Nonracemic α-Fluoro Aldehydes: Asymmetric Synthesis of 4-Deoxy-4-fluoro-D-arabinopyranose

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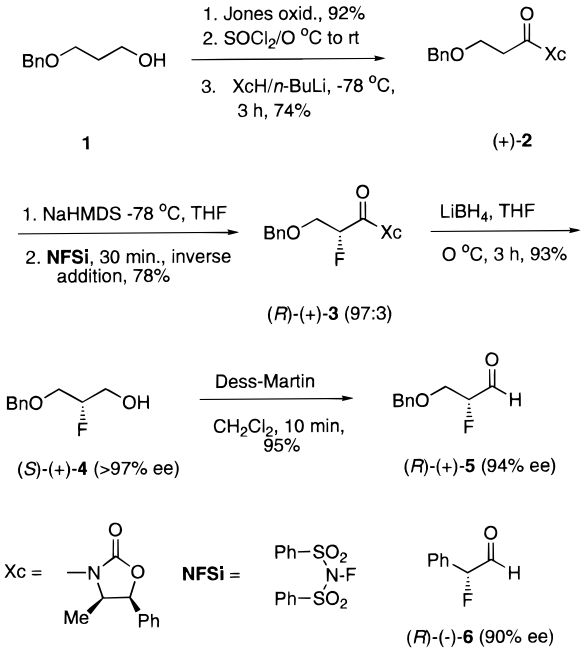
A well-known method for enhancing the biological and pharmacological activity of a molecule is the site-specific introduction of a fluorine atom.[1−5] Coupled with the importance of chirality in bioactive compounds, the development of new and improved methods for the enantioselective introduction of fluorine is of significance. Of particular interest in this regard are fluorinated carbohydrates because they exhibit significant biological activity and are useful probes of biochemical mechanisms.[6] These target molecules are generally prepared from carbohydrate substrates via multistep procedures requiring protection and/or functionalization of the sugar prior to fluorination.[7] In this paper, we describe the first enantioselective synthesis of epimerizable α-fluoro aldehydes and their utility as chiral building blocks by the asymmetric synthesis of 4-deoxy-4-fluoro-D-arabinopyranose **11**.

Nonracemic α-fluoro acids and α-fluoro ketones[3,4,8] have been reported, but by contrast α-fluoro aldehydes are rare.[9−13] Purrington et al. prepared racemic α-fluoro aldehydes by treatment of silyl enol ethers with 5% F_2/N_2 and described them as "unstable", decomposing on standing.[9] Similar observations were made by Suga and Schlosser.[10] A sugar-derived α-fluoro aldehyde diastereoisomer has been reported,[11] and a nonepimerizable tertiary α-fluoro aldehyde was prepared in a series of steps from (*S*)-monoethyl 2-fluoro-2-methylmalonate.[12] A potential source of nonracemic α-fluoro aldehydes is the oxidation of enantiopure 2-fluorohydrins readily available via reduction of α-fluoro carboximides (Scheme 1).

Scheme 1



The requisite α-fluoro carboximide **3** was prepared as follows: Jones oxidation of 3-(benzyloxy)-1-propanol (**1**) gave the corresponding acid in 92% yield. The acid, treated with $SOCl_2$, gave the acid chloride, which was not isolated but treated in situ with the lithium salt of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone, generated by reaction with 1.0 equiv of *n*-BuLi at −78 °C. Electrophilic fluorination of the sodium enolate of **2** with *N*-fluorobenzenesulfonimide (NFSi)[14,15] gave (+)-**3** in 78% yield and in a 97:3 dr.[16] Flash chromatography improved the dr to >99:1. The major diastereoisomer has the (*R*)-configuration because, as previously established, the bulky NFSi reagent approaches the enolate from the sterically least hindered direction.[15,17] Optimum conditions involved addition of the enolate of (+)-**2** to NFSi at −78 °C and quenching after 15−30 min. Longer reaction times and use of the lithium enolate resulted in the formation of benzyl 2-fluoro-3-(benzyloxy)propionate apparently formed by decomposition of the enolate.[18] Reduction of Cα-(*R*)-**3** with $LiBH_4$ gave the 2-fluorohydrin (*S*)-**4** in 93% yield and >97% ee.[19]

The oxidations of the fluorohydrin (*S*)-**4** and (*R*)-2-

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(16) Selected properties: (+)-**2**, gum, $[\alpha]^{20}_D$ +25.1 (*c* 1.95, $CHCl_3$); (*R*)-(+)-**3**, gum, $[\alpha]^{20}_D$ +27.9 (*c* 0.98, $CHCl_3$); (*S*)-(+)-**4**, oil, $[\alpha]^{20}_D$ +5.7 (*c* 1.13, MeOH); (*R*)-(+)-**5**, oil, $[\alpha]^{20}_D$ +9.3 (*c* 2.14, $CHCl_3$); (*R*)-(-)-**6**, oil, $[\alpha]^{20}_D$ −34.28 (*c* 0.7, $CHCl_3$); (*S*)-(-)-**7**, oil, $[\alpha]^{20}_D$ −21.80 (*c* 1.99, $CHCl_3$); (2*S*,3*S*,4*R*)-(+)-**8**, mp 70−3 °C, $[\alpha]^{20}_D$ +10.2 (*c* 1.08, $CHCl_3$); (+)-**9**, oil, $[\alpha]^{20}_D$ +14.33 (*c* 2.12, $CHCl_3$); (+)-**10**, oil, $[\alpha]^{20}_D$ +7.64 (*c* 3.86, MeOH); **11**, oil.

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(18) This compound gave satisfactory elemental analysis and had spectral properties consistent with its structure.

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Table 1. Selective Oxidation of Fluorohydrins to α-Fluoro Aldehydes 5 and 6

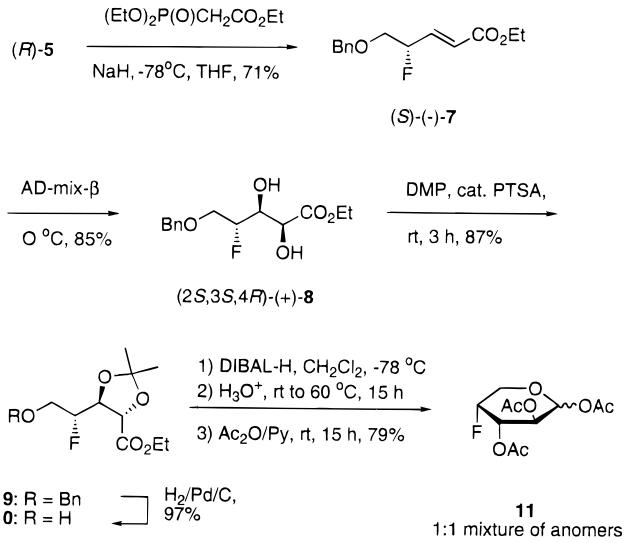
entry	Fluorohydrin	Oxidizing Reagent (time, min.)	α-Fluoroaldehydes 5 and 6 % ee[a]	% Yield[b]	δ ^{19}F ($CFCl_3$) ppm
1		Swern	0	41	
2		PCC	decomposition		
3		Dess-Martin (30)	60	90	
4		(10)	90	90	-192.5
5	(*S*)-**4**	Dess-Martin (10)	94	95	-204.8
6		Moffatt[c]	0	20	

[a] Determined by ^{19}F NMR on the corresponding imine of (*R*)-(+)-α-methylbenzylamine (ref 22). [b] Isolated yield of crude product. [c] $C_5H_5N{\cdot}SO_3$/DMSO/Et_3N, see ref 20.

phenyl-2-fluoroethanol[17] to α-fluoro aldehydes **5** and **6** was accomplished by treatment with an equivalent amount of the oxidizing reagent (Table 1). The Swern oxidation gave racemic material under a variety of conditions as did a modified Moffatt oxidation procedure (Table 1, entry 6).[20] PCC gave uncharacterizable materials (Table 1, entry 2). The only reagent to give satisfactory yields and ee's was the Dess−Martin periodinane[21] reagent in CH_2Cl_2 at rt (Table 1, entries 3−5). The oxidation time proved to be critical, and much lower ee's were observed on longer reaction times (Table 1, entry 3). Attempts to purify the α-fluoro aldehydes **5** and **6** by flash chromatography on silica gel resulted in decomposition so they were used in crude form in subsequent reactions (Scheme 2). α-Fluoro aldehydes **5** and **6** exhibit resonance absorption in the ^{1}H NMR at δ 9.76 and 9.81 ppm for the aldehydic proton and at δ −204.8 and −192.5 ppm, respectively, in the ^{19}F NMR. Treatment of **5** and **6** with (*R*)-(+)-α-methylbenzylamine in $CDCl_3$ gave the diastereomeric imines within a few minutes and was used to evaluate the enantiomeric purity by ^{19}F NMR (Table 1).[22]

Because of the enhanced acidity of the α-fluoro carbon proton α-fluoro carbonyl compounds are extremely sensitive to base-catalyzed epimerization.[17,23] Consequently, there was considerable concern about whether α-fluoro aldehydes **5** and **6** would be useful nonracemic building blocks. Horner−Wadsworth−Emmons reaction of (*R*)-**5** with NaH/triethylphosphonoacetate at −78 °C afforded a 92:8 *E*/*Z* mixture of the allyl fluoride **7**, which on purification by flash chromatography gave pure (*E*)-**7** in 71% yield. Significantly, no epimerization of the α-fluoro stereogenic center in **7** was detected, which was determined to be >97% ee by deprotection, reduction (H_2/Pd/C), and formation of the Mosher ester of the resulting saturated alcohol. Sharpless AD of **7** using AD-mix-β ($MeSO_2NH_2$ in *t*-BuOH/H_2O) for 2 days at rt gave the dihydroxy compound (2*S*,3*S*,4*R*)-**8** as a 97:3 mixture of diastereomers based on the Sharpless model.[24,25] Earlier

Scheme 2



we had shown that the adjacent fluorine atom in compounds related to **7** have little, if any, stereodirecting effects in OsO_4-catalyzed dihydroxylation.[15] If the AD-mix-β reagents were added separately using $K_2OsO_4{\cdot}2H_2O$, the reaction was complete within 30 min, affording **8** in 96% yield with no change in the dr. Crystallization from Et_2O/hexane afforded **8** as a single diastereoisomer. Protection with 2,2-dimethoxypropane (DMP) gave acetonide **9** (87%) followed by deprotection (H_2/Pd/C) afforded **10** in 97% yield. DIBAL-H reduction presumably gave an intermediate aldehyde or prealdehyde that could not be isolated.[26]

Consequently, the crude reaction mixture was treated in situ with 1% H_2SO_4 at 60 °C to remove the acetonide and acetylated with Ac_2O/pyridine to give 1,2,3-tri-*O*-acetyl-4-deoxy-4-fluoro-D-arabinopyranose (**11**) as a 1:1 mixture of anomers that could not be separated by flash chromatography. The combined yield for the 3 steps was 79%. The structure of **11** is supported by satisfactory elemental analysis and the similarity of its spectral properties to the related sugar 1-methyl-4-deoxy-4-fluoro-L-arabinopyranoside.[27]

In summary, the first examples of chiral nonracemic, epimerizable α-fluoro aldehydes were prepared, and their utility was demonstrated by the noncarbohydrate synthesis of 4-deoxy-4-fluoro-D-arabinopyranose **11**.

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Supporting Information Available: Experimental procedures and compound characterization data (17 pages).

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