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Catalytic Asymmetric Synthesis of a 1-Deoxy-1,1-difluoro-D-xylulose

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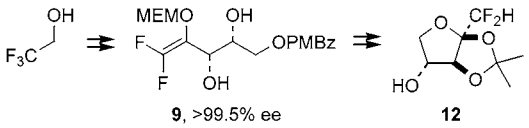
ABSTRACT



9, >99.5% ee **12**

A new route, of potential strategic importance, to a difluorosugar analogue has been developed. Key steps included a Stille coupling and a highly regio- and enantioselective dihydroxylation of a highly substituted diene. Protecting groups were chosen to enhance the reactivity of the disubstituted allylic fragment in the AD reaction and allow deprotection under orthogonal conditions.

Fluorosugars[1] are of considerable current interest because they retain much of the shape, electron distribution, and function of natural saccharides while lacking the ability to enter, as hydrogen bond donors, into critical hydrogen bonding interactions with nucleic acids or proteins. This makes them very useful molecular tools for identifying key interactions used by receptors in binding saccharide ligands.[2] Syntheses of difluorosugars using fluorination methods to transform a ketonic carbonyl group are common,[3] though not without difficulties caused by side reactions[4] associated with high electron demand (elimination, neighboring group participation, 1,2-shifts).[5] There are still few routes to fluorosugars that are based upon inexpensive and readily available fluorinated feedstocks or building blocks.[6] One important method for the de novo synthesis of monosaccharides[7] uses the Sharpless asymmetric dihydroxylation (AD) reaction of dienes.[8] We wished to develop the chemistry of fluorinated building block trifluoroethanol so that catalytic asymmetric[9] syntheses of fluorosugars would become available from dihydroxylation reactions of fluorinated dienes,[10] and we selected 1-deoxy-1,1-difluoro-D-xylulose as an illustrative target.

There is a high level of interest in 1-deoxy-D-xylulose currently due to its pivotal role in the biosyntheses of pyridoxol phosphate, thiamine pyrophosphate, and the phytyl chain of ubiquinone in *E. coli* (Scheme 1).[11]

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(1) Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Carbohydr. Res.* **2000**, *327*, 47.

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(5) Dax, K.; Albert, M. *Top. Curr. Chem.* **2001**, *215*, 193.

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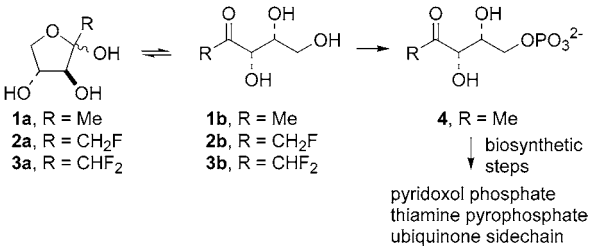
Scheme 1. 1-Deoxy-d-xylulose **1** and Putative Inhibitors **2** and **3** of Downstream Enzymes



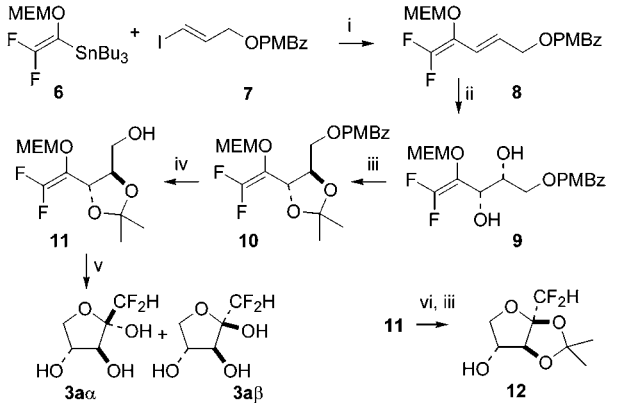
Bouvet and O'Hagan[12] proposed **2** and **3** as potential inhibitors of enzymes involved in the metabolism of 1-deoxy-D-xylulose and the 5-phosphate **4**. The compounds were inactive; however, both exist almost exclusively in cyclic forms **2a** and **3a**, preventing the key phosphorylation step.

Dihydroxylation of enone **5** was attempted during their synthesis, but the diol product could not be isolated cleanly from the reaction.

The same fluoroketone reactivity that prevents processing of **2** and **3** creates potential handling difficulties, so we planned a route in which the ketone is masked until a late stage, and significantly, one in which phosphorylation of the 5-hydroxyl group is possible.

Stannane **6** was synthesized on a 0.5 mol scale according to our published procedure[13] and coupled with protected iodoallylic alcohol **7** (synthesized from propiolic acid in four steps; hydroiodination,[14] esterification, selective reduction,[15] and esterification) under modified Farina−Liebeskind conditions[16] with full conversion to afford the crude diene product **8** with a clean ^{19}F NMR spectrum (Scheme 2).[17] The diene was freed from tin residues by KF treatment and could be chromatographed on basic alumina, an essential precaution considering the sensitivity of similar products[18] to even mildly acidic conditions. Overall, a moderate yield of diene (which should be used soon after synthesis) was obtained. Dihydroxylation occurred very slowly under standard conditions; typical reactions required 1 week to reach 70−85% conversion, and a significant fall in the pH of the medium was observed over this period. However, when the pH was maintained[19] in the range 11.0−12.0, the reaction reached

Scheme 2. Diene Synthesis and Elaboration to Xylulose Analogues[a]



[a] Reaction conditions: (i) $Pd(OAc)_2$ (2.6 mol %), CuI (20.8 mol %), Ph_3P (10.4 mol %), DMF, 30−50 °C, 41%; (ii) $K_2OsO_4 \cdot 2H_2O$ (2 mol %), $(DHQD)_2PHAL$ (4 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), 1:1 *t*-BuOH/H_2O, pH 11.0−12.0, rt, 54%; (iii) anhydrous $CuSO_4$ (2 equiv), PTSA (1 mol %), acetone, rt, 68%; (iv) 30% H_2O_2 (4.2 equiv), $LiOH \cdot H_2O$ (2.2 equiv), 3:1 THF/H_2O, 0 °C, 61%; (v) Me_3SiCl (1.2 equiv), MeOH, rt, 88%; (vi) HCl (12 M), THF, rt.

completion in only 1 h and we were able to isolate diol **9** in 55% yield. The effect of pH maintenance is spectacular and demonstrates the critical importance of rapid osmate ester turnover for efficient catalysis. The use of the PMBz protecting group is also relatively unusual;[20] ester hydrolysis probably prevents recovery of the diol in higher yield, and it is possible that a PMB ether[7b] or PMP ether[7a] would offer similar reactivity and greater stability under the reaction conditions. However, we wished to be able to cleave the primary hydroxyl group under mild nucleophilic conditions, so these possibilities were not investigated. The dihydroxylation failed completely when THP-protected dienol was exposed to the AD conditions, demonstrating clearly that the electronic complementarity between protecting group and catalyst is a requirement for this reaction to proceed efficiently.

The diol was protected in acetonide **10**, and then the synthesis was completed by hydrolysis of the ester (presenting an opportunity for phosphorylation of alcohol **11**) followed by removal of both acetals, to afford deoxy difluorosugar **3a** as a 1:3 mixture of α- and β-anomers. Resonances in the ^{1}H NMR were assigned fully (by gradient COSY/HSQC/HMBC experiments), allowing the unambiguous identification of the H-3 methine proton. The configuration of the major anomer (**3a**β) was assigned by a NOE experiment that showed a strong transfer of magnetization from the H-3 methine to the CF_2H proton in the major anomer. Both anomers converged on **12** when the mixture was treated with acetone and an acid catalyst.

The material exhibited the same magnitude and sign of rotation as that reported by Bouvet and O'Hagan, confirming

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(20) (a) Ref 7. (b) Report on slow AD reactions of a related alkenyl substrate: Yokomatsu, T.; Yamagishi, T.; Suemune, K.; Yoshida, Y.; Shibuya, S. *Tetrahedron* **1998**, *54*, 767.

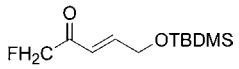

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Figure 1. Enone AD substrate used by Bouvet and O'Hagan.

that the sense of enantioselection conforms with the Sharpless model. Use of the $(DHQD)_2PHAL$ ligand predicts that **9** is the product; we determined an ee for the AD reaction by preparing the bis-(*S*)-Mosher ester (**13**) of **9** and the bis-(*S*)-Mosher ester of racemic diol **14** and examining their ^{19}F NMR spectra. Whereas the CF_3 region of the spectrum contained a number of peaks from esters and unreacted derivatizing agent that could not be deconvoluted, the CF_2 region of the spectrum of **13** contained only a single doublet for each of the vinylic fluorine atoms, even when a large number of data points (1579 between −90.0 and −95.0 ppm) and scans were recorded to optimize the signal-to-noise ratio (Figure 2a, Figure 3).

In contrast, two doublets were observed for each of the vinylic fluorine atoms in the bis-(*S*)-MTPA ester **14** of the racemic diol (Figure 2b); the ee is calculated as ≥99.5% on this basis.

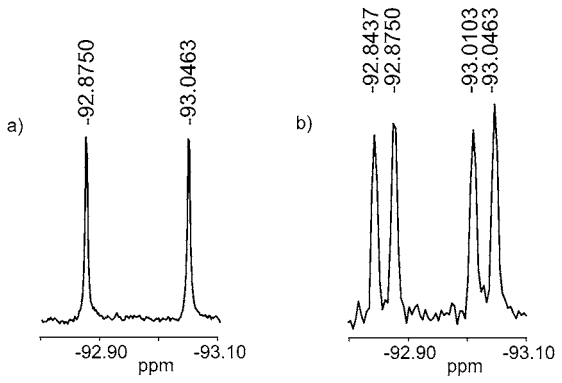

Figure 2. Partial ^{19}F NMR spectra [282 MHz, 300K, $CDCl_3$] of (a) **13** with enhanced signal-to-noise (1579 data points between −90.0 and −95.0 ppm) and (b) bis-(*S*)-Mosher ester of racemic diol **14**.

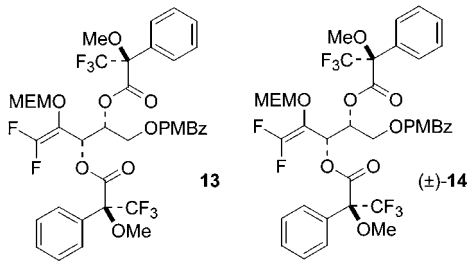

Figure 3. Mosher esters used for determination of ee.

Our method relies on Stille coupling to synthesize the key diene; obviously, methods that avoid the use of tin reagents and transition metal-catalyzed coupling would be preferable, and we are examining alternative routes currently. These findings do show that dienes such as **8** are useful substrates for Sharpless catalytic AD reactions, despite their relatively high lability. The dihydroxylation reaction is completely regioselective with the highly substituted alkenyl bond emerging untouched from the reaction. Sharpless and others have reported successful AD reactions of polyenes, but there are few examples where both alkenes bear deactivating substituents. Even with the use of a protecting group known to enhance AD reactivity, the dihydroxylation reaction was slow and pH control was essential, suggesting that **8** lies close to the lower limit of substrate reactivity. The AD products possess great potential for the synthesis of a wider range of difluorosugar analogues.

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Supporting Information Available: Full experimental procedures for **7**−**14**, characterization data for **7**−**12**, partial ^{19}F NMR data for **13** and **14**, HRMS for **13**, and ^{1}H, ^{19}F, and ^{13}C NMR spectra for **3a**α/**3a**β. This material is available free of charge via the Internet at http://pubs.acs.org.

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