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PAPER

Synthesis and properties of 1-(3′-dihydroxyboryl-2′,3′-dideoxyribosyl)-pyrimidines†

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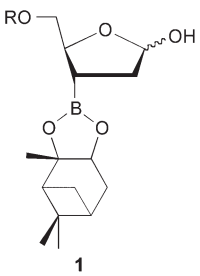
Nucleoside analogues having a boronic acid in place of the 3-hydroxyl group of deoxyribose have been synthesized. The synthesis of 3′-dihydroxyboryl-2′,3′-dideoxyribose was based on asymmetric homologation of boronic esters with (dihalomethyl)lithium, beginning from a (silyloxymethyl)boronic ester. A change of chiral director is required before introduction of the second stereocenter, and the direct displacement of (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol by (1*S*,2*S*,3*R*,5*S*)-pinanediol was used for this purpose. Coupling of the pinanediol ester of the 1-acetoxy-3-dioxyboryl-5-*tert*-butylsilyloxy deoxyribose analogue with silylated pyrimidine bases was accomplished with trimethylsilyl bromide. The boronic acid nucleoside analogues were not cytotoxic toward Hep G2 (human hepatocarcinoma) cells. Decomposition occurred over a period of several hours at 37 °C, pH 7.4, with liberation of free pyrimidine base.

Introduction

Several dideoxynucleosides are known to have clinically useful antiviral activity.[1] 5-Dihydroxyboryl-2′-deoxyuridine has been found to inhibit the growth of *Herpes simplex* 1 in cell culture.[2,3] 2′,3′-Dideoxyribonucleosides having a boronic acid function in place of the 3′-hydroxyl group have not been reported, and their synthesis presented an interesting chemical challenge. The synthetic route chosen was expected to provide new information about asymmetric synthesis *via* (α-haloalkyl)boronic esters.[4]

The first stage of the problem was to prepare the boronic acid analogue of deoxyribose in protected form, chosen as a pinanediol ester **1**. Subsequent connection of **1** to a pyrimidine or purine base followed by deprotection has led to the series of target compounds **2**.

The reaction of chiral boronic esters with (dichloromethyl)-lithium provides an efficient route for the highly stereoselective insertion and functionalization of two of the three stereocentres of **2**.[4] The steric relationship between these two centres requires either an inversion of one of them[5] or removal of the first chiral director and its replacement with a second that directs in the opposite sense, for which there are a few reported examples but no general method.[6–8] The use of alkyltrifluoroborate salts as intermediates or the direct replacement of 1,2-dicyclohexyl-1,2-ethanediol by pinanediol appeared most promising for general applicability.[8]



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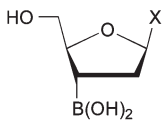

2 X =
a thymine
b 5-fluorouracil
c 5-iodouracil
d cytosine

The synthetic strategy also requires differential protection of the 4- and 5-hydroxyl groups of the (dideoxyribosyl)boronic acid unit so that the 5-membered ring can be closed and the pyrimidine or purine base connected before the 5-hydroxyl is unmasked. Hydroxyl protection used previously in the boronic ester chain extension has included benzyl,[9,10] *p*-methoxybenzyl,[5] and *tert*-butyldimethylsilyl.[11]

A possible alternative synthesis of **2a** from commercially available 2′,3′-didehydro-3′-deoxythymidine is suggested by the asymmetric hydroboration of 2,5-dihydrofuran with diisopinocampheylborane.[12] We chose the (α-haloalkyl)boronic ester route because of our interest in developing this chemistry and also because the polar groups near the hydroboration site might cause complications. After our work had begun, elaboration of the CH_2OH group of thymidine to $CH{=}CH_2$ and

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straightforward hydroboration leading to a $CH_2CH_2B(OH)_2$ substituent was reported.[13] However, yields were poor in hydroboration of analogous vinyl deoxycytosine and deoxyguanosine derivatives and hydroboration of a deoxyadenine derivative was unsuccessful.[14]

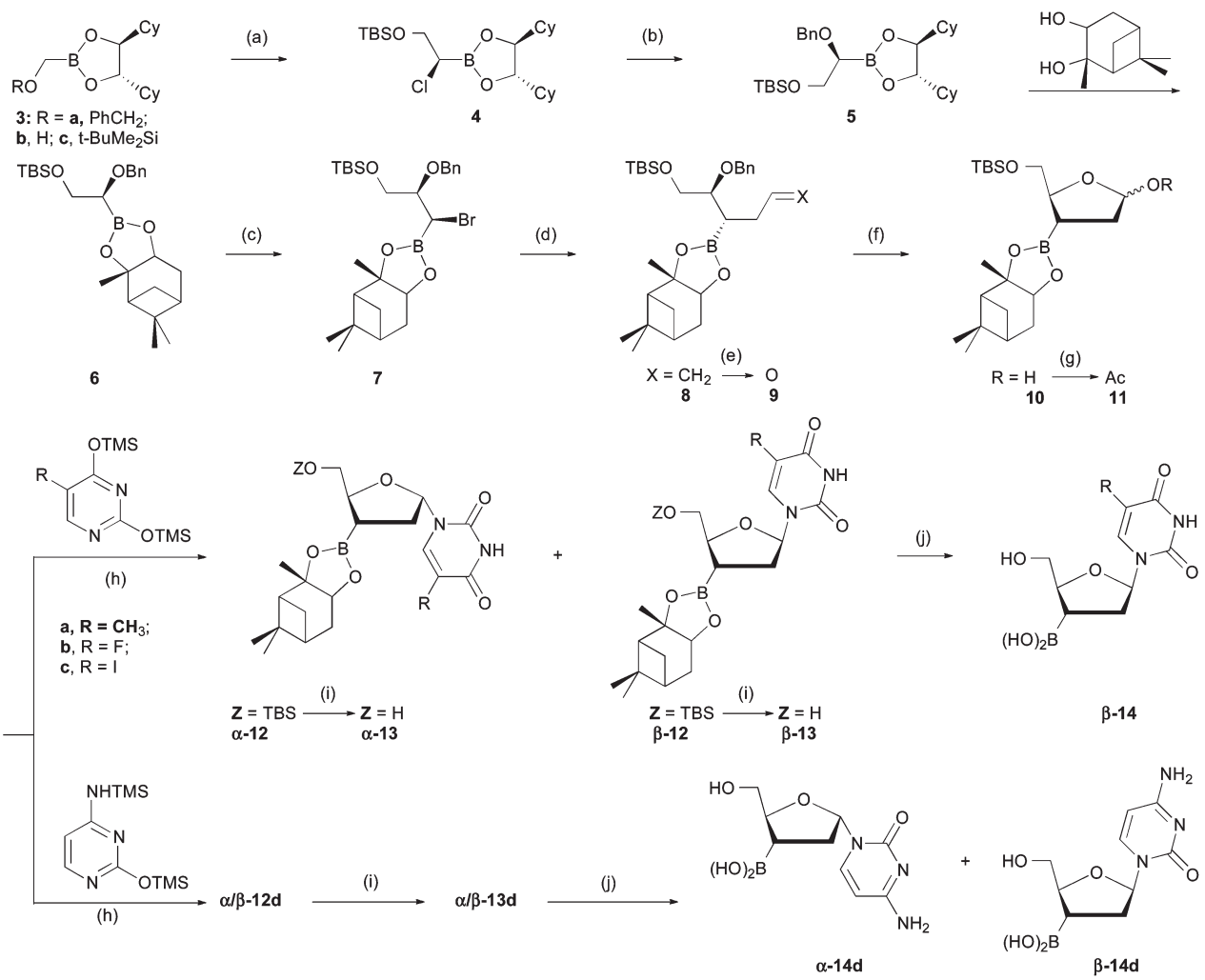
The removal and replacement of chiral directors is avoided in new methods of stereoselective synthesis involving insertion of an asymmetric α-substituted alkyllithium into a carbon–boron bond.[15–19] Although these methods work very well for sequential insertion of carbon-substituted stereocentres, their adaptation to introduction of oxygen-substituted stereocentres does not appear feasible.

Results

Synthesis of the protected deoxyribose analogue (10)

The chosen route to the needed steric relationship involved installation of the first stereocenter *via* homologation of an (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol (DICHED) (silyloxymethyl)-boronate[11] with (dichloromethyl)lithium followed by the direct displacement of DICHED from boron by (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol (from (+)-α-pinene). Our route began with (*S*)-DICHED [(*tert*-butyldimethylsilyloxy)methyl]boronate (**3c**) prepared from the (benzyloxymethyl)boronate **3a** *via* debenzylation to the (hydroxymethyl)boronic ester **3b** (Scheme 1).[11] (After this work was completed, an old, simpler route to **3b** *via* hydrolysis of acyclic, labile (halomethyl)boronic esters to (hydroxymethyl)-boronic acid dimer was revived and updated.[20]) Homologation of **3c** to **4** with (dichloromethyl)lithium, conversion to **5** with sodium benzyl oxide, and replacement of (*S*)-DICHED by (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol to form **6** proceeded smoothly. Several analogous displacements of other diols by pinanediol have been reported previously.[21–23] The rigid geometry of pinanediol minimizes entropy loss in formation of its cyclic esters with boron, and the displacement of DICHED is further favoured by its precipitation from the reaction mixture.

Reaction of **6** with (dibromomethyl)lithium (from LDA and dibromomethane *in situ*)[10] efficiently yielded bromo boronic ester **7**, which with allylmagnesium bromide was alkylated to **8**.



Scheme 1 (a) 1. $LiCHCl_2$, THF, −100 °C; 2. $ZnCl_2$, −70 to 25 °C, 15 h. (b) $PhCH_2ONa$. (c) 1. $LiCHBr_2(CH_2Br_2$, THF, −70 °C, add LDA); 2. $ZnCl_2$, −70 to 25 °C, 15 h. (d) $CH_2{=}CHCH_2MgBr$, −70 °C to 25 °C, 15 h. (e) $NaIO_4/K_2OsO_4$, 2,6-lutidine, dioxane/H_2O. (f) H_2/Pd. (g) Ac_2O, DMAP. (h) Me_3SiBr, CH_2Cl_2. (i) HCl, dioxane. (j) $PhB(OH)_2$, pentane/H_2O–CH_2OH.

The diastereomeric purity of intermediates **4–8** was expected to be >99% based on considerable precedent,[4] and the ^{1}H and ^{13}C NMR spectra did not indicate any noticeable amounts of diastereomers.

Oxidation of the terminal vinyl group of **8** with sodium periodate and concurrent diol cleavage catalysed by potassium osmate (or, less efficiently, ruthenium trichloride) led to aldehyde **9**. Catalytic hydrogenolysis over palladium completed the construction of the protected deoxyribose analogue **10**, which was acetylated to **11** for connection to the pyrimidine bases.

Connection to silylated pyrimidines

Connection of **11** to fully trimethylsilylated pyrimidine bases was accomplished by treatment with bromotrimethylsilane in dichloromethane, a modification of the Vorbrüggen nucleoside synthesis.[24] Bromotrimethylsilane proved superior to trimethylsilyl triflate for this purpose. Treatment of the reaction mixture from bis(trimethylsilyl)thymine with excess tetrabutylammonium fluoride followed by aqueous workup yielded a mixture of the silyloxy compounds **α-12a** and **β-12a**. TBS cleavage was accomplished with hydrogen chloride in dioxane to provide **α-13a** and **β-13a**.

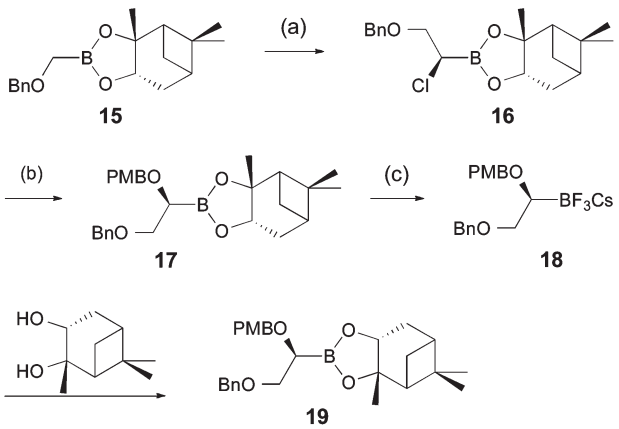
The **α-** and **β-13a** were separated by chromatography on silica. It appeared that the amounts of the two isomers were roughly equal at the beginning, but the loss of α-isomer during purification was greater and the isolated β/α ratio was ~3.6 : 1. The structure of the major isomer **β-13a** was assigned on the basis of oxidation with alkaline hydrogen peroxide, which yielded thymidine, confirmed by comparison of the proton NMR spectrum with that of authentic thymidine. Removal of the pinanediol to provide the boronic acids **α-** and **β-14a** was accomplished by treatment with phenylboronic acid in a two-phase system of water and nonpolar solvent, which is known to extract pinanediol phenylboronate into the nonpolar phase and leave free water-soluble boronic acids in the aqueous phase.[25]

Assignment of α or β to **13b-d** and **14b-d** was based on correlation of observed 4′–5′ ^{1}H coupling constants with the Karplus equation. The 5-fluorouracil derivative **β-13b** was isolated by thin layer chromatography but no **α-13b** was obtained. The isolated β/α ratio for the iodouracil derivatives **13c** was ~5 : 3. Approximately 1 : 1 β–α mixtures of the cytidine derivatives **12d–14d** were not separated or entirely freed from other impurities by the chromatographic techniques used. The nature of the impurities was not determined.

Unsuccessful alternative routes to 10

An alternative to **8** having a cyano group in place of the terminal vinyl, (1*S*,2*S*,3*R*,5*S*)-pinanediol [2-benzyloxy-l-cyanomethyl-3-(*t*-butyldimethylsilyloxy)propyl]-boronate (cyano analogue of aldehyde **9**), was prepared from bromo boronic ester **7** and lithioacetonitrile. Reduction of the crude cyano analogue of **9** with diisobutylaluminum hydride at −78 to 25 °C resulted in unanticipated desilylation. The product mixture after aqueous work up contained very little aldehyde, presumably because of cyclic hemiacetal formation with the free hydroxyl group.

In a brief exploration of another route to **10**, the (benzyloxymethyl)boronic ester **15** of (−)-(1*R*,2*R*,3*S*,5*R*)-pinanediol was converted *via* known chemistry[9,10,26–28] to chloro boronic ester **16**, and chloride displacement yielded *p*-methoxybenzyloxy derivative **17** (Scheme 2). However, the crude **17** was used directly and contained major impurities not immediately obvious from casual inspection of the ^{1}H NMR. Consequently the caesium alkyltrifluoroborate salt **18** failed to yield a crystalline precipitate under the usual reaction conditions,[29] leaving a significant equilibrium proportion of the pinanediol ester **17** among the products.[30] Laboriously obtained crystalline **18** contained ~30% of a second trifluoroborate, perhaps derived directly from **16**. An analytical sample of **18** was obtained by recrystallization. Reaction of the crude salt **18** with (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol in the presence of aqueous sodium bicarbonate yielded the pure boronic ester **19**, which has the correct chiral director for introduction of the next stereocenter.



Scheme 2 (a) 1. $LiCHCl_2$, THF, −100 °C; 2. $ZnCl_2$, −70 to 25 °C, 15 h. (b) *p*-$MeOC_6H_4CH_2OLi$ (=PMBOLi), −70 to 25 °C. (c) CsF + 3 HF, H_2O/Et_2O.

Cytotoxicity and instability of 14

Hep G2 (human hepatocarcinoma cell line) cells were incubated at 37 °C, pH 7.4, in a standard cell growth medium consisting of 90% RPMI-1640 and 10% FBS (foetal bovine serum). Cell growth inhibition by **β-14b** was observed at an activity level corresponding to ~5% of that of 2′-deoxy-5-fluorodeoxyuridine (FUdR) (Fig. 1), initial estimated CC_{50} for **β-14b** = 0.075 μM, for FUdR = 0.004 μM. Subsequent cytotoxicity measurements on different samples of **β-14b** ranged from CC_{50} = 0.03 to 0.16 μM. Measurements on FUdR ranged from CC_{50} = 0.007 to 0.0095 μM. 5-Fluorouracil (FU) is much less toxic, CC_{50} = 0.9–1.0 μM. The only compounds of the series that inhibited cell growth were the deoxyfluorouridine analogue **β-14b** and the deoxyiodouridine analogue **β-14c**.

Analysis of the solutions of the various **14** by HPLC showed that considerable degradation occurred in a few hours at 37 °C, pH 7.4. The HPLC retention times indicated that a major product of the degradation of **β-14b** was 5-fluorouracil (FU), confirmed by comparison with an authentic sample. The decomposition products of **β-14c** are presumably analogous though not as fully confirmed. Small percentages of the 2′-deoxynucleosides from air oxidation of various **14** were present

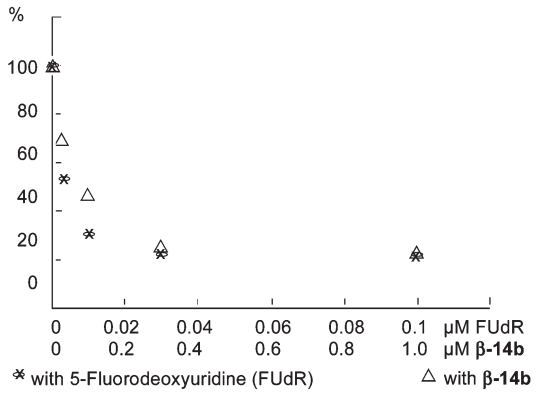


Fig. 1 Percentages of Hep G2 cells growing after 3 days in the presence of 2′,3′-dideoxy-5-fluorouridine-3′-boronic acid (**β-14b**) compared with 2′-deoxy-5-fluorodeoxyuridine (FUdR) in 90% RPMI-1640 and 10% FBS (foetal bovine serum) growth medium.

Table 1 Half-lives (hours) of **14** in growth media, pH 7.4, 37 °C

Medium: Compound	RPMI	RPMI–FBS 9 : 1	FBS
α-14a	73	455	769
β-14a	22	61	192
β-14b	13	18	27
α-14c	15	23	28
β-14c	6	10	18
α/β-14d	52	139	400

in all samples from the beginning and their HPLC integrals in proportion to those of the total mixture increased slowly over the course of three days.

Approximate first-order rates of fragmentation of **14** were observed in the cell growth media used, RPMI-1640 and foetal bovine serum (FBS) and mixtures of the two, pH 7.4, 37 °C. Approximate half-lives based on HPLC data are summarized in Table 1.

No reference standard was included in these studies, and the data are therefore only semiquantitative. It was assumed that the integrals of the HPLC peaks of all of the compounds in a given mixture are proportional to their molar concentrations. However, published ultraviolet spectral curves show a slightly higher ε for thymidine than for thymine.[31] Taking the molecular weights into account, the thymine–thymidine molarity ratio 2 : 1 would produce approximately equal HPLC peaks, and the actual half-lives may be somewhat shorter than those tabulated. It appears unlikely that ε for FU would be higher than that of **β-14b**.

In spite of the limitations of the data, first-order kinetic plots can be obtained. If the sum of the HPLC integrals for **β-14b** and 5-fluorouracil (FU) is taken as 100% and it is assumed that the molar extinction coefficients are equal, a first-order plot of the conversion of **β-14b** to FU in 90% RPMI-1640 and 10% FBS at 37 °C, pH 7.4, yields k_1 = 9.35 (±0.10) × 10^{-6} sec^{-1} (Fig. 2). An erroneous assumption about the relative extinction coefficients of **β-14b** and FU will alter k_1 but not change the rate law from first-order. For example, if it is assumed that the extinction coefficient of FU is half that of **β-14b**, then k_1 = 12.3 (±0.23) × 10^{-6} sec^{-1}, a 28% increase.

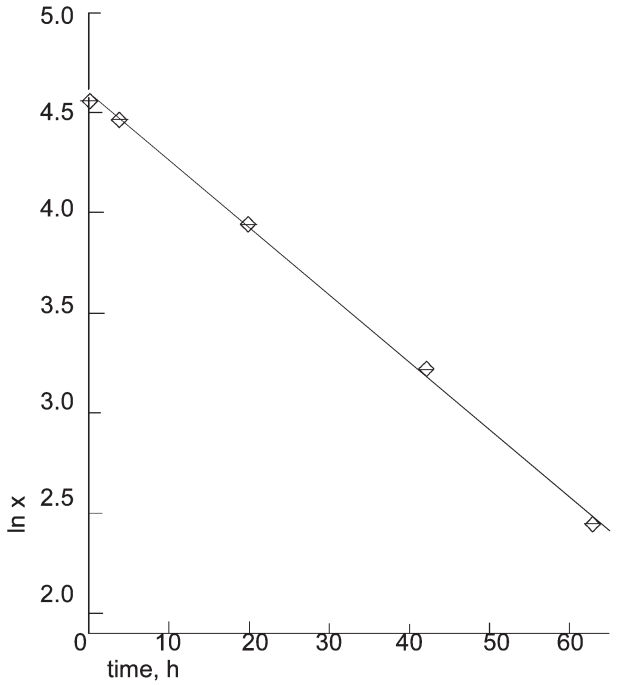


Fig. 2 First-order plot of the conversion of **β-14b** to FU in 90% RPMI-1640 and 10% FBS at 37 °C, pH 7.4, where x is the percent of **β-14b** remaining, molar values for the two compounds are assumed equal, and the sum of the two HPLC signals is taken as 100% at each point.

Measurement of the small amount of 5-fluoro-2′-deoxyuridine (FUdR) is highly dependent on the ratio of extinction coefficients of **β-14b** and FU. If the molar ε ratio for **β-14b**–FU is 1 : 1, there appears to be a small increase from ~3% to 7.7% during the course of the reaction. If it is 2 : 1, FUdR begins near 2.9%, rises to 4.9% in 4 h, and falls to 4.0% in 63 h. However, that appears to be beyond the limit, since such a low assumed ε results in an apparent decrease in the amount of FUdR present after the initial rise, and FUdR is stable under the solvolysis conditions.

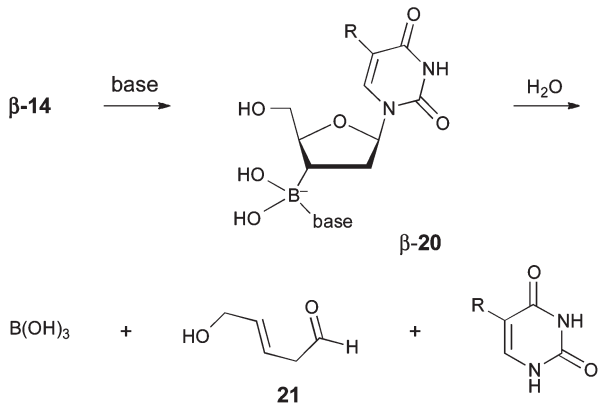
In human liver extract, the ratio of **β-14b**/FU after 12 h was ~60/40, in the same range as found in the various buffers. There is no measurable enzymatic degradation of **β-14b**.

Discussion

Instability of 14 under physiological conditions

The fragmentation of **14** had not been anticipated, in as much as β-alkoxy-substituted boronic esters are generally stable at room temperature. There is precedent for β-elimination of boron and oxygen in the partial decomposition of pinacol [1-chloro-2-(benzyloxy)hexyl]boronate during distillation at 125–130 °C, though the distillate yielded an analytically pure residue of the β-alkoxy compound after the volatile by-products were removed by short path vacuum distillation at 50–65 °C.[32] The mechanism of the facile β-elimination of boron and halide from (β-bromoalkyl)-boronic esters has been studied in detail.[33] A plausible mechanism for the fragmentation of **14** to a pyrimidine base and

β,γ-unsaturated aldehyde **21** *via* a borate complex **20** is illustrated. Since **21** would not be very stable under the reaction conditions, definitive evidence was not obtained, though the appearance of ill-defined NMR signals in the region expected for olefinic protons is in accord.



The differing rates of degradation in different buffers suggest general base catalysis. The measured half-life of **β-14b**, 15–27 h in the various buffers at pH 7.4, increases to 54 h at pH 5, much too small a change to be consistent with specific hydroxide ion catalysis. No measurable degradation was observed at pH 3. The faster fragmentation of the β-isomers at pH 7.4 contrasts with greater loss of the α-isomers during chromatography on silica.

Error evaluation

The identification of decomposition products of **β-14b** and **β-14c** and the rates of their formation were investigated in order to understand whether the cytotoxicities of **β-14b** and **β-14c** were properties of the compounds themselves or resulted from decomposition products. The data obtained are accurate enough for this purpose. Radical catalysed air oxidation of boronic acids is often encountered, and it is not surprising that a variable few per cent of the corresponding deoxyribonucleosides were found in the samples of **14**.

The assumption that the UV detector of the HPLC instrument responds equally to equal molar concentrations of **β-14b**, FUdR, and FU is likely a good approximation for **β-14b** and FUdR, in which the chromophore is remote from the structural difference. Accordingly, estimates of the relative concentrations of FUdR and **β-14b** in freshly prepared solutions of the latter are accurate enough for the conclusion that the FUdR accounts for the cytotoxicity.

Conclusions

1. A series of nucleoside analogues having a boronic acid function in place of the 3′-hydroxyl group has been synthesized *via* asymmetric boronic ester homologation with (dichloromethyl)-lithium.

2. The required change of chiral directors has been accomplished efficiently by direct displacement of (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol from boron with (+)-(1*S*,2*S*,3*R*,5*S*)-pinanediol.

3. None of the boron-substituted deoxyribonucleoside analogues synthesized has any significant cytotoxicity toward the Hep G2 cell line.

4. All of the boron-substituted deoxyribonucleoside analogues undergo gradual hydrolytic cleavage under physiological conditions, liberating the pyrimidine base.

5. The hydrolytic cleavages are pseudo-first-order, apparently base-catalysed, with half-lives on the order of several hours to days at 37 °C, pH 7.4.

6. The boronic acids oxidize slowly in air to produce small amounts of the corresponding deoxyribonucleosides.

7. No evidence of any enzymatic cleavage or oxidation was observed.

Experimental

(4*S*,5*S*)-2-[(1*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-(benzyloxy)-ethyl]-4,5-dicyclohexyl-1,3,2-dioxaborolane (5)

The preparation of (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol [DICHED] from 1,2-diphenyl-1,2-ethanediol (84 g, 0.39 mol) by the reported procedure[34] was modified during workup by addition of acetonitrile (300 mL) and potassium bifluoride (100 g, 1.28 mol) in water (500 mL), resulting in immediate precipitation of (*S*,*S*)-DICHED. (*S*,*S*)-DICHED (*tert*-butyldimethylsilyl)boronate (**3c**) was prepared by the published method.[11] (Dichloromethyl)lithium was prepared by addition of *n*-butyllithium (1.6 M in hexanes, 37 mL, 59 mmol) to dichloromethane (12 mL, 180 mmol) in THF (350 mL) at −100 °C under argon. A solution of (silyloxymethyl)boronic ester **3c** (19.5 g, 51.3 mmol) in THF (300 mL) was added, followed by the addition of anhydrous zinc chloride (1 M in ether, 100 mL, 100 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight. The solution was concentrated and diluted with 10% ether in pentane (500 mL). The organic layer was washed with saturated aqueous ammonium chloride, dried over magnesium sulphate, and concentrated under vacuum. Flash chromatography yielded the pure product **4** (21.8 g, 50.8 mmol). (Sometimes the reaction was not completed. The resulting materials (**3** and **4**) were purified on silica gel with pentane–ether (30 : 1 to 20 : 1), yield <50%.) A solution of sodium benzyl oxide in THF was prepared by treatment of benzyl alcohol (6.4 mL, 62 mmol) with sodium hydride (60% dispersed in mineral oil, 2.5 g, 62 mmol, washed twice with pentane) in THF (200 mL) overnight at room temperature. The sodium benzyl oxide solution was transferred to a solution of chloro boronic ester **4** (21.8 g, 50.8 mmol) in THF (100 mL) *via* cannula at room temperature. The resulting mixture was refluxed overnight. The progress of the reaction was monitored with TLC and NMR. The reaction was quenched with water at 0 °C, then diluted with ether and saturated aqueous ammonium chloride. The resulting solution was extracted with ether. The combined organic layer was dried over magnesium sulphate, filtered, and concentrated. The concentrate was quickly purified on silica gel eluting with pentane–ether (20 : 1) to give the pure liquid **5** (25 g, 97%): $[\alpha]_D^{22}$ −17.7° (*c* 0.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 4.66 (s, 2H), 3.94–3.80 (m, 4H), 3.46 (dd, J = 6.0, 5.7 Hz, 1H), 1.82–1.54 (m, 11H), 1.41–0.85 (m, 11H + s, 9H at δ 0.90), 0.06 (s, 6H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 139.5, 128.3, 127.9, 127.4, 83.9, 72.9, 70.3 (br, *C*-B), 64.8, 43.1, 28.4, 27.6, 26.6, 26.2, 26.16, 26.1, 18.6, −5.1; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{49}BNaO_4Si$ 523.3385; Found 523.3375; Calcd for $C_{29}H_{49}BKO_4Si$ 539.3125; Found 539.3112.

[(1*S*,2*S*,3*R*,5*S*)-Pinanediol (*S*)-[1-benzyloxy-2-(*tert*-butyldimethylsilyloxy)ethyl]boronate] (6)

The DICHED boronic ester **5** (28 g, 56 mmol) was transesterified with (1*S*,2*S*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptane-2,3-diol (pinanediol from (+)-α-pinene) (9.5 g, 56 mmol) in ether (100 mL) in the presence of water (10 mL). An hour later, DICHED had precipitated. The solution was concentrated under vacuum. Pentane was added and the precipitated DICHED was filtered, 9.7 g (77%). The filtrate was concentrated under reduced pressure, then **6** was quickly purified on silica gel with pentane–ether (30 : 1 to 20 : 1), liquid, 24 g (96%), $[\alpha]_D^{22}$ +9.5° (*c* 0.093, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 4.66 (s, 2H), 4.31 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.96–3.80 (m, 2H), 3.45 (dd, *J* = 5.7, 3.3 Hz, 1H), 2.38–2.28 (m, 1H), 2.24–2.14 (m, 1H), 2.07 (t, *J* = 4.8 Hz, 1H), 1.95–1.85 (m, 2H), 1.40 (s, 3H), 1.29 (s, 3H), 1.20 (d, *J* = 10.5 Hz, 1H), 0.90 (s, 9H), 0.84 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 128.4, 127.9, 127.4, 86.6, 78.3, 72.8, 70.3 (br, *C*-B), 64.7, 51.3, 39.6, 38.2, 35.6, 28.8, 27.3, 26.7, 26.2, 24.2, 18.6, −5.09, −5.1; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{41}BNaO_4Si$ 467.2759; Found 467.2744; $[M + K]^+$ Calcd for $C_{25}H_{41}BKO_4Si$ 483.2499; Found 483.2489.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol (1*S*,2*S*)-[1-allyl-2-benzyloxy-3-(*t*-butyldimethylsilyloxy)propyl]boronate (8)

The boronic ester **6** (12 g, 27 mmol) was dissolved in anhydrous THF (270 mL) under argon. Dibromomethane (5.7 mL, 81 mmol) was added by syringe. The solution was cooled to −78 °C and lithium diisopropylamide (2 M, 20 mL, 40.5 mmol) was added dropwise, followed by $ZnCl_2$ (1 M in diethyl ether, 135 mL). After overnight stirring, the mixture was quenched with water and diluted with pentane (500 mL). The organic layer was washed with ammonium chloride (3 × 100 mL), then dried over magnesium sulphate, filtered, and concentrated. Flash chromatography on silica with *n*-pentane–diethyl ether (30 : 1) yielded liquid (1*S*,2*S*,3*R*,5*S*)-pinanediol (1*S*,2*R*)-[2-benzyloxy-l-bromo-3-(*t*-butyldimethylsilyloxy)propyl]boronate (**7**) (12.1 g, 83%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 4.73 (AB, *J* = 21.0, 11.1 (11.4) Hz, 2H), 4.34 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.00–3.78 (m, 3H), 3.52 (d, *J* = 7.8 Hz, 1H), 2.40–2.28 (m, 1H), 2.19–2.09 (m, 1H), 2.08 (t, *J* = 6.0 Hz, 1H), 1.94–1.84 (m, 2H), 1.36 (s, 3H), 1.27 (s, 3H), 1.26 (d, *J* = 10.8 Hz, 1H), 0.9 (s, 9H), 0.83 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.4, 127.9, 127.6, 86.8, 81.8, 78.6, 73.3, 63.9, 51.5, 39.5, 38.5, 35.4, 29.7 (bs, *C*-B), 28.5, 27.2, 26.4, 26.2, 24.2, 18.6, −5.2; LRMS (ESI) Calcd for $C_{26}H_{42}$ $^{11}B^{78}BrNaO_4Si$ 559.2026; Found 558.2 (20%), 559.2 (97%), 560.2 (50%), 561.2 (100%), 562.2 (30%), 563.2 (10%). Bromo boronic ester **7** in THF at −70 °C was treated with allylmagnesium bromide (1.7 M, 16 mL, 27 mmol). The solution was warmed to room temperature and stirred overnight. After it was quenched with water at 0 °C, the mixture was extracted with ether. The organic layer was dried, filtered, and concentrated. Flash chromatography yielded liquid **8** (9.7 g, 86% from **7**); $[\alpha]_D^{22}$ 8.5° (*c* 0.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 5.83 (m, 1H), 5.10–4.90 (m, 2H), 4.80 (d, *J* = 11.7, 1H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.26 (dd, *J* = 9.0, 2.1 Hz, 1H), 3.82–3.60 (m, 3H), 2.48–2.10 (m, 3H), 2.05 (t, *J* = 5.4 Hz, 1H), 1.93–1.77 (m, 2H), 1.56–1.46 (m, 1H), 1.35 (s, 3H0, 1.29 (s, 3H), 1.19 (d, *J* = 10.5 Hz, 1H), 0.90 (s, 9H), 0.83 (s, 3H), 0.06 (s, 3H). 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 138.6, 128.4, 128.0, 127.5, 115.4, 85.8, 81.4, 77.9, 73.1, 66.7, 51.4, 39.7, 38.4, 35.8, 32.0, 29.0, 27.3, 26.7, 26.4 (bs, *C*-B), 24.3, 18.5, −5.12, −5.08; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{29}H_{47}BNaO_4Si$ 521.3229; Found 521.3218.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol (1*S*,2*S*)-[2-benzyloxy-3-(tert-butyldimethylsilyloxy)-1-(2-oxyethyl)-propyl]boronate (9)

The boronate **8** (0.8 g, 1.60 mmol, 1 eq.) was dissolved in 1,4-dioxane (15 mL) and water (5 mL). Potassium osmate dihydrate (11.82 mg, 0.032 mmol, 0.02 eq.), sodium periodate (1.373 g, 6.42 mmol, 4 eq.) and 2,6-lutidine (343.9 mg, 3.2 mmol, 375 µL, 2 eq.) were added and the mixture was stirred at room temperature and checked by TLC. The reaction was finished within 1 h. Water (30 mL) was added, followed by saturated ammonium chloride (15 mL) and ethyl acetate (50 mL). The water phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to a black oily residue. Chromatography on silica gel with 2–4% ethyl acetate in hexanes yielded colourless oily **9** (0.490 g, 63%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.7 (t, *J* = 1.5 Hz, 1H), 7.40–7.20 (m, 5H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.50 (d, *J* = 11.4, Hz, 1H), 4.27 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.86–3.66 (m, 2H), 2.66 (ddd, *J* = 6.9, 3.6, 1.2 Hz, 1H), 2.32 (ddt, *J* = 13.8, 9.0, 2.7 Hz, 1H), 2.21–2.11 (m, 1H), 2.03 (t, *J* = 5.4 Hz, 1H), 2.42–2.32 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H), 1.16 (d, *J* = 11.1 Hz, 1H), 0.90 (s, 9H), 0.83 (s, 3H). 0.054 (s, 3H), 0.049 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 139.1, 128.4, 128.1, 127.6, 86.1, 80.4, 78.1, 73.0, 65.8, 51.4, 42.0, 39.6, 38.4, 35.6, 28.7, 27.3, 26.5, 26.2, 24.2, 20.5 (bs, *C*-B), 18.5, −5.2; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{28}H_{45}BNaO_5Si$ 523.3022; Found 523.3019.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol (3*S*,4*S*)-5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxyribosyl-3-boronate (10)

The aldehyde boronate **9** (600 mg, 1.2 mmol) was treated with 10% palladium on charcoal (300 mg) in ethyl acetate (30 mL) under hydrogen. The mixture was stirred overnight, then monitored by TLC. If debenzylation of **9** was incomplete, 20% palladium hydroxide (50 mg) was added and hydrogenolysis continued. The mixture was filtered through a celite pad and the filtrate was concentrated. The residue was purified on silica gel with 5 : 1 pentane–ether to yield pure liquid mixture of dideoxyribosyl boronate anomers **10** (α and β); 81% (400 mg) to quantitative. The ratio of anomers α/β was ~0.5, based on NMR data: $[\alpha]_D^{22}$ +19.3° (*c* 0.035, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)

δ [5.51 (m, 0.33) + 5.38 (dd, J = 8.4, 3.0 Hz, 0.67) = 1H], 4.34–4.24 (m, 2H), 3.84 (dd, J = 10.8, 2.7 Hz, 1H), 3.70–3.40 (m, 2H), 2.39–2.17 (m, 2.5H), 2.10–2.00 (m, 2H), 1.97–1.78 (m, 4H), 1.61 (m, 0.5H), [1.39 (s, 1) + 1.38 (s, 2) = 3H], 1.29 (s, 3H), [1.11 (d, J = 11.1 Hz, 0.33H + 1.03 (d, J = 10.8 Hz, 0.67) = 1H], 0.93 (s, 9H), 0.89 (s, 3H), 0.84 (s, 3H), [0.113 (s, 2) + 0.111 (s, 2) + 0.06 (s, 2) = 6H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.6, 86.4, 86.1, 83.0, 81.4, 78.3, 78.2, 66.0, 64.8, 51.4, 39.61, 39.57, 38.34, 38.32, 36.2, 35.65, 35.57, 28.77, 28.74, 27.2, 26.65, 26.60, 26.17, 24.2, 18.66, 18.62, −5.05, −5.12, −5.24, −5.35; HRMS (EI-Q-TOF) m/z: $[M]^+$ Calcd for $C_{21}H_{38}BO_4Si$ 393.2637; Found 393.2643.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol (3*S*,4*S*)-1-acetyl-5-*O*-*tert*-butyldimethylsilyl-2,3-dideoxyribosyl-3′-boronate (11)

The dideoxyribose boronate **10** (300 mg, 0.73 mmol) was dissolved in dichloromethane (10 mL), then the solution was cooled to 0 °C, followed by the addition of a solution of acetic anhydride (0.21 mL, 2.19 mmol) and *N*,*N*-dimethylamino-4-pyridine (13 mg, 0.11 mmol) in methylene chloride (5 mL). The solution was stirred overnight. Water (10 mL) was added. The mixture was extracted with chloroform (3 × 100 mL). The chloroform solution was dried over magnesium sulphate, filtered, and concentrated. Chromatography on silica with 3 : 1 pentane–ether yielded liquid **11** (325 mg, 98%, α/β mixture); $[\alpha]_D^{22}$ +17.0° (*c* 0.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ [6.30 (dd, J = 5.1, 1.8 Hz, 0.33) + 6.26 (d, J = 4.5 Hz, 0.67) = 1H], 4.38–4.15 (m, 2H = [4.35 (m, 0.33) + 4.29 (dd, J = 8.4, 2.1 Hz, 0.33) + 4.27 (dd, J = 8.7, 1.8 Hz, 0.66) + 4.20 (m, 0.66)]), 3.76–3.62 (m, 2H), 2.28–2.45 (m, 1.5H), 2.27–2.14 (m, 2H), 2.11–2.03 (m, 1.5H), 1.39 + 1.38 (s, 3H), 1.293 + 1.289 (s, 3H), [1.14 (d, J = 11.1 Hz, 0.33) + 1.03 (d, J = 11.1 Hz, 0.67) = 1H], [0.91 (s, 6) + 0.88 (s, 3) = 9H], [0.85 + 0.84 (s, 3H)], [0.067 (s, 2) + 0.062 (2) + 0.053 (1) + 0.050 (1) = 6H]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.72, 170.68, 100.0, 99.2, 86.2, 85.6, 83.1, 78.2, 78.23, 78.19, 66.5, 65.2, 51.42, 51.37, 39.61, 39.58, 38.37, 38.31, 36.2, 35.63, 35.56, 35.1, 28.83, 28.76, 27.2, 26.65, 26.59, 26.22, 26.15, 24.15, 21.69, 21.34, 18.7, 18.6, −5.04, −5.10. −5.11, −5.14; LRMS (ESI) Calcd for $C_{23}H_{41}BNaO_6Si$ 475.3; Found 475.5; HRMS (EI-Q-TOF) m/z: $[M - C_2H_3O_2]^+$ Calcd for $C_{21}H_{38}BO_4Si$ 393.2637; Found 393.260.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol 5′-(*t*-butyldimethylsilyl)-3′-deoxythymidine-3′-boronate (α/β-12a)

To a mixture of the boronate **11** (200 mg, 0.442 mmol) and *O*,*O*′-bis(trimethylsilyl)-thymine (125 mg, 0.46 mmol) in dichloromethane (10 mL) was added bromotrimethylsilane (60 μL, 0.46 mmol) at 0–25 °C. *O*,*O*′-Bis(trimethylsilyl)thymine was dissolved at room temperature in the dichloromethane solution (5–30 min required). At this point, the reaction was completed. Tetrabutylammonium fluoride (1 M in THF, 0.9 mL, 0.9 mmol) was added and the mixture was stirred for an hour. After the reaction was quenched with water, the solution was extracted with chloroform (20 mL), then ethyl acetate (2 × 20 mL). The extracts were dried over magnesium sulphate, filtered, and concentrated. The residue was purified on silica with pentane–ether–acetone (2 : 1 : 1), then chloroform–acetone (9 : 1) to give the pure liquid mixture of isomers (ratio of α–β = 1 : 2, 140 mg, 61%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 1.2 Hz, 0.67H), 7.27 (d, J = 1.2 Hz, 0.33 H), 0.97 (d, J = 11.1 Hz); HRMS (ESI-Q/ICR) m/z: $[M + K]^+$ Calcd for $C_{26}H_{43}BKN_2O_6Si$ 557.2615; Found 557.2602.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol 3′-deoxythymidine-3′-boronate (α/β-13a)

The boronate **12** (80 mg, 0.154 mmol) was treated with HCl (4 M in dioxane, 0.1 mL) in THF (0.5 mL) at room temperature. After 1 h the reaction was complete. The solution was treated with water and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over magnesium sulphate, filtered, and concentrated. The concentrates were purified by thin layer chromatography. Useful eluting solvents for chromatography were *n*-pentane–ether–acetone (2 : 1 : 1), chloroform–ether–acetone (4 : 1 : 1), and chloroform–acetone (3 : 1). The liquid β-isomer eluted first: **β-13a** 36 mg (58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.8 (s, 1H), 7.65 (d, 0.9 Hz, 1H), 6.11 (dd, J = 6.9, 1.8 Hz, 1H), 4.30 (dd, J = 8.7, 2.1 Hz, 1H), 4.13 (dt, J = 11.4, 3.3 Hz, 1H), 4.10–4.00 (m, 1H), 3.88–3.78 (m, 1H), 2.56–2.18 (m, 4H, 2.05 (t, J = 4.5 Hz, 1H), 1.96–1.88 (m, 1H), 1.89 (d, J = 0.9 Hz, 3H), 1.86–1.78 (m, 1H), 1.39 (s, 1H), 1.29 (s, 1H), 1.00 (d, J = 10.8, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 150.5, 136.5, 110.2, 86.7, 86.0, 85.0, 78.4, 63.1, 51.2, 39.6, 38.3, 36.5, 35.5, 28.7, 27.2, 26.7, 24.1, 21.7 (bs, *C*-B), 12.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.4; HRMS (ESI-Q/ICR) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{29}BN_2NaO_6$ 427.2011; Found 427.1999. The presumed **α-13a** 10 mg (16%) (liquid): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.25 (d, J = 1.5 Hz, 1H), 6.12 (dd, J = 5.7 Hz, 1H), 4.39 (m, 1H), 4.30 (dd, J = 9.7, 1.8 Hz, 1H), 4.87–3.77 (m, 1H), 3.70–3.60 (m, 1H), 2.71–2.61 (m, 1H), 2.40–2.18 (m, 2H), 2.05 (t, J = 5.1 Hz, 1H), 2.02–1.70 (m, 2H), [1.95 (d, J = 0.9 Hz, 3H)], 1.39 (s, 3H), 1.29 (s, 3H), 1.01 (d, J = 10.8 Hz, 1H), 0.842 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.5, 135.5, 110.9, 87.0, 86.8, 84.0, 78.5, 65.0, 51.3, 39.6, 38.4, 35.8, 35.5, [31.2, 30.5, 29.9], 28.8, 27.2, 26.7, 24.2, 12.9.

Oxidation of deoxythymidine-3′-boronic ester β-13a

The boronic ester **β-13a** (20 mg, 0.05 mmol) was treated with sodium hydroxide (1 M aq. solution, 25 μL) and hydrogen peroxide (30% aq. solution, 7 μL) in THF at 0 °C, and warmed to room temperature. The reaction mixture was stirred for 4 h, then diluted with water (1 mL). The solution was extracted with ether (3 × 1 mL). The water layer was concentrated under vacuum to yield thymidine, identical with a purchased authentic sample by proton NMR.

β-3′-Deoxythymidine-3′-boronic acid (β-14a)

The deoxythymidine boronate **β-13a** (25 mg, 0.062 mmol) was stirred overnight with phenylboronic acid (7 mg, 0.056 mmol) in pentane (0.3 mL)–water (0.3 mL)–methanol (0.1 mL). The solution was diluted with 0.5 mL of water, then extracted with ether

(3 × 1 mL). Concentration of the aqueous phase yielded amorphous solid boronic acid **β-14a** (12.5 mg, 75%); ^{1}H NMR (300 MHz, D_2O) δ 7.78 (s, 1H), 6.08 (d, J = 7.2 Hz, 1H), 4.17 (m, 1H), 3.92 (dd, J = 12.3, 2.7 Hz, 1H), 3.77 (dd, J = 12.3, 4.2 Hz, 1H), 2.52–2.40 (m, 1H), 2.40–2.20 (m, 1H), 1.87 (s, 3H), 1.61 (m, 1H); ^{1}H NMR (300 MHz, CD_3OD) δ 8.1 (bs, 1H), 5.98 (dd, J = 6.3, 1.8 Hz, 1H), 4.10 (dt, J = 11.1 Hz, 1H), 3.94 (dd, J = 12.3, 2.4, 1H), 2.40–2.20 (m, 2H), 1.88 (d, J = 1.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 166.9, 152.5, 138.8, 110.3, 87.6, 87.5, 62.9, 37.6, 23.2 (broad s, *C*-B), 12.7; ^{11}B NMR (160 MHz, D_2O) δ 29.8; HRMS (MALDI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{10}H_{15}BN_2NaO_6$ 293.0915; Found 293.0907.

α-3′-Deoxythymidine-3′-boronic acid (α-14a)

Amorphous α-deoxythymidine boronic acid **α-14a** was obtained by a similar procedure to the preparation of 3-deoxythymidine boronic acid **β-14a**; 74%; ^{1}H NMR (300 MHz, D_2O) δ 7.61 (d, J = 1.2 Hz, 1H), 6.07 (AB, J = 6.0 Hz, 1H), 4.45 (m, 1H) 3.76 (dd, J = 12.3, 3.3 Hz, 1H), 3.61 (dd, J = 12.0, 5.4 Hz, 1H), 2.61 (m, 1H), 2.09 (m, 1H), 1.88 (s, [d, J = 0.9], 3H), [1.71 (m, 1H)]; ^{1}H NMR (500 MHz, CD_3OD) δ 7.54 (s, 1H), 6.08 (t, J = 6 Hz, 1H), 4.40 (m, 1H), 3.68 (dd, J = 12.0, 3.5 Hz, 1H), 3.55 (dd, J = 12.0, 5.0 Hz, 1H), 2.63 (m, 1H), 1.98–1.80 (m, 1H), 1.91 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 166.7, 152.6, 137.9, 111.4, 88.5, 86.2, 65.1, 36.8, 26.8 (bs, *C-B*), 12.6; ^{11}B NMR (160 MHz, D_2O) δ 30.2.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol 2′,3′-dideoxy-5-fluorouridine-3′-boronate (α/β-13b)

To a mixture of the boronic ester **11** (400 mg, 0.84 mmol) and *O*,*O*′-bis(trimethylsilyl)-5-fluorouridine (255 mg, 0.93 mmol) in dichloromethane (18 mL) was added bromotrimethylsilane (0.13 mL, 0.93 mmol) at 20–25 °C. The mixture was stirred for 50 min, tetrabutylammonium fluoride (1 M in THF, 0.9 mL, 0.9 mmol) was added, and stirring was continued for 1 h. After the reaction was treated with 10% HCl (1.5 mL), the solution was extracted with chloroform (20 mL), then ethyl acetate (2 × 20 mL). The extracts were dried over magnesium sulphate, filtered, and concentrated. The residue was purified on silica gel with pentane–acetone (5 : 1 to 3 : 1) to give a liquid mixture of anomers (α–β ratio ~1 : 2 by ^{1}H NMR). The resulting compound in methanol was treated with aq. 10% HCl (1.5 mL), then extracted with ethyl acetate (3 × 20 mL), dried, filtered, and concentrated. Thin layer chromatography yielded the liquid β-anomer, 60 mg (17.5%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (bs, 1H), 8.23 (d, J = 6.6 Hz, 1H), 6.03 (d, J = 6.6 Hz, 1H), 4.30 (dd, J = 9.0, 2.1 Hz, 1H), 4.13 (m, 1H), 3.86 (dd, J = 12.0, 2.7 Hz, 1H), 2.54–2.16 (m, 4H), 2.04 (t, J = 5.1 Hz, 1H), 1.97–1.70 (m, 2H), 1.39 (s, 3H), 1.29 (s, 3H), 0.98 (d, J = 11.1 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 (d, J = 26.6 Hz, 157.6, 157.2), 149.1, 141.8, 138.7, 125.4 (d, J = 34.6 Hz), 86.72 (86.68), 85.6, 78.4, 62.4, 51.2, 39.6, 38.3, 37.0, 35.5, 31.1, 28.7, 27.1, 26.7, 24.1, 20.6 (bs, *C*-B); ^{19}F NMR (282 MHz, $CDCl_3$) δ −166.76 (d, J = 4.5 Hz); ^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}BFN_2NaO_6$ 431.1760; Found 431.1758.

2′,3′-Dideoxy-5-fluorouridine-3′-boronic acid (β-14b)

2′,3′-Dideoxy-5-fluorouridine-3′-boronic ester (**α/β-13b**) (36 mg, 0.0875 mmol) and phenylboronic acid (10 mg, 0.083 mmol) were dissolved in water–ether–acetone (1.3 mL, 5 : 5 : 3). The solution was stirred overnight, then diluted with ether (2 mL) and water (1 mL). The water layer was separated and concentrated to give amorphous solid **β-14b** (19.5 mg, 82%); ^{1}H NMR (300 MHz, D_2O) δ 8.14 (d, J = 6.6 Hz, 1H), 6.01 (d(m), J = 6.6 Hz, 1H), 4.22–4.13 (m, 1H), 3.93 (dd, J = 12.6, 3.3 Hz, 1H), 3.77 (dd, J = 12.6, 4.8 Hz, 1H), 2.50–2.24 (m, 2H), 1.52 (m, 1H); ^{19}F NMR (282 MHz, D_2O) δ −167.98 (d, J = 5.9 Hz); ^{1}H NMR (300 MHz, CD_3OD) δ 8.55 (d, J = 6.9 Hz, 1H), 5.94 (d, J = 5.7 Hz, 1H), 4.11 (d, J = 10.8 Hz, 1H), 3.97 (dd, J = 12.3, 2.7 Hz, 1H), 3.69 (d, J = 12.0, 1H), 2.40–2.24 (m, 2H), 1.95–1.80 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.6 (d, J = 26.0 Hz, 158.8, 158.4), 149.5, 141.7, 138.6, 125.8 (d, J = 53.2 Hz, 126.0, 125.6), 86.6, 61.1, 36.5, 21.5 (bs, *C-B*); ^{19}F NMR (282 MHz, CD_3OD) δ −171.14 (d, J = 6.8 Hz); ^{11}B NMR (160 MHz, CD_3OD) δ 29.7; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_9H_{12}BFN_2NaO_6$ 297.0665, Found 297.0665. The sample in methanol apparently formed the monomethyl boronic ester: HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{10}H_{14}BFN_2NaO_6$ 311.0821; Found 311.0819; and the dimethyl ester: Calcd for $C_{11}H_{16}BFN_2NaO_6$ 325.0978; Found 325.0977.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol 2′,3′-dideoxy-5-iodouridine-3′-boronate (α/β-13c)

Iodouracil (714 mg, 3 mmol) was treated with hexamethyldisilazane (7 mL) followed by chlorotrimethylsilane (0.03 mL). The mixture was refluxed overnight, the hexamethyldisilazane was distilled, and the residue of the bis(trimethylsilyl)-5-iodouracil was kept under vacuum overnight. A solution of acylated dideoxyribosylboronate **11c** (180 mg, 0.4 mmol) and the disilylated 5-iodouracil (161 mg, 0.42 mmol) in dichloromethane (8 mL was treated with bromotrimethylsilane (0.06 mL, 0.42 mmol). After stirring for 1 h, the solvent was completely removed *in vacuo* overnight. The residue of silylated **12c** was redissolved in anhydrous acetonitrile (3 mL) followed by the addition of a solution of caesium fluoride (1.5 mL, 1 M). The solutions were stirred for 1 h, followed by the addition of 10% HCl (1 mL). The solutions were stirred for an additional 1 h, then extracted with ethyl acetate (3 × 20 mL). Solutions were concentrated under reduced pressure. After thin layer chromatography on silica with pentane–ether–acetone (1 : 1 : 1) liquid anomers of the deoxy-5-iodouridine boronic ester **13c** were obtained. Isolated yield, **α-13c** 99 mg (48%), **β-13c**, 52 mg (25%); **α-13c**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (br, 1H), 7.89 (s, 1H), 6.06 (t, J = 6.0 Hz, 1H), 4.43 (m, 1H), 4.31 (dd, J = 9.0, 2.1 Hz, 1H), 3.83 (dd, J = 11.7, 3.0 Hz, 1H), 3.64 (dd, J = 12.0, 5.1 Hz, 1H), 2.74 (m, 1H), 2.40–2.18 (m, 2H), 2.05 (t, J = 5.1 Hz, 1H), 2.02–1.72 (m, 3H), 1.39 (s, 3H), 1.29 (s, 3H), 0.98 (d, J = 10.8 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.4, 144.6, 88.0, 86.8, 84.5, 78.4, 68.2, 64.7, 51.2, 39.5, 38.3, 36.2, 35.4, 28.7, 27.1, 26.7, 24.1, 23.4 (bs, *C*-B); HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}BINaN_2O_6$ 539.0821; Found 539.0816; *m/z*: $[M + K]^+$

Calcd for $C_{19}H_{26}BIKN_2O_6$ 555.0560; found 555.0557. **β-13c**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 8.58 (s, 1H), 6.03 (d, J = 5.4 Hz, 1H), 4.30 (dd, J = 8.4, 1.5 Hz, 1H), 4.18 (dt, J = 11.7, 2.7 Hz, 1H), 4.12 (dd, J = 12.3, 2.1 Hz, 1H), 3.85 (dd, J = 12.3, 3.0 Hz, 1H), 2.76 (bs, 1H), 2.53–2.18 (m, 4H), 2.05 (t, J = 5.4 Hz, 1H), 1.93 (m, 1H), 1.86–1.74 (m, 2H), 1.39 (s, 3H), 1.29 (s, 3H), 0.98 (d, J = 11.1 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.2, 145.9, 87.1, 86.7, 85.9, 78.4, 66.8, 62.3, 51.2, 39.6, 38.3, 37.2, 35.5, 28.7, 27.2, 26.7, 24.1, 20.5 (bs, *C*-B); HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{26}BIN_2NaO_6$ 539.0821; Found 539.0823.

β-2,′3′-Dideoxy-5-iodouridine-3′-boronic acid (β-14c)

The boronic ester **β-13c** (99 mg, 0.19 mmol) in pentane–water–ether–methanol (2 : 2 : 1 : 1, 2 mL) was treated with phenylboronic acid (22 mg, 0.18 mmol). After overnight stirring, 3 mL of diethyl ether and 1 mL of water were added, the phases were separated, and the aqueous phase was extracted with two more 3 mL portions of ether. Crude pinanediol phenylboronate (47 mg, 98%) containing a small amount of unchanged **β-13c** was recovered from the organic phase, and concentration of the aqueous phase yielded the amorphous solid boronic acid **β-14c** (48 mg, 66%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.84 (s, 1H), 5.93 (dd, J = 5.4, 1.8 Hz, 1H), 4.14 (dt, J = 11.1, 3.0 Hz, 1H), 3.97 (dd, J = 12.3, 2.7 Hz, 1H), 3.67 (dd, J = 12.0, 2.4 Hz, 1H), 2.40–2.20 (m, 2H), 1.85 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 163.3, 152.2, 147.8, 88.4, 88.2, 66.8, 62.2, 38.1, 22.5 (bs, *C*-B); HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_9H_{12}BIN_2NaO_6$ 404.9725; Found 404.9731.

α-2′,3′-Dideoxy-5-iodouridine-3′-boronic acid (α-14c)

By the procedure used with **β-13c**, **α-13c** (52 mg, 0.1 mmol) was converted to crude pinanediol phenylboronate (25 mg, 98%) and amorphous boronic acid **α-14c** (28 mg, 73%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.09 (s, 1H), 6.03 (t, J = 6.0 Hz, 1H), 4.12 (m, 1H), 3.68 (dd, J = 12.3, 3.6 Hz, 1H), 3.54 (dd, J = 12.0, 5.4 Hz, 1H), 2.69 (m, 1H), 2.02–1.98 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 163.1, 152.2, 146.9, 89.4, 86.4, 67.9, 65.3, 36.9, 26.3 (bs, *C*-B); HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_9H_{12}BIN_2NaO_6$ 404.9725; Found 404.9726.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol 2,′3′-dideoxycytidine-3′-boronate (α/β-13d)

Reaction of acetylated deoxyriboseboronic acid **11** (320 mg, 0.71 mol) with bis(trimethylsilyl)cytosine (189 mg, 0.74 mol) by a procedure similar to that used with 5-iodouridine for the **c** series yielded the liquid silylated boronic ester **α/β-12d** (310 mg, 87%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.34 + 7.70 (d, J = 7.5 Hz + d, J = 7.2 Hz, ratio 2 : 1, 1H], 5.95 (m, possibly d, J = 6.3 Hz, obscuring δ 5.98, t, $J \sim 6$ Hz, 2 : 1, 1H), 5.90 + 5.81 (d, J = 7.5 Hz + d, J = 7.2 Hz, 1 : 2, 1H), 4.42 (m, weak), 4.33 + 4.31 (dd + dd, 3 : 1, J = 8.7, 1.8 Hz, 1H), 4.3–4.1 + 3.9–3.7 (m + m, 3H), 2.7–1.7 (m, 8H), 1.38 +1.34 (s + s, 3 : 1, 3H), 1.30 + 1.29 (s + s, 3 : 1, 3H), 1.05 + 1.01 (d + d, J = 10.8 Hz, 3 : 1, 1H), 0.96 + 0.93 (s + s, 3 : 1, 9H), 0.87 + 0.85 (s + s, 3 : 1, 3H), 0.15 + 0.14 + 0.10 (s + s + s, 1 : 1 : 0.7, 6H); HRMS (ESI-Q/ICR) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{43}BN_3O_5Si$ 504.3065, Found 504.3057; (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{42}BN_3NaO_5Si$ 526.2885; Found 526.2879. Desilylation of **α/β-12d** (250 mg, 0.5 mmol) in the usual manner, with some decomposition during chromatography, yielded (**α/β-13d**) (120 mg, 62%); ^{1}H NMR (300 MHz, CD_3OD) δ 8.63 + 8.06 (d, J = 7.8 Hz + d, J = 7.5 Hz, 3 : 1, 1H), 7.75 (d, J = 7.2 Hz, impurity), 6.12 + 6.05 (d, J = 7.5 Hz + d, J = 7.8 Hz, 1H), 6.03 (d, J = 7.2 Hz, impurity), 5.96 (m, 1H), 4.34 + 4.33 (dd + dd, J = 8.4, 1.8 Hz, 1H), [4.42 (m) + 4.16 (dt, J = 11 Hz, 2.7 Hz) + 4.00 (dd, J = 12.5 Hz, 2.3 Hz) + 3.76 (dd, J = 12.5 Hz, 2.9 Hz), 3.75–3.45 (m), 0.3 : 1 : 1 : 1 : 0.6, 3H], 2.7 (m, weak), 2.5–1.7 (m, 8H), 1.39, 1.37, 1.36 (s, s, s, ratio 2 : 0.3: 0.7, 3H), 1.302 + 1.296 (s, s, 3H) 1.07 (d, 0.7H, J = 10.8 Hz), 1.06 (d, ~0.3H, J = 10.8 Hz), 0.87, 0.86 (s, s, ratio 3 : 1, 3H) HRMS (ESI-Q/ICR) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{29}BN_3O_5^+$ 390.2200; Found 390.2188; HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{28}BN_3NaO_5$ 412.2020; Found 412.2014.

2,′3′-Dideoxycytidine-3′-boronic acid (a/β-14d)

Dideoxycytidine boronic ester (30 mg, 0.077 mmol) was transesterified with phenylboronic acid (9 mg, 0.073 mol) in the usual manner, and concentration of the aqueous phase yielded impure amorphous **α/β-14d** (66%, 13 mg); ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (s, impurity), 8.22 + 7.74 (d + d, J = 7.2 Hz, 7.8 Hz, 1H), 7.76 (s, impurity), 7.65 (br, 2H, merged with HDO in other fractions), 7.38 (m, absent in fractions that contain pinanediol), 6.30–5.80 (m, 2H), [4.38 (m) + 4.12 (dt, J = 11.4, 2.7 Hz) + 3.92 (dd, J = 12.3, 3.0 Hz) + 3.71 (dd, J = 12.0, 3.6 Hz, 1H) + 3.63–3.53 (m), 1 : 3 : 3 : 3 : 2, 3H], 2.73 + 2.40–2.16 (m, 2H), 1.82 + 1.70 (br, 1H); HRMS (ESI-Q/ICR) *m/z*: $[M + Na]^+$ Calcd for $C_9H_{15}BN_3O_5$ 256.1105; Found 256.1094; Calcd for $C_9H_{14}BN_3NaO_5$ 278.0924, Found 278.0920.

Caesium (1*S*)-[2-benzyloxy-1-(*p*-methoxybenzyloxy)ethyl]-trifluoroborate (18)

Pinanediol (1*R*)-(2-benzyloxy-1-chloroethyl)boronate (**16**) was prepared by the method described previously.[10] Crude **16** was added to lithium *p*-methoxybenzyl oxide in THF, the mixture treated with anhydrous DMSO as previously described,[10] and the product extracted and concentrated to yield crude (1*R*,2*R*,3*S*,5*R*)-pinanediol (1*S*)-(2-benzyloxy-1-*p*-methoxybenzyloxyethyl)boronate (**17**) (72.8 g, 90% from **3a**), which was used directly in the next step; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.832 (s, 3), 1.22 (d, J = 10.8 Hz, 1), 1.28 (s, 3), 1.38 (s, 3), 1.6 (m, ~1, impurity?) 1.9–2.4 (m, 5), 3.57 (m, 1), 3.69–3.80 (m, 2), 3.79 (s, 3), 3.81 (s, ~2, impurity?), 4.32 (dd, J = 2 Hz, J = 9 Hz, 1), 4.57 and 4.62 (AB, J = 6 Hz, 2), 4.59 (s, 2), 6.84 (m, 2), 6.89 (m, ~1.5 impurity?), 7.3 (m, 7 (+~1.5, impurity?)). Impurities consistent with the data include chloro boronic ester **16** and *p*-methoxybenzyl alcohol. A stock solution of caesium bifluoride in hydrofluoric acid was prepared by adding caesium fluoride (37 g, 0.244 mol) in small portions to well stirred 48% hydrofluoric acid (16.8 mL, 0.488 mol) in a 500 mL polyethylene bottle cooled with an ice bath [*CAUTION: Highly exothermic.*],

25.0 mL, 9.75 M in $CsHF_2$, 19.5 M in HF.[8] A portion of this solution (17.7 mL, 0.173 mol of $CsHF_2$) was added to a stirred solution of all of the **17** (72.8 g, 0.16 mol) in diethyl ether (250 mL) in a polyethylene bottle cooled with ice. No precipitate formed. After overnight, addition of pentane (150 mL) resulted in formation of 3 phases. The ether/pentane phase was decanted and concentrated to crude (1*R*,2*R*,3*S*,5*R*)-pinanediol (19.5 g, ~70%). The remainder was treated with water (180 mL) and 3 : 1 pentane–diethyl ether, again resulting in 3 liquid phases. The densest phase froze in the freezer (−19 °C) overnight. Further treatment of this phase with diethyl ether and cooling in the freezer led to solid crude **18** (25.6 g, ~30%). Evaporation of the aqueous (middle) phase led to a mixture of pinanediol and **18** (23 g), which was discarded. Two recrystallizations of crude **18** from acetonitrile by addition of diethyl ether yielded an analytical sample, mp > 275 °C: ^{1}H NMR (300 MHz, CD_3OD) δ 3.14 (unresolved m, $J \sim 4$ Hz, 1), 3.70 (s, 1), 3.72 (d, $J \sim 2$ Hz, 1), 3.76 (s, 3), 4.482 and 4.486 (AB, $J = 12$ Hz, 2), 4.58 + 4.62 (AB, $J = 11$ Hz, 2), 6.85 (d of m's, $J \sim 2$ Hz, $J = 7$ Hz, 2), 7.3 (m, 7); ^{13}C NMR (75 MHz, CD_3OD) δ 54.4, 72.5, 74.3, 113.3, 127.2, 127.7, 128.1, 129.6, 132.3 (w, poor S/N ratio obscured weaker peaks); ^{19}F NMR (282 MHz, CD_3OD) δ −147.0 (unresolved m). Anal. Calcd for $C_{17}H_{19}BCsF_3O_3$: C, 43.25; H, 4.06; B, 2.29; Cs, 28.16; F, 12.07. Found: C, 43.11; H, 3.83; B, 2.31; Cs, 30.3; F, 11.3. The unexplained deviations of the Cs and F values from those expected are typical of results frequently obtained with caesium alkyltrifluoroborates.

(1*S*,2*S*,3*R*,5*S*)-Pinanediol (1*S*)-(2-benzyloxy-1-*p*-methoxybenzyloxyethyl)boronate (19)

Caesium (1*S*)-[2-benzyloxy-1-(*p*-methoxybenzyloxy)ethyl]trifluoroborate (**18**) (24.6 g, 0.052 mol), (1*S*,2*S*,3*R*,5*S*)-pinanediol (8.95 g, 0.53 mol), and sodium bicarbonate (10 g, 0.12 mol) in a two-phase system of water (500 mL) and diethyl ether (200 ml) were stirred at 22 °C under argon. Reaction progress was monitored by comparison of the ^{1}H NMR signals of free pinanediol (δ 3.95, dd, $J \sim 6$ Hz, $J \sim 9$ Hz) and boronic ester **19** (δ 4.31, dd, $J = 1.9$ Hz, $J = 8.9$ Hz) in aliquots from the ether phase. Completion required ~8 days. The ether phase was separated, washed with water (100 mL), and concentrated on a rotary evaporator. The residue was dissolved in pentane (200 mL) and passed through a silica gel column with additional pentane. The solution was concentrated and stirred overnight under vacuum (0.24 torr), 16.3 g (69%) of liquid **19**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3), 1.20 (d, $J = 10.8$ Hz, 1), 1.27 (s, 3), 1.40 (s, 3) 1.83–1.9 (m, 2), 2.06 (m, 1), 2.15 (m, 1), 2.31 (m, 1), 3.56 (m, 1), 3.73 (m, 2), 3.77 (s, 3), 4.31 (dd, $J = 1.9$ Hz, $J = 8.9$ Hz), 4.52 and 4.61 (AB, 2, d + d, $J = 12$ Hz), 4.59 (s, 2), 6.84 (m, 2), 7.30 (m, 7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 26.7, 27.3, 28.9, 35.6, 38.3, 39.6, 51.3, 55.5, 68.2 (broad, *C*B), 71.8, 72.4, 73.4, 78.4, 86.8, 113.9, 127.6, 127.9, 128.4, 129.7, 131.3, 138.8, 159.3. HRMS (EI-double focusing magnetic sector) *m*/*z*: $[M]^+$ Calcd for $C_{27}H_{35}BO_5$ 450.2583; Found 450.2597; *m*/*z*: $[M - C_7H_7]^+$ Calcd for $C_{20}H_{28}BO_5$ 359.2034, Found 359.2039; *m*/*z*: $[M - C_8H_9O]^+$ Calcd for $C_{19}H_{26}BO_4$, 329.1928; Found 329.1932.

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