Pergamon

Tetrahedron 56 (2000) 5303–5310

TETRAHEDRON

Application of Oxazolidinone α-Fluoro Amide Chiral Building Blocks in the Asymmetric Synthesis of Fluorinated Carbohydrates: 2-Deoxy-2-fluoropentoses

Franklin A. Davis,* Hongyan Qi and Gajendran Sundarababu

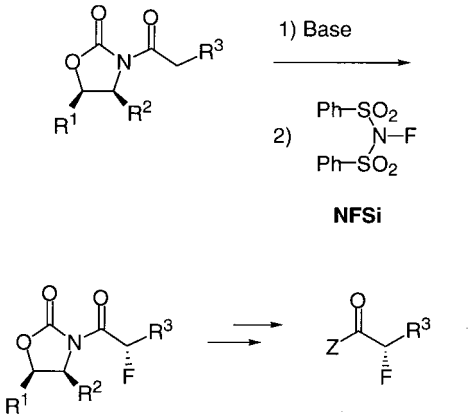
Department of Chemistry, Temple University, Philadelphia, PA 19122, USA

Received 21 April 2000; revised 23 May 2000; accepted 24 May 2000

Abstract—Deconjugative electrophilic fluorination of the lithium dienolate of *Z*-α,β-unsaturated imide (+)-**9** with *N*-fluorobenzenesulfonimide (**NFSi**) afforded the *E*-β,γ-unsaturated α-fluoro imide (+)-**10** as a single diastereoisomer. Dihydroxylation resulted in the formation of 2-fluoro-2-deoxy-γ-xylonic and -lyxonic lactones, **12a** and **12b**, respectively. Reduction and deprotection of the lactones afforded 2-deoxy-2-fluoro-xylo-D-pyranose (**15**) and 2-deoxy-2-fluoro-lyxo-L-pyranose (**17**).

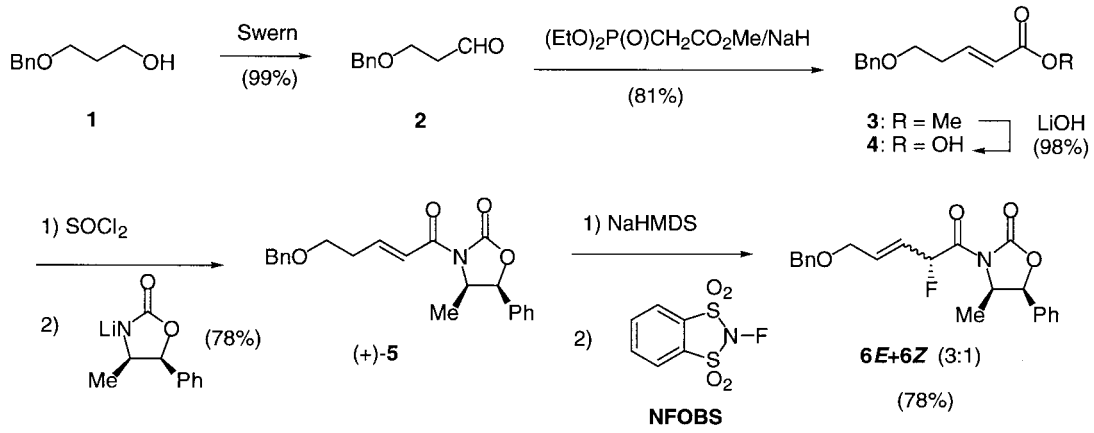
The strategic placement of fluorine in bioactive molecules is of considerable current interest because of the beneficial influence this element often has on physical, chemical and biological properties.[1–3] This is particularly true of carbohydrates where replacement of hydroxy by fluorine effects the acidity, basicity and overall reactivity of neighboring groups due to its extreme electronegativity. Since the van der Waal's radius of fluorine (1.47 Å) is not much different than oxygen (1.57 Å) only a minor steric perturbation on the sugar's geometry is expected.[4] However, replacement of hydroxyl by fluorine removes a hydrogen bond donor site while leaving intact a potential hydrogen bond acceptor site.[5,6] For these reasons fluorinated carbohydrates (deoxyfluorosugars) have proven to be useful probes of biochemical processes,[7] as diagnostic agents[8] and as potential antiviral and antitumor drugs.[7,9] Usually deoxyfluorosugars are prepared from carbohydrate substrates via multistep procedures which require tedious protection/deprotection chemistry as well as functionalization of the sugar prior to fluorination.[10,11] Furthermore, controlling the stereochemistry at adjacent stereocenters is often problematic. In this context the asymmetric synthesis of fluorinate carbohydrates from non-carbohydrates precursors[12] and, in particular, from α-fluoro carbonyl compounds offers significant potential for avoiding the limitations associated with carbohydrate precursors.

Nonracemic α-fluoro carbonyl compounds are useful intermediates for the asymmetric synthesis of fluoro organic compounds and have been prepared by a variety of means.[13,14] A particularly attractive method is the use of oxazolidone α-fluoro amides first introduced by us in 1992.[15] These building blocks are prepared in a highly stereodefined manner because the commercially available electrophilic fluorinating reagent, *N*-fluorobenzenesulfonimide (**NFSi**), approaches the *N*-aceyloxazolidinone enolate from the least hindered direction.[16,17] These building blocks have been used in asymmetric syntheses of α-fluoro aldehydes,[18–20] α-fluoro ketones,[16] β-fluoro hydrins,[15] and α-fluoro esters.[21] In this paper we report methodologies for the stereoselective synthesis of fluorinated carbohydrates from oxazolidone α-fluoro amides and details of the asymmetric synthesis of 2-deoxy-2-fluorpentoses.[22] This strategy involves the use of an appropriately substituted enantiopure β,γ-unsaturated α-fluoro carbonyl compound followed by dihydroxylation and cyclization to the deoxyfluorosugar.



Keywords: asymmetric synthesis; carbohydrates; fluorine compounds.
* Corresponding author. Tel.: +1-215-204-0477; fax: +1-215-204-0478; e-mail: fdavis@astro.ocis.temple.edu

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00444-0

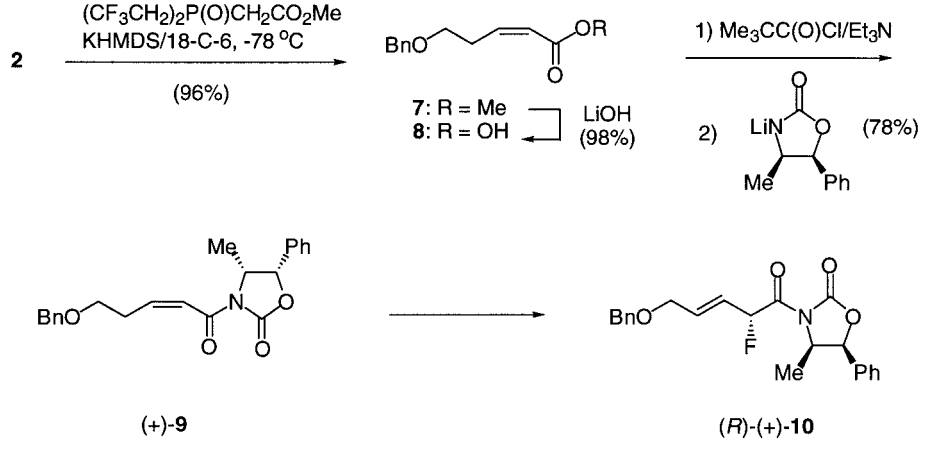


Scheme 1.

Results and Discussion

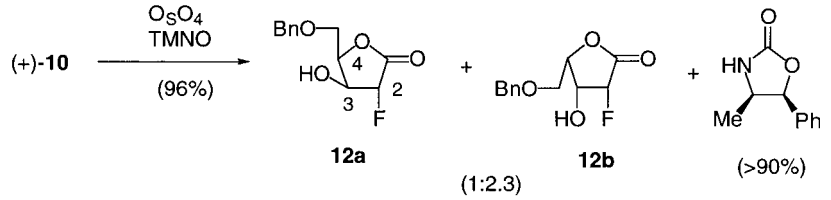
Our deoxyfluorosugar synthesis begins with 3-benzyloxy-1-propionaldehyde (**2**), prepared by Swern oxidation[23] of commercially available benzyloxy-1-propanol (**1**) in nearly quantitative yield (Scheme 1). Treatment of **2** with the ylide of triethyl phosphonoacetate in a Wadsworth–Horner–Emmons reaction afforded the *E*-α,β-unsaturated ester **3** in 81% yield following chromatography. Hydrolysis of **3** with LiOH[24] gave **4** (98% yield) which was converted to the acid chloride and treated with the lithium salt of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone. The *E*-α,β-conjugated chiral imide (+)-**5** was obtained in 78% yield. Deconjugative electrophilic fluorination of the sodium dienolate ion of (+)-**5** with *N*-fluorobenzenesulfonimide (**NFOBS**) at −78°C gave the α-fluoro β,γ-unsaturated amide **6** as an inseparable 3:1 mixture of *E*/*Z* isomers in 78% yield. Similar results were described by Kende and Toder for the alkylation of *E*-dienolate ions.[25] However these workers reported that alkylations of *Z*-dienolate ions were highly stereospecific, leading to *E*-3-alkenoate esters.

The *Z*-α,β-conjugated imide (+)-**9** was prepared as outlined in Scheme 2 and makes use of the Still modification of the Wittig reaction.[26] This procedure involves the reaction of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate with KHMDS/18-crown-6 to generate the ylide which on treatment with aldehyde **1** gave *Z*-**7** in 94% yield. A small amount of the *E*-alkene (<5%) was removed in the purification step. Attempts to convert acid **8** into the corresponding acid chloride with $SOCl_2$ resulted in complex mixtures and it was, therefore, converted into the pivaloyl anhydride with pivaloyl chloride.[11] The pivaloyl anhydride, without isolation, was transformed into (+)-**9** in 78% yield as described above. Deprotonation of (+)-**9** by NaHMDS followed by fluorination of the resulting dienolate with **NFOBS** afforded the *E*-α-fluoro imide **10** as the only product in 82% de and 78% yield. When LiHMDS was



Base	[F+]	% Yield (% De)
NaHMDS	**NFOBS**	78 (82)
LiHMDS	**NFOBS**	80 (88)
LiHMDS	**NFSi**	76 (>97)

Scheme 2.



Scheme 3.

used as the base the de improved to 88%. Significantly, fluorination of the lithium enolate of (+)-**9** with **NFSi** gave (2*R*)-**10** as a single diastereoisomer in 76% yield. The improved diastereoselectivity of **NSFi** compared to **NFOBS** is attributed to the greater steric bulk of the former reagent.

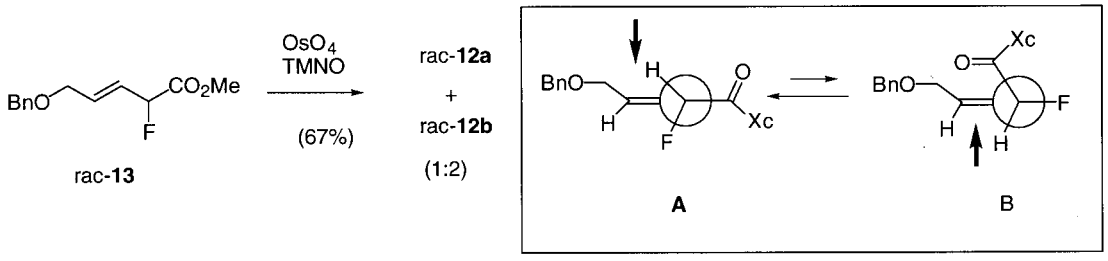
Dihydroxylation of (+)-**10** using a catalytic amount of osmium tetroxide with triethyl amine *N*-oxide (TMNO)[27] directly furnished diastereomeric γ-lactones **12a** and **12b** in a 1:2.3 ratio in 96% yield (Scheme 3). The intermediate β,γ-dihydroxy α-fluoro amides were not detected as they underwent rapid cyclization to the corresponding lactones **12** with recovery of the Evan's auxiliary in >90% yield (Scheme 3). The two lactones were readily separated by flash chromatography affording **12a** as a glassy oil and **12b** as a white solid in 86 and 94% yield, respectively, based on the theoretical yield. Structures were assigned from their NMR spectra as follows. Since the dihedral angle between H(3) and F(2) and H(3) and H(2) in lyxo-γ-lactone[28,29] approaches 90°, isomer **12b** with the smaller coupling constants, $J_{H(2)-H(3)}$=4.4 Hz and ($J_{H(3)-F(2)}$=0), was assigned the lyxo geometry where F(2) and H(3) are *syn* to each other. Conversely, the other isomer **12a**, with larger coupling constants ($J_{H(3)-H(2)}$=7.7 Hz and $J_{H(3)-F}$=22.0 Hz), was assigned the xylo geometry where F(2) and H(3) are *anti* to each other. These assignments were later confirmed by their transformation into the corresponding known 2-fluoropentoses **15** and **17** (see below).

The modest de observed for the dihydroxylation of (+)-**10** suggests that fluorine has little if any influence on the diastereoselectivity. Similar results were observed for 'HCN' addition to α-fluoro *N*-sulfinyl imines in the sulfinimine mediated asymmetric Strecker synthesis of β-fluoro α-amino acids.[19] The chiral auxiliary is also expected not to effect the diastereoselectivity because of its distance from the reactive site. Indeed dihydroxylation of racemic ester **13**, under similar conditions, afforded a 1:2 ratio of racemic lactones **12a** and **12b** (Scheme 4). These modest de's are in line with studies on the stereochemical outcome of electrophilic reactions at acyclic double bond where *Z*-olefins exhibit greater selectivity than *E*-olefins. According to the analyses of Kishi[30,31] and Vedejs[32] conformer **A**, where F adopts an 'inside' position, is expected to be less favorable than conformer **B** where $A^{1,3}$ strain is presumable lower. This is consistent with dihydroxylation of **B** taking place from the least hindered bottom face, *syn* to the hydrogen, resulting in **12b** as the major product. Although this model explains our results, electronic and secondary orbital effects of F on the selectivity cannot be excluded.

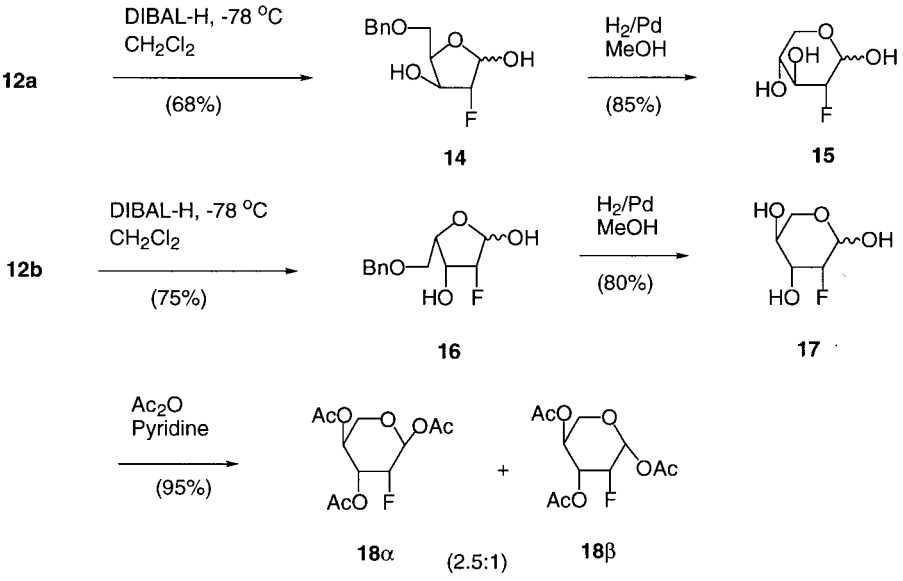
We next attempted to improve the diastereoselectivity of the dihydroxylation by treatment of (*R*)-**10** with Sharpless AD-mix-β. Unfortunately this led to recovery in >80% of the chiral auxiliary in the organic phase, and lactones **12** were not detected. This apparently resulted from faster saponification of the amide bond in **10**, as a consequence of the electron withdrawing α-fluoro group, under the basic AD-mix conditions.

Fluoro lactone **12a** was converted into 2-deoxy-2-fluoro-xylo-D-pyranose (**15**) by reduction with DIBAL in CH_2Cl_2 at −78°C to give lactal **14** in 68% yield (Scheme 5). Reductive removal of the benzyl group (H_2/Pd) afforded **15** in 85%.[7b,11h,29] The same reduction/deprotection sequence afforded 2-deoxy-2-fluoro-*lyxo*-L-pyranose (**17**)[11b,g] in 80%. The overall yields of **15** and **17** from **1** were 29 and 27%, respectively. Although the 2-fluorolyxose **17** is a known compound, reliable spectral data was lacking for comparison, and it was further transformed to 1,3,4-tri-*O*-acetyl-2-deoxy-2-fluoro-L-*lyxo*-pyranose (**18**α and **18**β) by acetylation with acetic anhydride in 95% yield to give a 2.5/1 mixture of anomers. The reported ^{1}H NMR and ^{13}C NMR spectra of the β-D isomer of **18** matches that of the minor product **18**β which is the enantiomer of the β-D isomer.[11g] Consequently, the major product of **18**α is assigned as the α-L anomer.

In summary, the asymmetric synthesis of 2-deoxy-2-fluoro-*xylo*-D-pyranose (**15**) and 2-deoxy-2-fluoro-*lyxo*-L-pyranose (**18**) was accomplished in 27–29% overall yields from a



Scheme 4.



Scheme 5.

noncarbohydrate precursor. The key step in this synthesis is the highly diastereoselective fluorination of a chiral enolate using the electrophilic fluorinating reagent *N*-fluorobenzenesulfonimide (**NFSi**).

Experimental

General procedure

Infrared spectra were recorded on a Mattson 4020 FTIR spectrometer using sodium chloride plates for liquids and potassium bromide disks for solids. ^{1}H and ^{13}C NMR spectra were referenced to $CDCl_3$ (7.26 and 77.0 ppm) using GE 300 and QE 500 MHz NMR spectrometers. ^{19}F NMR spectra were referenced to $CFCl_3$ (0.00) using QE 500 MHz NMR spectrometer. High resolution mass spectra were obtained on a Fissions ZAB HF double-focusing mass spectrometer. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh) purchased from Aldrich Chemical Co. Analytical and preparative thin layer chromatography were performed on pre-coated silica gel plates (250 and 1000 μm) purchased from Analtech Inc. TLC plates were visualized with UV light, $KMnO_4$ solution or an iodine chamber. Melting points were recorded on Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. THF was freshly distilled under nitrogen from sodium and benzophenone and CH_2Cl_2 from CaH_2. Elemental analyses were performed by the Department of Chemistry, University of Pennsylvania. *N*-Fluorobenzenesulfonimide (**NFOBS**)[17] was prepared as previously described and *N*-fluorobenzenesulfonimide (**NFSi**) was provided by AlliedSignal Inc. and is commercially available from Aldrich.

3-Benzyloxy-1-propionaldehyde (2). DMSO (1.6 mL, 22 mmol) was added to a solution of $(COCl)_2$ (1.0 mL, 11 mmol) in CH_2Cl_2 (100 mL) at −78°C. The reaction mixture was stirred for 10 min at which time 3-benzyl-1-propyl alcohol (**1**, Aldrich, 1.66 g, 10.0 mmol) was added dropwise in CH_2Cl_2 (5 mL). After 15 min, triethylamine (7.0 mL, 50 mmol) was added, the solution was stirred for 5 min at which time the reaction mixture was warmed to room temperature. After stirring for 30 min the reaction was quenched with saturated NH_4Cl (10 mL), and the aqueous phase was washed with CH_2Cl_2 (2×20 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2×10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:4) gave aldehyde **3** as a clear oil (1.63 g, 99%); ^{1}H NMR ($CDCl_3$) δ 7.2–7.4 (m, 5H), 4.5 (s, 2H), 3.8–3.9 (t, 2H, J=6.1 Hz), 2.6–2.7 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.2, 134.4, 129.7, 128.9, 128.4, 127.7, 127.6, 73.2, 63.2, 43.8; IR (neat) 1724 (C=O) cm^{-1}; Anal. calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 72.77; H, 7.25.

Ethyl 5-benzyloxy-2-(*E*)-pentenoate (3). Triethyl phosphonoacetate (9.81 mL, 49.5 mmol) was added to a suspension of NaH (60%, 2.28 g, 57 mmol) in benzene at 0°C. The mixture was stirred at room temperature for 1 h, cooled to 0°C and **3** (5.41 g, 33 mmol) was added. The reaction mixture was stirred at 0°C for 1 h, quenched with saturated NH_4Cl (20 mL), and the aqueous phase was washed with Et_2O (2×30 mL). The combined organic phases were washed with satd. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:9) gave 4.37 g (81%) of **3** as a clear oil: IR (neat) 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5H), 6.98 (dt, 1H, J=15.7, 6.9 Hz), 5.89 (dt, 1H, J=15.7, 1.5 Hz), 4.52 (s, 2H), 4.19 (q, 2H, J=7.1 Hz), 3.58 (t, 2H, J=6.5 Hz), 2.51 (dq, 2H, J=13.2, 6.6, 1.4 Hz), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.5, 138.0, 128.3, 128.1, 127.8, 127.6, 122.8, 72.9, 68.2, 60.1, 32.5, 14.2; Anal. Calcd for $C_{14}H_{18}O_2$: C, 71.79; H, 7.69. Found: C, 71.08; H, 7.74.

5-Benzyloxy-2-(*E*)-pentenecarboxylic acid (4). Ester **3** (3.70 g, 17.0 mmol) was dissolved in acetone (85 mL) and LiOH (1 M in H_2O, 85 mL) was added. After warming to room temperature and stirring for 1 h, the reaction mixture

was diluted with H_2O (85 mL), concentrated and washed with Et_2O (50 mL). The aqueous phase was acidified to pH 1 by addition of concentrated HCl and washed with Et_2O (3×50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), concentrated and placed under high vacuum for 8 h to give 3.40 g (97%) of acid **4** as a clear oil; IR (neat) 1654 (C═C), 1696 (C═O); ^{1}H NMR ($CDCl_3$) δ 7.47–7.30 (m, 5H), 7.11 (dt, 1H, J=16.6, 7.7 Hz), 6.91 (d, 1H, J=16.7 Hz), 4.53 (s, 2H), 3.61 (t, 2H, J=7.5 Hz), 2.56 (q, 2H, J=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.6, 148.6, 138.0, 128.4, 127.9, 127.78, 127.7, 122.2, 73.1, 68.0, 32.7; Anal. Calcd for $C_{12}H_{14}O_3$ C, 69.90; H, 6.80. Found: C, 69.72; H, 6.72.

(4*R*,5*S*)-(+)-(5-Benzyloxy-2-(*E*)-pentenoyl)-4-methyl-5-phenyl-2-oxazolidinone (5). Acid **4** (2.67 g, 13 mmol) was dissolved in $SOCl_2$ (5 mL) at 0°C, stirred for 1 h and concentrated. The residue was dissolved in benzene (10 mL), concentrated and repeated to remove all traces of $SOCl_2$. The residue was placed under high vacuum for 1 h and the crude acid chloride (2.80 g) was used without additional purification. In a separate flask, *n*-BuLi (2.5 M in hexane, 5.72 mL, 14.3 mmol) was added to a solution of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone (2.30 g, 13 mmol) in THF (60 mL) at −78°C. After 45 min, the resulting red solution was cannulated to a solution of the acid chloride in THF (10 mL) at −78°C. The reaction mixture was stirred for 2 h, quenched with satd. NH_4Cl solution (10 mL), warmed to rt and washed with Et_2O (3×30 mL). The combined organic phases were washed with satd. $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:4) gave 3.72 g (78%) of (+)-**5** as a clear oil; IR (neat) 1780, 1684, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 10H), 7.2–7.0 (m, 2H), 5.68 (d, 1H, J=7.2 Hz), 4.9–4.7 (m, 1H), 4.55 (s, 2H), 3.64 (t, 2H, J=6.5 Hz), 2.62 (q, 2H, J=7.5 Hz), 0.93 (d, 3H, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 164.1, 152.7, 148.0, 133.9, 128.7, 128.4, 127.7, 127.6, 125.6, 121.9, 79.0, 73.1, 68.3, 54.9, 33.1, 14.6; Anal. Calcd for $C_{22}H_{23}NO_4$ C, 72.32; H, 6.30. Found: C, 71.93; 6.24.

Attempted preparation of (4*R*,5*S*)-(+)-(5-benzyloxy-2-fluoro-3-(*E*)-pentenoyl)-4-methyl-5-phenyl-2-oxazolidinone (6). LiHMDS (1 M in hexane, 3.1 mL, 3.1 mmol) was added to a solution of (+)-**5** (0.92 g, 2.6 mmol) in THF (15 mL) at −78°C. After 1 h, **NFOBS** (1.23 g, 5.2 mmol) in THF (5 mL) was added dropwise, the solution was stirred for 2 h at −78°C and the reaction mixture was quenched with satd. NH_4Cl (10 mL). The solution was washed with Et_2O (2×30 mL) and the combined organic phases were washed with satd. KI (10 mL), $Na_2S_2O_3$ (10 mL) [to remove excess **NFOBS**], brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:9) gave 0.732 g (76%) of a 3:1 mixture of **6*E*** and **6*Z*** as a yellow oil; ^{19}F NMR ($CDCl_3$) δ −185.7 (d, J=48.8 Hz) and −187.0 J=47.0 Hz). HRMS calcd for $C_{22}H_{23}FNO_4$ (M+H), 384.1603 found 384.1611. Attempts to separate the *E*,*Z*-**6** isomers were unsuccessful.

Methyl 5-benzyloxy-2-(*Z*)-pentenoate (7). A solution of bis(2,2,2-trifluoroethyl)(methoxy)carbonylmethylphosphonate (0.318 g, 1 mmol, Aldrich) and 18-crown-6 (0.528 g, 2 mmol) in THF (20 mL) was cooled to −78°C and KHMDS (0.5 M in toluene, 2 mL, 1 mmol) was added. After 5 min, aldehyde **2** (0.164 g, 1 mmol) in THF (3 mL) was added and the solution was stirred for 30 min. At this time the reaction mixture was quenched at −78°C by addition of satd. NH_4Cl (5 mL) and washed with Et_2O (3×30 mL). The combined organic phases were washed with satd. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:9) gave 0.276 g (96%) of **7** as a yellow oil: IR (neat) 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40–7.27, (m, 5H), 6.36 (dt, 1H, J=11.5, 7.1 Hz), 5.86 (dt, 1H, J=11.5, 1.6 Hz), 4.53 (s, 2H), 3.71 (s, 3H), 3.59 (t, 2H, J=6.3 Hz), 3.00 (dq, 2H, J=6.6, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 147.1, 138.2, 128.2 (2 C), 127.5 (2 C), 127.4, 120.5, 72.7, 68.9, 50.9, 28.4.

5-Benzyloxy 2-(*Z*)-pentenoic acid (8). Ester **7** (3.09 g, 15 mmol) was hydrolyzed as described above affording 2.79 g (99%) of **8** as an oil: IR (neat) 1697, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.27 (m, 5H), 6.44 (dt, 1H, J=11.6, 7.2 Hz), 5.86 (dt, 1H, J=11.6, 1.7 Hz), 4.52 (s, 2H), 3.58 (t, 2H, J=6.3 Hz), 2.97 (dq, 2H, J=6.4, 1.7 Hz), 2.15 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.9, 148.9, 137.9, 130.5 (2C), 127.5 (3C), 120.5, 72.6, 68.6, 53.6; HRMS calcd for $C_{12}H_{15}O_3$ (M+H) 207.1021, found 207.1022.

(4*R*,5*S*)-(+)-(5-Benzyloxy-2-(*Z*)-pentenoyl)-4-methyl-5-phenyl-2-oxazolidinone (9). To a solution of acid **8** (0.194 g, 1.0 mmol) in THF (5 mL) at −78°C was added triethylamine (0.18 mL, 1.3 mmol) and pivaloyl chloride (0.13 mL, 1.1 mmol). The reaction mixture was stirred at −78°C for 1 h and the resulting pivaloyl anhydride was used without purification. In a separate flask, *n*-BuLi (2.5 M in hexane, 0.4 mL, 1.3 mmol) was added to a solution of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone (0.212 g, 1.2 mmol) in THF (5 mL) at −78°C. After 30 min, the resulting red solution was cannulated to a solution of the pivaloyl chloride at −78°C. The reaction mixture was stirred at this temperatue for 1 h, quenched with satd. NH_4Cl (2 mL), and washed with Et_2O (2×10 mL). The combined organic phases were washed with satd. $NaHCO_3$ (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:4) gave 0.276 g (78%) of **9** as a yellow oil; $[\alpha]_D^{20}$=6.1 (*c* 0.01, $CHCl_3$); IR (neat) 1782, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.27 (m, 10H), 7.13 (br d, 1H, J=11.6 Hz), 6.50 (dt, 1H, J=11.7, 7.1 Hz), 5.64 (d, 1H, J=7.3 Hz), 4.85–4.64 (m, 1H), 4.54 (s, 2H), 3.62 (t, 2H, J=6.3 Hz), 3.01–2.94 (m, 2H), 0.92 (d, 3H, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 164.3, 152.7, 148.1, 138.2, 133.0, 128.5, 128.2, 127.5, 127.4, 125.5 (10 C, 128.5–125.5), 120.3, 78.7, 72.7, 68.8, 54.5, 30.3, 14.4; HRMS calcd for $C_{22}H_{24}NO_4$ (M+H), 366.1707, found 366.1705.

(4*R*,5*S*)-(+)-(5-Benzyloxy-(2*R*)-fluoro-3-(*E*)-pentenoyl)-4-methyl-5-phenyl-2-oxazolidinone (10). LiHMDS (3.1 mL, 3.1 mmol, 1 M in hexane) was added to a solution of the imide (+)-**9** (0.92 g, 2.6 mmol) in THF (15 mL) at −78°C. After 1 h, **NFSi** (1.99 g, 5.2 mmol) in THF (5 mL) was added, the reaction mixture was stirred for 2 h and quenched at −78°C with satd. NH_4Cl (2 mL). The solution was washed with Et_2O (2×20 mL) and the combined

organic phases were washed with satd. KI (10 mL), $Na_2S_2O_3$ (10 mL) [to remove excess **NFSi**], brine (10 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:9) gave 0.732 g (76%) of **10** as a yellow oil; $[\alpha]_D^{20}$=4.3 (c=0.01, $CHCl_3$); IR (neat) 1781, 1721 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −185.7 (d, J=48.8); ^1H NMR ($CDCl_3$) δ 7.45–7.27 (m, 10H), 6.46 (ddd, 1H, J=48.4, 6.4, 0.9 Hz), 6.31–6.21 (m, 1H), 6.08–5.96 (m, 1H), 5.72 (d, 1H, J=7.2 Hz), 4.73 (m, 1H), 4.55 (s, 2H), 4.12–4.09 (m, 2H), 0.97 (d, 3H, J=6.61 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 167.6, 152.3, 137.8, 134.6, 134.5, 132.5, 128.9, 128.7, 128.4, 127.7 (6 C, 128.9–127.7), 125.6, 123.1, 122.8, 87.5 (d, J=296.2 Hz), 79.9, 72.6, 69.1, 55.2, 14.3; HRMS calcd for $C_{22}H_{23}FNO_4$ (M+H), 384.1603 found 384.1611.

5-*O*-Benzyl-2-deoxy-2-fluoro-D-γ-xylonic lactone (12a) and 5-*O*-benzyl-2-deoxy-2-fluoro-L-γ-lyxonic lactone (12b). To a solution of (+)-**10** (0.957 g, 2.5 mmol) in acetone and H_2O (20/1, 12.5 mL), were added trimethylamine *N*-oxide dihydrate (0.659 g, 6.25 mmol) and OsO_4 (2.5 mL of 2.5% w/w in *t*-BuOH). After 2 h at room temperature, solid $NaHSO_3$ (excess) was added, the solution was stirred for 10 min, diluted with EtOAc (20 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:1) afforded **12a** (0.115 g), **12b** (0.322 g) and a mixture of **12a** and **12b** (0.137 g) which was further purified. The total yield of **12a** (86%) and **12b** (94%) was 96%. Eluting after **12a**–**b** was (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone, 0.40 g (90%). Both lactones were initially obtained as slightly glassy yellow solids, but on standing **12b** solidified.

Properties of **12a**: $[\alpha]_D^{20}$=37.4 (c=0.01, $CHCl_3$); IR (neat) 1793, 1732 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −198.7 (dd, J=61.1, 24.4 Hz); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.32 (dd, H_2, J_{H2-F}=52.8 Hz, J_{H2-H3}=7.4 Hz), 4.73 (dt, H_3, J_{H3-F}=22.0 Hz, J_{H3-H2}=7.7 Hz), 4.64 (dt, H_4, J_{H4-H3}=8.1 Hz, $J_{H4-H5,H5'}$=1.8 Hz), 4.57 (AB, 2H (benzylic), J=11.7), 3.89 (dd, H_5, $J_{H5-H5'}$=11.4 Hz, J_{H5-H4}=1.8 Hz), 3.89 (dt, $H_{5'}$, $J_{H5'-H5}$=11.0 Hz, $J_{H5'-H4}$= 1.8 Hz, $J_{H5'-F}$=2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.7 (C1), 136.6, 128.7, 128.3, 127.8 (2C), 95.4 (d, C_2, J=192.8 Hz), 77.6 (benzylic), 73.9 (C_4), 73.0 (d, C_3, J=21.7 Hz), 66.8 (C_5); HRMS calcd for $C_{12}H_{13}FNaO_4$ ($M+Na^+$) 263.0691, found 263.0695.

Recrystallization from ether afforded **12b** as a white solid; mp 75–77°C; **10b**: $[\alpha]_D^{20}$=−4.3° (c=0.01, $CHCl_3$); IR (neat) 1793 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ −216.8 (d, J=48.4 Hz); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.14 (dd, H_2, J_{H2-F}=48.4 Hz, J_{H2-H3}=4.4 Hz), 4.55 (AB, 2H (benzylic) J=12.0 Hz), 4.60–4.52 (m, 3H, 2H (benzylic) and H_3), 4.51–4.48 (m, H_4), 3.88–3.81 (m, H_5, H_5'), 3.15 (bs, OH); ^{13}C NMR ($CDCl_3$) δ 170.2 (C_1), 137.1, 128.5, 128.4, 128.2, 128.0, 127.9, 86.5 (d, C_2 J=202.8 Hz), 78.1 (benzylic), 73.8 (C_4), 68.3 (d, C_3, J=18.8 Hz), 67.5 (C_5); HRMS calcd for $C_{12}H_{13}FNaO_4$ ($M+Na^+$) 263.0691, found 263.0695.

5-*O*-Benzyl-2-deoxy-2-fluoro-D-xylofuranose (14). DIBAL (1 M in toluene, 0.51 mL, 0.51 mmol) was added to a solution of γ-xylonic lactone **12a** (0.047 g, 0.19 mmol) in CH_2Cl_2 (2 mL) at −78°C. After 1 h, the reaction mixture was quenched with a few drops of H_2O, diluted with ether (20 mL) and stirred for 1 h at room temperature. The mixture was dried ($MgSO_4$), and concentrated to give 0.034 g (68%) of **14** as a colorless glassy oil as a 5:1 mixture of anomers by ^{19}F NMR; ^{19}F NMR ($CDCl_3$) δ −206.9 (d, J=61.0 Hz, major), −193.9 (d, J=48.8 Hz, minor); ^1H NMR (500 MHz, $CDCl_3$) major anomer: δ 7.45–7.27 (m, 5H), 5.36 (d, H_1, J=12.1 Hz), 4.85 (dd, H_2, J=49.7, 1.2 Hz), 4.65–4.55 (m, 2H); minor anomer: 5.56 (dd, H_1, J=10.3, 3.3 Hz), 4.78 (dt, H_2, J=51.7, 3.1 Hz); ^{13}C NMR ($CDCl_3$) major anomer: δ 136.8, 127.9 (2C), 128.2, 128.6 (2C), 100.4 (d, C_1, J=31 5 Hz), 98.0 (d, C_2, J=183.7 Hz), 80.22, 74.5 (d, C_3, J=26.4 Hz), 74.0, 68.8.

5-*O*-Benzyl-2-deoxy-2-fluoro-L-lyxofuranose (16). According to the procedure for the preparation of **14**, γ-lyxonic lactone **12b** (0.024 mg, 0.1 mmol) was reduced by DIBAL (0.3 mL, 0.3 mmol) to give 0.018 g (75%) of **16** as a colorless glassy oil that was a 2.7:1 mixture of anomers (by ^1H NMR) which equilibrated to a 1:1 mixture of anomers (by ^{19}F NMR and ^{13}C NMR); ^{19}F NMR ($CDCl_3$) δ −215.3 (d, J=48.8 Hz,), −209.2 (d, J=48.8 Hz); ^1H NMR (500 MHz, $CDCl_3$) major anomer: δ 5.55 (d, H_1, J=9.9 Hz), 4.77 (dd, H_2, J=53.0, 4.6 Hz), 4.64–4.53 (m, 3H), 4.35–4.32 (m, 1H), 4.02 (bs, OH), 3.81–3.68 (m, 2H), 3.11 (br d, OH, J=7.5 Hz); minor, 5.21 (dd, H_1, J=13.6, 4.4 Hz); ^{13}C NMR ($CDCl_3$) two anomers δ 137.4 and 137.1, 128.5 and 128.4, 128.0, 127.8 and 127.7, 98.6 (d, C_2, J=184.0 Hz) and 88.6 (d, C2, J=199.9 Hz), 77.8, 73.8, 71.4 (d, C_3, J=16.0 Hz) and 70.2 (d, C_3, J=16.0 Hz), 68.9.

2-Deoxy-2-fluoro-D-xylopyranose (15). Pd/C (0.028 g, 10%) was added to a solution of the **14** (0.028 g, 0.1 mmol) in MeOH (10 mL) and was subjected to H_2 at 1 atm provided by a balloon. After 2 h, the reaction mixture was filtered through filter paper and washed with MeOH and H_2O. The filtrate was concentrated to give 0.015 g (85%) of **15** as a colorless glassy oil with an anomeric ratio of β/α=1.3:1 (by ^{19}F NMR); minor: ^{19}F NMR ($CDCl_3$) δ −201.1 (d J=48 Hz), ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (d, H_1, J=3.7), 4.38 (ddd, H_2, J=49.0, 9.2, 3.7 Hz), 3.95–3.60 (m, H_3, H_4, H_5, H_5'); major: ^{19}F NMR ($CDCl_3$) δ −200.3 (d, J=36.6 Hz); ^1H NMR (500 MHz, $CDCl_3$) 4.80 (dd, H_1, J=7.7, 3.0 Hz), 4.05 (ddd, H_2, J=51.2, 8.4, 7.7 Hz), 3.31 (ddd, H_5, J=11.7, 10.3 Hz); ^{13}C NMR ($CDCl_3$) (both anomers) δ 94.2 (d, C_1, J=24.0 Hz) and 89.8 (d, C_1 J= 20.1 Hz), 92.8 (d, C_2, J=184.4 Hz) and 90.2 (d, C_2, J= 195.9 Hz), 24.1 (d, C_3, J=16.9 Hz) and 71.2 (d, C_3, J= 17.8 Hz), 68.9, 68.8, 65.2 and 60.8 (C_4 and C_5).

2-Deoxy-2-fluoro-L-lyxopyranose (17). Hydrogenaton of **16** (0.040 g, 0.15 mmol) in a similar manner afforded 0.018 (80%) of **17** as a colorless glassy oil with an anomeric ratio of α/β=2.6:1 (by ^{19}F NMR): ^{19}F NMR ($CDCl_3$) δ −223.1 (br s), −206.6 (dd, J=48.8, 24.4 Hz); ^1H NMR (500 MHz, D_2O) major δ 5.23 (t, H_1, J=2.9 Hz), 4.65 (dd, H_2, J=48.8, 2.9 Hz), 3.97–3.64 (m, 4H); ^{13}C NMR (D_2O) major: 91.9 (d, C_1, J=28.9 Hz), 91.2 (d, C_2, J=175.0 Hz), 69.8 (d, C_3, J=16.6 Hz), 67.6, 62.8; minor: 93.4 (d, C_1, J=15.7 Hz), 91.1 (d, C_2, J=180 Hz), 72.1 (d, C_3, J=16.7 Hz), 66.7, 65.2.

1,3,4-Triacetyl-2-deoxy-2-fluoro-L-lyxopyranose (18). 2-Fluorolyxose **17** (0.022 g, 0.145 mmol) was stirred with

acetic anhydride (0.136 mL, 1.45 mmol) and pyridine (0.234 mL, 2.9 mmol) at rt for 8 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with satd. NH_4Cl (3×5 mL), satd. $NaHCO_3$ (5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc/hexane 1:2) gave 1,3,4-triacetyl-2-deoxy-2-fluoro-α-L-lyxo-pyranose **18**α (0.0263 g) and 1,3,4-triacetyl-2-deoxy-2-fluoro-β-L-lyxopyranose **18**β (0.0224 g). The total yield of the two anomers was 95%; **18**α: ^{19}F NMR ($CDCl_3$) δ −205.9 (dd J=48.8, 24.4 Hz); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, H_1, J=5.9, 3.4 Hz), 5.30 (ddd, H_3, J=48.4, 5.0, 2.5 Hz), 5.25–5.20 (m, H_4), 4.79 (ddd, H_2, J=48.4, 5.0, 2.5 Hz), 4.00 (dd, H_5, J=11.8, 4.7 Hz), 3.70 (dd, H_5, 11.4, 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.6, 168.4, 90.2 (d, C_1, J=30.3 Hz), 85.8 (d, C_2, J=182.5 Hz), 68.7 (d, C_3, J=17.0 Hz), 66.4, 61.9, 20.8, 20.7, 20.6. **18**β: ^{19}F NMR ($CDCl_3$) δ −215.3 (br d, J=24.4 Hz); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, H_1, J=10.7, 2.5 Hz), 5.23 (ddd, H_3, J=17.6, 6.8, 2.9 Hz), 5.18–5.10 (m, H_4), 4.90 (dt, H_2, J=47.5, 2.8 Hz), 4.19 (dd, H_5, J=12.5, 4.3 Hz), 3.58 (ddd, H_5, J=12.5, 6.0, 1.6 Hz), 2.17, 2.15, 2.10; ^{13}C NMR ($CDCl_3$) δ 169.7, 169.5, 169.0, 89.4 (d, C_1, J=22.0 Hz), 84.5 (d, C_2, J=191.0 Hz), 68.5 (d, C_3, J=16.0 Hz), 67.5, 61.7, 20.7 (3C). The spectra properties of **18**β are in agreement with literature values.[11g]

Acknowledgements

We thank Christopher K. Murphy for preliminary studies and Mr George Kemmerer of the Temple NMR facilities for assistance in obtaining the ^{19}F NMR spectra. This work was supported by a grant from the National Science Foundation. We thank Prof. John T. Welch, SUNY Albany, for helpful discussions and Dr George A. Shia, AlliedSignal, for a generous gift of **NFSi**.

References

1. For reviews on biologically active organofluorine compounds see: (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996.

2. (a) Hudlicky, M.; Parlath; A. E., Eds. *Chemistry of Organic Fluorine Compounds II: A Critical Review*; Washington, DC, 1995. (b) Olah, G. A.; Chambers, R. D.; Prakash, G. K. S. *Synthetic Fluorine Chemistry*; Wiley: New York, 1992, Chapter 15.

3. For reviews on the synthesis and properties of chiral organofluorine compounds see: (a) Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661. (b) Yamazaki, T.; Welch, J. T.; Plummer, J. S.; Gimi, R. H. *Tetrahedron Lett.* **1991**, *32*, 4267.

4. (a) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441. (b) O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1997**, 645.

5. The ability of fluorine bonded to cabon to form hydrogen bonds is controversal. See: (a) Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. *Tetrahedron* **1996**, *52*, 12613. (b) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.

6. For an X-ray structure supporting fluorine hydrogen bonding in fluorohydrins see: Desmarteau, D. D.; Xu, Z. Q.; Witz, M. *J. Org. Chem.* **1997**, *57*, 629.

7. For reviews on fluorinated carbohydrates see: (a) Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91. (b) Penglis, A. A. E. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 195. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (d) Mann, *J. Chem. Soc. Rev.* **1987**, *16*, 381. (e) Curd, P. J. *J. Carbohydr. Chem.* **1985**, *4*, 451.

8. Dwek, R. A. *CIBA Foundation Symposium: Carabon Fluorine Compounds*; Elsevier: Amsterdam, 1977, p 239.

9. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

10. For a recent review on the asymmetric synthesis of fluorinated carbohydrates see: Novo, B.; Resnati, G. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999; Chapter 11, p 349.

11. (a) Albano, E. L.; Tolman, R. L.; Robins, R. K. *Carbohydr. Res.* **1971**, *19*, 63. (b) Butchard, C. G.; Kent, P. W. *Tetrahedron* **1971**, *27*, 3457. (c) Wright, J. A.; Fox, J. J. *Carbohydr. Res.* **1970**, *13*, 297. (d) Reichman, U.; Watanabe, K. A.; Fox, J. J. *Carbohydr. Res.* **1975**, *42*, 233. (e) Su, T.-S.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 1790. (f) Lundt, K.; Pedersen, C. *Mikrochem. Acta S.* **1966**, 126. (g) Dax, K.; Glänzer, B. I. *Carbohydr. Res.* **1987**, *162*, 13. (h) Bols, M.; Lundt, I. *Acta Chem. Scand.* **1990**, *44*, 252.

12. For examples, and leading references to the synthesis of fluorinated carbohydrates from non-carbohydrate sources see: (a) Yan, F.; Nguyen, B. V.; York. C.; Hudlicky, T. *Tetrahedron*, **1997**, *53*, 11541. (b) Welch, J. T.; Eswarakrishna, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186. (c) Ref. 10.

13. For reviews on α-fluoro carbonyl compounds see: (a) Davis, F. A.; Kasu, P. V. N. *Org. Procd. Int.* **1999**, *31*, 127. (b) Rozen, S.; Filler, R. *Tetrahedron* **1985**, *41*, 1111.

14. For reviews on the asymmetric synthesis of fluoro organic compounds which includes sections on α-fluoro carbonyl compounds see: (a) Resnati, G. *Tetrahedron* **1989**, *45*, 5703. (b) Iseki, K.; Kobayashi, Y. *Rev. Heteroatom Chem.* **1995**, *12*, 211. Davis, F. A.; Qi, H.; Sundarababu, G. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999; Chapter 1.

15. Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153.

16. Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135.

17. Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60*, 4730.

18. Davis, F. A.; Kasu, P. V. N.; Sundarababu, G.; Qi, H. *J. Org. Chem.* **1997**, *62*, 7546.

19. Davis, F. A.; Srirajan, V.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 6931.

20. (a) Less, S. L.; Handa, S.; Millburn, K.; Leadlay, P. F.; Dutton, C. J., Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3515. (b) Less, S. L.; Leadlay, P. F.; Dutton, C. J.; Staunton, J. *Tetrahedron Lett.* **1996**, *37*, 3519.

21. Siddiqui, M. A.; Marquez, V. E.; Driscoll, J. S.; Barchi Jr., J. J. *Tetrahedron Lett.* **1994**, *35*, 3263.

22. Some aspects of this work have been published earlier. Davis, F. A.; Qi, H.; *Tetrahedron Lett.* **1996**, *37*, 4345.

23. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

24. Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, G. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.

25. Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 162.

26. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

27. Hanser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236.

28. Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F.; Perkin, I. *J. Chem. Soc., Perkin Trans 1* **1975**, 1480.

29. Csuk, R.; Glänzer, B. I. *Adv. Carbohydr. Chem. Biochem.* **1988**, *46*, 73.
30. For comprehensive discussions of dihydroxylation stereoselectivity see: Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761.
31. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
32. Vedjejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094.