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S-Ribosylhomocysteine analogues with the carbon-5 and sulfur atoms replaced by a vinyl or (fluoro)vinyl unit

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Abstract

Treatment of the protected ribose or xylose 5-aldehyde with sulfonyl-stabilized fluorophosphonate gave (fluoro)vinyl sulfones. Stannyldesulfonylation followed by iododestannylation afforded 5,6-dideoxy-6-fluoro-6-iodo-D-*ribo* or *xylo*-hex-5-enofuranoses. Coupling of the hexenofuranoses with alkylzinc bromides gave ten-carbon ribosyl- and xylosylhomocysteine analogues incorporating a fluoroalkene. The fluoroalkenyl and alkenyl analogues were evaluated for inhibition of *Bacillus subtilis S*-ribosylhomocysteinase (LuxS). One of the compounds, 3,5,6-trideoxy-6-fluoro-D-*erythro*-hex-5-enofuranose, acted as a competitive inhibitor of moderate potency (K_I = 96 μM).

Keywords

LuxS enzyme; Negishi coupling; *S*-ribosylhomocysteine; vinyl fluorides; vinyl stannanes

1. Introduction

S-Adenosyl-L-homocysteine (SAH) is a byproduct of many methyltransferase reactions and a potent inhibitor of the methyltransferases. In eukaryotes and some bacteria, detoxification of SAH is mediated by SAH hydrolase (EC 3.3.1.1), which effects hydrolytic cleavage of SAH to L-homocysteine (Hcy) and adenosine (Figure 1).[1] Hcy appears to be a risk factor for coronary artery diseases.[2] Alternatively, most bacteria utilize enzyme 5′-methylthioadenosine (MTA)/SAH nucleosidase (EC 3.2.2.9) to irreversibly cleave SAH yielding adenine and *S*-ribosyl-L-homocysteine (SRH).[3] The SRH is then converted to Hcy and 2,4-dihydroxy-2,3-pentadione (DPD) by a metalloenzyme *S*-ribosylhomocysteinase (LuxS).[4] DPD[5] spontaneously cyclizes and complexes with borate to form a furanosyl borate diester, which acts as a type 2 autoinducer for bacterial interspecies quorum sensing.[6] Since quorum sensing regulates many bacterial behaviors such as virulence and biofilm formation, LuxS and other proteins involved in quorum sensing have been proposed as attractive targets for novel antibacterial drug design.[7] Several substrate analogues of SRH (e.g., **1** and **2**) showed submicromolar inhibition of LuxS.[4e,h]

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We have previously observed that SAH hydrolase is capable of the addition of water across 5′,6′ isolated double bond of adenosine analogues **3** and **4** (Figure 2).[1c,8] The resulting adduct (or its derivative) caused covalent modification and inactivation[8b] of the enzyme, a process which required the catalytic activity of the enzyme. Since LuxS catalyzes a similar reaction as SAH hydrolase (i.e., overall elimination of Hcy), we designed analogues of SRH with the vinyl or halovinyl moieties incorporated in place of the carbon-5 and sulfur atoms (e.g., **5**). We envisaged that these ribosyl analogues might serve as mechanistic probes to study the mechanism of action of LuxS and evaluate the similarities between SAH hydrolase and LuxS. As mentioned above, LuxS inhibitors may provide a novel class of antibacterial agents. We now describe the syntheses of SRH analogues with the carbon-5 and sulfur atoms replaced by vinyl or (6-fluoro)vinyl motifs and discuss their interactions with LuxS enzyme.

2. Chemistry

Our initial plan to prepare compound **5** and its congeners is illustrated in Scheme 1. Treatment of the diacetone 3-*O*-benzoylglucose **6** or allose **7** with periodic acid selectively removed the 5,6-*O*-isopropylidene group. Subsequent oxidative cleavage of the exposed vicinal diol[9a] gave the corresponding 5-aldehydes **8** and **9**, respectively, in high yields (Scheme 1). Wittig olefination of aldehyde **8** with the ylide derived from commercially available [4-ethoxy-4-oxobutyl)triphenylphoshonium bromide provided a complex mixture of products. Column chromatography yielded protected 5,6,7,8-tetradeoxy-α-D-*xylo*-non-5(*Z*)-enofuranuronate **10** (18% yield). The stereochemistry was assigned as *Z*, based on the magnitude of the coupling constants for olefinic protons ($^3J_{5\text{-}6}$ = 11.1 Hz), and literature precedence for the Wittig condensations of aliphatic aldehydes with the nonstabilized ylides.[9b] Similarly, Wittig-treatment of *ribo* 5-aldehyde **9** gave **11**; a nine-carbon analogue of SRH. Unfortunately, our attempts to add bromine (CH_2Cl_2/0 °C) across the double bond of **10** or **11** (as well as **16**) produced a complex mixture which did not give the desired SRH analogues of type **5** bearing a (6-bromo)vinyl unit when treated with DBU.[10]

In an alternative approach, we attempted a synthesis of 6-bromoalkenyl analogues **5** (X = Br) *via* Pd-catalyzed monoalkylation[11–13] of the readily available (*gem*-dibromo)vinyl sugar precursors (e.g. **12**, **13**) with the corresponding alkylzinc reagents. Thus, dibromolefination of *xylo* 5-aldehyde **8** by the Corey-Fuchs procedure[14] gave 5-(dibromomethylene)-5-deoxyxylose **12** (81% from **6**; Scheme 2). Analogous treatment of the *ribo* 5-aldehyde **9** afforded **13**.[15] Treatment of **12** with 3 equiv. of 4-ethoxy-4-oxobutylzinc bromide in the presence of $Pd(PPh_3)_4$ at 55 °C gave monoalkylated 5,6,7,8,9-pentadeoxy-α-D-*xylo*-dec-5(*E*)-enofuranuronate **14** (18%, $^3J_{5\text{–}6}$ = 15.4 Hz) and dialkylated **18** (48%) products, but did not yield the desired 6-bromoalkenyl product **15**. Analogous Negishi coupling of 5-(dibromomethylene)-5-deoxyribose **13** afforded only dialkylated product **19** (54%). Changing catalyst [($Pd_2(dba)_3$)], solvent (THF), reaction temperature (r.t. to 60 °C) as well as adding additives (CuI, tricyclohexylphosphine) did not lead to the formation of **15** or **17** but instead produced dialkylated byproducts **18** and **19** (3-49%) in agreement with a recent report.[13b]

We next explored stereoselective coupling of the *gem*-dihalovinyl sugars containing two different halogens. We chose 5-deoxy-5-(fluoroiodomethylene) hexenofuranoses **26** and **27** because the iodo and fluoro substituents are known to have quite different reactivity towards oxidative-addition in Pd-mediated couplings.[11b,16,17] The precursors **26** and **27** were prepared employing McCarthy's stannyldesulfonylation methodology.[18,19] Thus, treatment of the *xylo* aldehyde **8** with the enolate generated from the sulfonyl-stabilized fluorophosphonate[20] gave (fluoro)vinyl sulphones **20** (*E/Z*, 7∶3; 76%; Scheme 3). The stereoselective radical-mediated stannyldesulfonylation of **20** with Bu_3SnH produced (fluoro) vinyl stannanes **23** (*E/Z*, 7∶3; 95%). Iododestannylation of **23** with *N*-iodosuccinimide (NIS) quantitatively afforded 6-fluoro-6-iodo-*xylo*-hex-5-enofuranoses **26** with retention of the *E/Z*

configuration. The *ribo* analogue **27** (*E/Z*, 3:2; 57% overall yield from **9**) was similarly prepared. The isomeric ratio for the fluorinated sugars could be distinguished by the magnitude of the $^3J_{F\text{-}H5}$ in the NMR spectra.

Pd-mediated cross-coupling of the *xylo* analogue **26** (*E/Z*, 4:1) with 2 equiv. of 4-ethoxy-4-oxobutylzinc bromide resulted in selective consumption of (*E*)-**26** to afford (*Z*)-**29** in 61% isolated yield or 76% based on consumption of (*E*)-**26** (Scheme 4). A small amount of (*E*)-**29** was also isolated, although monocoupling with *gem*-dihalovinyl substrates is considered to be *trans* selective.[12,13b,16] Similar monoalkylation of the *ribo* analogue **27** (*E/Z*, 3:2) with $BrZn(CH_2)_3COOEt$ yielded (*Z*)-**30** [54%, 90% based on the conversion of (*E*)-**27**][21] and (*E*)-**30** [12%, 30% from (*Z*)-**27**]. Coupling of the (iodo)vinyl (*E*)-**28**, prepared as depicted in Scheme 3 (**9** → **22** → **25** → **28**), with $BrZn(CH_2)_3COOEt$ gave the unfluorinated analogue (*E*)-**16** (56%) with the retention of configuration. Treatment of (*Z*)-**29** with NH_3/MeOH removed the benzoyl group and converted the ethyl ester into a methyl ester (*Z*)-**31** (74%). Subsequent removal of the isopropylidene group with aqueous trifluoroacetic acid (TFA) at 0 °C gave (Z)-**33** (61%; α/β, 1:1). Successive treatment of (*Z*)-**30** with NH_3/MeOH followed by TFA/H_2O gave (*Z*)-**34** (52% overall yield; α/β, 3:7); a ten-carbon 6-fluoroalkenyl analogue of SRH.

The 5,6-dideoxy-6-fluorohex-5-enofuranoses **42** and **43**, depurinated analogues of **3** (X = F), were synthesized by protiodestannylation of the (fluoro)vinyl stannanes **23** and **24**. Thus, treatment of **23** (*E/Z*, 7:3) with NH_3/MeOH at 25 °C resulted in the removal of 3-*O*-benzoyl group to give **36** (Scheme 5). However, prolonged heating of **36** (or **23**) with NH_3/MeOH at 65 °C for 48 h effected protiodestannylation to yield a separatable mixture of (*E*)-**39** (29%) and (*Z*)-**39** (48%). Treatment of (*E*)-**39** with TFA/H_2O at 0 °C gave (*E*)-**42** (α/β, ~1:1). Analogous debenzoylation and protiodestannylation of **24** (*E/Z*, 1:1) with NH_3/MeOH yielded (*E*)-**40** (32%) and (*Z*)-**40** (26%). Acid-catalyzed removal of the isopropylidene group in (*E*)-**40** gave 5,6-dideoxy-6-fluoro-D-*ribo*-hex-5-enofuranose (*E*)-**43** (67%; α/β, ~1:4). Alternatively, concomitant protiodestannylation and removal of acetone unit in **36** or **37** with TFA also afforded **42** and **43**.

The 3,5,6-trideoxy 6-fluorohex-5-enofuranose **44**, which lacks a hydroxyl group at C3 and therefore cannot participate in the second enolization step of the LuxS catalyzed reaction,[4b] was also prepared. Thus, oxidation of the diacetone 3-deoxyglucose[22] with H_5IO_6[9a] and *in situ* treatment of the rather unstable 3-deoxyribose 5-aldehyde with the enolate generated from the sulfonyl-stabilized fluorophosphonate[20] gave the (fluoro)vinyl sulfones **35** (48%; *E/Z*, 2:1;). Subjection of **35** to the stannyldesulfonylation/protiodestannylation[18b] sequence afforded 3-deoxy (6-fluoro)vinyl sugar **41**, which was deprotected to yield **44** (12% from **35**). Alternatively, treatment of vinyl stannanes **38** with TFA affected simultaneous protiodestannylation and removal of the acetone unit to give **44** (23% from **35**; *E/Z* ~1:3, α/β ~1:4).

3. Inhibition of LuxS

The (6-fluoro)vinyl *xylo*- (**42**) and *ribo*-hexofuranoses (**43**) and their 3-deoxy analogue **44** as well as (6-fluoro)vinyl *xylo*- and *ribo*-decofuranoses (**33** and **34**) were evaluated[4h] as potential inhibitors of *Bacillus subtilis S*-ribosylhomocysteinase (LuxS). Compound **44** exhibited competitive inhibition of moderate potency, with a K_I value of 96 ± 3 μM (Figure 3). None of the other compounds showed significant inhibition under the assay conditions.

4. Summary and Conclusions

We have developed synthesis of six-, nine- and ten-carbon analogues of ribosyl- and xylosylhomocysteines in which the carbon-5 and sulfur atoms are replaced by a vinyl or (fluoro)

vinyl unit. These fluoroalkenyl and alkenyl analogues of SRH were synthesized employing either the Wittig reaction or Pd-catalyzed coupling routes. They were evaluated against *Bacillus subtilis S*-ribosylhomocysteinase (LuxS). Only 3,5,6-trideoxy-6-fluoro-D-*erythro*-hex-5-enofuranose acted as competitive inhibitor of moderate potency with K_I = 96 μM.

5. Experimental Section

^{1}H (Me_4Si) NMR spectra were determined with solution in $CDCl_3$ at 400 or 600 MHz, ^{13}C (Me_4Si) at 100.6 MHz and ^{19}F ($CFCl_3$) at 376.5 MHz unless otherwise noted. Mass spectra (MS) were obtained by atmospheric pressure chemical ionization (APCI) and HRMS by electron impact techniques unless otherwise noted. Reagent grade chemicals were used as received. Solvents were dried by reflux over and distillation from CaH_2 under an argon atmosphere except THF (K/benzophenone). TLC was performed on Merck kieselgel 60-F_{254} with MeOH/$CHCl_3$ (1:9) and EtOAc/MeOH (95:5) as developing systems, and products were detected with 254 nm light or by visualization with $Ce(SO_4)_2$/$(NH_4)_6Mo_7O_{24}$•$4H_2O$/H_2SO_4/H_2O reagent. Merck kieselgel 60 (230-400 mesh) was used for column chromatography. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN.

Ethyl 3-*O*-Benzoyl-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-α-D-*xylo*-non-5(*Z*)-enofuranuronate (10)

Step (a). H_5IO_6 (150 mg, 0.66 mmol) was added to a stirred solution of **6** (200 mg, 0.55 mmol) in dried EtOAc at ambient temperature. A precipitate appeared within the first five minutes and the resulting solution was stirred for 90 min. The precipitate was filtered off and was washed with EtOAc (2 × 5 mL). The combined organic layer was washed with $NaHCO_3$/H_2O (10 mL), NaCl/H_2O (10 mL), dried (Na_2SO_4) and evaporated to yield 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**8**; 160 mg, 95%; approx. 90% pure based on ^{1}H NMR): ^{1}H NMR δ 1.35 & 1.48 (2 × s, 2 × 3, 2 × CH_3), 4.76 (d, $J_{4\text{-}3}$ = 3.2 Hz, 1, H4), 4.88 (d, $J_{2\text{-}1}$ = 3.1 Hz, 1, H2), 5.77 (d, $J_{1\text{-}2}$ = 3.1 Hz, 1, H1), 6.18 (d, $J_{3\text{-}4}$ = 3.3 Hz, 1, H3), 7.42-8.01 (m, 5, Ar), 9.78 (s, 1, H5). Step (b). LHMDS (1M/THF; 0.69 mL, 0.69 mmol) was added dropwise to a stirred solution of $Ph_3PCH_2CH_2CH_2CO_2Et$/Br (314 mg, 0.69 mmol) in anhydrous THF (4 mL) in a flame-dried flask under N_2 at ambient temperature. After 15 minutes, a solution of the crude, preferentially freshly prepared, aldehyde **8** (160 mg of the material from step a) in THF (2 mL) was added via syringe and stirring was continued overnight. EtOAc (30 mL) and $NaHCO_3$/H_2O (10 mL) was added and the separated organic was washed with NaCl/H_2O (10 mL), dried (Na_2SO_4), and evaporated. Column chromatography (10 → 30% hexanes/EtOAc) gave **10** (39 mg, 18%) as an oil: ^{1}H NMR δ 1.24 (t, J = 7.2 Hz, 3, CH_3), 1.37 & 1.62 (2 × s, 2 × 3, 2 × CH_3), 2.41 (t, $J_{8\text{-}7/7'}$ = 6.9 Hz, 2, H8/8′), 2.50 ("q", $J_{7\text{-}6/8/8'}$ = 7.3 Hz, 2, H7/7′), 4.15 (q, J = 7.1 Hz, 2, CH_2), 4.71 (d, $J_{2\text{-}1}$ = 3.8 Hz, 1, H2), 5.22 (dd, $J_{4\text{-}5}$ = 7.7 Hz, $J_{4\text{-}3}$ = 2.8 Hz, 1, H4), 5.46 (d, $J_{3\text{-}4}$ = 2.8 Hz, H3), 5.58 (dd, $J_{5\text{-}6}$ = 11.1 Hz, $J_{5\text{-}4}$ = 7.9 Hz, 1, H5), 5.68 (dt, $J_{6\text{-}5}$ = 11.1 Hz, $J_{6\text{-}7/7'}$ = 7.1 Hz, 1, H6), 6.05 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 7.48-8.04, (m, 5, Ar); ^{13}C NMR δ 14.62 (CH_3), 24.08 (C7), 26.62 & 27.19 (CMe_2), 34.23 (C8), 60.90 (CH_2), 75.54 (C2), 78.59 (C3), 84.20 (C4), 105.02 (C1), 112.47 (CMe_2), 123.90 (C6), 128.91 (Bz), 129.78 (Bz), 130.15 (Bz), 133.85 (Bz), 134.39 (C5), 165.64 (Bz), 173.09 (C9); MS *m/z* 391 (100, MH^+). HRMS (AP-ESI) *m/z* calcd for $C_{21}H_{26}O_7Li$ (MLi^+) 397.1839; found 397.1833.

Ethyl 3-*O*-Benzoyl-5,6,7,8-tetradeoxy-1,2-*O*-isopropylidene-α-D-*ribo*-non-5(*Z*)-enofuranuronate (11)

Step (a) Oxidation of **7** (200 mg, 0.55 mmol) with H_5IO_6 (150 mg, 0.66 mmol), as described for **10**, gave 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*ribo*-pentodialdo-1,4-furanose (**9**; 145 mg, 85%; approx. 90% pure, ^{1}H NMR): ^{1}H NMR δ 1.39 & 1.61 (2 × s, 2 × 3, 2 × CH_3), 4.64 (dd, $J_{4\text{-}5}$ = 2.2 Hz, $J_{4\text{-}3}$ = 9.2 Hz, 1, H4), 5.01 (t, $J_{2\text{-}1/3}$ = 4.2 Hz, 1, H2), 5.13 (dd, $J_{3\text{-}4}$ = 9.2

Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 6.02 (d, $J_{1\text{-}2}$ = 3.4 Hz, 1, H1), 7.48-8.03 (m, 5, Ar), 9.77 (d, $J_{5\text{-}4}$ = 2.2 Hz, 1, H5). Step (b). Treatment of the crude **9** (145 mg) with $Ph_3P(CH_2)_3CO_2Et/Br$ (275 mg, 0.60 mmol) and LHDMS (1M/THF; 0.60 mmol, 0.60 mL), as described for **10**, gave **11** (18 mg, 12%): ^{1}H NMR δ 1.26 (t, *J* = 7.1 Hz, 3, CH_3), 1.36 & 1.62 (2 × s, 2 × 3, 2 × CH_3), 2.38 (t, $J_{8\text{-}7/7'}$ = 8.2 Hz, 2, H8/8′), 2.46-2.55 (m, 1, H7), 2.55-2.67 (m, 1, H7′), 4.15 (q, *J* = 7.1 Hz, 2, CH_2), 4.74 (dd, $J_{3\text{-}4}$ = 9.1 Hz, $J_{3\text{-}2}$ = 4.8 Hz, 1, H3), 4.96 ("t", $J_{2\text{-}1/3}$ = 4.3 Hz, 1, H2), 5.20 (t, $J_{4\text{-}3/5}$ = 8.7 Hz, 1, H4), 5.50 (ddt, $J_{5\text{-}6}$ = 10.9 Hz, $J_{5\text{-}4}$ = 8.7 Hz, $J_{5\text{-}7/7'}$ = 1.0 Hz, 1, H5), 5.72 (dt, $J_{6\text{-}5}$ = 10.9 Hz, $J_{6\text{-}7/7'}$ = 7.1 Hz, 1, H6), 5.93 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.48-8.04, (m, 5, Ar); ^{13}C NMR δ 14.30 (CH_3), 24.01 (C7), 26.99 & 27.04 (CMe_2), 34.53 (C8), 60.89 (CH_2), 73.39 (C4), 77.34 (C2), 77.56 (C3), 104.61 (C1), 113.40 (CMe$_2$), 127.26 (C5), 128.90 (Bz), 129.80 (Bz), 130.28 (Bz), 133.80 (Bz), 135.14 (C6), 166.25 (Bz), 173.06 (C9). HRMS (AP-ESI) *m/z* calcd for $C_{21}H_{26}O_7Li$ (MLi^+) 397.1839; found 397.1828.

3-*O*-Benzoyl-5,6-dideoxy-6,6-dibromo-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (12)

(Dibromomethylene)triphenylphosphorane [generated *in situ* by stirring CBr_4 (8.09 g, 24.5 mmol), Ph_3P (6.46 g, 24.5 mmol) and activated Zn (dust; 1.60 g, 24.5 mmol) in dried CH_2Cl_2 (100 mL) at 0 °C (ice-bath) for 30 min followed by stirring at ambient temperature under N_2 for 3h] was added to the solution of freshly prepared aldehyde **8** [prepared as described for **10** (step a) from **6** (4.68 g, 12.9 mmol) and dried for 1 h under vacuum prior to use] in CH_2Cl_2 (75 mL). After stirring for 14 h at ambient temperature, the reaction mixture was partitioned ($NaHCO_3/H_2O//CHCl_3$), and the organic layer was washed (H_2O, brine), dried ($MgSO_4$), and the volatiles were evaporated. Column chromatography (15 → 25% EtOAc/hexane) gave **12** (4.68 g, 81% overall from **6**) as a solidifying viscous oil: ^{1}H NMR δ 1.34 & 1.58 (2 × s, 2 × 3, 2 × CH_3), 4.68 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 5.04 (dd, $J_{4\text{-}5}$ = 7.6 Hz, $J_{4\text{-}3}$ = 3.0 Hz, 1, H4), 5.54 (d, $J_{3\text{-}4}$ = 3.0 Hz, 1, H3), 6.00 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.60 (d, $J_{5\text{-}4}$ = 7.6 Hz, 1, H5), 7.48 (t, *J* = 7.6 Hz, 2 Ar), 7.60 (tt, *J* = 1.3, 7.6 Hz, 1 Ar), 8.02 ("dd", *J* = 1.4, 7.7 Hz, 2 Ar); ^{13}C NMR δ 24.96 & 25.51 (CMe_2), 75.71 (C3), 78.18 (C4), 82.04 (C2), 93.26 (C6), 103.30 (C1), 111.26 (CMe$_2$), 127.31 (Bz), 127.73 (Bz), 128.44 (Bz), 130.49 (C5), 132.37 (Bz), 163.81 (Bz); MS *m/z* 451 (5, MH^+ [$^{81}Br_2$]), 449 (10, MH^+ [$^{81/79}Br_2$]), 447 (5, MH^+ [$^{79}Br_2$]).

Ethyl 3-*O*-Benzoyl-5,6,7,8,9-pentadeoxy-1,2-*O*-isopropylidene-α-D-*xylo*-dec-5(*E*)-enofuranuronate (14) and Ethyl 3-*O*-Benzoyl-6-[3-(ethoxycarbonyl)propyl]- 5,6,7,8,9-pentadeoxy-1,2-*O*-isopropylidene-α-D-*xylo*-dec-5-enofuranuronate (18)

$Pd[P(Ph)_3]_4$ (22 mg, 0.014 mmol) was added to a stirred solution of **12** (42 mg, 0.094 mmol) in anhydrous benzene (3 mL) in a flame dried flask under N_2 at ambient temperature. After 2 minutes, 4-ethoxy-4-oxobutylzinc bromide (0.5 M/THF; 0.56 mL, 129 mg, 0.28 mmol) was added and the resulting mixture was heated at 55 °C for 6 h. The reaction mixture was cooled down to ambient temperature and was partitioned between EtOAc (30 mL) and $NaHCO_3$/H_2O (10 mL). The separated organic layer was washed with H_2O (10 mL), NaCl/H_2O (10 mL), dried (Na_2SO_4), and evaporated. Column chromatography (10 → 30% EtOAc/hexanes) gave recovered **12** (7 mg, 13%), **14** (7 mg, 18%) and **18** (19 mg, 48%). Compound **14** had: ^{1}H NMR δ 1.23 (t, *J* = 7.1 Hz, 3, CH_3), 1.28 & 1.58 (2 × s, 2 × 3, 2 × CH_3), 1.68 (quint, $J_{8\text{-}7/7'/9/9'}$ = 7.5 Hz, 2, H8/8′), 2.07 ("q", $J_{7\text{-}6/8/8'}$ = 7.0 Hz, 2, H7/7′), 2.23 (t, $J_{9\text{-}8/8'}$ = 7.4 Hz, 2, H9/9′), 4.15 (q, *J* = 7.1 Hz, 2, CH_2), 4.70 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 4.86 (dd, $J_{4\text{-}5}$ = 7.1 Hz, $J_{4\text{-}3}$ = 2.8 Hz, 1, H4), 5.42 (d, $J_{3\text{-}4}$ = 2.7 Hz, 1, H3), 5.56 (dd, $J_{5\text{-}6}$ = 15.4 Hz, $J_{5\text{-}4}$ = 7.3 Hz, 1, H5), 5.92 (dt, $J_{6\text{-}5}$ = 15.4 Hz, $J_{6\text{-}7/7'}$ = 6.9 Hz, 1, H6), 6.03 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 7.46-8.05, (m, 5, Ar); ^{13}C NMR δ 14.59 (CH_3), 23.34 (C8), 26.69 & 27.16 (CMe_2), 30.10 (C7), 34.05 (C9), 60.74 (CH_2), 75.90 (C2), 81.58 (C3), 85.44 (C4), 105.00 (C1), 112.52 (CMe$_2$), 128.35 (C5), 130.17 (Bz), 130.65 (Bz), 132.47 (Bz), 133.60 (Bz), 135.50 (C6), 165.89 (Bz), 173.74 (C10); MS *m/z* 405 (100, MH^+). Compound **18** had: ^{1}H NMR δ 1.21 (t, *J* = 7.1 Hz, 3, CH_3), 1.29 (t, *J* = 7.1 Hz, 3, CH_3), 1.36 & 1.61 (2 × s, 2 × 3, 2 × CH_3), 1.69 (quint, *J* = 7.5 Hz, 2H), 1.71-1.80

(m, 2H), 2.05 (t, *J* = 7.5 Hz, 2H), 2.10-2.26 (m, 4H), 2.33 (t, *J* = 7.2 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2, CH_2), 4.18 (q, *J* = 7.1 Hz, 2, CH_2), 4.70 (d, $J_{2\text{-}1}$ = 3.8 Hz, 1, H2), 5.14 (dd, $J_{4\text{-}5}$ = 8.7 Hz, $J_{4\text{-}3}$ = 2.9 Hz, 1, H4), 5.35 (d, $J_{5\text{-}4}$ = 8.4 Hz, 1, H5), 5.41 (d, $J_{3\text{-}4}$ = 2.8 Hz, 1, H3), 6.02 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.47-8.06, (m, 5, Ar); ^{13}C NMR δ 14.60 (CH_3), 14.65 (CH_3), 26.65 & 27.15 (C*Me*$_2$), 23.32 & 23.84 (C8/8′), 30.53 & 36.22 (C7/7′), 34.04 & 34.08 (C9/9′), 60.59 (CH_2), 60.75 (CH_2), 75.90 (C4), 78.71 (C3), 84.24 (C2), 104.84 (C1), 112.36 (*C*Me$_2$), 119.09 (C5), 146.90 (C6), 128.92 (Bz), 128.92 (Bz), 129.81 (Bz), 130.17 (Bz), 133.83 (Bz), 165.70 (Bz), 173.62 & 173.75 (C10/10′); MS *m/z* 519 (100, MH^+).

Ethyl 3-*O*-Benzoyl-5,6,7,8,9-pentadeoxy-1,2-*O*-isopropylidene-α-D-*ribo*-dec-5(*E*)-enofuranuronate (16)

Treatment (55 °C, 3 h) of **28** (*E*; 20 mg, 0.048 mmol) with 4-ethoxy-4-oxobutylzinc bromide (0.5 M/THF; 0.19 mL, 65 mg, 0.096 mmol) as described for **14**/**18** gave **16** (11 mg, 56%): ^{1}H NMR δ 1.24 (t, *J* = 7.1 Hz, 3, CH_3), 1.35 & 1.59 (2 × s, 2 × 3, 2 × CH_3), 1.72 (quint, $J_{8\text{-}7/7'/9/9'}$ = 7.4 Hz, 2, H8/8′), 2.13 ("q", $J_{7\text{-}6/8/8'}$ = 7.2 Hz, 2, H7/7′), 2.28 (t, $J_{9\text{-}8/8'}$ = 7.6 Hz, 2, H9/9′), 4.10 (q, *J* = 7.1 Hz, 2, CH_2), 4.65 (dd, $J_{4\text{-}5}$ = 7.6 Hz, $J_{4\text{-}3}$ = 8.9 Hz, 1, H4), 4.74 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 4.96 (t, $J_{2\text{-}1/3}$ = 4.3 Hz, 1, H2), 5.53 (dd, $J_{5\text{-}6}$ = 15.4 Hz, $J_{5\text{-}4}$ = 7.3 Hz, 1, H5), 5.89 (d, $J_{1\text{-}2}$ = 4.0 Hz, 1, H1), 5.91 (dt, $J_{6\text{-}5}$ = 15.8 Hz, $J_{6\text{-}7/7'}$ = 6.8 Hz, 1, H6), 7.46-8.05, (m, 5, Ar); ^{13}C NMR δ 14.62 (CH_3), 24.40 (C8), 26.92 & 27.00 (C*Me*$_2$), 31.99 (C7), 33.89 (C9), 60.65 (CH_2), 76.92 (C2), 77.65 (C3), 78.60 (C4), 104.37 (C1), 113.35 (*C*Me$_2$), 127.04 (C5), 128.85 (Bz), 129.83 (Bz), 130.28 (Bz), 133.76 (Bz), 136.28 (C6), 166.29 (Bz), 173.84 (C10); MS *m/z* 405 (100, MH^+).

Ethyl 3-*O*-Benzoyl-5,6,7,8,9-pentadeoxy-6-[3-(ethoxycarbonyl)propyl]-1,2-*O*-isopropylidene-α-D-*ribo*-dec-5-enofuranuronate (19)

Treatment of **13**[15] (42 mg, 0.094 mmol) with Pd[P(Ph)$_3$]$_4$ (22 mg, 0.014 mmol) and 4-ethoxy-4-oxobutylzinc bromide (0.56 mL, 129 mg, 0.28 mmol) as described for **14**/**18** gave **19** (26 mg, 54%): ^{1}H NMR δ 1.22 (t, *J* = 7.1 Hz, 6, 2 × CH_3), 1.37 & 1.62 (2 × s, 2 × 3, 2 × CH_3), 1.75 (quint, *J* = 7.5 Hz, 4H), 2.11 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 9.0 Hz, 2H), 2.26 (t, *J* = 9.0 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2, CH_2), 4.16 (q, *J* = 7.1 Hz, 2, CH_2), 4.74 (dd, $J_{3\text{-}4}$ = 9.0 Hz, $J_{3\text{-}2}$ = 4.8 Hz, 1, H3), 4.95 (t, $J_{2\text{-}3}$ = 4.3 Hz, 1, H2), 5.01 (t, $J_{4\text{-}5}$ = 9.0 Hz, 1, H4), 5.26 (d, $J_{5\text{-}4}$ = 8.9 Hz, 1, H5), 5.89 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H1), 7.40-8.10 (m, 5, Ar); ^{13}C NMR δ 14.55 (CH_3), 14.61 (CH_3), 21.48 (C8/8′), 23.11 & 27.03 (C*Me*$_2$), 30.08 & 30.12 (C7/7′), 32.34 & 34.04 (C9/9′), 60.73 (CH_2), 60.83 (CH_2), 73.86 (C4), 78.71 (C3), 84.24 (C2), 104.37 (C1), 113.28 (*C*Me$_2$), 122.65 (C5), 128.92 (Bz), 128.92 (Bz), 129.81 (Bz), 130.17 (Bz), 133.83 (Bz), 143.90 (C6), 165.70 (Bz), 170.57 & 171.62 (C10/10′); MS *m/z* 519 (100, MH^+).

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-1,2-*O*-isopropylidene-6-phenylsulfonyl-α-D-*xylo*-hex-5-enofuranose (20)

LHMDS (0.84 mL, 140 mg, 0.84 mmol) was added dropwise to a solution of diethyl fluoro (phenylsulfonyl)methylphosphonate[20] (260 mg, 0.84 mmol) in anhydrous THF (8 mL) in a flame dried flask under N_2 at −78 °C. After 30 minutes, a solution of **8** (265 mg, 0.82 mmol) in THF (4 mL) was added and stirring was continued for 1.5 h. EtOAc (30 mL) and NH_4Cl/H_2O (10 mL) were added and reaction mixture was allowed to warm to ambient temperature. The separated organic layer was washed with $NaHCO_3$/H_2O (10 mL), NaCl/H_2O (10 mL), dried (Na_2SO_4), and evaporated. Column chromatography (10 → 30% EtOAc/hexanes) gave **20** (166 mg, 76%; *E*/*Z*, 7:3) as inseparable mixture of isomers: HRMS (AP-ESI) *m/z*: calcd for $C_{22}H_{22}FO_7S$ (MH^+) 449.1065, found 449.1071; ^{19}F NMR δ −110.25 (d, $J_{F\text{-}H5}$ = 18.8 Hz, 0.30F, *Z*), −119.30 (d, $J_{F\text{-}H5}$ = 32.1 Hz, 0.70F, *E*). Compound (*E*)-**20** had: ^{1}H NMR δ 1.35 & 1.56 (2 × s, 2 × 3, 2 × CH_3), 4.73 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 5.23 (dt, $J_{4\text{-}5}$ = 7.4 Hz, $J_{4\text{-}3/F}$ = 2.3

Hz, 1, H4), 5.49 (d, *J*3-4 = 3.1 Hz, 1, H3), 6.03-6.05 (m, 1, H1), 6.43 (dd, $J_{5\text{-}F}$ = 32.4 Hz, $J_{5\text{-}4}$ = 7.2 Hz, 1, H5), 7.48-8.03 (m, 10, Ar); ^{13}C NMR δ 26.55 & 27.10 (C*Me*$_2$), 73.78 (C4), 78.21 (C3), 83.77 (C2), 105.31 (C1), 113.13 (*C*Me$_2$), 112.10 (d, $^2J_{5\text{-}F}$ = 3.3 Hz, C5), 128.99 (Ph), 129.08 (Bz), 129.13 (Bz), 129.79 (Ph), 129.94 (Ph), 130.12 (Ph), 130.17 (Bz), 134.25 (Bz), 135.02 (Ph), 156.00 (d, $^1J_{6\text{-}F}$ = 300.0 Hz, C6), 165.36 (Bz). Compound (*Z*)-**20** had: ^{1}H NMR δ 1.38 & 1.69 (2 × s, 2 × 3, 2 × CH$_3$), 4.76 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 5.68 (d, $J_{3\text{-}4}$ = 2.8 Hz, 1, H3), 5.99 (dd, $J_{5\text{-}F}$ = 19.3 Hz, $J_{5\text{-}4}$ = 8.6 Hz, 1, H5), 6.05-6.07 (m, 1, H1), 6.07-6.09 (m, 1, H4), 7.48-8.03 (m, 10, Ar); ^{13}C NMR δ 26.98 & 27.32 (C*Me*$_2$), 73.15 (d, $^3J_{4\text{-}F}$ = 10.14 Hz, C4), 79.06 (C3), 83.93 (C2), 105.37 (C1), 113.35 (*C*Me$_2$), 114.10 (d, $^2J_{5\text{-}F}$ = 15.0 Hz, C5), 128.99 (Ph), 129.08 (Bz), 129.13 (Bz), 129.79 (Ph), 129.94 (Ph), 130.12 (Ph), 130.17 (Bz), 134.25 (Bz), 135.02 (Ph), 155.58 (d, $^1J_{6\text{-}F}$ = 292.3 Hz, C6), 165.36 (Bz). Note: Freshly prepared aldehyde **8**, dried under vacuum for 2 h at ambient temperature prior the use, gave the best results.

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-1,2-*O*-isopropylidene-6-phenylsulfonyl-α-D-*ribo*-hex-5-enofuranose (21)

Treatment of **9** (200 mg, 0.68 mmol) with diethyl fluoro(phenylsulfonyl) methylphosphonate[20] (212 mg, 0.68 mmol) and LHMDS (0.68 mL, 114 mg, 0.68 mmol) as described for **20** gave **21** (216 mg, 71%; *E/Z*, 6:4): HRMS (AP-ESI) *m/z*: calcd for $C_{22}H_{22}FO_7S$ (MH^+) 449.1065, found 449.1069; ^{19}F NMR δ −108.98 (d, $J_{F\text{-}H5}$ = 22.6 Hz, 0.40F, *Z*), −121.25 (d, $J_{F\text{-}H5}$ = 30.1 Hz, 0.60F, *E*). Compound (*E*)-**21** had: ^{1}H NMR δ 1.28 & 1.38 (2 × s, 2 × 3, 2 × CH$_3$), 4.85 (dd, $J_{3\text{-}4}$ = 9.0 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 5.00 ("t", $J_{2\text{-}1/3}$ = 4.5 Hz, 1, H2), 5.10 (t, $J_{4\text{-}3/5}$ = 8.2 Hz, 1, H4), 5.94 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.37 (dd, $J_{5\text{-}F}$ = 31.3 Hz, $J_{5\text{-}4}$ = 8.3 Hz, 1, H5), 7.44-8.20 (m, 10, Ar); ^{13}C NMR δ 26.86 & 26.93 (C*Me*$_2$), 71.36 (d, $^3J_{4\text{-}F}$ = 2.2 Hz, C4), 76.64 (d, $^4J_{3\text{-}F}$ = 1.8 Hz, C3), 77.54 (C2), 104.96 (C1), 114.10 (*C*Me$_2$), 114.22 (d, $^2J_{5\text{-}F}$ = 3.1 Hz, C5), 128.88 (Ph), 129.13 (Bz), 129.18 (Bz), 129.88 (Ph), 130.28 (Ph), 133.98 (Bz), 135.10 (Ph), 136.96 (Ph), 156.91 (d, $^1J_{6\text{-}F}$ = 306.0 Hz, C6), 165.96 (Bz). Compound (*Z*)-**21** had: ^{1}H NMR δ 1.28 & 1.38 (2 × s, 2 × 3, 2 × CH$_3$), 4.84 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 5.01 ("t", $J_{2\text{-}1/3}$ = 4.6 Hz, 1, H2), 5.86 (dd, $J_{5\text{-}F}$ = 19.8 Hz, $J_{5\text{-}4}$ = 9.9 Hz, H5), 5.96 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.07 (t, $J_{4\text{-}3/5}$ = 10.4 Hz, 1, H4), 7.44-8.20 (m, 10, Ar); ^{13}C NMR δ 27.17 & 27.39 (C*Me*$_2$), 70.71 (d, $^3J_{4\text{-}F}$ = 8.5 Hz, C4), 77.17 (C3), 77.86 (C2), 104.82 (C1), 114.37 (*C*Me$_2$), 116.23 (d, $^2J_{5\text{-}F}$ = 16.2 Hz, C5), 128.95 (Ph), 129.22 (Bz), 129.46 (Bz), 129.80 (Ph), 130.02 (Ph), 133.61 (Bz), 134.00 (Ph), 135.19 (Ph), 156.62 (d, $^1J_{6\text{-}F}$ = 296.3 Hz, C6), 166.30 (Bz).

(*E*)-3-*O*-Benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-phenylsulfonyl-α-D-*ribo*-hex-5-enofuranose (22)

Treatment of **9** (150 mg, 0.50 mmol) with diethyl (phenylsulfonyl)methylphosphonate[20] (146 mg, 0.50 mmol) and LHMDS (0.50 mL, 84 mg, 0.50 mmol) as described for **20** gave **22** (166 mg, 82%): ^{1}H NMR δ 1.33 & 1.55 (2 × s, 2 × 3, 2 × CH$_3$), 4.76 (dd, $J_{3\text{-}4}$ = 9.5 Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 4.92 (ddd, $J_{4\text{-}5}$ = 3.7 Hz, $J_{4\text{-}6}$ = 1.7 Hz, $J_{4\text{-}3}$ = 9.5 Hz, 1, H4), 5.01 ("t", $J_{2\text{-}3/1}$ = 4.2 Hz, 1, H2), 5.90 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.79 (dd, $J_{6\text{-}4}$ = 1.8 Hz, $J_{6\text{-}5}$ = 15.0 Hz, 1, H6), 7.09 (dd, $J_{5\text{-}6}$ = 15.0 Hz, $J_{5\text{-}4}$ = 3.8 Hz, 1, H5), 7.50-8.05 (m, 10, Ar); MS *m/z* 431 (100, MH^+).

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-1,2-*O*-isopropylidene-6-tributylstannyl-α-D-*xylo*-hex-5-enofuranose (23)

Bu_3SnH (407 mg, 0.38 mL, 1.4 mmol) was added dropwise to a degassed solution of **20** (300 mg, 0.70 mmol; *E/Z*, 7:3) in anhydrous toluene (5 mL) in a flame-dried flask under N_2 at ambient temperature. After an additional 10 minutes of degassing with N_2, AIBN (86 mg, 0.53 mmol) was added and the reaction mixture was refluxed at 110 °C with stirring for 5 h. The volatiles were evaporated and the residue was partitioned between EtOAc (50 mL) and

$NaHCO_3/H_2O$ (30 mL). The organic layer was washed with $NaCl/H_2O$ (30 mL), dried (Na_2SO_4), and evaporated. Column chromatography (hexanes → 10% EtOAc/hexanes) gave **23** (794 mg, 95%; *E/Z*, 7:3) as an inseparable mixture: MS *m/z* 599 (89, MH^+, ^{120}Sn), 597 (63, MH^+, ^{118}Sn), 595 (33, MH^+, ^{116}Sn), 541 (100, M-57, ^{120}Sn), 539 (78, M-57, ^{118}Sn), 537 (42, M-57, ^{116}Sn); ^{19}F NMR δ −87.67 (d, $J_{F\text{-}H5}$ = 34.3 Hz, 84% of 0.30F, *Z*), −87.67 (dd, $J_{F\text{-}Sn}$ = 229.5 Hz, $J_{F\text{-}H5}$ = 34.8 Hz, 16% of 0.30F, *Z*), −92.73 (d, $J_{F\text{-}H5}$ = 52.7 Hz, 84% of 0.70F, *E*), −92.73 (ddd, $J_{F\text{-}Sn}$ = 213.1 Hz, $J_{F\text{-}H5}$ = 52.7 Hz, $J_{F\text{-}H4}$ = 4.9 Hz, 16% of 0.70F, *E*). Compound (*E*)-**23** had: ^1H NMR δ 0.90-1.60 (m, 27, 3 × Bu), 1.34 & 1.36 (2 × s, 2 × 3, 2 × CH_3), 4.71 (d, $J_{2\text{-}1}$ = 3.8 Hz, 1, H2), 5.10 (dd, $J_{5\text{-}F}$ = 52.6 Hz, $J_{5\text{-}4}$ = 7.4 Hz, 1, H5), 5.32 (d, $J_{3\text{-}4}$ = 3.0 Hz, 1, H3), 5.47-5.49 (m, 1, H4), 6.02 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.47-8.06 (m, 5, Ar); ^{13}C NMR δ 10.33 (Bu), 11.15 (Bu), 17.90 (Bu), 27.42 & 27.54 (CMe_2), 28.24 (Bu), 70.56 (d, $^3J_{4\text{-}F}$ = 17.6 Hz, C4), 77.21 (C3), 77.52 (C2), 104.31 (C1), 113.07 (*C*Me_2), 120.53 (d, $^2J_{5\text{-}F}$ = 3.9 Hz, C5), 128.75 (Bz), 129.83 (Bz), 130.25 (Bz), 133.61 (Bz), 166.16 (Bz), 177.14 (d, $^2J_{6\text{-}F}$ = 262.0 Hz, C6). Compound (*Z*)-**23** had: ^1H NMR δ 0.90-1.60 (m, 27, 3 × Bu), 1.38 & 1.69 (2 × s, 2 × 3, 2 × CH_3), 4.69 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H2), 4.75 (d, $J_{3\text{-}4}$ = 7.9 Hz, 1, H3), 5.47-5.49 (m, 1, H4), 5.98 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 6.02 (dd, $J_{5\text{-}F}$ = 34.3 Hz, $J_{5\text{-}4}$ = 9.2 Hz, 1, H5), 7.47-8.06 (m, 5, Ar); ^{13}C NMR δ 10.33 (Bu), 11.15 (Bu), 17.90 (Bu), 27.42 & 27.54 (CMe_2), 28.24 (Bu), 74.73 (d, $^3J_{4\text{-}F}$ = 22.2 Hz, C4), 77.38 (d, $^4J_{3\text{-}F}$ = 1.4 Hz, C3), 77.52 (C2), 104.53 (C1), 113.47 (*C*Me_2), 121.24 (d, $^2J_{5\text{-}F}$ = 9.5 Hz, C5), 128.75 (Bz), 129.88 (Bz), 130.34 (Bz), 133.73 (Bz), 166.35 (Bz), 180.03 (d, $^2J_{6\text{-}F}$ = 254.3 Hz, C6).

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-1,2-*O*-isopropylidene-6-tributylstannyl-α-D-*ribo*-hex-5-enofuranose (24)

Treatment of **21** (300 mg, 0.70 mmol; *E/Z*, 3:2) with Bu_3SnH (407 mg, 0.38 mL, 1.4 mmol) and AIBN (86 mg, 0.53 mmol) as described for **23** gave **24** (397 mg, 95%; *E/Z*, 3:2): MS *m/z* 599 (89, MH^+, ^{120}Sn), 597 (63, MH^+, ^{118}Sn), 595 (33, MH^+, ^{116}Sn), 541 (100, M-57, ^{120}Sn), 539 (78, M-57, ^{118}Sn), 537 (42, M-57, ^{116}Sn); ^{19}F NMR δ −87.58 (d, $J_{F\text{-}H5}$ = 33.1 Hz, 84% of 0.40F, *Z*), −87.58 (ddd, $J_{F\text{-}Sn}$ = 226.7 Hz, $J_{F\text{-}H5}$ = 32.8 Hz, $J_{F\text{-}H4}$ = 4.1 Hz, 16% of 0.40F), −94.80 (d, $J_{F\text{-}H5}$ = 51.1 Hz, 84% of 0.60F, *E*), −94.80 (ddd, $J_{F\text{-}Sn}$ = 213.9 Hz, $J_{F\text{-}H5}$ = 50.8 Hz, $J_{F\text{-}H4}$ = 4.5 Hz, 16% of 0.60F, *E*). Compound (*E*)-**24** had: ^1H NMR δ 0.70-1.70 (m, 27, 3 × Bu), 1.24 & 1.26 (2 × s, 2 × 3, 2 × CH_3), 4.62 (dd, $J_{3\text{-}4}$ = 9.3 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 4.86-4.87 (m, 1, H2), 4.90 (dd, $J_{5\text{-}F}$ = 51.0 Hz, $J_{5\text{-}4}$ = 8.4 Hz, 1, H5), 5.28 ("t", $J_{4\text{-}3/5}$ = 8.9 Hz, 1, H4), 5.79 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H1), 7.57-8.06 (m, 5, Ar); ^{13}C NMR δ 11.15 (Bu), 14.03 (Bu), 29.96 (Bu), 27.48 & 27.59 (CMe_2), 29.23 (Bu), 70.55 (d, $^3J_{4\text{-}F}$ = 18.1 Hz, C4), 77.36 (C3), 77.48 (C2), 104.50 (C1), 113.54 (*C*Me_2), 120.59 (d, $^2J_{5\text{-}F}$ = 3.8 Hz, C5), 128.77 (Bz), 129.81 (Bz), 130.38 (Bz), 133.69 (Bz), 166.44 (Bz), 176.10 (d, $^1J_{6\text{-}F}$ = 260.0 Hz, C6). Compound (*Z*)-**24** had: ^1H NMR δ 0.70-1.70 (m, 27, 3 × Bu), 1.28 & 1.30 (2 × s, 2 × 3, 2 × CH_3), 4.47 ("t", $J_{4\text{-}3/5}$ = 9.3 Hz, 1, H4), 4.71 (dd, $J_{3\text{-}4}$ = 9.0 Hz, $J_{3\text{-}2}$ = 4.8 Hz, 1, H3), 4.85-4.86 (m, 1, H2), 5.81 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 5.83 (dd, $J_{5\text{-}F}$ = 33.7 Hz, $J_{5\text{-}4}$ = 9.5 Hz, 1, H5), 7.57-8.06 (m, 5, Ar); ^{13}C NMR δ 11.15 (Bu), 14.03 (Bu), 29.96 (Bu), 27.48 & 27.59 (CMe_2), 29.23 (Bu), 74.72 (d, $^3J_{4\text{-}F}$ = 22.0 Hz, C4), 77.16 (C3), 77.67 (C2), 104.28 (C1), 113.13 (*C*Me_2), 121.18 (d, $^2J_{5\text{-}F}$ = 9.9 Hz, C5), 128.77 (Bz), 129.76 (Bz), 130.28 (Bz), 130.80 (Bz), 166.24 (Bz), 177.00 (d, $^1J_{6\text{-}F}$ = 255.0 Hz, C6).

(*E*)-3-*O*-Benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-tributylstannyl-α-D-*ribo*-hex-5-enofuranose (25)

Treatment of **22** (*E*; 300 mg, 0.70 mmol) with Bu_3SnH (407 mg, 0.38 mL, 1.4 mmol) and AIBN (86 mg, 0.53 mmol) as described for **23** gave **25** (385 mg, 95%): ^1H NMR δ 1.51-1.90 (m, 33, 3 × Bu & 2 × CH_3), 4.66 (dd, $J_{4\text{-}5}$ = 6.5 Hz, $J_{4\text{-}3}$ = 8.4 Hz, 1, H4), 4.77 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 4.97 (t, $J_{2\text{-}1/3}$ = 3.6 Hz, 1, H2), 5.93 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 6.10 (dd, $J_{5\text{-}6}$ = 19.1 Hz, $J_{5\text{-}4}$ = 6.5 Hz 1, H5), 6.50 (dd, $J_{6\text{-}5}$ = 19.1 Hz, $J_{6\text{-}4}$ = 0.9 Hz, 1, H6), 7.57-8.06

(m, 5, Ar); MS *m/z* 581 (89, MH^+, ^{120}Sn), 579 (63, MH^+, ^{118}Sn), 577 (33, MH^+, ^{116}Sn), 523 (100, M-57, ^{120}Sn), 521 (78, M-57, ^{118}Sn), 519 (42, M-57, ^{116}Sn).

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-6-iodo-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (26)

A solution of NIS (50 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise to a stirred solution of **23** (90 mg, 0.15 mmol; *E/Z*, 7:3) in CH_2Cl_2 (5 mL) under N_2 at −20 °C. After 1h, $CHCl_3$ (30 mL) and diluted $NaHSO_3/H_2O$ (10 mL) were added. The separated organic layer was washed with $NaHCO_3/H_2O$ (10 mL), NaCl/H_2O (10 mL), dried (Na_2SO_4), and evaporated. Column chromatography (hexanes → 30% EtOAc/hexanes) gave **26** (155 mg, 83%; *E/Z*, 8:2) as an inseparable mixture: MS *m/z* 435 (100, MH^+); ^{19}F NMR δ −56.54 (d, $J_{F\text{-}H5}$ = 15.8 Hz, 0.20F, *Z*), −60.98 (d, $J_{F\text{-}H5}$ = 33.1 Hz, 0.80F, *E*). Compound (*E*)-**26** had: ^1H NMR δ 1.35 & 1.38 (2 × s, 2 × 3, 2 × CH_3), 4.69 (d, $J_{2\text{-}1}$ = 3.8 Hz, 1, H2), 5.28 (ddd, $J_{4\text{-}5}$ = 9.8 Hz, $J_{4\text{-}3}$ = 2.9 Hz, $J_{4\text{-}6}$ = 1.6 Hz, 1, H4), 5.45 (d, $J_{3\text{-}4}$ = 3.0 Hz, 1, H3), 5.58 (dd, $J_{5\text{-}F}$ = 33.0 Hz, $J_{5\text{-}4}$ = 8.7 Hz, 1, H5), 5.99 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 7.47-8.06 (m, 5, Ar); ^{13}C NMR δ 26.60 & 27.12 (CMe_2), 74.04 (d, $^3J_{4\text{-}F}$ = 4.4 Hz, C4), 77.88 (C3), 83.73 (C2), 104.74 (C1), 107.89 (d, $^1J_{6\text{-}F}$ = 338.7 Hz, C6), 112.85 (*C*Me_2), 116.80 (d, $^2J_{5\text{-}F}$ = 5.4 Hz, C5), 129.04 (Bz), 129.50 (Bz), 130.18 (Bz), 134.09 (Bz), 165.54 (Bz). Compound (*Z*)-**26** had: ^1H NMR δ 1.35 & 1.68 (2 × s, 2 × 3, 2 × CH_3), 4.71 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H2), 4.84 (dd, $J_{4\text{-}5}$ = 8.7 Hz, $J_{4\text{-}3}$ = 2.7 Hz, 1, H4), 5.48 (d, $J_{3\text{-}4}$ = 3.0 Hz, 1, H3), 5.77 (dd, $J_{5\text{-}F}$ = 15.4 Hz, $J_{5\text{-}4}$ = 8.8 Hz, 1, H5), 6.03 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 7.47-8.06 (m, 5, Ar); ^{13}C NMR δ 26.78 & 27.27 (CMe_2), 77.88 (C3), 80.06 (d, $^3J_{4\text{-}F}$ = 8.2 Hz, C4), 83.84 (C2), 105.04 (C1), 112.94 (d, $^2J_{5\text{-}F}$ = 16.9 Hz, C5), 112.95 (*C*Me_2), 114.78 (d, $^1J_{6\text{-}F}$ = 332.0 Hz, C6), 129.04 (Bz), 129.40 (Bz), 130.18 (Bz), 134.14 (Bz), 165.54 (Bz).

(*E/Z*)-3-*O*-Benzoyl-5,6-dideoxy-6-fluoro-6-iodo-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (27)

Treatment of **24** (250 mg, 0.42 mmol; *E/Z*, 3:2) with NIS (142 mg, 0.63 mmol) as described for **26** gave **27** (155 mg, 85%; *E/Z*, 3:2) as an inseparable mixture: HRMS (AP-FAB) *m/z*: calcd for $C_{16}H_{16}FIO_5Li$ (MLi^+) 441.0181; found 441.0192; ^{19}F NMR δ −56.42 (d, $J_{F\text{-}H5}$ = 15.1 Hz, 0.40F, *Z*), −63.30 (d, $J_{F\text{-}H5}$ = 33.5 Hz, 0.60F, *E*). Compound (*E*)-**27** had: ^1H NMR δ 1.36 & 1.60 (2 × s, 2 × 3, 2 × CH_3), 4.75 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 4.98 (t, $J_{2\text{-}1/3}$ = 4.5 Hz, 1, H2), 5.16 (t, $J_{4\text{-}3/5}$ = 9.0 Hz, 1, H4), 5.49 (dd, $J_{5\text{-}F}$ = 32.7 Hz, $J_{5\text{-}4}$ = 8.7 Hz, 1, H5), 5.89 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.50-8.10 (m, 5, Ar); ^{13}C NMR δ 26.96 & 27.11 (CMe_2), 72.45 (d, $^3J_{4\text{-}F}$ = 4.3 Hz, C4), 76.74 (d, $^4J_{3\text{-}F}$ = 2.1 Hz, C3), 77.32 (C2), 104.39 (C1), 113.78 (*C*Me_2), 114.96 (d, $^1J_{6\text{-}F}$ = 331.5 Hz, C6), 119.90 (d, $^2J_{5\text{-}F}$ = 5.5 Hz, C5), 128.92 (Bz), 129.46 (Bz), 130.50 (Bz), 133.94 (Bz), 166.21 (Bz). Compound (*Z*)-**27** had: ^1H NMR δ 1.38 & 1.64 (2 × s, 2 × 3, 2 × CH_3), 4.72-4.75 (m, 1, H4), 4.84 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 4.98 (t, $J_{2\text{-}3/1}$ = 4.5 Hz, 1, H2), 5.68 (dd, $J_{5\text{-}F}$ = 15.3 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 1, H5), 5.91 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.50-8.14 (m, 5, Ar); ^{13}C NMR δ 26.96 & 27.11 (CMe_2), 76.85 (d, $^4J_{3\text{-}F}$ = 2.1 Hz, C3), 77.63 (C2), 78.13 (d, $^3J_{4\text{-}F}$ = 8.3 Hz, C4), 104.54 (C1), 108.75 (d, $^1J_{6\text{-}F}$ = 339.4 Hz, C6), 113.90 (*C*Me_2), 115.77 (d, $^2J_{5\text{-}F}$ = 16.2 Hz, C5), 128.91 (Bz), 129.49 (Bz), 130.37 (Bz), 133.95 (Bz), 166.21 (Bz).

(*E*)-3-*O*-Benzoyl-5,6-dideoxy-6-iodo-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (28)

Treatment of **25** (150 mg, 0.25 mmol) with NIS (85 mg, 0.38 mmol) as described for **26** gave **28** (93 mg, 87%): ^1H NMR δ 1.35 & 1.62 (2 × s, 2 × 3, 2 × CH_3), 4.67 (dd, $J_{2\text{-}3}$ = 9.2 Hz, $J_{2\text{-}1}$ = 4.6 Hz, 1, H2), 4.77 (dd, $J_{3\text{-}4}$ = 3.4 Hz, $J_{3\text{-}2}$ = 9.2 Hz, 1, H3), 4.97 (t, $J_{4\text{-}3/5}$ = 4.2 Hz, 1, H4), 5.91 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 6.61-6.70 (m, 2, H5/6), 7.49-8.08 (m, 5, Ar); ^{13}C NMR δ 26.95 & 26.96 (CMe_2), 76.37 (C4), 77.59 (C3), 79.61 (C2), 81.32 (C6), 104.43 (C1), 113.68

(*C*Me$_2$), 128.89 (Bz), 129.60 (Bz), 130.94 (Bz), 133.89 (Bz), 141.58 (C5), 166.08 (Bz); MS *m/z* 417 (100, MH$^+$).

Ethyl 3-*O*-Benzoyl-5,6,7,8,9-pentadeoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-dec-5-(*E/Z*)-enofuranuronate (29)

Pd[P(Ph)$_3$]$_4$ (5 mg, 0.004 mmol) was added to a stirred solution of **26** (30 mg, 0.07 mmol; *E/Z*, 4:1) in anhydrous benzene (3 mL) under N_2 at ambient temperature. After 2 minutes, 4-ethoxy-4-oxobutylzinc bromide (0.5M/THF; 0.28 mL, 65 mg, 0.14 mmol) was added and the resulting mixture was heated at 55 °C for 5 h. EtOAc (30 mL) and $NaHCO_3/H_2O$ (10 mL) were added and the separated organic layer was washed with H_2O (10 mL), NaCl/H_2O (10 mL), dried (Na_2SO_4), and then was evaporated. Column chromatography (10 → 30% EtOAc/hexanes) gave (*Z*)-**29** (18 mg, 61%, 76% based on the conversion of the *E*-isomer), (*E*)-**29** (2 mg, 7%, 35% based on the conversion of the *Z*-isomer) and more polar byproduct tentatively assigned as 3-*O*-debenzoylated-(*Z*)-**26** [~5%, TLC; ^{19}F NMR δ −57.21 ($J_{F\text{-}H5}$ = 16.4 Hz)]. Compound (*Z*)-**29** had: ^{1}H NMR δ 1.22 (t, *J* = 7.1 Hz, 3, CH_3), 1.36 & 1.61 (2 × s, 2 × 3, 2 × CH_3), 1.81 ("quint", $J_{8\text{-}7/7'/9/9'}$ = 7.4 Hz, 2, H8/8′), 2.26 (dt, $J_{7\text{-}F}$ = 18.1 Hz, $J_{7\text{-}8/8'}$ = 7.4 Hz, 2, H7/7′), 2.30 (t, $J_{9\text{-}8/8'}$ = 7.4 Hz, 2, H9/9′), 4.09 (q, *J* = 7.1 Hz, 2, CH_2), 4.69 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 4.84 (dd, $J_{5\text{-}F}$ = 35.8 Hz, $J_{5\text{-}4}$ = 8.4 Hz, H5), 5.33 (dd, $J_{4\text{-}5}$ = 8.5 Hz, $J_{4\text{-}3}$ = 2.8 Hz, 1, H4), 5.45 (d, $J_{3\text{-}4}$ = 2.8 Hz, 1, H3), 6.00 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 7.48-8.04, (m, 5, Ar); ^{13}C NMR δ 14.59 (CH_3), 21.49 (C8), 26.64 & 27.11 (C*Me*$_2$), 31.61 (d, $^2J_{7\text{-}F}$ = 25.4 Hz, C7), 33.34 (C9), 60.75 (CH_2), 73.37 (d, $^3J_{4\text{-}F}$ = 6.6 Hz, C4), 77.63 (C2), 78.33 (C3), 100.03 (d, $^2J_{5\text{-}F}$ = 10.9 Hz, C5), 104.78 (C1), 112.60 (*C*Me$_2$), 128.97 (Bz), 129.70 (Bz), 130.16 (Bz), 133.93 (Bz), 162.94 (d, $^1J_{6\text{-}F}$ = 260.7 Hz, C6), 165.61 (Bz), 173.32 (C10); ^{19}F NMR δ −99.93 (dt, $J_{F\text{-}H5}$ = 35.8 Hz, *J* = 18.0 Hz); HRMS (AP-FAB$^+$) *m/z* calcd for $C_{22}H_{27}FO_7Li$ (MLi$^+$) 429.1910; found 429.1900. Compound (*E*)-**29** had: ^{1}H NMR δ 1.28 (t, *J* = 7.1 Hz, 3, CH_3), 1.35 & 1.61 (2 × s, 2 × 3, 2 × CH_3), 1.85-1.95 (m, 2, H8/8′), 2.38 (t, $J_{9\text{-}8/8'}$ = 7.2 Hz, 2, H9/9′), 2.39-2.50 (m, 2, H7/7′), 4.15 (q, *J* = 7.1 Hz, 2, CH_2), 4.69 (d, $J_{2\text{-}1}$ = 3.8 Hz, 1, H2), 4.93 ("dt", $J_{4\text{-}5}$ = 9.3 Hz, $J_{4\text{-}F/3}$ = 2.5 Hz, 1, H4), 5.30 (dd, $J_{5\text{-}F}$ = 18.6 Hz, $J_{5\text{-}4}$ = 9.4 Hz, H5), 5.38 (d, $J_{3\text{-}4}$ = 2.9 Hz, 1, H3), 6.00 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.48-8.04 (m, 5, Ar); ^{19}F NMR δ −94.53 ("q", *J* = 22.1 Hz). HRMS (AP-FAB$^+$) *m/z* calcd for $C_{22}H_{27}FO_7Li$ (MLi$^+$) 429.1910; found 429.1903.

Ethyl 3-*O*-Benzoyl-5,6,7,8,9-pentadeoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*ribo*-dec-5(*E/Z*)-enofuranuronate (30)

Treatment of **27** (42 mg, 0.097 mmol; *E/Z*, 3:2) with Pd[P(Ph)$_3$]$_4$ (22 mg, 0.01 mmol) and 4-ethoxy-4-oxobutylzinc bromide (0.5M/THF; 0.30 mmol, 0.60 mL) as described for **29** followed by column chromatography (10 → 40% EtOAc/hexanes) gave (*Z*)-**30** (22 mg, 54%; 90% based on the conversion of *E*-isomer), (*E*)-**30** (5 mg, 12%; 30% based on the conversion of the *Z*-isomer), and more polar 3-*O*-debenzoylated-(*Z*)-**27** (3 mg, 10%). Compound (*Z*)-**30** had: ^{1}H NMR δ 1.24 (t, *J* = 7.1 Hz, 3, CH_3), 1.37 & 1.60 (2 × s, 2 × 3, 2 × CH_3), 1.84 ("quint", $J_{8\text{-}7/7'/9/9'}$ = 7.4 Hz, 2, H8/8′), 2.25 (dt, $J_{7\text{-}F}$ = 17.6 Hz, $J_{7\text{-}8/8'}$ = 7.5 Hz, 2, H7/7′), 2.32 (t, $J_{9\text{-}8/8'}$ = 7.4 Hz, 2, H9/9′), 4.09 (q, *J* = 7.1 Hz, 2, CH_2), 4.72 (dd, $J_{3\text{-}4}$ = 9.2 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 4.75 (dd, $J_{5\text{-}F}$ = 35.0 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 1, H5), 4.95 (t, $J_{2\text{-}1/3}$ = 4.3 Hz, 1, H2), 5.19 (t, $J_{4\text{-}3/5}$ = 9.1 Hz, 1, H4), 5.89 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.48-8.09 (m, 5, Ar); ^{13}C NMR δ 14.60 (CH_3), 21.45 (C8), 26.95 & 27.00 (C*Me*$_2$), 31.63 (d, $^2J_{7\text{-}F}$ = 26.5 Hz, C7), 33.32 (C9), 60.79 (CH_2), 71.39 (d, $^3J_{4\text{-}F}$ = 6.3 Hz, C4), 77.54 (C2), 73.63 (C3), 103.40 (d, $^2J_{5\text{-}F}$ = 11.8 Hz, C5), 104.39 (C1), 113.52 (*C*Me$_2$), 128.84 (Bz), 129.71 (Bz), 130.33 (Bz), 133.77 (Bz), 164.13 (d, $^1J_{6\text{-}F}$ = 272.7 Hz, C6), 165.33 (Bz), 173.30 (C10); ^{19}F NMR δ −102.14 (dt, $J_{F\text{-}H5}$ = 34.1 Hz, $J_{F\text{-}H7/7'}$ = 17.6 Hz). HRMS (AP-ESI) *m/z* calcd for $C_{22}H_{28}FO_7$ (MH$^+$) 423.1814; found 423.1815. Compound (*E*)-**30** had: ^{1}H NMR δ 1.26 (t, *J* = 7.1 Hz, 3, CH_3), 1.36 & 1.61 (2 × s, 2 × 3, 2 × CH_3), 1.90 ("quint", $J_{8\text{-}7/7'/9/9'}$ = 6.9 Hz, 2, H8/8′), 2.38 (t, $J_{9\text{-}8/8'}$ = 6.9 Hz, 2, H9/9′), 2.50 (dt, $J_{7\text{-}F}$ = 23.0 Hz, $J_{7\text{-}8/8'}$ = 7.3 Hz, 2, H7/7′), 4.14 (q, *J* = 7.1 Hz, 2, CH_2), 4.75-4.80 (m,

2, H3/4), 4.95 (t, $J_{2\text{-}1/3}$ = 4.0 Hz, 1, H2), 5.17 (dd, $J_{5\text{-}F}$ = 19.2 Hz, $J_{5\text{-}4}$ = 8.7 Hz, 1, H5), 5.88 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1), 7.48-8.09 (m, 5, Ar); ^{13}C NMR δ 14.63 (CH_3), 21.99 (C8), 26.92 & 27.00 (C*Me*$_2$), 28.49 (d, $^2J_{7\text{-}F}$ = 27.0 Hz, C7), 33.67 (C9), 60.78 (CH_2), 73.65 (d, $^3J_{4\text{-}F}$ = 14.7 Hz, C4), 77.50 (C2), 77.61 (C3), 104.58 (d, $^2J_{5\text{-}F}$ = 25.8 Hz, C5), 104.37 (C1), 113.39 (*C*Me$_2$), 128.88 (Bz), 129.64 (Bz), 130.25 (Bz), 133.83 (Bz), 165.15 (d, $^1J_{6\text{-}F}$ = 256.5 Hz, C6), 165.99 (Bz), 173.21 (C10); ^{19}F NMR δ - 94.73 ("q", $J_{F\text{-}H5/7/7'}$ = 22.8 Hz). HRMS (AP-ESI) *m/z* calcd for $C_{22}H_{28}FO_7$ (MH^+) 423.1814; found 423.1819. The 3-*O*-debenzoylated-(*Z*)-**27** had: ^{1}H NMR δ 1.27 & 1.58 (2 × s, 2 × 3, 2 × CH_3), 3.82-3.84 (m, 1, H3), 4.18 (t, $J_{4\text{-}3/5}$ = 8.8 Hz, 1, H4), 4.60-4.62 (m, 1, H2), 5.61 (dd, $J_{5\text{-}F}$ = 15.1 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 1, H5), 5.83 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1); ^{13}C NMR δ 26.99 & 27.07 (C*Me*$_2$), 76.63 (C3), 78.56 (C2), 80.47 (d, $^3J_{4\text{-}F}$ = 8.0 Hz, C4), 104.16 (C1), 115.85 (d, $^1J_{6\text{-}F}$ = 344.1 Hz, C6), 113.70 (*C*Me$_2$), 115.85 (d, $^2J_{5\text{-}F}$ = 15.7 Hz, C5); ^{19}F NMR δ −56.50 (d, $J_{F\text{-}H5}$ = 15.1 Hz); MS *m/z* 331 (100, MH^+).

Methyl 5,6,7,8,9-Pentadeoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-dec-5(*Z*)-enofuranuronate (31)

Compound (*Z*)-**29** (26 mg, 0.062 mmol) was dissolved in MeOH (6 mL) and saturated NH_3/MeOH (3 mL) was added at 0 °C (ice bath). The resulting mixture was stirred for 48 h (0 °C → ambient temperature). The volatiles were evaporated and the residue was column chromatographed (15 → 50% EtOAc/hexanes) to give **31** (14 mg, 74%): ^{1}H NMR δ 1.35 & 1.55 (2 × s, 2 × 3, 2 × CH_3), 1.90 (quint, $J_{8\text{-}7/7'/9/9'}$ = 7.2 Hz, 2, H8/8′), 2.23-2.40 (m, 2, H7/7′), 2.41 (t, $J_{9\text{-}8/8'}$ = 7.2 Hz, 2, H9/9′), 3.70 (s, 3, CH_3), 4.17 (d, $J_{3\text{-}4}$ = 2.6 Hz, 1, H3); 4.59 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 4.84 (dd, $J_{5\text{-}F}$ = 37.6 Hz, $J_{5\text{-}4}$ = 7.7 Hz, 1, H5), 5.08 ("dm", $J_{4\text{-}5}$ = 7.6 Hz, 1, H4), 5.95 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1); ^{13}C NMR δ 21.40 (C8), 26.59 & 27.12 (C*Me*$_2$), 31.65 (d, $^2J_{7\text{-}F}$ = 26.6 Hz, C7), 33.29 (C9), 52.08 (CH_3), 75.29 (d, $^3J_{4\text{-}F}$ = 4.9 Hz, C4), 76.74 (d, $^4J_{3\text{-}F}$ = 1.0 Hz, C3), 85.51 (C2), 101.15 (d, $^2J_{5\text{-}F}$ = 11.0 Hz, C5), 104.74 (C1), 112.08 (*C*Me$_2$), 161.86 (d, $^1J_{6\text{-}F}$ = 261.8 Hz, C6), 174.02 (C10); ^{19}F NMR δ −100.23 (dt, $J_{F\text{-}H5}$ = 38.0 Hz, $J_{F\text{-}H7}$ = 18.0 Hz); MS *m/z* 305 (100, MH^+).

Methyl 5,6,7,8,9-Pentadeoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*ribo*-dec-5(*Z*)-enofuranuronate (32)

Saturated NH_3/MeOH (3 mL) was added to a solution of (*Z*)-**30** (26 mg, 0.062 mmol) in MeOH (3 mL) and the mixture was stirred at 0 °C for 48 h to ambient temperature. The volatiles were evaporated and the residue was column chromatographed (15 → 60% EtOAc/hexanes) to give **32** (13 mg, 69%): ^{1}H NMR δ 1.39 & 1.62 (2 × s, 2 × 3, 2 × CH_3), 1.90 (quint, $J_{8\text{-}7/7'/9/9'}$ = 7.3 Hz, 2, H8/8′), 2.31 (dt, $J_{7\text{-}F}$ = 17.6 Hz, $J_{7\text{-}8/8'}$ = 7.4 Hz, 2, H7/7′), 2.40 (t, $J_{9\text{-}8/8'}$ = 6.9 Hz, 2, H9/9′), 3.75 (s, 3, CH_3), 4.56-4.72 (m, 4, H2/3/4/5), 5.82 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H1); ^{13}C NMR δ 21.44 (C8), 26.81 & 26.94 (C*Me*$_2$), 31.74 (d, $^2J_{7\text{-}F}$ = 26.1 Hz, C7), 33.20 (C9), 52.07 (CH_3), 73.94 (d, $^3J_{4\text{-}F}$ = 5.1 Hz, C4), 76.80 (C2), 78.62 (C3), 103.63 (d, $^2J_{5\text{-}F}$ = 11.6 Hz, C5), 104.00 (C1), 113.07 (*C*Me$_2$), 163.91 (d, $^1J_{6\text{-}F}$ = 262.70 Hz, C6), 173.90 (C10); ^{19}F NMR δ -100.23 (dt, $J_{F\text{-}H5}$ = 37.1 Hz, $J_{F\text{-}H7/7'}$ = 18.1 Hz). HRMS (AP-ESI) *m/z* calcd for $C_{14}H_{22}FO_6$ (MH^+) 305.1395; found 305.1396.

Methyl 5,6,7,8,9-Pentadeoxy-6-fluoro-α/β-D-*xylo*-dec-5(*Z*)-enofuranuronate (33)

A solution of **31** (17 mg, 0.056 mmol) in TFA/H_2O (9:1, 3 mL) was stirred for 45 min at 0 °C and was evaporated and coevaporated [toluene (3×), CH_3CN (2×)]. The residue was dissolved in H_2O and the aqueous layer was extracted with ether (2×). The water layer was evaporated to give **33** (9 mg, 61%; α/β, 1:1): ^{1}H NMR (MeOH-d_4) δ 1.81-1.94 (m, 2, H8/8′), 2.27-2.38 (m, 2, H7/7′), 2.38-2.45 (m, 2, H9/9′), 3.67 (m, 3, CH_3), 3.92 (dd, $J_{3\text{-}4}$ = 3.8 Hz, $J_{3\text{-}2}$ = 1.8 Hz, 0.5, H3), 3.97 (dd, $J_{3\text{-}4}$ = 3.9 Hz, $J_{3\text{-}2}$ = 2.6 Hz, 0.5, H3), 4.00-4.04 (m, 1, H2), 4.91 (d, $J_{4\text{-}5}$ = 8.9 Hz, 0.5, H4), 4.99 (d, $J_{4\text{-}5}$ = 9.1 Hz, 0.5, H4), 5.04-5.12 (m, 1, H5), 5.08 (s, 0.5, H1β), 5.37 (d, $J_{1\text{-}2}$ = 4.0 Hz, 0.5, H1α); ^{19}F NMR δ −106.29 (dt, $J_{F\text{-}H5}$ = 37.2 Hz, $J_{F\text{-}H7}$ = 17.6 Hz, 0.5F),

−106.87 (dt, $J_{F\text{-}H5}$ = 37.8 Hz, $J_{F\text{-}H7}$ = 18.2 Hz, 0.5F). HRMS (AP-ESI) *m/z* calcd for $C_{11}H_{18}FO_6$ (MH^+) 265.1082; found 265.1088.

Methyl 5,6,7,8,9-Pentadeoxy-6-fluoro-α/β-D-*ribo*-dec-5(*Z*)-enofuranuronate (34)

A solution of **32** (12 mg, 0.04 mmol) in TFA/H_2O (9:1, 3 mL) was stirred for 30 min at 0 °C and was evaporated and coevaporated [toluene (3×)]. The residue was dissolved in H_2O and the aqueous layer was extracted with ether (2×). The water layer was evaporated to give **34** (8 mg, 76%; α/β, 3:7): ^{1}H NMR (D_2O) δ 1.72-1.76 (m, 2, H8/8′), 2.20 (dt, $J_{7\text{-}F}$ = 18.1 Hz, $J_{7\text{-}8/8'}$ = 8.4 Hz, 2, H7/7′), 2.31-2.38 (m, 2, H9/9′), 3.59 (d, $J_{2\text{-}3}$ = 2.4 Hz, 0.7, H2), 3.82-3.85 (m, 0.3, H2), 3.90-3.93 (s, 0.7, H3), 3.90-4.06 (m, 4.3, H3/H4/CH_3), 4.64-4.77 (m, 1, H5), 5.12 (s, 0.7, H1), 5.28 (d, $J_{1\text{-}2}$ = 3.7 Hz, 0.3, H1); ^{19}F NMR δ −104.06 (dt, $J_{F\text{-}H5}$ = 36.4 Hz, $J_{F\text{-}H7/7'}$ = 17.8 Hz, 0.3, α); −105.04 (dt, $J_{F\text{-}H5}$ = 35.8 Hz, $J_{F\text{-}H7/7'}$ = 18.8 Hz, 0.7F, β). HRMS (AP-ESI) *m/z* calcd for $C_{11}H_{18}FO_6$ (MH^+) 265.1082; found 265.1090.

(*E/Z*)-3,5,6-Trideoxy-6-fluoro-1,2-*O*-isopropylidene-6-phenylsulfonyl-α-D-*erythro*-hex-5-enofuranose (35)

Step (a). Treatment of diacetone 3-deoxyglucose[22] (204 mg, 0.83 mmol) with H_5IO_6 (228 mg, 1.00 mmol), as described for **10** (Step *a*, except no aqueous workup was performed) gave 3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentdialdo-1,4-furanose [~85% pure; ^{1}H NMR δ 9.75 (d, $J_{5\text{-}4}$ = 4.8 Hz, H5)] which was directly used in the next step. Step (b) Treatment of the crude aldehyde with diethyl fluoro(phenylsulfonyl)methylphosphonate[20] (297 mg, 0.96 mmol) and LHMDS (0.96 mL, 0.96 mmol), as described for **20**, gave **35** (150 mg, 48%; *E/Z*, 2:1) as an inseparable mixture of isomers. Compound (*E*)-**35** had: ^{1}H NMR δ 1.30 & 1.47 (2 × s, 2 × 3, 2 × CH_3), 1.71 (ddd, $J_{3\text{-}4}$ = 10.9 Hz, $J_{3\text{-}3'}$ = 15.5 Hz, $J_{3\text{-}2}$ = 4.6 Hz, 1, H3), 2.28 (dd, $J_{3'\text{-}4}$ = 4.5 Hz, $J_{3'\text{-}3}$ = 13.4 Hz, 1, H3′), 4.77 (t, $J_{2\text{-}1/3}$ = 4.0 Hz, 1, H2), 4.93-4.97 (m, 1, H4), 5.85 (d, $J_{1\text{-}2}$ = 3.6 Hz, 1, H1), 6.31 (dd, $J_{5\text{-}F}$ = 32.4 Hz, $J_{5\text{-}4}$ = 7.5 Hz, 1, H5), 7.56-7.97 (m, 5, Ar); ^{13}C NMR δ 26.42 & 27.00 (C*Me*$_2$), 39.25 (d, $^4J_{3\text{-}F}$ = 2.0 Hz, C3), 71.26 (d, $^3J_{4\text{-}F}$ = 2.4 Hz, C4), 80.69 (C2), 105.90 (C1), 112.01 (*C*Me$_2$), 116.77 (d, $^2J_{5\text{-}F}$ = 3.7 Hz, C5), 129.17 (Ph), 129.91 (ph), 135.08 (Ph), 137.22 (Ph), 155.54 (d, $^1J_{6\text{-}F}$ = 301.9 Hz, C6); ^{19}F NMR δ −122.72 (d, $J_{F\text{-}H5}$ = 32.5 Hz, 0.66). Compound (*Z*)-**35** had: ^{1}H NMR δ 1.34 & 1.60 (2 × s, 2 × 3, 2 × CH_3), 1.68 (ddd, $J_{3\text{-}4}$ = 10.5 Hz, $J_{3\text{-}3'}$ = 15.2 Hz, $J_{3\text{-}2}$ = 4.7 Hz, 1, H3), 2.46 (ddd, $J_{3'\text{-}4}$ = 4.6 Hz, $J_{3'\text{-}3}$ = 13.2 Hz, 1, H3′), 4.79 (t, $J_{2\text{-}1/3}$ = 3.9 Hz, 1, H2), 5.71 (ddd, $J_{4\text{-}5}$ = 8.7 Hz, $J_{4\text{-}3}$ = 10.6 Hz, $J_{4\text{-}3'}$ = 4.5 Hz, 1, H4), 5.84-5.85 (m, 1, H1), 5.86 (dd, $J_{5\text{-}F}$ = 20.1 Hz, $J_{5\text{-}4}$ = 8.6 Hz, H5), 7.56-7.97 (m, 5, Ar); ^{19}F NMR δ −114.04 (d, $J_{F\text{-}H5}$ = 20.0 Hz, 0.33); MS *m/z* 329 (100, MH^+).

(*E/Z*)-3,5,6-Trideoxy-6-fluoro-1,2-*O*-isopropylidene-6-tributylstannyl-α-D-*erythro*-hex-5-enofuranose (38)

Treatment of **35** (128 mg, 0.39 mmol) with Bu_3SnH (0.21 mL, 228 mg, 0.78 mmol,) and AIBN (481 mg, 0.29 mmol), as described for **23**, gave **38** (83 mg, 44%; *E/Z*, 1:1): ^{19}F NMR δ −92.83 (d, $J_{F\text{-}H5}$ = 33.9 Hz, 84% of 0.50F, *Z*), −92.83 (ddd, $J_{F\text{-}Sn}$ = 230.4 Hz, $J_{F\text{-}H5}$ = 34.7 Hz, $J_{F\text{-}H4}$ = 5.2 Hz 16% of 0.50F, *Z*), −96.75 (d, $J_{F\text{-}H5}$ = 52.7 Hz, 84% of 0.50F, *E*), −96.75 (ddd, $J_{F\text{-}Sn}$ = 221.1 Hz, $J_{F\text{-}H5}$ = 52.7 Hz, $J_{F\text{-}H4}$ = 4.9 Hz, 16% of 0.50F, *E*); MS *m/z* 479 (100, MH^+, ^{120}Sn), 477 (73, MH^+, ^{118}Sn), 475 (48, MH^+, ^{116}Sn). Compound (*E*)-**38** had: ^{1}H NMR δ 0.98-1.70 (m, 34, 3 × Bu/2 × CH_3/H3), 2.26 (dd, $J_{3'\text{-}4}$ = 4.3 Hz, $J_{3'\text{-}3}$ = 13.4 Hz, 1, H3), 4.45-4.55 (m, 1, H4), 4.75 (t, $J_{2\text{-}1/3}$ = 4.2 Hz, 1, H2), 4.96 (dd, $J_{5\text{-}F}$ = 52.9 Hz, $J_{5\text{-}4}$ = 7.5 Hz, 1, H5), 5.83 (d, $J_{1\text{-}2}$ = 3.8 Hz, 1, H1); ^{13}C NMR δ 10.31 (Bu), 11.00 (Bu), 13.97 (Bu), 27.04 & 27.08 (C*Me*$_2$), 27.50 (Bu), 40.19 (d, $^2J_{3\text{-}F}$ = 1.6 Hz, C3), 71.25 (d, $^3J_{4\text{-}F}$ = 17.3 Hz, C4), 81.06 (C2), 105.47 (C1), 111.41 (*C*Me$_2$), 123.42 (d, $^2J_{5\text{-}F}$ = 3.7 Hz, C5), 174.29 (d, $^1J_{5\text{-}F}$ = 323.5 Hz, C6). Compound (*Z*)-**38** had: ^{1}H NMR δ 0.98-1.70 (m, 34, 3 × Bu/2 × CH_3/H3), 2.11 (dd, $J_{3'\text{-}4}$ = 4.3 Hz, $J_{3'\text{-}3}$ = 13.4 Hz, 1, H3′), 4.73 (t, $J_{2\text{-}1/3}$ = 4.2 Hz, 1, H2), 5.21 (ddd, $J_{4\text{-}5}$ =

7.5 Hz, $J_{4\text{-}3}$ = 4.4 Hz, $J_{4\text{-}3'}$ = 15.2 Hz, 1, H4), 5.81 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 5.84 (dd, $J_{5\text{-}F}$ = 34.2 Hz, $J_{5\text{-}4}$ = 9.2 Hz, 1, H5); ^{13}C NMR δ 10.31 (Bu), 11.00 (Bu), 13.97 (Bu), 27.04 & 27.08 (C*Me*$_2$), 27.50 (Bu), 41.00 (d, $^2J_{3\text{-}F}$ = 1.8 Hz, C3), 74.73 (d, $^3J_{4\text{-}F}$ = 21.7 Hz, C4), 80.83 (C2), 105.69 (C1), 111.17 (*C*Me$_2$), 123.26 (d, $^2J_{5\text{-}F}$ = 8.1 Hz, C5), 177.16 (d, $^1J_{6\text{-}F}$ = 316.5 Hz, C6).

(*E/Z*)-5,6-Dideoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (39)

Step (a). Compound **23** (200 mg, 0.34 mmol; *E/Z*, 7:3) was dissolved in saturated NH_3/MeOH (20 mL) and the resulting solution was stirred overnight at ambient temperature. The volatiles were evaporated to give **36** in quantitative yield of sufficient purity to use in the subsequent reaction. Step (b). Compound **36** (crude from step *a*, 0.34 mmol) was dissolved in NH_3/MeOH (20 mL) and the resulting mixture was heated in a pressure Ace tube at 65 °C for 18 h. The volatiles were evaporated and the residue was column chromatographed (hexanes/EtOAc, 8:2 → 3:7) to give (*E*)-**39** (20 mg, 29% from **23**) and (*Z*)-**39** (33 mg, 48% from **23**). Compound (*E*)-**39** had: ^{1}H NMR δ 1.35 & 1.58 (2 × s, 2 × 3, 2 × CH_3), 1.78 (br s, 1, OH3), 4.32 (d, $J_{3\text{-}4}$ = 2.5 Hz, 1, H3), 4.59 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 4.69 ("dm", $J_{4\text{-}5}$ = 7.0 Hz, 1, H4), 5.53 (ddd, $J_{5\text{-}F}$ = 18.1 Hz, $J_{5\text{-}6}$ = 11.2 Hz, $J_{5\text{-}4}$ = 7.1 Hz, 1, H5), 5.94 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.86 (ddd, $J_{6\text{-}F}$ = 82.9 Hz, $J_{6\text{-}5}$ = 11.2 Hz, $J_{6\text{-}4}$ = 1.0 Hz, 1, H6); ^{13}C NMR δ 26.47 & 27.06 (C*Me*$_2$), 76.48 (d, $^4J_{3\text{-}F}$ = 2.0 Hz, C3), 76.80 (d, $^3J_{4\text{-}F}$ = 12.6 Hz, C4), 85.31 (C2), 104.87 (C1), 106.20 (d, $^2J_{5\text{-}F}$ = 13.7 Hz, C5), 112.25 (*C*Me$_2$), 153.79 (d, $^1J_{6\text{-}F}$ = 262.6 Hz, C6); ^{19}F NMR δ −122.18 (dd, $J_{F\text{-}H5}$ = 17.8 Hz, $J_{F\text{-}H6}$ = 82.9 Hz). Compound (*Z*)-**39** had: 1.35 & 1.54 (2 × s, 2 × 3, 2 × CH_3), 1.81 (br s, 1, OH3), 4.22 (br s, 1, H3), 4.58 (d, $J_{2\text{-}1}$ = 3.7 Hz, 1, H2), 5.07 (ddd, $J_{5\text{-}F}$ = 40.1 Hz, $J_{5\text{-}6}$ = 4.9 Hz, $J_{5\text{-}4}$ = 7.5 Hz, 1, H5), 5.12-5.15 (m, 1, H4), 5.96 (d, $J_{1\text{-}2}$ = 3.7 Hz, 1, H1), 6.63 (dd, $J_{6\text{-}F}$ = 82.7 Hz, $J_{6\text{-}5}$ = 4.8 Hz, $J_{6\text{-}4}$ = 1.2 Hz, 1, H6); ^{13}C NMR δ 26.57 & 27.10 (C*Me*$_2$), 74.49 (d, $^3J_{4\text{-}F}$ = 5.1 Hz, C4), 76.74 (d, $^4J_{3\text{-}F}$ = 1.9 Hz, C3), 85.47 (C2), 104.80 (C1), 106.24 (C5), 112.24 (*C*Me$_2$), 150.20 (d, $^1J_{6\text{-}F}$ = 265.2 Hz, C6); ^{19}F NMR δ −121.02 (dd, $J_{F\text{-}H5}$ = 41.1 Hz, $J_{F\text{-}H6}$ = 83.3 Hz). MS (APCI$^+$) *m/z* 205 (100, MH$^+$). Anal. Calcd for $C_9H_{13}FO_4$ (204.19): C, 52.94; H, 6.42. Found: C, 53.19; H, 6.63.

(*E/Z*)-5,6-Dideoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*ribo*-hex-5-enofuranose (40)

Step (a). Compound **24** (200 mg, 0.34 mmol; *E/Z*, 1:1) was dissolved in NH_3/MeOH (20 mL) and stirred overnight at ambient temperature. The volatiles were evaporated to give **37** in quanitative yield of sufficient purity to use in the subsequent step. Step (b). Treatment of **37** (crude, 0.34 mmol) with NH_3/MeOH (20 mL) at 65 °C, as described for **39**, gave unchanged **37** (17 mg, 10% from **24**; *E/Z*, 2:3) and **40** as separable isomers (*E*; 22 mg, 32% from **24**) and (*Z*; 18 mg, 26% from **24**). Compound (*E*)-**40** had: ^{1}H NMR δ 1.40 & 1.60 (2 × s, 2 × 3, 2 × CH_3), 2.37 (d, $J_{OH3\text{-}3}$ = 10.0 Hz, 1, OH3), 3.70-3.73 (m, 1, H3), 4.12 (t, $J_{4\text{-}5/3}$ = 8.3 Hz, 1, H4), 4.60 (t, $J_{2\text{-}1/3}$ = 4.6 Hz, 1, H2), 5.53 (ddd, $J_{5\text{-}F}$ = 17.1 Hz, $J_{5\text{-}6}$ = 11.2 Hz, $J_{5\text{-}4}$ = 7.8 Hz, 1, H5), 5.84 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H1), 6.82 (ddd, $J_{6\text{-}F}$ = 82.4 Hz, $J_{6\text{-}5}$ = 11.1 Hz, $J_{6\text{-}4}$ = 0.7 Hz, 1, H6); ^{13}C NMR δ 26.75 & 26.84 (C*Me*$_2$), 76.55 (d, $^3J_{4\text{-}F}$ = 17.0 Hz, C4), 76.49 (C3), 78.57 (C2), 104.08 (C1), 109.44 (d, $^2J_{5\text{-}F}$ = 12.9 Hz, C5), 113.11 (*C*Me$_2$), 152.81 (d, $^1J_{6\text{-}F}$ = 262.1 Hz, C6); ^{19}F NMR δ −123.67 (dd, $J_{F\text{-}H5}$ = 17.1 Hz, $J_{F\text{-}H6}$ = 82.5 Hz). Compound (*Z*)-**40** had: 1.40 & 1.60 (2 × s, 2 × 3, 2 × CH_3), 2.39 (d, $J_{OH3\text{-}3}$ = 11.0 Hz, 1, OH3), 3.74 (ddd, $J_{3\text{-}OH3}$ = 10.9 Hz, $J_{3\text{-}4}$ = 8.9 Hz, $J_{3\text{-}2}$ = 5.1 Hz, 1, H3), 4.60 (t, $J_{2\text{-}1/3}$ = 4.5 Hz, 1, H2), 4.70 (t, $J_{4\text{-}3/5}$ = 8.8 Hz, 1, H4), 4.89 (ddd, $J_{5\text{-}F}$ = 40.0 Hz, $J_{5\text{-}6}$ = 4.9 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 1, H5), 5.84 (d, $J_{1\text{-}2}$ = 3.9 Hz, 1, H1), 6.69 (ddd, $J_{6\text{-}F}$ = 82.7 Hz, $J_{6\text{-}5}$ = 4.9 Hz, $J_{6\text{-}4}$ = 0.8 Hz, 1, H6); ^{13}C NMR δ 26.79 & 26.92 (C*Me*$_2$), 73.18 (d, $^3J_{4\text{-}F}$ = 5.1 Hz, C4), 76.74 (d, $^4J_{3\text{-}F}$ = 2.0 Hz, C3), 78.58 (C2), 104.20 (C1), 108.69 ($^2J_{5\text{-}F}$ = 1.9 Hz, C5), 113.17 (*C*Me$_2$), 153.71 (d, $^1J_{6\text{-}F}$ = 265.8Hz, C6); ^{19}F NMR δ −123.90 (dd, $J_{F\text{-}H5}$ = 40.1 Hz, $J_{F\text{-}H6}$ = 82.6 Hz): MS (APCI$^+$) *m/z* 205 (100, MH$^+$). Anal. Calcd for $C_9H_{13}FO_4$ (204.19): C, 52.94; H, 6.42. Found: C, 53.07; H, 6.67.

(*E/Z*)-3,5,6-Trideoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-*erythro*-hex-5-enofuranose (41)

Treatment of **38** (100 mg, 0.21 mmol; *E/Z*, 1:1) with NH_3/MeOH (15 mL) and C_sF (51 mg, 0.33 mmol) at 65 °C for 4 h, as described for **39** (Step b), gave **41** (16 mg, 40%; *E/Z*, ~45:55): ^{19}F NMR δ −124.79 (dd, $J_{F\text{-}H5}$ = 41.8 Hz, $J_{F\text{-}H6}$ = 83.0 Hz, 0.55F), −125.95 (dd, $J_{F\text{-}H5}$ = 16.7 Hz, $J_{F\text{-}H6}$ = 82.9 Hz, 0.45F); MS (APCI$^+$) *m/z* 189 (100, MH$^+$). Compound (*E*)-**41** had: ^{1}H NMR δ 1.35 & 1.55 (2 × s, 2 × 3, 2 × CH_3), 1.55-1.68 (m, 1, H3), 2.20 (dd, $J_{3'\text{-}3}$ = 13.5 Hz, $J_{3'\text{-}4}$ = 4.3 Hz, 1, H3′), 4.62 (ddd, $J_{4\text{-}3}$ = 11.5 Hz, $J_{4\text{-}5}$ = 8.2 Hz, $J_{4\text{-}3'}$ = 4.3 Hz, 1, H4), 4.75-4.79 (m, 1, H2), 5.42 (ddd, $J_{5\text{-}F}$ = 16.8 Hz, $J_{5\text{-}6}$ = 11.2 Hz, $J_{5\text{-}4}$ = 8.3 Hz, 1, H5), 5.82-5.84 (m, 1, H1), 6.80 (dd, $J_{6\text{-}F}$ = 82.7 Hz, $J_{6\text{-}5}$ = 11.2 Hz, 1, H6). Compound (*Z*)-**41** had: 1.28 & 1.57 (2 × s, 2 × 3, 2 × CH_3), 1.55-1.68 (m, 1, H3), 2.28 (dd, $J_{3'\text{-}3}$ = 13.5 Hz, $J_{3'\text{-}4}$ = 4.3 Hz, 1, H3′), 4.75-4.79 (m, 1, H2), 4.92 (ddd, $J_{5\text{-}F}$ = 41.3 Hz, $J_{5\text{-}4}$ = 8.1 Hz, $J_{5\text{-}6}$ = 4.8 Hz, 1, H5), 5.13 (ddd, $J_{4\text{-}3}$ = 11.5 Hz, $J_{4\text{-}5}$ = 8.0 Hz, $J_{4\text{-}3'}$ = 4.1 Hz, 1, H4), 5.82-5.84 (m, 1, H1), 6.53 (dd, $J_{6\text{-}F}$ = 82.8 Hz, $J_{6\text{-}5}$ = 4.8 Hz, 1, H6).

(*E*)-5,6-Dideoxy-6-fluoro-α/β-D-*xylo*-hex-5-enofuranose (42)

A solution of (*E*)-**39** (13 mg, 0.064 mmol) in TFA/H_2O (9:1; 3 mL) was stirred for 50 min at 0 °C (ice bath). The volatiles were evaporated, coevaporated [toluene (3×) and MeCN (2×)], and the residue was flash column chromatographed (50 → 95% EtOAc/hexanes) to give **42** (4 mg, 38%; α/β, 1:1): ^{1}H NMR (MeOH-d_4) δ 3.91-4.03 (m, 2 H2/3), 4.56-4.63 (m, 1, H4), 5.07 (s, 0.5, H1β), 5.37 (d, $J_{1\text{-}2}$ = 4.0 Hz, 0.5, H1α), 5.51 (ddd, $J_{5\text{-}F}$ = 17.8 Hz, $J_{5\text{-}6}$ = 11.2 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 0.5, H5), 5.65 (ddd, $J_{5\text{-}F}$ = 17.9 Hz, $J_{5\text{-}6}$ = 11.1 Hz, $J_{5\text{-}4}$ = 8.9 Hz, 0.5, H5), 6.87 (dd, $J_{6\text{-}F}$ = 84.0 Hz, $J_{6\text{-}5}$ = 11.0 Hz, 0.5, H6), 6.90 (dd, $J_{6\text{-}F}$ = 83.7 Hz, $J_{6\text{-}5}$ = 11.0 Hz, 0.5, H6); ^{13}C NMR (MeOH-d_4) δ 75.29 (d, $^3J_{4\text{-}F}$ = 13.8 Hz, C4), 77.00 & 77.20 (C3), 77.73 (C2), 78.17 (d, $^3J_{4\text{-}F}$ = 13.7 Hz, C4), 81.26 (C2), 96.72 (C1α), 103.17 (C1β), 108.71 (d, $^2J_{5\text{-}F}$ = 12.0 Hz, C5), 109.32 (d, $^2J_{5\text{-}F}$ = 11.7 Hz, C5), 152.14 (d, $^1J_{6\text{-}F}$ = 258.7 Hz, C6), 152.24 (d, $^1J_{6\text{-}F}$ = 259.2 Hz, C6); ^{19}F NMR (MeOH-d_4) δ - 126.55 (dd, $J_{F\text{-}H5}$ = 17.8 Hz, $J_{F\text{-}6}$ = 83.9 Hz, 0.5F), −126.85 (dd, $J_{F\text{-}H5}$ = 18.1 Hz, $J_{F\text{-}H6}$ = 84.0 Hz, 0.5F); MS (APCI$^-$) *m/z* 163 (100, MH$^-$).

Analogous treatment of **39** (*E/Z*, 1:1; 20 mg, 0.040 mmol) gave **42** (5 mg, 76%) as a mixture (*E/Z*, ~1:1; α/β, ~1:1). Compound (*E/Z*)-**37** had: ^{19}F NMR (MeOH-d_4) δ −126.55 (dd, $J_{F\text{-}H5}$ = 17.3 Hz, $J_{F\text{-}H6}$ = 84.0 Hz; *E*, 0.25, β), −126.85 (dd, $^3J_{F\text{-}H5}$ = 17.5 Hz, $^2J_{F\text{-}H6}$ = 84.0 Hz; *E*, 0.25, β), −127.66 (dd, $J_{F\text{-}H5}$ = 41.5 Hz, $J_{F\text{-}H6}$ = 84.9 Hz; *Z*, 0.25, β), −128.34 (dd, $J_{F\text{-}H5}$ = 42.2 Hz, $J_{F\text{-}H6}$ = 84.8 Hz; *Z*, 0.25, α); MS(APCI$^-$) *m/z* 163 (100, MH$^-$).

Treatment of the crude **36** [from step (a) for the preparation of **39**] with TFA/H_2O (1 h, 0 °C) followed by evaporation, coevaporation [toluene (2×) and MeCN (1×)], partition (H_2O/ethyl ether), and evaporation of the aqueous layer also gave **42** (55% from **23**, α/β, 1:1).

(*E*)-5,6-Dideoxy-6-fluoro-α/β-D-*ribo*-hex-5-enofuranose (43)

Treatment of (*E*)-**40** (13 mg, 0.064 mmol) with TFA/H_2O (9:1, 3 mL), as described for **42**, gave **43** (7 mg, 67%; α/β, 1:4): ^{1}H NMR (MeOH-d_4) δ 3.77 (t, $J_{3\text{-}2/4}$ = 6.1 Hz, 0.2, H3), 3.87 (d, $J_{2\text{-}1}$ = 4.5 Hz, 0.8, H2), 4.01-4.05 (m, 1, H2α & H3β), 4.20 (t, $J_{4\text{-}3/5}$ = 8.0 Hz, 0.8, H4), 4.30 (dd, $J_{4\text{-}5}$ = 8.2 Hz, $J_{4\text{-}3}$ = 6.4 Hz, 0.2, H4), 5.12 (br s, 0.8, H1), 5.28 (d, $J_{1\text{-}2}$ = 4.1 Hz, 0.2, H1), 5.42 (ddd, $J_{5\text{-}F}$ = 17.5 Hz, $J_{5\text{-}6}$ = 11.1 Hz, $J_{5\text{-}4}$ = 8.3 Hz, 0.2, H5), 5.49 (ddd, $J_{5\text{-}F}$ = 17.6 Hz, $J_{5\text{-}6}$ = 11.1 Hz, $J_{5\text{-}4}$ = 8.5 Hz, 0.8, H5), 6.86 (dd, $J_{6\text{-}F}$ = 83.9 Hz, $J_{6\text{-}5}$ = 11.1 Hz, 0.8, H6), 6.87 (dd, $J_{6\text{-}F}$ = 83.7 Hz, $J_{6\text{-}5}$ = 11.0 Hz, 0.2, H6); ^{13}C NMR (MeOH-d_4) δ 70.90 (C2α), 75.32 (d, $^4J_{3\text{-}F}$ = 2.6 Hz, C3α), 75.5 (d, $^4J_{3\text{-}F}$ = 2.5 Hz, C3β), 76.13 (C2β), 77.55 (d, $^3J_{4\text{-}F}$ = 13.6 Hz, C4α), 77.88 (d, $^3J_{4\text{-}F}$ = 13.7 Hz, C4β), 96.63 (C1α), 102.09 (C1β), 111.19 (d, $^2J_{5\text{-}F}$ = 11.4 Hz, C5α), 112.65 (d, $^2J_{5\text{-}F}$ = 10.6 Hz, C5β), 151.98 (d, $^1J_{6\text{-}F}$ = 258.6 Hz, C6β), 152.17 (d, $^1J_{6\text{-}F}$ = 258.7 Hz, C6α); ^{19}F NMR (MeOH-d_4) δ −128.55 (dd, $J_{F\text{-}H5}$ = 17.4 Hz, $J_{F\text{-}H6}$ = 83.5 Hz, 0.2F, α), −129.00 (dd, $J_{F\text{-}H5}$ = 17.3 Hz, $J_{F\text{-}H6}$ = 83.7 Hz, 0.8F, β); MS (APCI$^-$) *m/z* 163 (100, MH$^-$).

Analogous treatment of **40** (*E/Z*, 1:1; 16 mg, 0.032 mmol) gave **43** (3 mg, 57%) as a mixture (*E/Z*, ~3:1; α/β, ~1:4 for *E* isomer and α/β, ~1:15 for *Z* isomer): ^{19}F NMR (MeOH-d_4) δ −128.01 (dd, $J_{F\text{-}H5}$ = 41.3 Hz, $J_{F\text{-}H6}$ = 83.4 Hz; *Z*, 0.02F, α) −128.55 (dd, $J_{F\text{-}H5}$ = 17.6 Hz, $J_{F\text{-}H6}$ = 84.2 Hz; *E*, 0.14F, α), −129.00 (dd, $J_{F\text{-}H5}$ = 17.5 Hz, $J_{F\text{-}H6}$ = 83.8 Hz; *E*, 0.60F, β), −129.69 (dd, $J_{F\text{-}H5}$ = 40.8 Hz, $J_{F\text{-}H6}$ = 84.4 Hz; *Z*, 0.24F, β); MS(APCI$^-$) *m/z* 163 (100, MH$^-$).

Treatment of the crude **37** [from step (a) for the preparation of **40**] with TFA/H^{2}O (1 h, 0 °C) followed by evaporation, coevaporation [toluene (2×) and MeCN (1×)], partition (H_2O/ethyl ether), and evaporation of the aqueous layer also gave **43** (45% from **24**, α/β, 1:3).

(*E/Z*)-3,5,6-Trideoxy-6-fluoro-α-D-*erythro*-hex-5-enofuranose (44)

Treatment of **38** (62 mg, 0.13 mmol; *E/Z*, 3:2) with TFA/H_2O (9:1, 1mL; 1 h, 0 °C) followed by evaporation, coevaporation [toluene (2×) and MeCN (1×)], partition (H_2O/ethyl ether), and evaporation of the aqueous layer gave **44** (10 mg, 52%; *E/Z* ~1:3, α/β, ~1:4): ^{1}H NMR (D_2O) δ 1.85-2.10 (m, 2, H3,3'), 4.05-4.25 (m, 1, H2), 4.58-4.75 (m, 1, H4), 4.86 (ddd, $J_{5\text{-}F}$ = 41.7 Hz, $J_{5\text{-}4}$ = 8.9 Hz, $J_{5\text{-}6}$ = 4.7, Hz, 0.15, H5), 4.92 (ddd, $J_{5\text{-}F}$ = 41.6 Hz, $J_{5\text{-}4}$ = 8.9 Hz, $J_{5\text{-}6}$ = 4.7 Hz, 0.6, H5), 5.12 (s, 0.15, H1β), 5.13 (s, 0.6, H1β), 5.24 (d, $J_{1\text{-}2}$ = 3.5 Hz, 0.05, H1α), 5.25 (d, $J_{1\text{-}2}$ = 3.8 Hz, 0.2, H1α), 5.39 (ddd, $J_{5\text{-}F}$ = 17.4 Hz, $J_{5\text{-}6}$ = 11.2 Hz, $J_{5\text{-}4}$ = 9.3 Hz, 0.2, H5), 5.45 (ddd, $J_{5\text{-}F}$ = 17.6 Hz, $J_{5\text{-}6}$ = 11.1 Hz, $J_{5\text{-}4}$ = 9.1 Hz, 0.05, H5), 6.52 (ddd, $J_{6\text{-}F}$ = 83.7 Hz, $J_{6\text{-}5}$ = 4.7 Hz, $J_{6\text{-}4}$ = 1.0 Hz, 0.15, H6), 6.55 (dd, $J_{6\text{-}F}$ = 83.7 Hz, $J_{6\text{-}5}$ = 4.7 Hz, $J_{6\text{-}4}$ = 1.0, 0.60, H6), 6.77 (dd, $J_{6\text{-}F}$ = 83.9 Hz, $J_{6\text{-}5}$ = 10.7 Hz, 0.05, H6), 6.78 (dd, $J_{6\text{-}F}$ = 83.9 Hz, $J_{6\text{-}5}$ = 11.0 Hz, 0.20, H6); ^{19}F NMR (D_2O) δ −126.35 (dd, $J_{F\text{-}H5}$ = 17.3 Hz, $J_{F\text{-}H6}$ = 83.6 Hz; *E*, 0.20F, β), −126.45 (dd, $J_{F\text{-}H5}$ = 17.2 Hz, $J_{F\text{-}H6}$ = 82.8 Hz; *E*, 0.05F, α), −126.81 (dd, $J_{F\text{-}H5}$ = 42.0 Hz, $J_{F\text{-}H6}$ = 83.7 Hz; *Z*, 0.15F, α), −127.55 (dd, $J_{F\text{-}H5}$ = 42.0 Hz, $J_{F\text{-}H6}$ = 83.8 Hz; *Z*, 0.60F, β); HRMS (LCT-ESI) *m/z*: calcd for $C_6H_9FO_3$ [M + Na]$^+$ 171.0433; found 171.0434.

Analogous treatment of **41** (10 mg, 0.053 mmol; *E/Z*, ~45:55) with TFA/H_2O gave **44** (5 mg, 64%; *E/Z* ~1:2, α/β ~1:3).

Enzymatic assay

Inhibition assays were performed in a buffer containing 50 mM HEPES (pH 7.0), 150 mM NaCl, 150 μM 5,5′-dithio-bis-(2-nitrobenzoic acid),[23] and various concentrations of SRH (0–55 μM) and inhibitors (0–1 mM). The reactions were initiated by the addition of Co^{2+}-substituted LuxS from *Bacillus subtilis* (final concentration 0.4–0.5 μM) and monitored continuously at 412 nm (ε = 14150 M^{-1} cm^{-1}) in a Perkin-Elmer λ25 UV-VIS spectrophotometer at room temperature. The initial rates recorded from the early regions of the progress curves were fitted into the Lineweaver-Burk equation $1/V = K_M'/(k\text{cat}\ [E]_0) \times 1/[S] + 1/(k\text{cat}\ [E]0)$ and the Michaelis-Menten equation $V = k\text{cat}\ [E]0\ [S]/(K_M' + [S])$ using KaleidaGraph 3.5 to determine the inhibition pattern. K_I values were calculated from the equation $K_M' = K_M \times (1 + [I]/K_I)$, where K_M = 2.2 μM.

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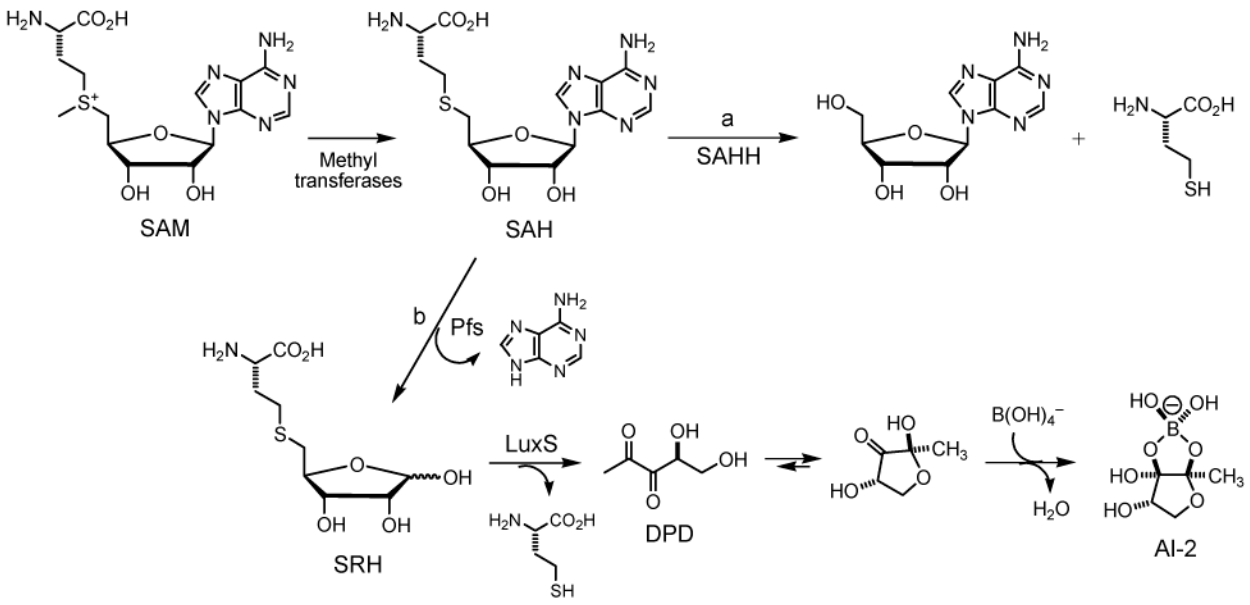


Figure 1.
Reaction pathways for SAH detoxification in eukaryotes (a) and the majority of bacteria (b). The latter is also utilized by the bacteria to produce the type 2 autoinducer.

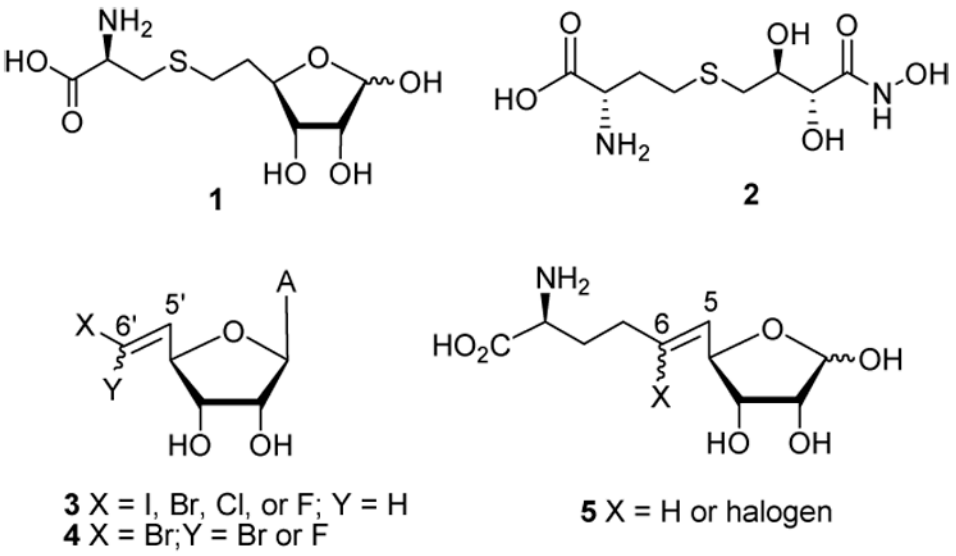


Figure 2.

Inhibitors of LuxS enzyme (**1**, **2**).[4e,h] 5′-Deoxy-5′-(halomethylene)adenosine analogues (**3**, **4**) which serve as suicide substrates for SAH hydrolase[8] and targeted SRH analogues (**5**) in which the sulfur and C5 atoms are replaced by a vinyl unit.

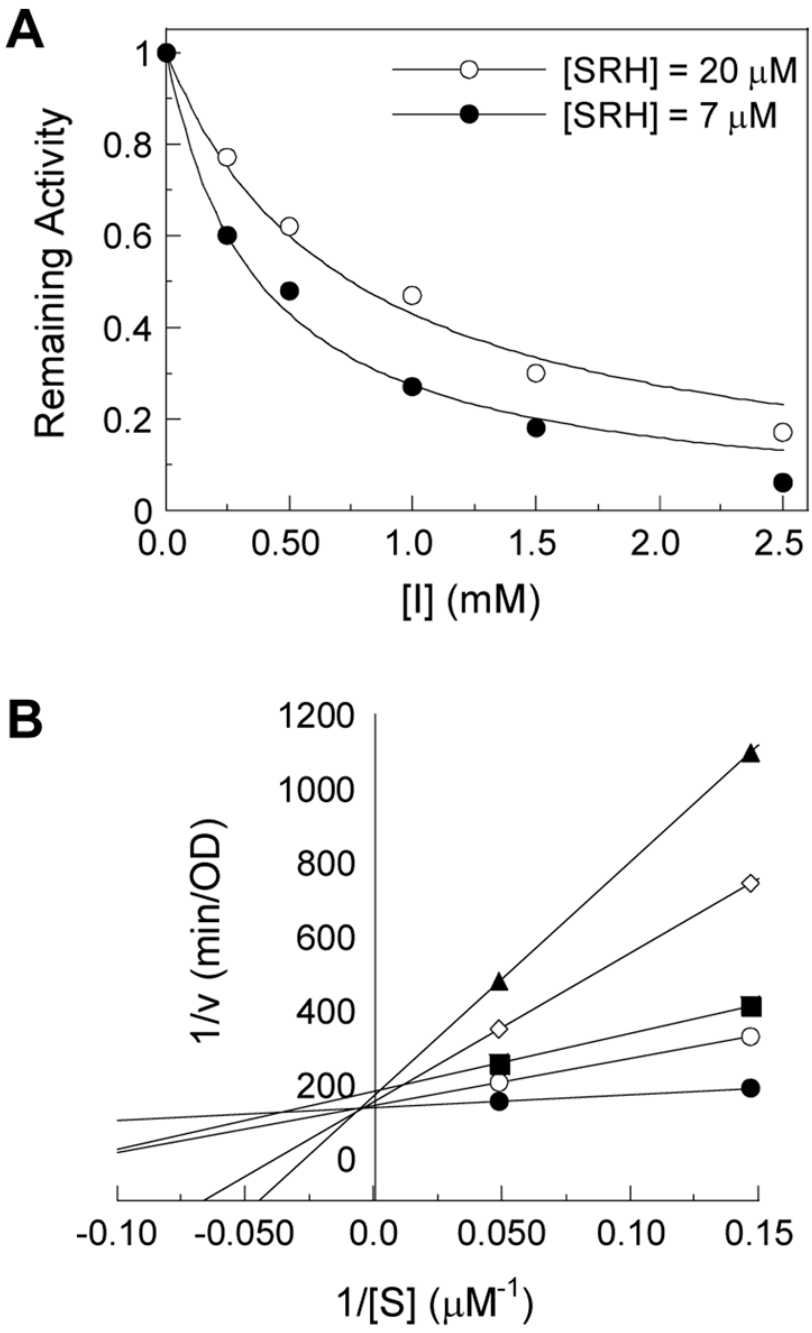
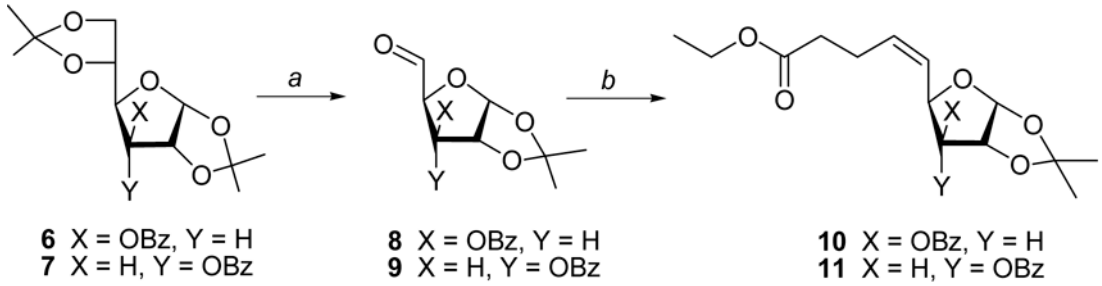
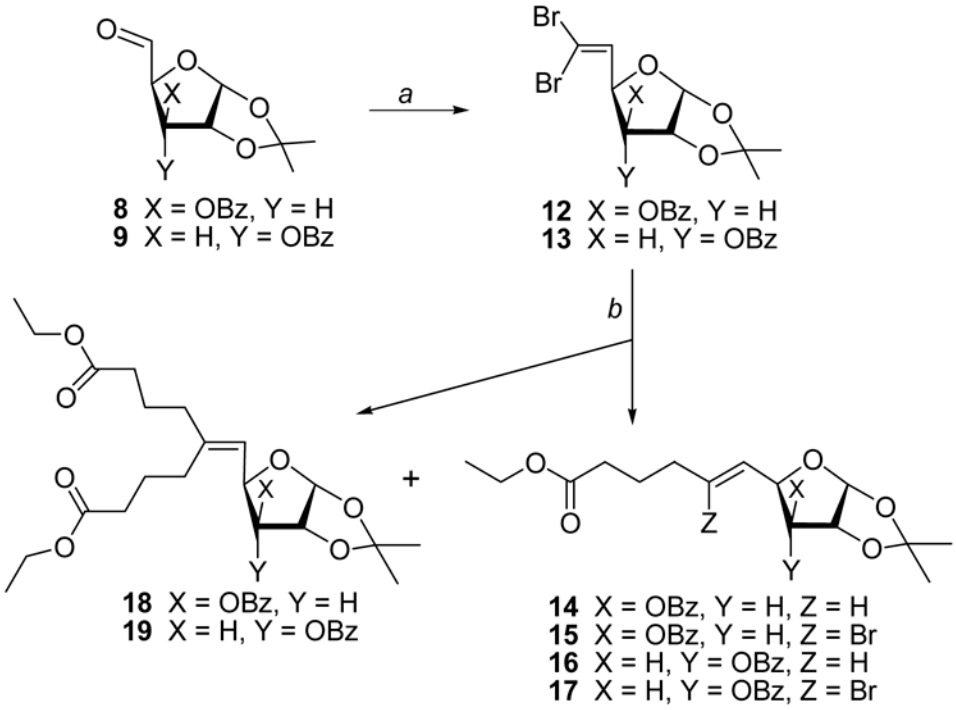


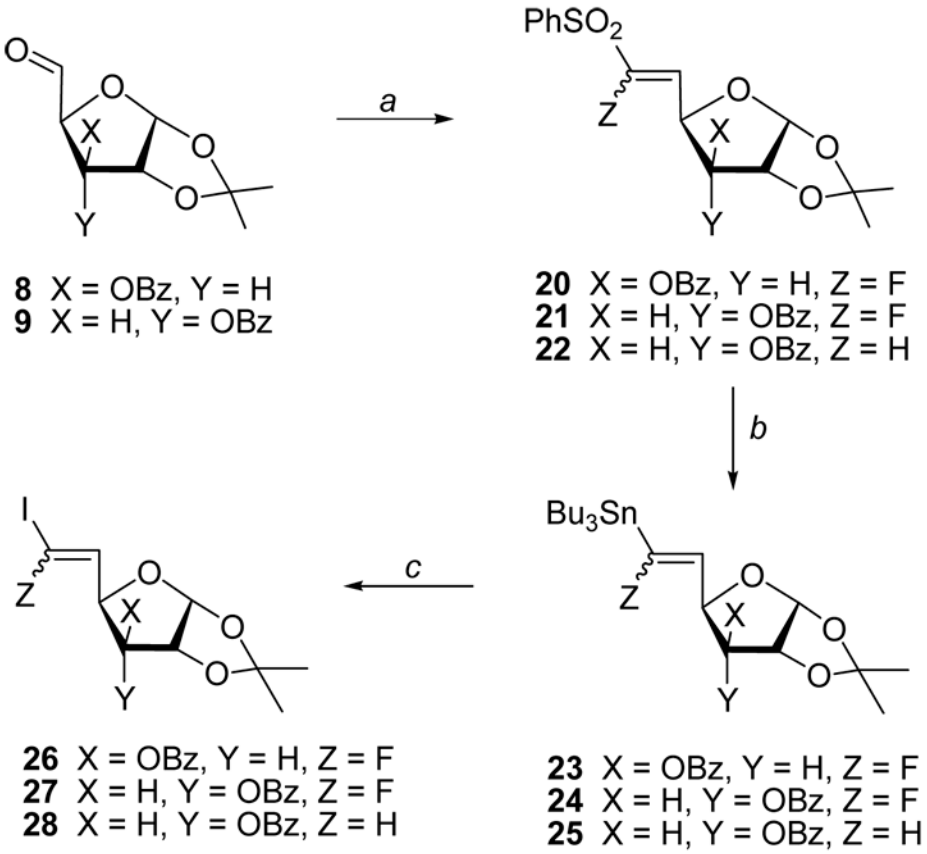
Figure 3.
Inhibition of Co^{2+}-substituted *B. subtilis* LuxS by compound **44**. (A) Plot of remaining LuxS activity (relative to that in the absence of inhibitor) as a function of [I]. (B) Lineweaver-Burke plot of data from part A to show the competitive inhibition mode.



Scheme 1.
(*a*) H_5IO_6/EtOAc; (*b*) $Ph_3PCH_2CH_2CH_2CO_2Et$/HMDS/THF.

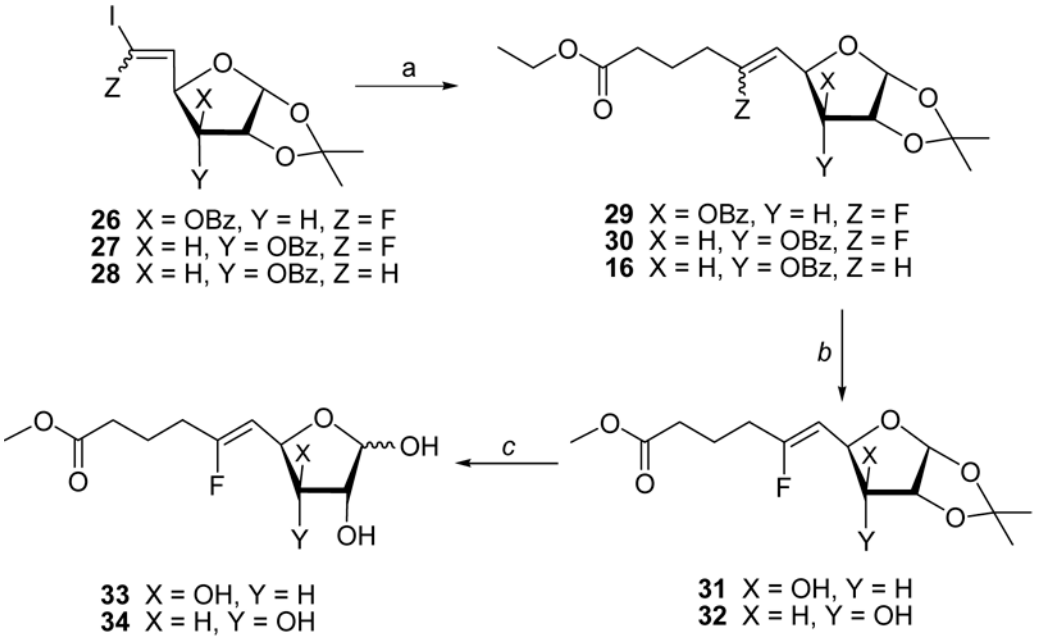


Scheme 2.
(*a*) PPh_3/CBr_4; (*b*) $BrZn(CH_2)_3CO_2Et/Pd(PPh_3)_4$/benzene/Δ



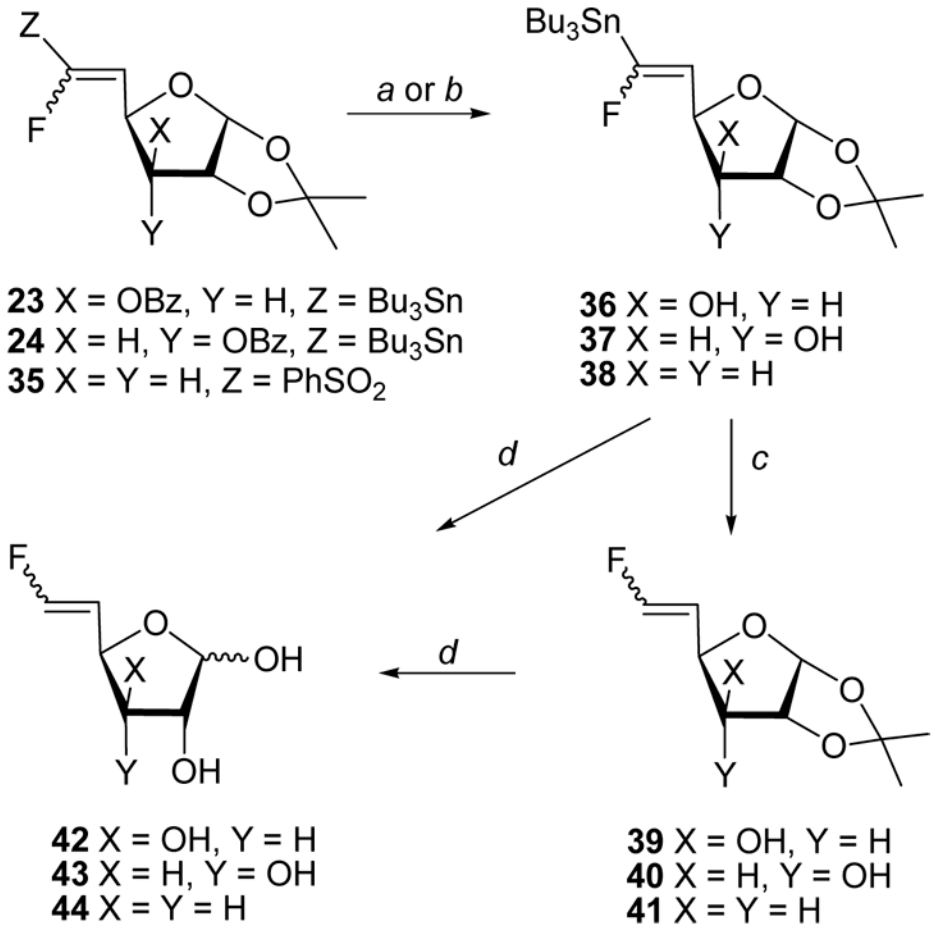
Scheme 3.

(*a*) $PhSO_2CHFPO(OEt)_2$ or $PhSO_2CH_2PO(OEt)_2$/LHMDS/THF/-78 °C; (*b*) Bu_3SnH/AIBN/toluene/85 °C; (*c*) NIS/CH_2Cl_2



Scheme 4.

(*a*) $BrZn(CH_2)_3CO_2Et/Pd(PPh_3)_4$/benzene/Δ; (*b*) NH_3/MeOH; (*c*) TFA/H_2O



Scheme 5.

(*a*) NH_3/MeOH/25 °C; (*b*) Bu_3SnH/AIBN/toluene/85 °C;(*c*) NH_3/MeOH/65 °C or NH_3/MeOH/CsF/65 °C; (d) TFA/H_2O