Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1687–1688

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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

Vincent Jeanneret, Pierre Vogel*

Institut de chimie organique de l'Université de Lausanne, BCH, CH-1015 Lausanne-Dorigny, Switzerland

Patrice Renaut, Jean Millet, Jocelyne Theveniaux and Véronique Barberousse

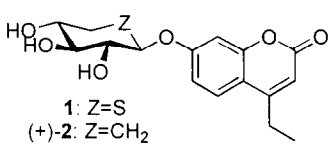
Laboratoires Fournier, S. A., Centre de Recherche, 50 rue de Dijon, F – 21121 Daix, France

Received 3 April 1998; accepted 28 May 1998

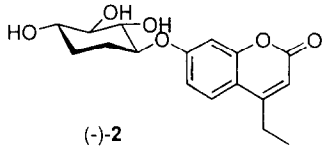
Abstract: A (-)-conduritol F derivative was condensed with 4-ethyl-7-hydroxy-2H-1-benzopyran-2-one and converted into (+)-4-ethyl-7-[(1'R,2'S,3'S,4'R)-2',3',4'-trihydroxycyclohexyloxy]-2H-1-benzopyran-2-one ((+)-**2**). Enantiomer (-)-**2** was obtained from a (+)-conduritol F derivative. The carbaxyloside (-)-**2** with the L-xylose configuration was more active than (+)-**2** in the Wessler's model. © 1998 Elsevier Science Ltd. All rights reserved.

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



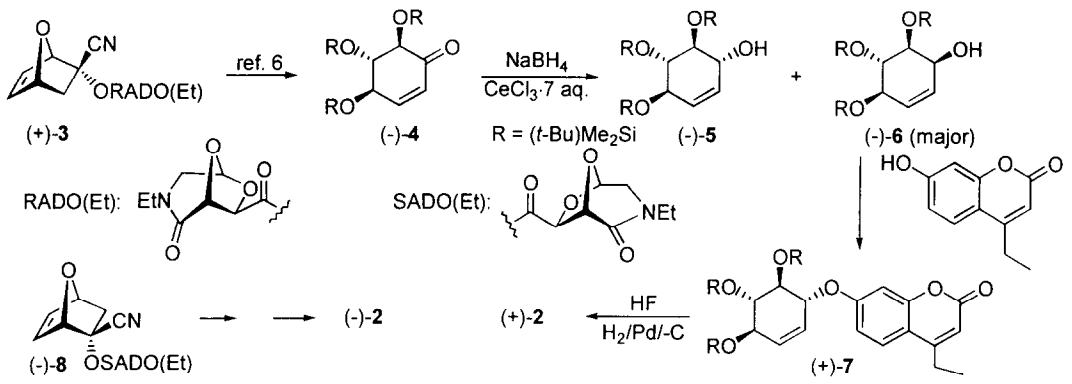
(-)-**2**

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]

* Fax: 0041 21 692 39 75; E-mail: pierre.vogel@ico.unil.ch

PII: S0960-894X(98)00283-2



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.

Acknowledgments: We are grateful to the *Swiss National Science Foundation* (Bern) for partial financial support.

References

1. Okayama, M.; Kimata, K.; Suzuki, S.J.; *Biochem (Tokyo)* **1973,** *74,* 1069-1073; Schwartz, N.B.; Galligani, L.; Ho, P.L.; Dorfman, A. *Proc. Nat. Acad. Sci.* USA **1974,** *71,* 4047-4051; Schwartz, N.B. *J. Biol. Chem.* **1977,** *252,* 6316-6321; Mani, K.; Hausmark, B.; Persson, S.; Kaneda, Y.; Yamamoto, H.; Sakurai, K.; Ashikari, S.; Habuchi, H.; Suzuta, S.; Kimata, K.; Malmström, A.; Westergren-Thorsson, G.; Fransson, L.-A. *Cancer Res.* **1998**, *58*, 1099-1104.
2. Bellamy, F.; Barberousse, V.; Martin, N.; Masson, P.J.; Millet, J.; Samreth, S.; Sepulchre, C.; Theveniaux, J.; Horton, D. *Eur. J. Med. Chem.* **1995**, Suppl. to Vol. 30, 101s-115s.
3. Bellamy, F.; Horton, D.; Millet, F.; Picart, F.; Samreth, S.; Chazan, J.B. *J. Med. Chem.* **1993**, *36*, 898-903; see also: Fritz, T.A.; Lugemwa, F.N.; Sarkar, A.K.; Esko, J.D. *J. Biol. Chem.* **1994**, *269*, 300-307; Lugemwa, F.N.; Sarkar, A.K.; Esko, J.D. *Ibid.* **1996**, *271*, 19159-19165; Bozó, E.; Borasa, S.; Kuszmann, J. *Carbohydr. Res.* **1997**, *299*, 59-67. Idem. *Ibid.* **1997**, *301,* 23-32.
4. Martin, N.B.; Masson, P.J.; Sepulchre, C.; Theveniaux, J.; Millet, J.; Bellamy, F. *Seminars in Thrombosis & Hemostasis.* **1996**, *22*, 247-251.
5. Reymond, J.L.; Vogel, P. *Tetrahedron Asymmetry* **1990**, *1*, 729-736.
6. Le Drian, C.; Vionnet, J.P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161-168.
7. Mitsunobu, O. *Synthesis* **1981**, 1-28; Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639-1642.
8. Ahluwalia, V.K.; Sunita, *Indian J. Chem., Sect. B,* **1977**, *15B*, 240-241.
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)).
10. Millet, J.; Theveniaux, J.; Brown, N.L. *Thromb. Haemost.* **1992**, *67*, 176-179.
11. Wessler, S.; Reimer, M.; Shap, M. J. *Appl. Physiol.* **1957**, *14*, 943-946.