. Mp > 240 °C decomp.;  $[\alpha]_{\text{D}}^{25} + 31.2$  (c 0.12, MeOH);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 500 MHz)  $\delta$  2.17–2.22 (m, 1H), 2.27–2.32 (m, 1H), 3.69 (dd,  $J = 11.5$  and 5.7 Hz, 1H), 3.93 (dd,  $J = 11.5$  and 5.7 Hz, 1H), 4.38 (d,  $J = 3.4$  Hz, 1H), 5.63–5.67 (m, 1H), 5.83 (t,  $J = 5.7$  Hz, 1H), 6.04 (d,  $J = 5.2$  Hz, 1H), 6.41 (br-s, 1H), 7.18 (dd,  $J_{\text{H,F}} = 79.0$  Hz and  $J = 2.9$  Hz, 1H), 7.70 (s, 1H), 10.59 (br-s, 1H).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 125 MHz)  $\delta$  38.6, 51.2, 53.2 (d,  $J_{\text{C,F}} = 4.8$  Hz), 64.1, 71.2, 116.4, 120.2, 121.4 (d,  $J_{\text{C,F}} = 8.4$  Hz), 136.1, 150.3 (d,  $J_{\text{C,F}} = 263.9$  Hz), 150.8,

153.3, 156.7.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 470 MHz)  $\delta$  -124.2 (d,  $J_{\text{H,F}} = 88.0$  Hz). ESI-MS ( $m/z$ ): 321 [ $\text{M}^+ + \text{H}$ ], 343 [ $\text{M}^+ + \text{Na}$ ]. HRMS (ESI+): calcd for  $\text{C}_{13}\text{H}_{14}\text{FN}_6\text{O}_3$  321.1106, found 321.1110 [ $\text{M}^+ + \text{H}$ ].

## 4.2. Anti-HBV and cytotoxicity assay

Anti-HBV assays were conducted as previously described.<sup>14,15</sup> Briefly, HepG2 2.15 cells were seeded in 96-well cell culture plates at a density of  $4 \times 10^3$  cells in 200  $\mu\text{L}$  per well together with various concentrations of a compound. On days 3 and 7 after plating, the culture medium was removed and the fresh medium and a drug were replenished. On day 14, the cells were harvested for DNA collection and the DNA samples were extracted from the cells using QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions and were re-suspended in 100  $\mu\text{L}$  Tris-EDTA buffer. Total cellular DNA samples were amplified using the Genesig Advanced Kit for quantification of hepatitis B virus genomes (PrimerDesign™ Ltd., Southampton, UK) and Applied Biosystems® 7500 Fast Real-time PCR System (Life Technologies Japan Ltd., Tokyo Japan). PCR preparations were incubated at 95 °C for 10 min, followed by 50 cycles at 95 °C for 10 s and 60 °C for 1 min. The data were analyzed using 7500 Fast Software Version 2.0.6 (Life Technologies Japan Ltd., Tokyo Japan), and threshold cycle (CT) values were obtained. To derive the HBV copy numbers from the CT values, a standard curve was generated with 10-fold serial dilutions of an HBV plasmid. The amount of HBV DNA in each assay sample with a test compound was compared to no-compound control samples, and 50% effective concentration ( $\text{EC}_{50}$ ) was determined using the Forecast function of Microsoft Excel software. The cytotoxicities of the compounds in HepG2.2.15 cells were also determined. Cells were plated in a 96-well plate at a density of  $2 \times 10^3$  cells in 200  $\mu\text{L}$  per well and were continuously exposed to the compound at a certain concentration for 14 days. The number of viable cells in each well was determined using the Cell Counting Kit-8 (Dojindo, Kumamoto, Japan), compared to no-compound control samples, and 50% cytotoxicity concentration ( $\text{CC}_{50}$ ) values were determined.

## 4.3. Methods – molecular modeling

We used the previously published<sup>12,14</sup> ternary complexes of HBV-reverse transcriptase (RT) with entecavir triphosphate (ETV-TP) as a template for building a model of the structural interactions of (E)-6 with HBV-RT<sub>WT</sub> in the presence of primer-templates (pt). The HBV-RT model was built by homology modeling using sequence homology between HBV-RT and HIV-RT.<sup>12</sup> (E)-6-TP was generated by suitable modifications to ETV-TP. Minimization of the (E)-6-HBV-RT<sub>WT</sub> (pt) complex in the OPLS3 force field as implemented in Maestro version 10.7.015 (Schrödinger, LLC, New York) was carried out. Figures of structural interactions were generated using Pymol version 2.5.4.

## Author contributions

H. K.: conceptualization, investigation, synthetic methodology, and writing-original draft. N. H.-K.: investigation and writing a part of the original draft. S. H.: investigation. D. D.: molecular





modeling and writing a part of the original draft. H. B.: molecular modeling and writing a part of the original draft. R. T.: investigation. S. I.: investigation. K. O.: investigation. Y. H.: investigation. Y. O.: formal analysis. S. S.-M.: formal analysis. K. H.: investigation. Y. T.: conceptualization, methodology, and investigation. H. M.: conceptualization, methodology, supervision, and writing-review and editing. All authors have read, commented, and given approval to the final version of the manuscript.

## Conflicts of interest

The authors have no conflict of interest to declare.

## Acknowledgements

The present work was supported in part by a grant for the Development of Novel Drugs for Treating HBV Infection from the Japan Agency for Medical Research and Development (YT; JP20fk0310101, HM: JP16fk0310501 and JP20fk0310113); grants for the Research Program on HIV/AIDS from the Japan Agency for Medical Research and Development under grant number JP18fk0410001 (HM); grants from Japan Society for the Promotion of Sciences (HM: 17H04222 and 17K19577), and the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health (HM, DD). The authors are grateful to Kyoko Hattori and Asuka Fujiwara for their technical help. This study utilized the high-performance computational capabilities of the Biowulf Linux cluster at the NIH, Bethesda, MD (<https://hpc.nih.gov>).

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