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Boron trifluoride as a promoter and fluoride donor in the aldol reaction of *trans* α,β-epoxyaldehydes. Access to 5- and 6-fluoro heptulosonic ester analogues

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Abstract

A direct synthesis of 5- and 6-fluoro heptulosonic esters is achieved by reaction of *trans* α,β-epoxyaldehydes with 2-(trimethylsilyloxy)acrylate in presence of $BF_3 \cdot Et_2O$.

Keywords: aldol reactions; epoxides; halohydrin; fluorine compounds.

Higher 3-deoxy-2-ulosonic acids are widespread natural carbohydrates. The first compound of this family is 3-deoxy-D-arabino-heptulosonic acid which in its 7-phosphate form (DAHP) is an important intermediate in the shikimic acid pathway along which the aromatic aminoacids and a multitude of other aromatic and alicyclic compounds are biosynthesized in bacteria, fungi and plants.[1] Other ulosonic acids like the 3-deoxy-D-manno-octulosonic acid (KDO)[2] and the 5-*N*-acetyl neuraminic acid[3] play an important role in many biological phenomena.[4]

Further study on the medicinal chemistry and biochemistry of these ulosonic acids requires practical routes to the natural, unnatural derivatives and analogues of these sugars. In the case of the heptulosonic acid, biosynthesis and chemical synthesis of this compound has been reported by many groups.[3,5,6] Its synthesis has almost exclusively employed aldehydes derived from sugars. The methodology we have developed some years ago was different and was based on the use of α,β-epoxyaldehydes. It led to the synthesis of protected heptulosonic ester through 4+2+1 carbon atoms incorporation, that may also allow modification at the C1 position, in 11 steps and 19% total yield.[7]

In our search to achieve more direct access to heptulosonic analogues, we explored a method that makes use of ethyl pyruvate derivatives. Only a few cases have been reported in the literature by three groups.[8,9] Recently, enol trimethylsilylethers of the pyruvate esters were reacted in Mukaiyama aldol reactions with non-optically active aldehydes or acetals. Among various Lewis acids tested the boron-trifluoride promoted reaction gave the best results.

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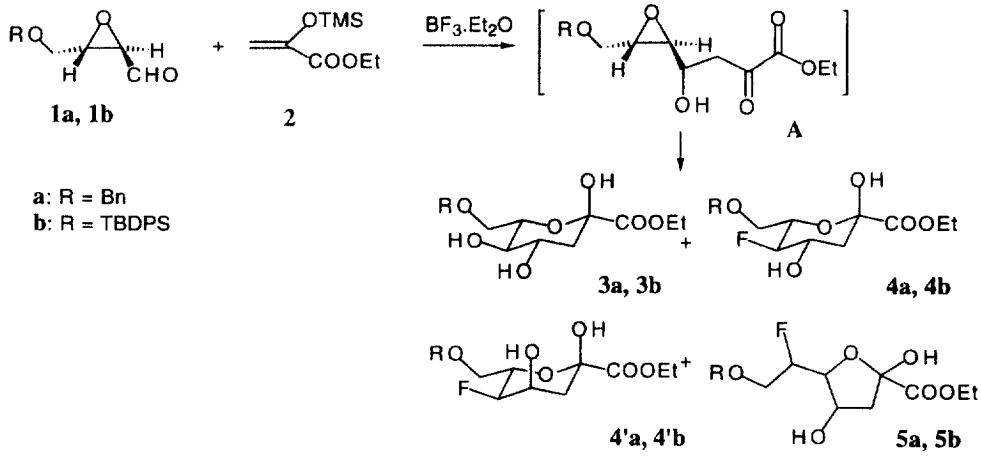
In our case, we studied the Mukaiyama aldol reaction of epoxyaldehydes **1a**, **1b** with 2-(trimethylsilyloxy)acrylate **2** which has been prepared in 70% yield from the corresponding pyruvate, by treatment with trimethylsilylchloride and triethylamine in presence of a catalytic amount of DMAP.[8] Epoxyaldehydes **1a**, **1b** have been prepared in a four steps procedure starting from commercially available *cis*-1,4-butene-2-diol in 65% and 75% overall yield.[10]

In some initial experiments compounds **1a** and **2** were treated with several promoters ($BiCl_3/ZnI_2$ or NaI, $Eu(fod)_3$, $LiClO_4$, $Sn(OTf)_2$, TMSOTf, $BF_3 \cdot Et_2O$); we have already successfully used many of them in the Lewis acid promoted aldolisation reaction between an α,β-epoxyaldehyde and the enolsilylether of *tert*-butylacetate.[11] The reactions have been carried out either by using a catalytic amount of Lewis acid or one equivalent at rt, –40°C ($Sn(OTf)_2$) or 0°C ($BF_3 \cdot Et_2O$). The results showed that for all Lewis acids used except for $BF_3 \cdot Et_2O$ the condensation reaction either did not take place or gave traces of the aldol compounds in a very complex reaction mixture ($LiClO_4$, TMSOTf).

The best result was obtained when using boron-trifluoride promoter. In a typical experiment, to a solution of **2** and $BF_3 \cdot Et_2O$ (1 equiv.) in CH_2Cl_2 at 0°C was added dropwise a solution of epoxyaldehyde **1a** or **1b**. After 6 h at 0°C, 0.5 equiv. of $BF_3 \cdot Et_2O$ was added and 10 h later the reaction mixture was quenched and the organic phase extracted. We were grateful to see that after careful purifications and analysis of the compounds obtained from the complex mixture, some very interesting futures arised. The reaction yielded three types of compounds, the expected heptulosonic esters **3** and mainly the fluoro heptulosonic esters **4** and **5** in a six- or five-membered form (Scheme 1).



Scheme 1. Reagents and conditions: $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 6 h then 0.5 equiv. $BF_3 \cdot Et_2O$, rt, 10 h

Compounds **4**, **4′** were obtained in 15–18% yield in a ratio 2:1 in favor of compounds **4**, while, compounds **5** are obtained in 25% yield (anomer ratio α:β 1:1). Finally, compounds **3** have been obtained in 3% yield. Spectroscopic analysis of **3a** (^1H, ^{13}C NMR and COSY experiments) showed unambiguously the arabino form of the heptulosonic ester in agreement with previous results.[6,7] The absolute configurations on C-4, C-5 carbon atoms for compounds **4** and **5**, their furanosidic or pyranosidic form and the position of the fluorine atom have been established by ^{19}F, ^1H and ^{13}C NMR spectroscopy.

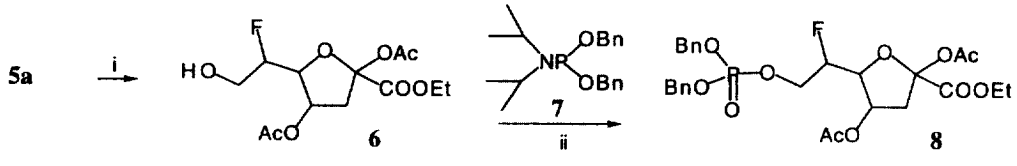
The pyranosidic forms for compounds **3**, **4**, **4′** and the furanosidic one for **5** were confirmed by the ^{13}C chemical shifts of C-2 and C-3 carbon atoms. In fact, the signals for C-2 and C-3 appear at δ C-2=102–105 ppm and δ C-3>45 ppm for compound **5** in contrast to that of **3**, **4** and **4′** which resonate at δ C-2=92–98 ppm and δ C-3<41 ppm. Comparable shift differences for ulosonic esters have been observed by Zbiral et al.[12] and Barton et al.[13]

For fluoropyranosidic compounds **4** and **4′** we observe by ^{1}H NMR spectroscopy (400 MHz), large coupling constants for **4** ($J_{H3-H4} \approx 11.3$ Hz; $J_{H4-H5} \approx 9.2$ Hz and $J_{H5-H6} = 9.1$ Hz) while for compounds **4′** the values are 3.5–4.8 Hz, 3.2 Hz and 9.9 Hz, respectively. These values clearly indicate the equatorial (**4**) and axial (**4′**) position of the 4-OH group which is clearly correlated to the synthesis of the two diastereoisomeric β-hydroxyesters **A** in the condensation step. Finally, taking into account the relative configurations of **1a**, **1b** and spectroscopic data of **5a**, **5b**, in agreement with furanosidic compounds reported,[14] a C4/C5 *threo* configuration can be assigned.

It is noteworthy that there is only another one-pot synthesis of furanosidic ulosonic analogues in the literature. Shiba et al.[14] have reported that condensation of D-glucose with oxaloacetic acid followed by treatment with HCl in MeOH leads to pyranosidic and furanosidic nonulosonic esters in 3% and 15% yields, respectively.

Introduction of fluorine when using an epoxide and a boron trifluoride ether complex is not a common result. We have first checked by ^{19}F NMR spectroscopy that there is no other compound except **4**, **4″** and **5** in the reaction mixture possessing a fluorine atom. We have also performed the reaction of α,β-epoxyaldehyde **1a** with $BF_3 \cdot Et_2O$ under the same conditions as for the aldolisation reaction. While degradation of **1a** occured after several hours no introduction of fluorine is observed in the final reaction mixture. Thus, fluoride attack on the epoxide ring proceeds after the aldolisation reaction. This seems in agreement with the results concerning fluorohydrin formation from epoxysteroids[15,16] where a carbonyl group (ketone or ester) should be suitably positioned for the reaction to occur. Even if the precise origin of the fluoride nucleophile is not clear, fluoride attack on the epoxide ring proceeds with inversion of configuration on each carbon of the epoxide.

The α,β-anomers of compound **5a** have been transformed in a three step procedure (Scheme 2) and 85% yield to give the protected fluoro benzylphosphates **8**.[17] The anomers can be separated by HPLC chromatography (eluant PE:isopropylalcohol 95/5; α:β 40:60). Under analytical conditions (microporosil 12 μm, flow rate 1 ml/min) the retention times are 26.87 min (α) and 28.93 min (β). We were also grateful to see that pure anomers of **8** can be resolved on a Chiracel OD column (see for example, the β-anomer Fig. 1).



Scheme 2. Reagents and conditions: (i) DMAP, Ac_2O, rt 2 h, then HF pyridine, rt, 15 h; (ii) tetrazole, **7**, CH_2Cl_2, rt 2 h, then mcpba, –40°C, 50 min

In conclusion, we have found a new synthetic methodology based on the use of non-carbohydrate starting compounds that can lead in one-step to the synthesis of 5- and 6-fluoro heptulosonic analogues. Work is in progress to optimize the reaction conditions and to understand how the fluorine transfer occurs. The 7-phosphate fluoro heptulosonic analogues, after purification and deprotection, will be tested as inhibitors of the DHQ synthase, the enzyme that transforms the 3-deoxy-D-arabino heptulosonic acid 7-phosphate to the 3-dehydroquinic acid in the shikimic acid pathway. These results also open the possibility for an access to higher modified ulosonic acids.

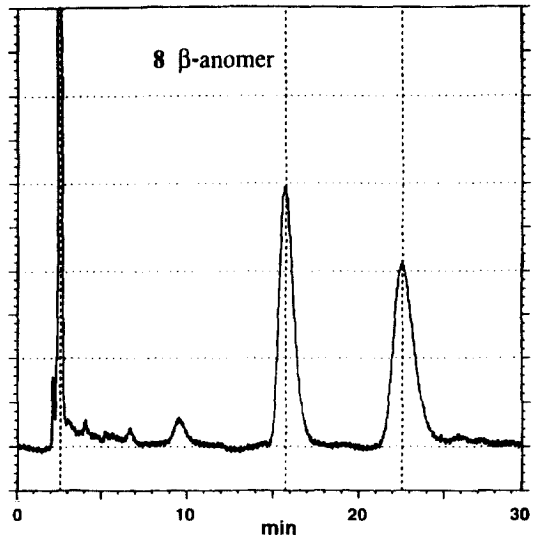


Figure 1. Enantiomeric separation of the β-anomer of compound **8** on a Chiracel OD column. Conditions: isopropylalcohol/hexane 20/80, flow rate 1.3 ml/min (λ=220 nm)

Acknowledgements

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17. Compound **8α**: ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm)=1.23 (t, 3H, J=7.1 Hz, CH_3(*Et*)); 2.01 (s, 3H, CH_3(*OAc*)); 2.04 (s, 3H, CH_3(*OAc*)); 2.63 (dd, 1H, $J(H_{3a}H_4)$=6.2 Hz, $J(H_{3a}H_{3b})$=15.6 Hz, H_{3a}); 2.73 (dd, 1H, $J(H_{3b}H_4)$=2.5 Hz, $J(H_{3a}H_{3b})$=15.6 Hz, H_{3b}); 4.20 (q, 2H, J=7.1 Hz, CH_2(*Et*)); 4.25 (dddd, 1H, $J(H_{7a}F)$=28.8 Hz, $J(H_{7a}P)$=7.2 Hz, $J(H_{7a}H_6)$=5.0 Hz, $J(H_{7a}H_{7b})$=12.2 Hz, H_{7a}); 4.41 (dddd, 1H, $J(H_{7b}F)$=25.2 Hz, $J(H_{7b}P)$=6.1 Hz, $J(H_{7b}H_6)$=1.9 Hz, $J(H_{7b}H_{7a})$=12.2 Hz, H_{7b}); 4.44 (ddd, 1H, $J(H_5F)$=6.00 Hz, $J(H_5H_4)$=4.3 Hz, $J(H_5H_6)$=8.21 Hz, H_5); 4.85 (ddddd, 1H, $J(H_6F)$=46.1 Hz, $J(H_6P)$=1.74 Hz, $J(H_6H_5)$=8.26 Hz, $J(H_6H_{7a})$=4.7 Hz, $J(H_6H_{7b})$=1.7 Hz, H_6); 5.02 and 5.04 (2d, 4H, CH_2(*OBn*)); 5.44 (ddd, 1H, $J(H_4H_{3b})$=2.5 Hz, $J(H_4H_{3a})$=6.1 Hz, $J(H_4H_5)$=4.3 Hz, H_4); 7.31 (s, 10H, H_{ar}(*OBn*)); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm)=13.96 (CH_3(*Et*)); 20.84 (CH_3(*OAc*)); 43.31 (C_3); 62.44 (CH_2(*Et*)); 66.69 (dd, $^{2}J(C_7F)$=19.17 Hz, $^{2}J(C_7P)$=5.45 Hz, C_7); 69.48 (d, $^{2}J(CP)$=5.48 Hz, CH_2(*OBn*)); 71.83 (C_4); 78.89 (d, $^{2}J(C_5F)$=30.70 Hz, C_5); 87.53 (dd, $^{1}J(C_6F)$=175.63 Hz, $^{3}J(C_6P)$=7.35 Hz, C_6); 104.48 (C_2); 135.79/135.85/128.83/128.05 (OBn); 166.32 (C_1); 169.49 and 169.90 (C(*OAc*)); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm)=−121.51 (dddd, $^{3}J(H_{7b}F)$=25.71 Hz, $^{3}J(H_{7a}F)$=29.54 Hz, $^{3}J(H_5F)$=5.75 Hz, $^{2}J(H_6F)$=46.1 Hz); ^{31}P NMR (160 MHz, $CDCl_3$): δ (ppm)=−0.56. MS CI/NH_4^+ *m/z*=600 [(M+18)$^+$, 100]. Compound **8β**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.21 (t, 3H, J=7.1 Hz, CH_3(*Et*)); 2.04 (s, 3H, CH_3(*OAc*)); 2.05 (s, 3H, CH_3(*OAc*)); 2.53 (d, 1H, $J(H_{3a}H_{3b})$=15.5 Hz, H_{3a}); 2.77 (dd, 1H, $J(H_{3b}H_4)$=5.7 Hz, $J(H_{3a}H_{3b})$=15.5 Hz, H_{3b}); 4.17 (q, 2H, J=7.1 Hz, CH_2(*Et*)); 4.20 (m, 1H, $J(H_{7a}P)$=7.1 Hz, $J(H_{7a}H_6)$=5.2 Hz, $J(H_{7a}H_{7b})$=12.2 Hz, H_{7a}); 4.40 (dddd, 1H, $J(H_{7b}F)$=26.0 Hz, $J(H_{7b}P)$=6.0 Hz, $J(H_{7b}H_6)$=1.8 Hz, $J(H_{7b}H_{7a})$=12.2 Hz, H_{7b}); 4.39 (ddd, 1H, $J(H_5F)$=5.1 Hz, $J(H_5H_4)$=5.1 Hz, $J(H_5H_6)$=8.6 Hz, H_5); 4.83 (ddddd, 1H, $J(H_6F)$=46.2 Hz, $J(H_6P)$=1.7 Hz, $J(H_6H_5)$=8.4 Hz, $J(H_6H_{7a})$=4.8 Hz, $J(H_6H_{7b})$=1.7 Hz, H_6); 5.02 and 5.03 (2d, 4H, J=8.0 Hz and J=8.0 Hz, CH_2(*OBn*)); 5.49 (ddd, 1H, $J(H_4H_{3b})$=4.9 Hz, $J(H_4H_5)$=4.9 Hz, H_4); 7.32 (s, 10H, H_{ar}(*OBn*)); ^{19}F NMR (400 MHz, $CDCl_3$): δ (ppm)=−119.96 (dddd, $^{3}J(H_{7b}F)$=27 Hz, $^{3}J(H_{7a}F)$=27 Hz, $^{3}J(H_5F)$=5.25 Hz, $^{2}J(H_6F)$=46.2 Hz); ^{31}P NMR (160 MHz, $CDCl_3$): δ (ppm)=−0.57. MS CI/NH_4^+ *m/z*=600 [(M+18)$^+$, 100].