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Carbaxylosides of 4-Ethyl-2-oxo-2H-benzopyran-7-yl as Non-hydrolyzable, Orally Active Venous Antithrombotic Agents

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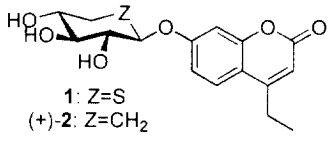
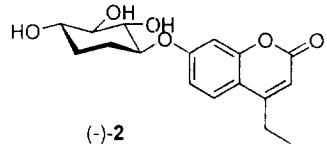
Abstract: A (-)-conduritol F derivative was condensed with 4-ethyl-7-hydroxy-2H-1-benzopyran-2-one and converted into (+)-4-ethyl-7-[(1'R,2'S,3'S,4'R)-2',3',4'-trihydroxycyclohexyloxy]-2H-1-benzopyran-2-one ((+)-**2**). Enantiomer (-)-**2** was obtained from a (+)-conduritol F derivative. The carbaxyloside (-)-**2** with the L-xylose configuration was more active than (+)-**2** in the Wessler's model.

Keywords: anticoagulants; coumarins; inositols; mimetics

Since the demonstration that *p*-nitrophenyl β-D-xylopyranoside[1] can be a substrate for galactosyltransferase 1 (GT1) and can act as a primer for the biosynthesis of glycosaminoglycan (GAG), it has been shown that β-D-xylopyranosides of aglycones making these compounds able to penetrate the plasmic membranes are antithrombotic agents in animals that can be taken orally.[1] Among the various xylosides and analogues tested,[3] iliparcil (**1**), a coumarin derivative, has shown very interesting activity.[2,4]



1: Z=S
(+)-**2**: Z=CH_2



(-)-**2**

The antithrombotic activity of **1** is limited by its hydrolysis *in vivo*. In order to increase the bioavailability of xylosides such as **1** we have prepared the carbapyranoside analogue (+)-**2** and its enantiomer (-)-**2**. Strickingly, (-)-**2** which has the configuration of L-xylose is found to be significantly more active as oral antithrombotic agent in the rat than (+)-**2**. Its activity is closer to that of iliparcil[2] than to that of (+)-**2** !

Enantiomerically pure cyclohexenone (-)-**4** ($[\alpha]^{25}_D$ = -65, c = 2.5, $CHCl_3$) was derived from the "naked sugar of the first generation" (+)-**3**[5] following Le Drian's method.[6] Reduction ($NaBH_4$, $CeCl_4 \cdot 7$ aq./CH_2Cl_2) gave a 2:5 mixture of allylic alcohols (-)-**5** and (-)-**6** which was reacted with 4-ethyl-7-hydroxycoumarin[7] in the presence of 1,1'-(azodicarbonyl)dipiperidine and (n-Bu)$_3$P in anhydrous THF (0-25°C).[8] This gave (+)-**7** (63%) together with unreacted (-)-**5**. After flash chromatography on silical gel, pure (+)-**7** was hydrogenated (AcOEt, 20% Pd/C, H_2 1 atm) and desilylated (HF/MePh, MeCN, 20°C, 24 h) into (+)-**2** in 62% yield.[9] The carba-L-xyloside (-)-**2** was obtained in the same way starting from (-)-**8**.[5]

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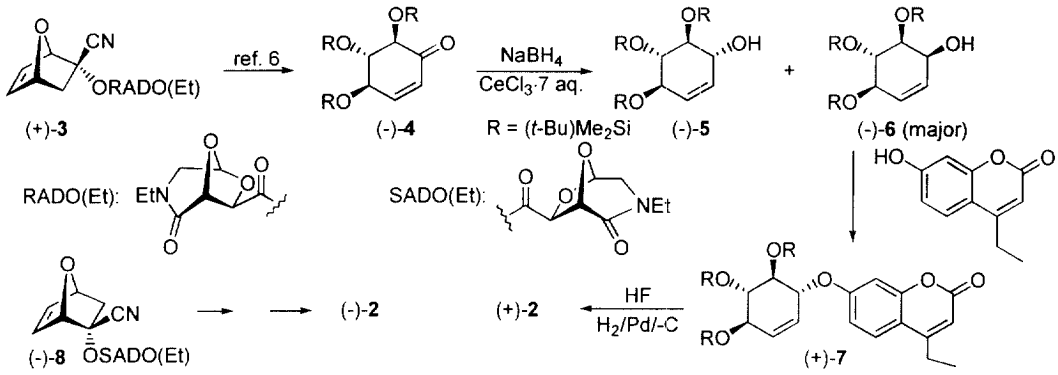

The carbaxylosides (+)-**2** and (-)-**2** were tested for their venous antithrombotic activity in the rat[10] (modified Wessler's model[11]). Oral administration of these compounds 4 hours before the injection of the thrombogenic stimulus factor X_a reduced thrombus weight. For a 20 mg/kg dose the carba-D-xyloside (+)-**2** showed a weak activity of 20±10% whereas the carba-L-xyloside (-)-**2** had a antithrombotic activity of 96±3% which is of same range of potency as that observed for O- and S-D-xylosides (**1**: 71% at dose of 3 mg/kg[2]).

For the first time carbaxylosides of coumarins have been demonstrated to have significant potential as oral antithrombotic agents. Unexpectedly, the carbaxyloside with the L-xylose configuration is more active than its enantiomer. This raises the question whether thio-L-xylosides should also be antithrombotic agents.

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9. Data for (+)-**2**: m.p. 140-150°C, $[\alpha]^{25}_D$ = 8 (c = 0.9, CH_2Cl_2/MeOH 1:1), ^{1}H-NMR (400 MHz, DMSO-d_6): 7.68 ppm (d, ^3J = 8.9 Hz), 7.04 (d, ^4J = 2.4), 6.97 (dd, ^3J = 8.9, ^4J = 2.4), 6.13 (s), 4.27 (ddd, ^3J = 10.1, 8.8, 4.5), 3.29 (dd, ^3J = 8.9, 8.8), 3.25 (ddd, ^3J = 10.9, 8.8, 4.7), 3.06 (dd, ^3J = 8.9, 8.8), 2.78 (q, ^3J = 7.4), 1.95 (dm, ^3J = 7.4)).
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