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Synthesis of (2*S*)-2-Chloro-2-fluororibolactone via Stereoselective Electrophilic Fluorination

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Abstract

A novel and efficient route for the preparation of (2*S*)-2-chloro-2-fluorolactone **29** is described. This approach takes advantage of a highly efficient diastereoselective electrophilic fluorination reaction (94% yield; >50:1 dr)

Graphical Abstract

INTRODUCTION

Hepatitis C virus (HCV) a flavivirus that causes significant morbidity and mortality, affects at least 71 million people worldwide.¹ Globally, this major public health concern is responsible for approximately 27% of liver cirrhosis and around 25% of hepatocellular carcinoma.² Since the discovery of HCV in 1989, several antiviral drug regimens have been developed.³ Until 2011, subcutaneous pegylated interferon alfa and oral ribavirin were used as the main HCV treatment. Since then, the addition of protease inhibitors (PIs) and the development of interferon-free therapies considerably increased the rates of treatment tolerability and sustained virological response. Further improvement was recently achieved with Epclusa, the first all-oral, pan-genotypic, single tablet regimen for chronic HCV infection (combination of NS5B inhibitor sofosbuvir and NS5A inhibitor velpatasvir).⁴

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Supporting Information

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¹H, ¹³C, and ¹⁹F NMR spectra for newly synthesized compounds and crystallography data for compound **15** and **30** (PDF)

CIF data for **15** (CIF)

CIF data for **30** (CIF)

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Despite these advances, new potent pan-genotypic nucleosides analogues that can reduce treatment duration (~12 weeks) are needed. Recently, our group and other laboratories paid special attention to the (*S*)-2'-chloro-2'-fluoro-deoxyribouridine prodrug **1** (Figure 1)⁵ which displays high pan-genotypic potency against HCV in subgenomic 1a replicon assays ($EC_{50} = 0.1 \mu M$).^{5d} This prodrug was rapidly metabolized in human hepatocytes to its active metabolite, 2'-chloro-2'-fluoro-deoxyribonucleoside 5'-triphosphate, which inhibits the NS5B polymerase by competing with natural uridine triphosphate. With a sofosbuvir-like C2'-exopuckered sugar, this prodrug also exhibited a favorable resistance and safety profile which makes it a potential candidate for clinical development.

The synthesis of this nucleoside analogue is particularly challenging due to the unusual (2' *S*)-Cl,F substitution on the sugar moiety. One of the key intermediates required for the synthesis of **1** is lactone **4**, which can be prepared in four steps from 2-deoxy-D-ribose (Scheme 1a).^{5d,6} However, the reported synthesis is hampered by the lack of stereoselectivity of the fluorination/chlorination sequence. These halogenation reactions also suffer from undesired side reactions such as β -elimination⁶ or overfluorination, resulting in low yields and difficult chromatographic separations.

Modified riboside moieties are generally prepared from natural sugars such as ribose or 2'-deoxyribose but also from D-glyceraldehyde via Reformatsky, Wittig, or aldol reactions. The latter approach was successfully used for the synthesis of several 2'-modified nucleosides such as sofosbuvir⁷ or gemcitabine.⁸ Regarding the formation of *gem*-Cl-F-carbons, there are only a few examples in the literature and most of them are synthesized via electrophilic fluorination of an α -chloro carbonyl compound.⁹ Partial stereoselectivity is usually achieved by using chiral transition metal complexes (Ni, Pd, Ti)¹⁰ with or without organocatalysts such as spiro oxazoline ligands,¹¹ cinchona alkaloid esters,¹² *N*-acyloxazolidinones,¹³ and the Jørgensen catalyst.¹⁴ It is worth mentioning that there are only a few examples reporting the stereoselective electrophilic chlorination of α -fluoro carbonyl compounds.^{14a}

Herein we report an alternative route for the preparation of the (*S*)-2-chloro-2-fluorolactone intermediate **4** using stereoselective aldolization and fluorination reactions (Scheme 1b). This strategy allows us to introduce directly the chlorine atom during the aldol step and therefore avoid an additional chlorination step. Using this approach, we expect the stereochemistry of the C3 hydroxyl group to be controlled by the C4 chiral center, mostly favoring a 3,4-*trans* configuration. Also, according to literature precedents, the use of (*S*)-4-benzyloxazolidinone (Xc) as chiral auxiliary could potentially improve the chiral induction toward the desired (3*R*) configuration.¹⁵

RESULTS AND DISCUSSION

Initially, we investigated the aldolization between ethyl chloroacetate **9** and glyceraldehyde **8** (Table 1). The reaction of a lithium enolate of **9**, generated by using either LiHMDS or LDA, gave the aldol product **11** in moderate yields as a mixture of the four possible diastereomers (entries 1 and 2).¹⁶ The yield increased to 62% when we used a boron enolate but, as mentioned earlier, no apparent diastereoselectivity was observed (entry 4).¹⁷ On the other hand, the use of a titanium enolate was found to be incompatible with our reactants as

only degradation was observed (entry 3).¹⁸ The lack of selectivity of this reaction along with the possible side reactions (such as self-Claisen^{7b} or Darzens¹⁶ condensations) that could occur during the process led us to investigate an aldol reaction between *N*-(α -chloroacetyl)-oxazolidinone **10** and glyceraldehyde **8**. Unfortunately, standard conditions with either TiCl₄ or Bu₂BOTf only gave traces of the desired compound **12** with complete recovery of the starting materials (entries 5 and 6).¹⁹ However, when the reaction was performed with a lithiated base such as LiHMDS or LDA, only one diastereomer was obtained in 54% and 44% yield, respectively (entries 7 and 8). Despite our efforts, we were not able to improve this yield, as compound **12** seems to undergo partial retroaldolization during workup.²⁰

Although our ultimate goal was to introduce a fluorine atom at C2, it was important to fully define the newly set stereocenters in compound **12**. Unfortunately, we were unable to assign the absolute configuration at this stage, and therefore product **12** was further converted to the lactone **15** using the chemistry depicted in Scheme 2. Thus, compound **12** was first silylated with TBSOTf in the presence of 2,6-lutidine to give compound **13** in 94% yield. Our initial attempt to directly convert **13** to **15** using a standard LiOH-H₂O₂ hydrolysis resulted in epimerization at C2.²¹ Therefore, the oxazolidinone was first cleaved by careful treatment with 0.5 equiv of sodium ethoxide at -78 °C to afford ester **14** in 91% yield as a single diastereomer.²² Compound **14** was finally cyclized in acidic conditions followed by 5-TBS-protection to give the 2-chlorolactone **15** which was identified as the (2*R*,3*R*) isomer by X-ray crystallography (Figure 2).

Fluorination of oxazolidinone derivative **13** was attempted using 1.3 equiv of LiHMDS and 1.5 equiv of NFSI (Scheme 3), but unfortunately no fluorinated product was observed under these standard conditions.²³ We hypothesized that the approach of the fluorinating reagent toward the C2 center might be restricted by the presence of the nearby bulky oxazolidinone and therefore prevent the fluorination.

To confirm this hypothesis, the less hindered ethyl ester **11** was prepared from the Evans oxazolidinone **10** through a one-pot aldolization/auxiliary cleavage sequence (Scheme 4). Thus, the aldol reaction of **10** with glyceraldehyde **8** was performed in the presence of LiHMDS and quenched by addition of ethanol at -78 °C to provide ester **11** in 67% with an excellent stereoselectivity at C3. However, despite an improvement in yield and simpler one-pot reaction versus Table 1 entry 7, ethanol quenching led to significant epimerization at C2 (ratio 7:3, determined by ¹H NMR). As the subsequent fluorination step in our approach goes through an enolate intermediate, racemization had limited consequences and **11** was directly reacted with TBSOTf and 2,6-lutidine to afford protected compound **14** almost quantitatively.

Fluorination of the epimeric mixture **14** was attempted following the conditions described above (Table 2, entry 1). Surprisingly, the reaction afforded only a single diastereomer, which was later confirmed to be the desired (2*S*)-isomer. Unfortunately, the reaction was not complete after 1 h at -78 °C and gave 15% of the elimination product **18**.²⁴ Interestingly, we were able to remove the undesired olefin **18** during workup by treatment of the crude mixture with solid potassium permanganate.^{7a} It is noteworthy that warming the reaction to

room temperature or increasing the reaction time affected neither the conversion rate nor the diastereoselectivity.

Nevertheless, complete conversion was finally achieved using 2.5 equiv of both LiHMDS and NFSI (Table 2, entry 2) which afforded (2*S*)-**17** in 94% yield along with approximately 5% of elimination product **18** (ratio *Z/E*, 33:1). To investigate the role of the chelating effect of the counterion in the diastereoselectivity of this particular reaction, the fluorination of compound **14** was attempted using NaHMDS and KHMDS (entries 3 and 4). Although these reactions yielded the fluorinated product in good yields, only partial diastereoselectivity was observed (16:1 and 10:1 with NaHMDS and KHMDS, respectively). Interestingly, fluorination in the presence of a stronger base such as LDA²⁵ also gave compound **17** as a single diastereomer but with a low yield due to rapid elimination of the β -OTBS group and formation of compound **18** (entry 5).

The mechanism illustrated in Scheme 5 was postulated in an attempt to rationalize the stereoselectivity of this fluorination step. Thus, the reaction performed with LiHMDS might go through a transition state in which the lithium ion simultaneously chelates the enolate and the oxygen atom at the β -position, forming a Zimmerman–Traxler-like six-membered ring. The loss of diastereoselectivity observed with sodium and potassium cations could be explained by their weaker interaction with oxygen relative to lithium,²⁶ which might destabilize the aforementioned six-membered ring transition state. This hypothesis is supported by the fact that LDA, another lithiated base, led to complete diastereoselectivity as well. Additionally, this transition state allows the axial attack of the electrophilic fluorinating agent without steric hindrance from the ethoxy moiety, leading only to the formation of the 2-chloro-2-fluoro isomer (2*S*)-**17**.

As a side note, the γ -isopropylidene group and its C4 chiral center seems to have no effect on the diastereoselectivity because similar selectivities were observed on substrates lacking a chiral center at this position (Table 3). α -Chloro- β -hydroxyester derivatives **22–24** were prepared by aldol reaction between ethyl chloroacetate **9** and achiral alkyl or aromatic aldehydes followed by protection with TBSOTf.^{27,28} Interestingly, unlike for compound **14**, treatment of substrates **22–24** with LiHMDS resulted only in partial deprotonation and prompted us to use the stronger base, LDA, instead. Obtaining the desired 2-chloro-2-fluoro compounds **25–27** as single *S* diastereomers at the 2 position (ratio >50:1, 24–39%) indicates that the isopropylidene moiety and its chirality at the C4-center are not influencing the diastereoselectivity of the fluorination of compounds such as **14**.

Finally, with compound **17** in hand, the desired 2-chloro-2-fluorolactone **29** was readily obtained by cyclization and 5-TBS-protection (Scheme 6). As our attempts to crystallize the TBS-lactone **29** to determine the absolute configuration at C2 were unsuccessful, introduction of different protecting groups at position 5 was investigated. X-ray crystallography of the 5-*p*-nitrobenzoyl-protected lactone **30**, prepared from intermediate **28** by reaction with *p*-nitrobenzoyl chloride and triethylamine in 1,4-dioxane (Figure 3), revealed the *S* configuration of the C2 position.

CONCLUSION

We developed an alternative pathway to prepare a key intermediate required for the synthesis of the prodrug **1**. The 2-chloro-2-fluorolactone **29** was obtained in five steps with an improved 40% overall yield compared to the 10% overall yield of the original four-step synthesis. This new route starts with an efficient one-pot synthesis of 2-chloroacetate **11** from **10** and takes advantage of the diastereoselective electrophilic fluorination of this derivative to form the (2*S*)-Cl,F-stereocenter in high yield. Further investigations are underway to determine the scope and limitations of this ligand-free diastereoselective fluorination.

EXPERIMENTAL SECTION

General Information.

NMR spectra were recorded on a Bruker Ascend 400 MHz Fourier transform spectrometer at rt in CDCl₃ or DMSO-*d*₆ as indicated. Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard. NMR treatment was performed with MestReNova version 10.0.2–15465 using the following abbreviations for signal characterization: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal), dd (doublet of doublets), or heptd (heptuplet of doublet). High-resolution mass spectra (HRMS) were recorded on a Thermo-Fisher Q Exactive Plus orbitrap high-resolution mass spectrometer with electrospray ionization positive (ESI+) or negative (ESI–).

Reactions were monitored by thin-layer chromatography (TLC) and visualized by ultraviolet irradiation and/or KMnO₄ dip. Purifications were performed on silica gel column chromatography (60 Å, 63–200 μm, or 40–75 μm) with CombiFlash Rf 200. Anhydrous solvents were purchased from Aldrich Chemical Co., Inc. (Milwaukee). Reagents were purchased from commercial sources and used without further purification.

(*S*)-4-Benzyl-3-(2-chloroacetyl)oxazolidin-2-one (**10**).

To a solution of (*S*)-4-benzyl-2-oxazolidinone (5 g, 28.2 mmol) in dry THF (150 mL) at –78 °C under N₂ was added *n*-BuLi (2.5 M in hexanes, 13.5 mL, 33.9 mmol). The solution was stirred at –78 °C for 15 min, and chloroacetyl chloride (2.47 mL, 31.0 mmol) was added in one portion. After full conversion (typically 30 min), the reaction was quenched by addition of a saturated aqueous solution of NH₄Cl and allowed to reach rt. The mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The crude residue was purified via column chromatography on silica gel to afford a colorless syrup (5.1 g, 71%), which crystallized while standing. Alternatively, precipitation could be initiated by dilution of the syrup in cold diethyl ether to afford a white solid after filtration. ¹H and ¹³C NMR data matched those reported in the literature.²⁹

Ethyl 2-Chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypropanoate (**11**).

Procedure A: Ethyl chloroacetate **9** (5.0 g, 40.8 mmol) was added to a solution of LDA (1 M in THF/hexanes, 53 mL, 53.0 mmol) in dry THF (300 mL) at –78 °C under N₂. After 15 min, (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **8** (6.1 mL, 49.0 mmol)³⁰ was

introduced to the mixture and the reaction was stirred for an additional 1 h at -78°C . The reaction was quenched with 1 M HCl at -78°C . The mixture was extracted with ethyl acetate, washed with water and brine, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by flash column chromatography (hexanes/EtOAc 9:1 to 8:2) to afford compound **11** (colorless oil, 4.8 g, 47%) as a diastereomeric mixture of four isomers. NMR data matched those reported in the literature.³¹ Procedure B: To a solution of LiHMDS (1 M in THF, 5.9 mL, 5.90 mmol) in dry THF (20 mL) at -78°C under N_2 was added dropwise via cannula a solution of **10** (1 g, 3.94 mmol) in THF (2 mL). The mixture was stirred 30 min at this temperature, and a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **8** (736 μL , 5.90 mmol) in THF (2 mL) was added dropwise via cannula. After 30 min, anhydrous ethanol (5 mL) was added at -78°C and the reaction mixture was further stirred for 15 min before addition of silica (10 g). The mixture was filtered on a silica gel pad prior to concentration under reduced pressure. The crude residue was purified via column chromatography on silica gel (hexanes/EtOAc 95:5 to 70:30) to afford the desired aldol product **11** as a mixture of two diastereomers in 67% yield (670 mg, 2*R*/2*S* ratio 7:3, colorless oil). HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{18}\text{ClO}_5$ 253.0843, found 253.0838.

(*S*)-4-Benzyl-3-((2*R*,3*R*)-2-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxypropanoyl)oxazolidin-2-one (12**).**

To a solution of LiHMDS (1 M in THF, 1.48 mL, 1.48 mmol) in dry THF (5 mL) at -78°C under N_2 was added dropwise via cannula a solution of **10** (250 mg, 0.99 mmol) in THF (2 mL). The mixture was stirred 30 min at this temperature, and a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **8** (115 μL , 1.28 mmol) in THF (2 mL) was added dropwise via cannula. After 30 min, the reaction was quenched at -78°C by addition of 1 M HCl. The mixture was rapidly diluted with EtOAc and then washed with water and brine. The organic layer was dried over MgSO_4 and filtered on a silica gel pad prior to concentration under reduced pressure. The crude residue was purified via column chromatography on silica gel (hexanes/EtOAc 95:5 to 70:30) to afford the desired aldol product as a single diastereoisomer in 54% yield as a white solid (205 mg). ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 3H), 7.25 (d, J = 6.9 Hz, 2H), 5.77 (d, J = 6.1 Hz, 1H), 4.79–4.72 (m, 1H), 4.38–4.08 (m, 6H), 3.31 (dd, J = 13.6, 3.3 Hz, 1H), 3.27 (bs, 1H), 2.85 (dd, J = 13.5, 9.2 Hz, 1H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 152.4, 134.7, 129.5, 129.1, 127.6, 109.9, 75.9, 73.7, 66.4, 65.9, 55.5, 52.7, 37.6, 26.6, 25.1; HRMS (ESI-TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{23}\text{ClNO}_6$ 384.1214, found 384.1201.

(*S*)-4-Benzyl-3-((2*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoyl)-oxazolidin-2-one (13**).**

To a solution of compound **12** (230 mg, 0.60 mmol) in dry CH_2Cl_2 (6 mL) at 0°C under N_2 were sequentially added 2,6-lutidine (280 μL , 2.4 mmol) and TBSOTf (275 μL , 1.2 mmol). The mixture was stirred 1 h at 0°C and quenched by addition of 1 M HCl (5 mL). The mixture was extracted with CH_2Cl_2 (2×10 mL). Combined organic layers were washed with water and brine, dried over MgSO_4 , and concentrated in vacuo. The crude residue was purified via column chromatography on silica gel (hexanes/EtOAc, 95:5) to afford the desired silylated derivative **13** in 94% yield as a white solid (281 mg). ^1H NMR (400 MHz,

CDCl₃) δ 7.47–7.23 (m, 5H), 5.71 (d, J = 4.0 Hz, 1H), 4.78–4.70 (m, 1H), 4.54 (dd, J = 6.1, 4.0 Hz, 1H), 4.43 (dd, J = 13.4, 6.3 Hz, 1H), 4.32–4.22 (m, 1H), 4.10 (dd, J = 8.2, 6.4 Hz, 1H), 3.92 (t, J = 7.8 Hz, 1H), 3.52 (dd, J = 13.3, 2.8 Hz, 1H), 2.65 (dd, J = 13.2, 10.6 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 0.93 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 165.9, 152.9, 135.2, 129.3, 129.1, 127.5, 109.3, 74.6, 72.4, 67.1, 66.3, 62.0, 56.1, 38.0, 26.6, 25.7, 25.4, 18.1, –4.5, –4.9; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₂₄H₃₇ClNO₆Si 498.2079, found 498.2075.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (14**).**

Procedure A: To a solution of compound **13** (52 mg, 0.10 mmol) in a mixture of anhydrous EtOH (1.5 mL) and THF (1.5 mL) at –78 °C was added NaOEt (21 wt % in EtOH, 0.02 mL, 0.5 mmol). The mixture was stirred 30 min at –78 °C and quenched by addition of 1 M HCl (5 mL). After dilution with EtOAc, the organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude residue was purified via column chromatography on silica gel (hexanes/EtOAc, 95:5) to afford the desired ethyl ester **14** as a colorless oil (35 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 4.60 (d, J = 2.7 Hz, 1H), 4.34–4.28 (m, 1H), 4.25 (qd, J = 7.2, 1.1 Hz, 2H), 4.20 (dd, J = 7.2, 2.7 Hz, 1H), 4.07 (dd, J = 8.4, 6.3 Hz, 1H), 3.89 (dd, J = 8.4, 5.4 Hz, 1H), 1.40 (s, 3H), 1.36–1.30 (m, 6H), 0.90 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.8, 109.4, 75.8, 75.6, 66.6, 62.2, 61.3, 26.6, 25.7, 25.1, 18.0, 14.1, –4.3, –4.7; HRMS (ESI-TOF) m/z [M + H]⁺ calcd for C₁₆H₃₂ClO₅Si 367.1708, found 367.1701.

Procedure B: To a solution of compound (3*R*)-**11** (2.32 g, 9.18 mmol) in dichloromethane (10 mL) at 0 °C was added 2,6-lutidine (4.28 mL, 36.72 mmol) followed by TBSOTf (4.22 mL, 18.36 mmol). The reaction mixture was stirred for 2 h and then quenched with a saturated aqueous solution of NaHCO₃. The crude mixture was extracted with ethyl acetate, washed with 1 M HCl and brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 95/5) afforded the two major diastereoisomers (2*R*,3*R*)-**14** and (2*S*,3*R*)-**14** in 99% yield (colorless oil, 3.33 g, ratio 7:3).

(3*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-chlorodihydrofuran-2(3*H*)-one (15**).**

To a solution of compound **14** (29 mg, 0.08 mmol) in acetonitrile (0.2 mL) were added water (0.01 mL) and acetic acid (0.05 mL). The reaction mixture was refluxed for 1 h and coevaporated with toluene under reduced pressure. The crude 2-chlorolactone was dissolved in DMF (0.2 mL), and TBSCl (24 mg, 0.16 mmol) and imidazole (14 mg, 0.20 mmol) were added. The reaction was stirred at rt for 2 h and quenched with water (5 mL). The mixture was extracted with EtOAc/Et₂O (1:1). The organic layer was washed with water (3 × 10 mL), a saturated aqueous solution of NH₄Cl (10 mL), and brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to afford the protected lactone **15** as a white solid (30.7 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 4.62 (d, J = 5.4 Hz, 1H), 4.51 (dd, J = 5.6, 2.7 Hz, 1H), 4.41 (d, J = 2.5 Hz, 1H), 3.94 (dd, J = 12.0, 2.7 Hz, 1H), 3.82 (dd, J = 12.0, 2.0 Hz, 1H), 0.93 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C

NMR (101 MHz, CDCl₃) δ 171.1, 85.8, 70.4, 61.4, 55.7, 25.7, 25.6, 18.3, 18.2, -4.9, -5.1, -5.5, -5.6; mp 85–86 °C; HRMS (ESI-TOF) m/z : [M - H]⁻ calcd for C₁₇H₃₆ClO₄Si₂ 395.1841, found 395.1830.

Ethyl (2*S*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-fluoropropanoate (17).

A solution of LiHMDS (1 M in THF, 0.34 mL, 0.34 mmol) was added dropwise to a mixture of compound (3*R*)-**14** (50 mg, 0.14 mmol) and NFSI (107 mg, 0.34 mmol) in anhydrous THF (0.5 mL) at -78 °C. After 1 h, the reaction was quenched with a saturated aqueous solution of NH₄Cl and extracted with EtOAc. Solid potassium permanganate (300 mg) and water (0.5 mL) were added to the organic layer (consumption of the elimination compound was monitored by TLC, hexanes/EtOAc 9:1, R_f = 0.57). A saturated aqueous solution of Na₂S₂O₃ (20 mL) was added to the heterogeneous mixture, and formation of a brown precipitate was observed after vigorous shaking. The mixture was treated with 1 M HCl (10 mL). The organic layer was separated and washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 95/5) to give compound **17** as a colorless oil (49 mg, 94%, ratio 2*S*/2*R* > 50:1). ¹H NMR (400 MHz, CDCl₃) δ 4.42–4.21 (m, 4H), 4.10–4.00 (m, 1H), 3.93 (dd, J = 8.2, 6.4 Hz, 1H), 1.41 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.33 (s, 3H), 0.93 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H); ¹⁹F NMR (377 MHz, CDCl₃) δ -127.12 (d, J = 18.2 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 164.8 (d, J = 27.6 Hz), 108.9, 104.8 (d, J = 261.4 Hz), 77.2 (d, J = 21.4 Hz), 75.3 (d, J = 4.0 Hz), 65.6 (d, J = 1.5 Hz), 63.1, 25.9, 25.8, 24.6, 18.3, 13.9, -4.0, -4.2, -4.2; HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₁₆H₃₁ClFO₅Si 385.1613, found 385.1607.

Ethyl 2-Chloro-3-hydroxy-4-methylpentanoate (19).

To a solution of **9** (0.22 mL, 2.04 mmol) in CH₂Cl₂ (20 mL) at -78 °C were added dibutylboryl trifluoromethanesulfonate (1.0 M in CH₂Cl₂, 4.1 mL, 4.08 mmol) and DIPEA (1 mL, 6.12 mmol). The mixture was stirred 2 h at -78 °C, and isobutyraldehyde (0.28 mL, 3.06 mmol) was added. The reaction was stirred at this temperature for 1 h and for another 1 h at 0 °C. The mixture was quenched with a (1:1) mixture of methanol/phosphate buffer (20 mL, pH 7.2) followed by H₂O₂ (10 mL, 30% w/w in water), and the solution was stirred 16 h at rt. After removal of the solvent under reduced pressure, the solution was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (hexanes/EtOAc, 9:1) to give compound **19** as an anti/syn mixture (2.3:1) (colorless oil, 350 mg, 88%). ¹H and ¹³C NMR data matched those reported in the literature.³² Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 4.30–4.22 (m, 2H), 4.20 (d, J = 7.9 Hz, 1H), 3.81 (dd, J = 8.0, 4.1 Hz, 1H), 2.72 (bs, 1H), 2.12–2.04 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H). HRMS (ESI-TOF) m/z : [M + H]⁺ calcd for C₈H₁₆ClO₃ 195.0788, found 195.0785.

Ethyl 2-Chloro-3-cyclopentyl-3-hydroxypropanoate (20).

Compound **20** was prepared following the procedure described for **19** using cyclopentanecarboxaldehyde to give **20** as an anti/syn mixture (2.3:1) (colorless oil, 76%). Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 4.29–3.85 (m, 4H), 2.75 (bs, 1H), 2.26–2.14 (m, 1H), 1.94–1.35 (m, 8H), 1.32 (t, $J = 7.2$ Hz, 3H); mixture: ^{13}C NMR (101 MHz, CDCl_3) δ 168.8, 168.7, 76.1, 76.0, 62.4, 62.2, 61.9, 58.7, 43.1, 41.8, 29.0, 28.9, 28.9, 27.1, 25.6, 25.4, 25.4, 25.4, 14.0, 13.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{10}\text{H}_{18}\text{ClO}_3$ 221.0944, found 221.0939.

Ethyl 2-Chloro-3-hydroxy-3-phenylpropanoate (21).

Compound **21** was prepared following the procedure described for **19** using benzaldehyde to give **21** as an anti/syn mixture (1.8:1) (colorless oil, 88%). ^1H and ^{13}C NMR data matched those reported in the literature.³² Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.33 (m, 5H), 5.07 (dd, $J = 7.7, 5.5$ Hz, 1H), 4.41 (d, $J = 7.5$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 3.07 (d, $J = 5.0$ Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H).

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-4-methylpentanoate (22).

Compound **22** was prepared following conditions described for **14** (procedure B) with **19** (250 mg, 1.28 mmol), TBSOTf (0.6 mL, 2.56 mmol), and 2,6-lutidine (0.6 mL, 5.12 mmol) in CH_2Cl_2 (6 mL) to afford **22** (colorless oil, 366 mg, 92%) as an anti/syn mixture (2.4:1). Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 4.27–4.19 (m, 2H), 4.17 (d, $J = 7.7$ Hz, 1H), 4.00 (dd, $J = 7.7, 3.3$ Hz, 1H), 2.17 (heptd, $J = 6.9, 3.2$ Hz, 1H), 1.32 (t, $J = 7.1$ Hz, 3H), 0.99–0.88 (m, 15H), 0.10–0.03 (m, 6H); mixture: ^{13}C NMR (101 MHz, CDCl_3) δ 169.0, 168.8, 61.9, 61.8, 61.2, 58.2, 31.9, 30.3, 26.1, 26.0, 20.2, 19.5, 18.5, 18.4, 16.5, 16.0, 13.9, 13.9, –3.8, –4.0, –4.2, –4.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{30}\text{ClO}_3\text{Si}$ 309.1653, found 309.1647.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-3-cyclopentylpropanoate (23).

Compound **23** was prepared following conditions described for **14** (procedure B) with **20** (250 mg, 1.13 mmol), TBSOTf (0.5 mL, 2.26 mmol) and 2,6-lutidine (0.5 mL, 4.52 mmol) in CH_2Cl_2 (5 mL) to afford **23** (colorless oil, 364 mg, 96%) as an anti/syn mixture (2:1). Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 4.31–4.29 (m, 1H), 4.27–4.20 (m, 2H), 4.10–4.04 (m, 1H), 2.38–2.24 (m, 1H), 1.80–1.36 (m, 7H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.28–1.16 (m, 1H), 0.89 (s, 9H), 0.12–0.08 (m, 6H); mixture: ^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 168.2, 62.5, 62.0, 61.9, 61.2, 43.9, 43.2, 29.7, 28.9, 28.0, 27.8, 26.0, 25.9, 25.5, 25.9, 25.2, 25.1, 18.4, 18.3, 14.0, –3.9, –4.0, –4.2, –4.3; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{32}\text{ClO}_3\text{Si}$ 335.1809, found 335.1801.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-3-phenylpropanoate (24).

Compound **24** was prepared following conditions described for **14** (procedure B) with **21** (410 mg, 1.79 mmol), TBSOTf (0.82 mL, 3.58 mmol) and 2,6-lutidine (0.83 mL, 7.16 mmol) in CH_2Cl_2 (20 mL) to afford **24** (colorless oil, 582 mg, 95%) as an anti/syn mixture (1.6:1). Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 7.44–7.29 (m, 5H), 4.95 (d, $J = 9.1$ Hz, 1H), 4.33–4.25 (m, 2H), 4.23 (d, $J = 9.1$ Hz, 1H), 1.36 (t, $J = 7.1$ Hz, 3H), 0.83 (s, 9H),

0.12—0.24 (m, 6H); mixture: ^{13}C NMR (101 MHz, CDCl_3) δ 168.9, 167.9, 139.9, 139.7, 128.5, 128.2, 128.1, 127.5, 127.1, 63.7, 61.9, 61.7, 60.3, 25.6, 25.5, 18.1, 17.9, 14.0, 13.7, -4.7, -5.0, -5.4; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{28}\text{ClO}_3\text{Si}$ 343.1496, found 343.1491.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-2-fluoro-4-methylpentanoate (25).

To a solution of diisopropylamine (0.09 mL, 0.65 mmol) in dry THF (1 mL) at -78°C under N_2 was added dropwise *n*-BuLi (2.5 M in hexanes, 0.26 mL, 0.65 mmol). After 10 min at -78°C , compound **22** (100 mg, 0.32 mmol) in dry THF (0.3 mL) was introduced dropwise to the reaction mixture. A solution of NFSI (224 mg, 0.70 mmol) in anhydrous THF (0.5 mL) was immediately added. After 1 h at -78°C , the reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with EtOAc. Solid potassium permanganate (300 mg) and water (0.5 mL) were added to the organic layer (consumption of the elimination product was monitored by TLC, hexanes/EtOAc 95:5, R_f = 0.54). A saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) was added to the heterogeneous mixture, and formation of a brown precipitate was observed after vigorous shaking. The mixture was treated with 1 M HCl (10 mL). The organic layer was separated, washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc 95:5 as eluent) to give compound **25** (colorless oil, 17.3 mg, 33%). ^1H NMR (400 MHz, CDCl_3) δ 4.35 (q, J = 7.1 Hz, 2H), 4.04 (dd, J = 20.0, 2.2 Hz, 1H), 2.00 (heptd, J = 6.8, 2.3 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.97 (s, 9H), 0.94 (dd, J = 6.8, 1.8 Hz, 3H), 0.21 (s, 3H), 0.15 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ -126.02 (d, J = 20.2 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 165.5 (d, J = 27.9 Hz), 106.9 (d, J = 263.9 Hz), 80.3 (d, J = 19.2 Hz), 63.0, 30.9, 26.0, 22.1, 18.6, 16.2 (d, J = 3.6 Hz), 13.9, -4.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{29}\text{ClFO}_3\text{Si}$ 327.1559, found 327.1553.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-3-cyclopentyl-2-fluoropropanoate (26).

Compound **26** was prepared following the procedure described for **25** with **23** (50 mg, 0.15 mmol), LDA (2 M in THF/heptane/ethylbenzene, 0.1 mL, 0.20 mmol), and NFSI (118 mg, 0.37 mmol) in THF (1.5 mL) to afford **26** (colorless oil, 12.6 mg, 24%). ^1H NMR (400 MHz, CDCl_3) δ 4.34 (qd, J = 7.1, 1.1 Hz, 2H), 4.19 (dd, J = 17.8, 3.6 Hz, 1H), 2.25–2.08 (m, 1H), 1.85–1.73 (m, 1H), 1.72–1.40 (m, 7H), 1.37 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H), 0.19 (d, J = 1.0 Hz, 3H), 0.14 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ -123.05 (d, J = 18.0 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 165.3 (d, J = 28.1 Hz), 106.8 (d, J = 261.3 Hz), 78.9 (d, J = 20.4 Hz), 63.0, 42.3 (d, J = 1.8 Hz), 31.1, 26.5 (d, J = 2.3 Hz), 26.0, 25.3 (d, J = 16.1 Hz), 18.6, 13.9, -4.0 (d, J = 2.7 Hz), -4.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{31}\text{ClFO}_3\text{Si}$ 353.1715, found 353.1703.

Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-2-chloro-2-fluoro-3-phenylpropanoate (27).

Compound **27** was prepared following the procedure described for **25** with **24** (50 mg, 0.15 mmol), LDA (2 M in THF/heptane/ethylbenzene, 0.15 mL, 0.30 mmol), and NFSI (118 mg, 0.37 mmol) in THF (1.5 mL) to afford **30** (colorless oil, 20.4 mg, 39%). ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.39 (m, 2H), 7.37–7.31 (m, 3H), 5.17 (d, J = 17.0 Hz, 1H), 4.21 (q, J

= 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.14 (s, 3H), -0.10 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ -130.11 (d, J = 17.2 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 164.8 (d, J = 26.9 Hz), 136.6, 128.9, 128.5, 128.5, 127.9, 106.3 (d, J = 263.0 Hz), 78.2 (d, J = 21.3 Hz), 63.0, 25.6, 18.2, 13.8, -4.9, -5.2; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{27}\text{ClFO}_3\text{Si}$ 361.1402, found 361.1396.

(2S)-2-Deoxy-2-chloro-2-fluoro-3-O-(*tert*-butyldimethylsilyl)-5-hydroxy-d-ribonolactone (28).

To a solution of compound **9** (150 mg, 0.39 mmol) in acetonitrile (0.5 mL) were added water (0.05 mL) and acetic acid (0.3 mL). The reaction mixture was stirred at 80 °C for 2 h and coevaporated with toluene under reduced pressure. Compound **28** was obtained in 88% yield and used in the next step without further purification. A sample was purified for analysis by flash column chromatography (hexanes/EtOAc, 8:2) to afford chlorofluorolactone **28** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.56 (dd, J = 13.2, 6.5 Hz, 1H), 4.41 (dt, J = 6.4, 3.1 Hz, 1H), 4.09 (dd, J = 13.0, 2.3 Hz, 1H), 3.83 (d, J = 12.9 Hz, 1H), 2.02 (bs, 1H), 0.95 (s, 9H), 0.25 (s, 3H), 0.20 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ -134.91 (d, J = 13.3 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 164.9 (d, J = 25.7 Hz), 102.4 (d, J = 258.3 Hz), 83.4, 74.2 (d, J = 16.3 Hz), 59.2, 25.5, 18.0, -4.3, -5.2; HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{11}\text{H}_{19}\text{ClFO}_4\text{Si}$ 297.0725, found 297.0732.

(2S)-2-Deoxy-2-chloro-2-fluoro-3,5-di-O-(*tert*-butyldimethylsilyl)-d-ribonolactone (29).

To a solution of compound **28** (3.89 g, 13 mmol) in DMF (30 mL) were added imidazole (2.3 g, 52 mmol) and TBSCl (3.9 g, 26 mmol). The mixture was stirred 2 h at 25 °C and quenched with water. The solution was extracted with ethyl acetate/diethyl ether (1:1), and the organic layer was washed with water (3 $\times$ 30 mL), a saturated aqueous solution of NH_4Cl (30 mL), and brine (30 mL), dried over MgSO_4 , and concentrated under reduced pressure. The crude was purified by flash column chromatography (hexanes/EtOAc, 95:5) to afford protected lactone **29** as a colorless oil (5.0 g, 94%). ^1H NMR (400 MHz, CDCl_3) δ 4.58 (dd, J = 12.0, 5.7 Hz, 1H), 4.37–4.32 (m, 1H), 3.98 (dd, J = 12.1, 3.7 Hz, 1H), 3.84 (dd, J = 12.1, 2.9 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ -134.67 (d, J = 11.9 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 165.2 (d, J = 26.0 Hz), 102.1 (d, J = 259.6 Hz), 83.6, 74.1 (d, J = 16.0 Hz), 59.5, 25.7, 25.5, 18.2, 18.0, -4.4, -5.2, -5.4, -5.5; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{35}\text{ClFO}_4\text{Si}_2$ 413.1746, found 413.1739.

((2R,3R,4S)-3-((*tert*-Butyldimethylsilyl)oxy)-4-chloro-4-fluoro-5-oxotetrahydrofuran-2-yl)methyl 4-Nitrobenzoate (30).

To a solution of lactone **28** (140 mg, 0.47 mmol) in 1,4-dioxane (2 mL) were added *p*-nitrobenzoyl chloride (93 mg, 0.50 mmol) and triethylamine (0.09 mL, 0.65 mmol). The reaction mixture was stirred at rt for 45 min and quenched with 1 M HCl (10 mL). The organic layer was washed with a saturated aqueous solution of NaHCO_3 and brine, dried over MgSO_4 , and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc, 95:5) afforded compound **30** (102 mg, 49%) as a white solid. A small amount was recrystallized by slow evaporation from pentane/ Et_2O for X-ray analysis. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, J = 8.9 Hz, 2H), 8.24 (d, J = 8.9 Hz, 2H),

4.79 (dd, $J = 12.3, 3.5$ Hz, 1H), 4.75–4.69 (m, 1H), 4.62 (dd, $J = 12.3, 5.9$ Hz, 1H), 4.45 (dd, $J = 8.4, 4.9$ Hz, 1H), 0.95 (s, 9H), 0.24 (s, 3H), 0.19 (s, 3H); ^{19}F NMR (377 MHz, CDCl_3) δ –136.48 (d, $J = 8.5$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 164.4 (d, $J = 26.6$ Hz), 164.0, 151.0, 134.2, 130.9, 123.8, 100.6 (d, $J = 263.7$ Hz), 81.4, 75.6 (d, $J = 16.9$ Hz), 62.6, 25.5, 18.1, –4.4, –5.2; mp 99–100 °C; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{24}\text{ClFNO}_7\text{Si}$ 448.0995, found 448.0984.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Structure of sofosbuvir and novel 2'-Cl,2'-F nucleoside analogue **1**.

Figure 2.
Crystal structure of (2*R*,3*R*)-2-chlorolactone **15** showing thermal ellipsoids at the 50% probability level.

Figure 3.
Crystal structure of (2*S*,3*R*)-2-Cl,2-F-lactone **30** showing thermal ellipsoids at the 50% probability level.

a- Previous work **b- This work** **Scheme 1.**

Reported Synthesis and Retrosynthetic Approach for the Preparation of (2*S*)-2-Chloro-2-fluororibolactone **4**

Scheme 2.
Synthesis of 2-Cl Lactone 15

Scheme 3.
Fluorination Attempt on Compound 13

Scheme 4.
Synthesis of Compound 14

Scheme 5.

Proposed Mechanism for the Fluorination of Compound 14

Scheme 6.
Synthesis of Ribolactones 29 and 30

Table 1.

Aldol Reaction Optimization

entry	Rx	conditions	product (yield, ratio) ^{a,b}
1	9	LiHMDS, THF, -78 °C	11 (39%, 2:2:5:1)
2	9	LDA, THF, -78 °C	11 (47%, 6:1:8:1)
3	9	TiCl ₄ , DIPEA, CH ₂ Cl ₂ , -78 °C	11 (0%)
4	9	Bu ₂ BOTf, DIPEA, CH ₂ Cl ₂ , -78 to 0 °C	11 (62%, 3:1:3:3)
5	10	Bu ₂ BOTf, DIPEA, CH ₂ Cl ₂ , -78 to 0 °C	12 (traces)
6	10	TiCl ₄ , DIPEA, CH ₂ Cl ₂ , -78 °C	12 (traces)
7	10	LiHMDS, THF, -78 °C	(<i>2R,3R</i>)- 12 (54%, >50:1)
8	10	LDA, THF, -78 °C	(<i>2R,3R</i>)- 12 (44%, >50:1)

^a Isolated yield.^b Ratio determined by ¹H NMR analysis.

Table 2.

Fluorination Conditions Screening

entry	base (equiv)	NFSI (equiv)	conversion (%) ^a	<i>S/R</i> - 17 ^b
1	LiHMDS, 1.3	1.5	70	>50:1
2	LiHMDS, 2.5	2.5	100 (94)	>50:1
3	NaHMDS, 2.5	2.5	100 (79)	16:1
4	KHMDS, 2.5	2.5	96 (92)	10:1
5	LDA, 1.3	1.5	100 (33)	>50:1

^aDetermined by ¹H NMR, isolated yield in parentheses.

^b(2*S*:2*R*) ratio determined by ¹H NMR or ¹⁹F NMR.

Table 3.

Preparation of the γ -Modified Chloroacetate Derivatives 25–27

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{COOEt} + \text{R}-\text{CHO} \xrightarrow[\text{-78}^\circ\text{C to } 0^\circ\text{C}]{\text{Bu}_2\text{BOTf, DIPEA, CH}_2\text{Cl}_2} \text{R}-\text{CH}(\text{OH})-\text{CH}(\text{Cl})-\text{COOEt} \quad \mathbf{19-21} \\ \mathbf{9} \end{array} $				
$ \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{COOEt} \xrightarrow[\text{0}^\circ\text{C, 2 h}]{\text{TBSOTf, 2,6-lutidine, CH}_2\text{Cl}_2} \text{R}-\text{CH}(\text{OTBS})-\text{CH}(\text{Cl})-\text{COOEt} \quad \mathbf{22-24} \\ \mathbf{19-21} \end{array} $				
$ \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{COOEt} \xrightarrow[\text{-78}^\circ\text{C, 1 h}]{\text{LDA, NFSI, THF}} \text{R}-\text{CH}(\text{OTBS})-\text{CH}(\text{F})(\text{Cl})-\text{COOEt} \quad \mathbf{25-27} \\ \mathbf{22-24} \end{array} $				
entry	R	aldolization	protection	yield ^a (ratio of fluorination) ^b
1	<i>i</i> -Pr	19 , 88% (2.3:1)	22 , 92% (2.4:1)	25 , 33% (>50:1)
2	cyclopentyl	20 , 76% (2.3:1)	23 , 96% (2:1)	26 , 24% (>50:1)
3	Ph	21 , 88% (1.8:1)	24 , 95% (1.6:1)	27 , 39% (>50:1)

^a Isolated yield; ratio determined by ¹H NMR.^b LDA (2.5 equiv), NFSI (2.5 equiv).