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First synthesis of 5-fluoro-(+)-MK7607, its 1-epimer and 6-deoxy derivative

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ABSTRACT

(+)-MK7607 is a patented naturally occurring unsaturated pseudo-carbasugar possessing herbicidal activity. We present herein the first synthesis of the 5-fluorinated analogue (1*S*, 2*S*, 3*R*, 4*R*)-5-fluoro-6-(hydroxymethyl)cyclohex-5-ene-1,2,3,4-tetrol as well as that of two related compounds, namely its 1-epimer and its 6-deoxy derivative.

The (non-detachable) prefix 'carba-' signifies replacement of a heteroatom by carbon in general natural product nomenclature, and may be applied to replacement of the hemiacetal ring oxygen in carbohydrates if there is a desire to stress homomorphic relationships.[1] Therefore, carbasugars are sugar analogues in which the endocyclic oxygen has been replaced by a methylene group or its derivatives.[1,2] However, this definition is misconstrued by many authors, who include carbocyclic polyols containing a non-substituted carbon, which should be called pseudo-carbasugars because they do not have a homomorphic sugar associated.[2] As mimics of substrates in their ground-state, carbasugars do not display very high inhibitory activity towards glycosidases. Therefore, nature selected carbasugar-based inhibitors by adding an amine or a double bond in the cycle to mimic transition states of the substrates of these enzymes. Valienamine or (+)-MK7607 enters this category of pseudo-carbasugars possessing interesting biological activity (Fig. 1). (+)-MK7607 is a patented naturally occurring herbicide, produced through fermentation of *Curvularia eragrostidis* D2452.[3] Besides, its 1-*epi*-MK7607 also presents a high affinity to galactose-recognizing lactin (ML I).[4] So far, racemic MK7607,[5] non natural enantiomer (−)-MK7607[6] and 1-*epi*-(+)-MK7607[7] were synthesized. In the context of biological activity, addition of a fluorine atom is definitely a bonus as reporter group[8] or to improve physicochemical properties.[9] We present herein the first synthesis of fluoro-(+)-MK 7607, as well as that of two derivatives, namely its 1-epimer and the 6-deoxy analogue. Preliminary studies on their inhibitory activity against an array of glycosidases are also reported.

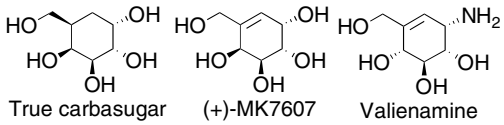

Figure 1.

We have been involved in the synthesis of carbasugars, and our strategy is based on a Lewis acid induced rearrangement of a sugar bearing an enol ether, which possesses an electron donating group.[10] This reaction was successfully applied to the synthesis of carbamonosaccharides, carbadisaccharides,[11] *gem*-difluorocarbaglucose,[12] and more recently to *gem*-difluorocarbagalactose.[13] The synthesis of this compound starts from known primary alcohol **1**[14] that was transformed into alkyne **2** through Swern oxidation and Corey–Fuchs reaction. The PMP group was oxidatively cleaved to obtain the corresponding lactol. Oxidation followed by olefination[15] of the resulting lactone using CBr_2F_2 afforded the key *gem*-difluoroalkene **3**. Formation of the Cobalt-cluster on the triple bond, followed by TIBAL induced rearrangement and subsequent removal of the Cobalt gave the carbocyclic products **4α** and **4β** in 64% yield over three-step as an almost 1:1 mixture of axial and equatorial alcohols (Scheme 1).

Next steps usually comprise partial hydrogenation and reductive ozonolysis. When separately applied to compounds **4α** and **4β**, the expected compounds **5α** and **5β** were obtained as major products in each case, but after careful separation, which involved an acetylation-separation sequence, a secondary product was

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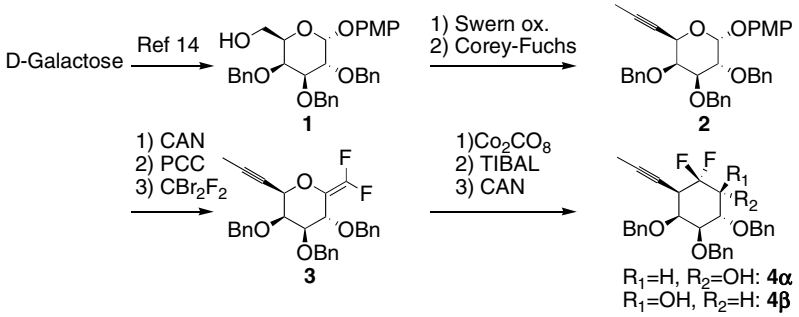
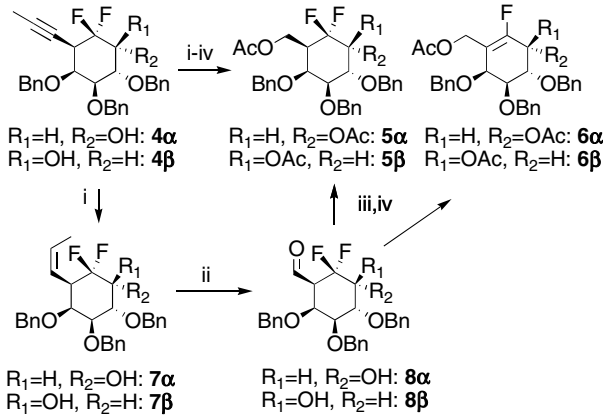


Scheme 1. Synthesis of *gem*-difluorocarbagalactose derivatives **4α** and **4β**.



Scheme 2. Cleavage of the triple bond. Reagents and conditions: (i) $Pd/CaCO_3$, H_2, EtOAc, 2 h; (ii) O_3, CH_2Cl_2, −78 °C, 2 min; (iii) $NaBH_4$, CH_2Cl_2/EtOH (1:5), rt, 45 min; (iv) Ac_2O, Pyr., 2 h, rt; 92% yield over four steps for both isomers **5α** or **β**:**6α** or **β**, **3**:**2**.

isolated and identified as the unsaturated compound **6α** or **6β**. The formation of those compounds was attributed to an elimination reaction occurring during the three-step process to convert the triple bond into CH_2OH. The expected α,β-elimination of HF from the transient aldehydes **8α** and **8β** with DBU was investigated and led only to complex mixtures (Scheme 2).

Conventional hydrogenolysis of **6α** surprisingly led to 6-deoxy-5-fluoro-(+)-MK7607[16] via peracetylated **9α**, putatively through a π-allyl intermediate accounting for the abstraction of the acetate group (Scheme 3). Prior deacetylation of **6β** followed by hydrogenolysis of **10β** led to a complex mixture of products. Finally, benzyl ethers were cleaved with a Lewis acid (BCl_3) and the desired 5-fluoro-(+)-MK7607[17] and its 1-*epi*-(+)-MK7607[18] were delivered in 78% and 75% yield from **6α** and **6β**, respectively via the corresponding peracetylated **11α** and **11β** (Scheme 3).

These three compounds were tested as glycosidase inhibitors for bovine kidney α-L-fucosidase, coffee beans α-galactosidase, *Escherichia coli* and *Aspergillus oryzae* β-galactosidase, rice and yeast α-glucosidase, *Aspergillus niger* amyloglucosidase, almonds β-glucosidase, jack beans α-mannosidase, snail β-mannosidase, *A. niger* β-xylosidase, bovine kidney and jack beans β-*N*-acetylglucosaminidase but no interesting activity was detected.

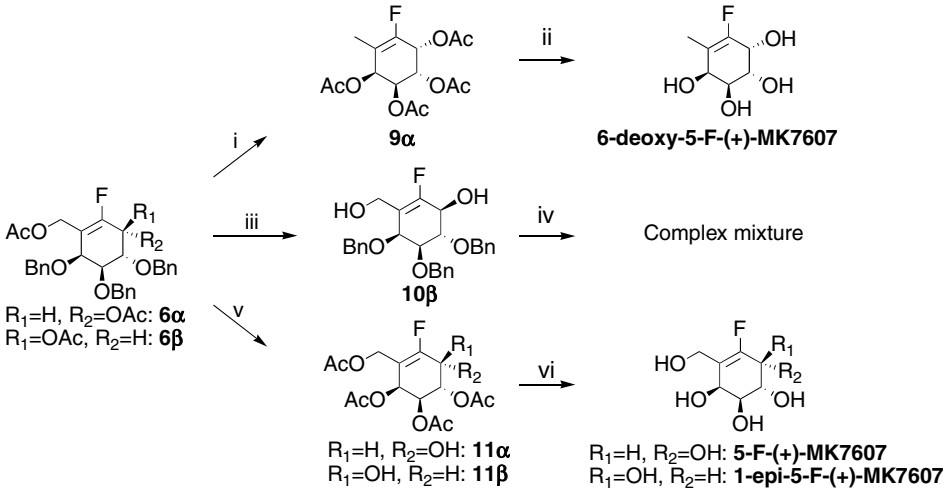
In conclusion, we have synthesized three fluorinated derivatives of the naturally occurring product (+)-MK7607, which biological interest may rely on the evaluation of their herbicidal activity to be carried out in the near future.

Acknowledgments

The authors thank Fundação para a Ciência e Tecnologia (FCT Portugal) for research grant (João Sardinha) as well as Claudia Bello and Professor Pierre Vogel for testing inhibitory activity.

Supplementary data

Experimental procedure and spectroscopic data for the synthesis of **6α** and **6β** as well as **5-fluoro-(+)-MK7607**, **1-epi-5-fluoro-**



Scheme 3. Synthesis of fluoro-MK7607 and derivatives. Reagents and conditions: (i) (1) Pd/C, H_2, EtOAc/MeOH, 1.5 h; (2) Ac_2O, Pyr., 2 h, rt, 94% over two steps; (ii) MeONa, MeOH, rt, 2 h, quant.; (iii) MeONa, MeOH, rt, 2 h, 89%; (iv) Pd/C, H_2, EtOAc/MeOH, 1.5 h; (v) (1) BCl_3, DCM, −78 °C, 3.5 h; (2) Ac_2O, Pyr., 2 h, rt, 75% or 78% over two steps; (vi) MeONa, MeOH, rt, 2 h, quant.

(+)-MK7607 and **6-deoxy-5-fluoro-(+)-MK7607** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.070.

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16. *6-Deoxy-5-fluoro-(+)-MK7607*: $[\alpha]_D^{20}$ +88.5 (*c* 0.13, MeOH); ^{1}H NMR (D_2O, 400 MHz): δ 4.28 (ddd, 1H, J = 0.9 Hz, $J_{5,6}$ = 4.6 Hz, $J_{1,F}$ = 9.7 Hz, H-6), 4.08 (dd, 1H, $J_{3,4}$ = 4.1 Hz, J = 6.5 Hz, H-3), 3.81 (ddd, 1H, J = 1.0 Hz, $J_{5,6}$ = 4.6 Hz, $J_{4,5}$ = 10.9 Hz, H-5), 3.71 (dd, 1H, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 10.9 Hz, H-4), 1.65 (d, 3H, J = 2.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.97 (d, $^1J_{C,F}$ = 256.8 Hz, C-1), 114,86 (d, $^2J_{C,F}$ = 12.1 Hz, C-2), 69.70 (d, $^3J_{C,F}$ = 11.0 Hz, C-3), 68.29 (d, $^4J_{C,F}$ = 1.8 Hz, C-4), 67.94 (d, $^3J_{C,F}$ = 11.0 Hz, C-3), 66.90 (d, $^2J_{C,F}$ = 25.7 Hz, C-6), 11.73 (d, $^3J_{C,F}$ = 5.0 Hz, C-7); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −118.15 (s, 1F); HRCIMS calcd for $C_7H_{15}FNO_4$ $(M+NH_4)^+$: 196.0985, found: 196.0988.
17. *5-Fluoro-(+)-MK7607*: $[\alpha]_D^{20}$ +41.3 (*c* 0.14, MeOH); ^{1}H NMR (D_2O, 400 MHz): δ 4.31–4.25 (m, 3H, H-3, H-6, H-7a), 3.93 (ddd, 1H, J = 1.1 Hz, $J_{5,6}$ = 3.4 Hz, $J_{4,5}$ = 12.7 Hz, H-7b), 3.80 (ddd, 1H, $J_{x,x}$ = 0.7 Hz, $J_{5,6}$ = 4.6 Hz, $J_{4,5}$ = 10.7 Hz, H-4), 3.67 (dd, 1H, $J_{3,4}$ = 4.1 Hz, $J_{4,5}$ = 10.7 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.79 (d, $^1J_{C,F}$ = 266.7 Hz, C-1), 116.61 (d, $^2J_{C,F}$ = 9.5 Hz, C-2), 68.00 (d, $^4J_{C,F}$ = 1.6 Hz, C-4), 67.28 (d, $^3J_{C,F}$ = 10.9 Hz, C-5), 66.38 (d, $^2J_{C,F}$ = 25.2 Hz, C-6), 65.45 (d, $^3J_{C,F}$ = 10.2 Hz, C-3), 54.40 (d, $^3J_{C,F}$ = 6.2 Hz, C-7); ^{19}F NMR ($CDCl_3$, 235 MHz) δ −115.80 (s, 1F); HRCIMS calcd for $C_7H_{15}FNO_5$ $(M+NH_4)^+$: 212.0934, found: 212.0935.
18. *1-epi-5-Fluoro-(+)-MK7607*: $[\alpha]_D^{20}$ +17.5 (*c* 0.2, MeOH); ^{1}H NMR (D_2O, 400 MHz): δ 4.44–4.31 (m, 2H, H-3, H-7a), 4.19 (d, 1H, $J_{5,6}$ = 7.6 Hz, H-6), 4.03 (ddd, 1H, J = 0.6 Hz, J = 3.8 Hz, $J_{4,5}$ = 12.5 Hz, H-7b), 3.73 (dd, 1H, $J_{5,6}$ = 7.6 Hz, $J_{4,5}$ = 10.8 Hz, H-5), 3.53 (dd, 1H, $J_{3,4}$ = 4.0 Hz, $J_{4,5}$ = 10.8 Hz, H-4); ^{13}C NMR (D_2O, 100 MHz) δ 155.67 (d, $^1J_{C,F}$ = 266.6 Hz, C-1), 115.16 (d, $^2J_{C,F}$ = 9.6 Hz, C-2), 71.85 (d, $^3J_{C,F}$ = 8.2 Hz, C-5), 70.04 (d, $^2J_{C,F}$ = 21.6 Hz, C-6), 70.03 (d, $^4J_{C,F}$ = 2.6 Hz, C-4), 66.04 (d, $^3J_{C,F}$ = 9.9 Hz, C-3), 54.60 (d, $^3J_{C,F}$ = 6.4 Hz, C-7); ^{19}F NMR (D_2O, 235 MHz) δ −122.06 (s, 1F); HRCIMS calcd for $C_7H_{15}FNO_5$ $(M+NH_4)^+$: 212.0934, found: 212.0933.