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Note

An improved synthesis of an umbelliferyl 5-thioxylopyranoside, precursor of the antithrombotic drug Iliparcil

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Abstract

4-Ethyl-2-oxo-2*H*-1-benzopyran-7-yl 2,3,4-tri-*O*-acetyl-5-thio-β-D-xylopyranoside, a synthetic intermediate of the orally active antithrombotic compound Iliparcil, has been prepared in 44–47% isolated yield. Different conditions were used for the glycosylation of 4-ethyl-2*H*-7-hydroxy-1-benzopyran-2-one **6** applying 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl bromide (**2**), the analogous β-chloride **3** or the α-trichloroacetimidate **5** as donors. With halides **2** and **3**, the reaction was carried out in the presence of ZnO–$ZnCl_2$ or ZnO alone. Both promoters are cheap, safe and therefore compatible with large-scale industrial processes.

Keywords: 5-Thioxyloside; Antithrombotic; Zinc oxide; Glycosylation

In the course of our search for an orally active antithrombotic product [1–4], we have identified Iliparcil [5] (4-ethyl-2-oxo-2*H*-1-benzopyran-7-yl 5-thio-β-D-xylopyranoside (**1**)) as a suitable candidate for clinical development. Iliparcil **1** (Scheme 1) shows a potent antithrombotic activity according to the Wessler model [6] in rats in which thrombosis is induced by Factor Xa. When administered 4 h before the induction of thrombosis, it effectively prevents the formation of thrombus with an ED_{50} of 6 mg/kg. Unfortunately, the original synthesis of this compound [5] proved to be problematic because of the poor yield of the glycosylation step and, thus, an optimization of this glycosylation using various methods and reaction conditions appeared desirable. Herein, we report our efforts resulting in an optimized yield of the desired glycoside **1**, compatible with large-scale industrial syntheses.

Iliparcil was initially obtained from a protected 5-thioxylopyranosyl donor reacting with the 4-ethylumbelliferone **6** [7], followed by a deprotection step [5] with a 15% overall yield. The production of **1** on an industrial scale required an improved overall yield, as well as the use of suitable promoters. How-

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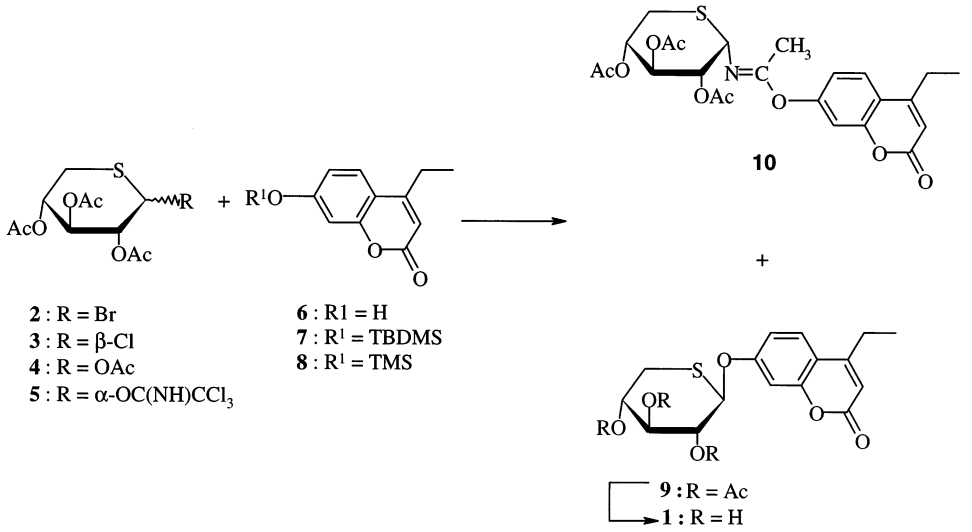

Scheme 1.

ever, there are only a limited number of glycosidation reactions of 5-thioxylose reported in the literature [1–5,8–14].

We first tried to overcome the poor solubility of the aglycone by silylating it as described by Yegorov et al. [15] or by Courtin-Duchateau and Veyrières [16]. Whereas its protection by a trimethylsilyl or by a *tert*-butyldimethylsilyl group [15–17] could be realized in quantitative yields, the glycosylation reactions did not succeed in our hands (Table 1, Entries 2 and 3).

These disappointing results led us to study different conditions for the reaction between **6** and various 5-thio-D-xylopyranosyl donors. Using the readily available peracetate **4** [18] (Table 1, Entry 6) and $BF_3{\cdot}Et_2O$ as promoter [19], the glycosylation reaction also failed. The use of bromide **2** [20] and zinc oxide, which is known to be a good catalyst for glycosylation [11,21–23] and to be suitable for industrial applications, seemed more promising, in that we obtained **9** with a much better yield of 44% (Table 1, Entry 4).

To further improve the yield, different parameters such as solvent, temperature, reaction time and catalyst were studied in two sets of experiments, one using 1 g of aglycone and 2 g of bromide **2** [11] (α/β ratio of 7:13, Table 2) and another starting with 5 g of aglycone and 10 g of bromide **2** [11] (α/β ratio 47:3, Table 3).

Interestingly, acetonitrile led to the formation of the imidate intermediate **10**, probably formed via the nitrilium ion [24], which seemed to disappear in the course of certain reactions, according to TLC analysis.

Table 1
Synthesis of **9** under various conditions (using 1 equiv of each reactant)

Entry	Starting materials		Promoter	Solvent	Time (h)	Temperature (°C)	Yield **9** (%)
1	**2**	**6**	ImAg [a]–$ZnCl_2$	toluene–CH_3CN	24	55	17 [b]
2	**2**	**7**	Bu_4NF	THF	20	0	trace [c]
3	**2**	**8**	$BF_3{\cdot}Et_2O$	toluene	20	20	[c]
4	**2**	**6**	ZnO–$ZnCl_2$	toluene–CH_3CN	20	60	44 [b]
5	**3**	**6**	ZnO	CH_3CN	20	60	47 [d]
6	**4**	**6**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	4	40	[c]
7	**5**	**6**	BF_3 Et_2O	$(CH_2Cl)_2$	1.5/2	−20/−5	46 [d]

[a] Silver imidazolate.
[b] Isolated yield.
[c] Compound **6** and glycosyl donor recovered.
[d] Determined by GC.

Table 2
Glycosylation of **2** ($\alpha/\beta = 7{:}13$) with aglycone **6** used on the 1 g scale (using 1 equiv of each component)

Entry	Temperature (°C)	Solvent	Time (h)	Promoter	Yield **9** (%)
1	110	toluene–CH_3CN	1	ZnO	0 [a]
2	60	toluene–CH_3CN	8	ZnO–$ZnBr_2$	0 [b]
3	60	toluene–CH_3CN	20	ZnO–$ZnCl_2$	44 [c]
4	55	toluene–CH_3CN	20	$ZnCl_2$	0 [a]
5	75	$(CH_2Cl)_2$	20	ZnO–$ZnCl_2$	17 [d]

[a] Compound **6** and glycosyl donor recovered.
[b] Degradation
[c] Isolated yield.
[d] Determined by GC.

Otherwise, Entry 3 in Table 2 clearly indicates that both ZnO and $ZnCl_2$ are necessary in order to get an acceptable yield. This led us to assume that the β-chlorinated derivative **3** [25] could be formed during the reaction as a transient intermediate and prompted us to carry out the glycosidation step starting with **3**. In these conditions, **9** [5] was obtained in a 47% yield (Table 1, Entry 5), implying a transient acetoxonium intermediate formed via participation of the 2-acetoxy group.

Finally, Schmidt's procedure starting with trichloroacetamidate **5** [11] led to the target compound **9** [5] with 46% yield (Table 1, Entry 7).

In conclusion, we have developed two methods which lead to Iliparcil **1** in 44–47% isolated yield. Since 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl trichloroacetimidate **5** requires a multistep preparation, the route using the readily prepared bromo sugar **2** appears more efficient. Its advantage lies in the effectiveness of a zinc oxide and zinc chloride mixture for multigram glycosylation of 4-ethyl-2*H*-7-hydroxy-1-benzopyran-2-one with 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl bromide. Since deacetylation of the 5-thio-β-D-xylopyranoside derivative **9** under Zemplén's conditions (catalytic NaOMe in MeOH) [5] leads to Iliparcil **1** in 87% yield, this two-step procedure produced the target compound in an improved (40%) overall yield.

1. Experimental

General methods.—TLC was performed on precoated plates of Silica Gel $60F_{254}$ (E. Merck); components were detected by UV light and by spraying the plates with 10% H_2SO_4 and subsequent heating. Melting points were determined with a Koffler apparatus and are uncorrected. Specific rotations were recorded with a Perkin–Elmer 241 polarime-

Table 3
Glycosylation of **2** ($\alpha/\beta = 47{:}3$) with aglycone **6** used on the 5 g scale in the presence of ZnO–$ZnCl_2$ (using 1 equiv of each component)

Entry	Temperature (°C)	Solvent	Time (h)	Yield (%)	
				9	**10**
1	60	CH_3CN	48	26 [a]	11 [b]
2	65	CH_3CN	24	10 [a]	3 [b]
3	60	toluene–CH_3CN	20	17 [a]	19 [b]
4	60	toluene–CH_3CN	48	26 [a]	
5	60	toluene–DMF 5%	46	28 [a]	
6	70	toluene–DMF 10%	24	34 [b]	

[a] Determined by GC.
[b] Isolated yield.

ter. ^{1}H NMR spectra were recorded with a Bruker ACP-300 spectrometer and chemical shifts refer to an internal standard of Me_4Si ($\delta = 0.00$). Elemental analyses were performed with a Perkin–Elmer CHN 2400. GC analyses were carried out with a FID detector ($F_{air} =$ 300 mL/min, $F_{H_2} = 25$ mL/min, $F_{He} = 10$ mL/min), a Macrobore CP Sil 5 CB Column (10 m × 0.52 mm × 2 μm) in EtOAc at 260 °C. High-resolution mass spectra were recorded on a ZabSpec TOF Micromass under ESI conditions.

*4-Ethyl-2-oxo-2*H*-1-benzopyran-7-yl 2,3,4-tri*-O*-acetyl-5-thio-β*-D*-xylopyranoside* (**9**)

Procedure A: using zinc oxide and zinc chloride. A mixture of **6** (8 g, 42 mmol), ZnO (3.77 g, 46 mmol), $ZnCl_2$ (6.3 g, 46 mmol), molecular sieves 13 X in toluene (150 mL) and MeCN (150 mL) was stirred at 60 °C under an inert atmosphere. After 15 min, **2** (α/β = 7:13, 8.5 g, 24 mmol) was added followed by another portion (8 g) 3 h later. Exactly 17 h later, the mixture was filtered and washed (1 M NaOH, water). The organic layer was concentrated under reduced pressure. The expected compound **9** precipitated in EtOAc–diethyl ether (8.4 g, 44%); mp 186–188 °C, lit. 189 °C [5]; $[\alpha]_D$ −63° (*c* 0.8, CH_2Cl_2); ^{1}H NMR (200 MHz, CD_3CN): δ 7.70 (d, 1 H, *J* 8.7 Hz, Ar), 7.06 (d, 2 H, *J* 2.4 Hz, Ar), 7.00 (dd, 1 H, *J* 8.7 Hz, 2.4 Hz, Ar), 6.16 (s, 1 H, Ar), 5.57 (d, 1 H, $J_{1,2}$ 8.8 Hz, H-1), 5.44 (t, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 5.19 (t, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 5.06 (ddd, 1 H, $J_{4,5e}$ 5.6 Hz, $J_{4,5a}$ 9.4 Hz, H-4), 3.00–2.86 (m, 2 H, H-5a, H-5e), 2.79 (q, 2 H, H–CH_2CH$_3$), 2.01 (s, 3 H, H–OAc), 2.00 (s, 3 H, H–OAc), 1.96 (s, 3 H, H–OAc), 1.27 (t, 3 H, H–CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.3 (CH$_3$*C*O), 161.1, 159.2, 157.3, 155.0 (Ar), 125.4 (Ar), 114.6 (Ar), 113.4, 111.0, 103.9 (Ar), 79.2 (C-1), 73.7, 72.1, 71.8 (C-2, C-3, C-4), 27.3 (C-5), 24.7 (*C*H$_2$CH$_3$), 20.8, 20.6, 20.6 (*C*H$_3$CO), 12.1 (CH$_2$*C*H$_3$).

The mother liquor was chromatographed on silica gel (6:1 toluene–EtOAc) to yield traces of **10** : mp 162 °C; $[\alpha]_D^{22}$ +304° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, 1 H, Ar), 7.20 (dd, 1 H, Ar), 7.12 (d, 1 H, Ar), 6.28 (s, 1 H, CH=), 5.26 (t, 1 H, $J_{2,3}$ 9.7 Hz, H-3), 5.13 (dd, 1 H, H-2), 5.00 (m, 1 H, H-4), 4.67 (d, 1 H, $J_{1,2}$ 3.1 Hz, H-1), 2.89–2.51 (m, 4 H, H-5, H-5′, CH_2CH$_3$), 2.12–1.93 (m, 12 H, OAc, CH_3C(=N)O), 1.35 (t, 3 H, CH$_2$CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.0 (C=O), 162.3–154.4 (CN, ArO, OC=O, C=), 124.5–108.5 (Ar, C_2H_5–*C*=), 76.2–70.2 (C-2, C-3, C-4), 57.8 (C-1), 25.6–12.0 (C-5, *C*H$_2$CH$_3$, 3*C*H$_3$–C=O, *C*H$_3$CN, CH$_3$*C*H$_2$); *m/z* Calcd for $C_{24}H_{28}NO_9S$: 506.1485 [M + H]; Found: 506.1427.

Procedure B: using chloride **3**. A mixture of **6** (250 mg), ZnO (110 mg, 1 equiv) and molecular sieves 13 X in MeCN (10 mL) was stirred under an inert atmosphere for 15 min. Then **3** (410 mg) was added (1 equiv) and the mixture was heated to 60 °C. After 20 h, it was filtered and washed (1 M HCl, water, 1 M NaOH, water, saturated NaCl solution, water). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. A GC analytical method was used to estimate the amount of **9** (47%).

Procedure C: using Schmidt's procedure. Boron trifluoride etherate (40 μL, 0.3 mmol) was added to a stirred dichloroethane solution containing **6** (435 mg, 2.3 mmol), **5** (1 g, 2.3 mmol) and 10 Å molecular sieves, protected from moisture by an inert atmosphere. The mixture was stirred for 1.5 h at −20 °C and then for a further 2 h at −5 °C. It was then quenched with a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried with $MgSO_4$ and concentrated under reduced pressure. According to GC, **9** was formed in a yield of 46%.

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