5a-Carba-β-D-, 5a-Carba-β-L- and 5-Thio-β-L-xylopyranosides as New Orally Active Venous Antithrombotic Agents

by **Patrice Renaut**, **Jean Millet**, **Christiane Sepulchre**, **Jocelyne Theveniaux**, and **Véronique Barberousse**

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

and **Vincent Jeanneret**[1]) and **Pierre Vogel***

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

Mitsunobu displacement of (−)-(1*S*,4*R*,5*S*,6*S*)-4,5,6-tris{[(*tert*-butyl)dimethylsilyl]oxy}cyclohex-2-en-1-ol ((−)-**12**; a (−)-conduritol-F derivative) with 4-ethyl-7-hydroxy-2*H*-1-benzopyran-2-one (**16**) provided a 5a-carba-β-D-pyranoside (+)-**17** that was converted into (+)-4-ethyl-7-[(1′*R*,4′*R*,5′*S*,6′*R*)-4′,5′,6′-trihydroxycyclohex-2′-en-1′-yloxy]-2*H*-1-benzopyran-2-one ((+)-**5**) and (+)-4-ethyl-7-[(1′*R*,2′*R*,3′*S*,4′*R*)-2′,3′,4′-trihydroxycyclohexyloxy]-2*H*-1-benzopyran-2-one ((+)-**6**). The 5a-carba-β-D-xyloside (+)-**6** was an orally active antithrombotic agent in the rat (venous *Wessler*'s test), but less active than racemic carba-β-xylosides (±)-**5** and (±)-**6**. The 5a-carba-β-L-xyloside (−)-**6** was derived from the enantiomer (+)-**12** and found to be at least 4 times as active as (+)-**6**. (+)-4-Cyanophenyl 5-thio-β-L-xylopyranoside ((+)-**3**) was synthesized from L-xylose and found to maintain *ca*. 50% of the antithrombotic activity of its D-enantiomer. Compounds (±)-**5**, (±)-**6**, and (−)-**6** are *in vitro* substrates for galactosyltransferase 1.

Introduction. – Thromboembolic disorders are a major cause of morbidity and mortality. Dermatan sulfate, the chondroitin sulfates, and heparan sulfate have *in vivo* antithrombotic activities [1][2]. Since the demonstration that 4-nitrophenyl β-D-xylopyranoside [3][4] can be 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 that can be taken orally [5]. Among the various xylosides and analogues tested (more than 700) [6], naroparcil (**1**), beciparcil ((−)-**2**), and iliparcil (**4**) have the most interesting activities [7]. Naroparcil (**1**) was shown to be a primer for the free GAG chain synthesis after oral administration in the rabbit [8]. The GAG's extracted from the plasma were found to enhance inhibition of thrombin by heparin cofactor II and contained dermatan-sulfate-like compounds that can be responsible for the antithrombotic effect [8].

The observed plasma level of inactive aglycone following oral administration of xyloside **4** suggests that hydrolysis may reduce the antithrombotic potency of such systems. In order to increase their bioavailability, we have envisioned to replace the β-D-xylopyranoside by carba-pyranoside analogues such as the conduritol-B derivative (+)-**5** and its dihydro analogue (+)-**6**.

In a preliminary communication [9], we have shown that (+)-**6** has a weak activity as oral antithrombotic agent in the rat (modified *Wessler*'s model). Surprisingly, its

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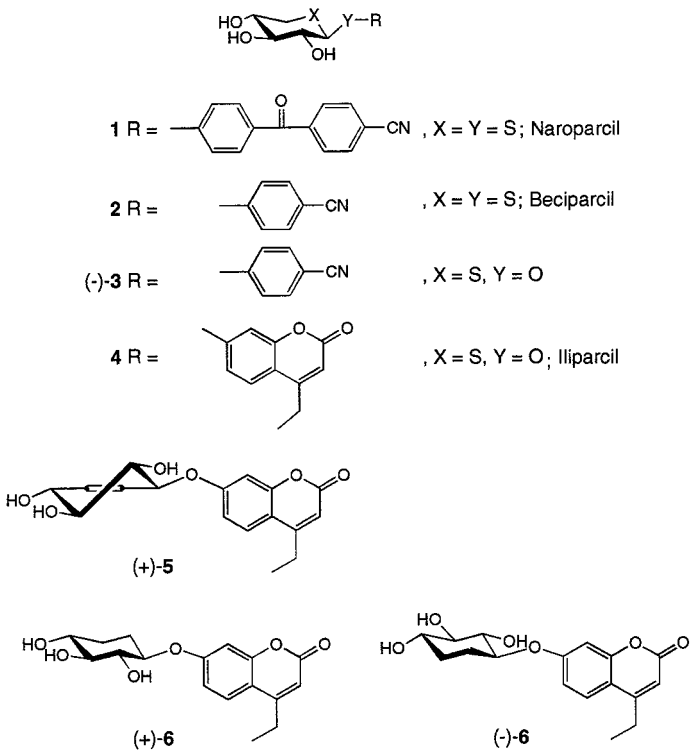
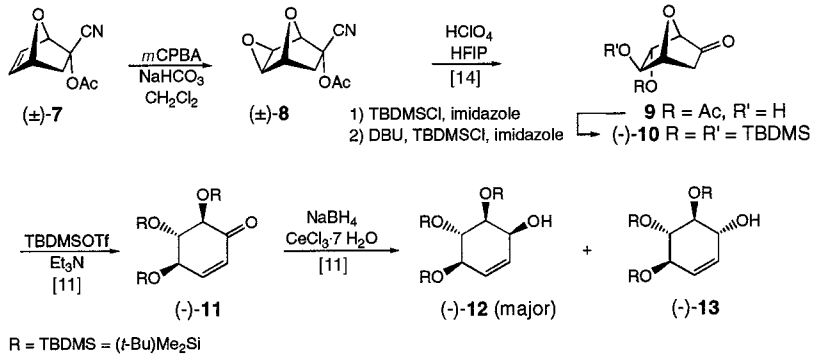
[1]) Present address: *Scribbs Research Institute*, La Jolla, CA, USA.



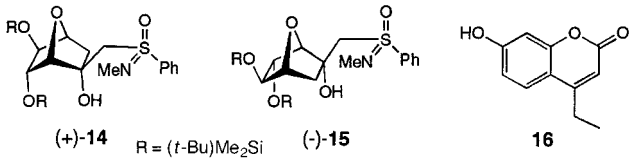
enantiomer (−)-**6** which has the configuration of L-xylose was found to have an activity close to that of iliparcil (**4**). We report here the details of these studies and answer the question whether thio-L-xylopyranosides should also be antithrombotic agents. As we shall see, (+)-4-cyanophenyl 5-thio-β-L-xylopyranoside ((+)-**3**) derived from L-xylose maintains *ca*. 50% of the antithrombotic activity of (−)-**3**.

Syntheses. – Since the ethereal link between the conduritol-B moiety and the aglycone (4-ethyl-7-hydroxy-2*H*-1-benzopyran-2-one) will be generated through a S_N2 displacement, a suitably semi-protected conduritol-F intermediate was required. Among the numerous synthesis of conduritol-F that have been proposed [10], the one by *Le Drian* [11] has demonstrated that racemic (±)-**12** can be derived from the *Diels-Alder* adduct (±)-**7** of furan to 1-cyanovinyl acetate *via* (±)-**8**–**11**, whereas enantiomerically pure (+)-**12** and (−)-**12** can be derived with the same ease from the *Diels-Alder* adducts of furan to enantiomerically pure 1-cyanovinyl esters [12]. The synthesis of (±)-**12** [11] involves the base-induced isomerization of the 7-oxabicyclo[2.2.1]heptan-2-one derivative (±)-**10** into cyclohex-2-enone (±)-**11** (91%). The reduction of (±)-**11** under *Luche*'s conditions [13] provided a 2.5 : 1 mixture of conduritol derivatives (±)-**12** and (±)-**13** in 84% yield. Compound (±)-**10** was obtained in 8 steps and 50% yield following *Le Drian*'s method [11]. Applying *Allemann*'s modification [14], (±)-**10** was derived from (±)-**7** in 4 steps and 37% overall yield (*Scheme 1*).

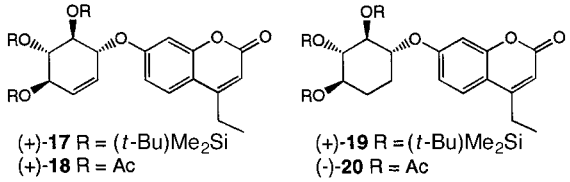
Scheme 1



Enantiomerically pure (−)-**10** was prepared according to the *Le Drian*'s method [11]. Alternatively, it was obtained by the *Johnson-Zeller* [15] resolution of (±)-**10**: The products of addition of the lithium conjugate base of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximide to (±)-**10** were separated by flash chromatography (silica gel) yielding (+)-**14** (42%) and (−)-**15** (39%). Pyrolysis of (−)-**15** (100–200°/0.2 Torr) gave (−)-**10** in 94% yield. The latter was transformed to (−)-**12** as described in the racemic series.

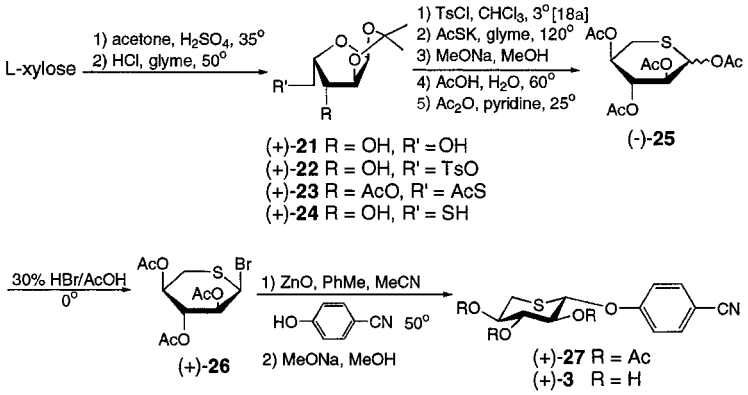


The *Mitsunobu* [16] displacement of (−)-**12** with hydroxycoumarine **16** [17] provided (+)-**17**. The reaction produced a low yield using Ph_3P and diethyl azodicarboxylate (< 30%). With 1,1′-(azodicarbonyl)bispiperidine and $(Bu)_3P$ in anh. THF (0–25°), (+)-**17** was isolated in 63% yield when starting with a 5 : 2 mixture of (−)-**12** and (−)-**13**. Probably for steric reasons, (−)-**13** did not react under the *Mitsunobu* conditions and was recovered after chromatographic purification. Treatment of (+)-**17** with 40% aqueous HF solution (PhMe, MeCN, 20°, 24 h) provided crude (+)-**5**. Acetylation (Ac_2O, pyridine, cat. 4-(dimethylamino)pyridine (DMAP), 20°, 24 h) gave the triacetate (+)-**18** (79%), the ammonolysis of which with NH_3/MeOH (20°, 48 h) produced pure (+)-**5**. Hydrogenation of (+)-**17** (AcOEt, 20% Pd/C, H_2, 1 atm) gave (+)-**19** (92%), and desilylation (HF/PhMe, MeCN) produced crude (+)-**6**. Acetylation (Ac_2O/pyridine, cat. DMAP) led to (−)-**20** (71%), the ammonolysis (NH_3/MeOH) of which furnished pure (+)-**6** (86%). The racemic (±)-**5** and (±)-**6** were prepared in the same way using a 5 : 2 mixture of (±)-**12** and (±)-**13**.



The carba-xylopyranoside analogues (+)-**5**, (±)-**5**, (+)-**6**, and (±)-**6** were submitted to *in vivo* and *in vitro* tests (see below) and found to be active as antithrombotic agents. Strikingly, the racemic carba-xyloside (±)-**6** appeared to be more active than the enantiomerically pure (+)-**6** with the D-*xylo* configuration. We thus prepared the carba-β-L-pyranoside (−)-**6** starting from diastereoisomeric sulfoximide (+)-**14** (from (±)-**10**) and confirmed that the carba-β-L-xylopyranoside (−)-**6** is more potent than its β-D-enantiomer (+)-**6** as oral antithrombotic agent in the rat. This led us to prepare 4-cyanophenyl 5-thio-β-L-xylopyranoside ((+)-**3**) starting from (+)-**26** (*via* (+)-**27**). Glycosyl bromide (+)-**26** was obtained from L-xylose which was protected (→(+)-**21**) and then tosylated [18a] (→(+)-**22**; *Scheme 2*). Subsequently, the 5-*O*-tosyl derivative (+)-**22** was transformed according to a procedure similar to that reported by *Ingles* and *Whistler* [18b] for the thio-D-xyloside (→(+)-**23**→(+)-**24**→(−)-**25**→(+)-**26**; see *Scheme 2* and *Exper. Part*), the main modification consisting in using AcSK instead of BnSNa. In the thio-xylopyranoside series, the β-L-enantiomer (+)-**3** is less active than the β-D-enantiomer (−)-**3**, in contrast to the carba-β-xyloside enantiomers (+)- and (−)-**6**.

Scheme 2



Biological Assays. – The carba-xylosides (±)-**5**, (±)-**6**, (+)-**6**, and (−)-**6** and the thio-xylosides (+)-**3** and (−)-**3** [19] were tested for their oral venous antithrombotic activity in the rat [6a][20] (modified *Wessler*'s test [21]). Oral administration of these compounds 4 h before the injection of the thrombogenic stimulus X_a factor reduced thrombus weight in a dose-related manner as shown in the *Table*. In parallel (see *Table*), we examined the *in vitro* ability of these compounds to be substrates for galactosyltransferase 1 (GT-1), the second enzyme involved in the biosynthesis of the glycosaminoglycan-linkage region. The enzyme was extracted from the epiphyses of femurs and tibias of chick embryos [22]. It is worth noting that the oral antithrombotic activity parallels the K_m values.

Conclusion. – For the first time, we demonstrate that carba analogues of coumarine β-xylopyranosides have a significant potential as oral antithrombotic agents. Because these compounds are expected to be hydrolyzed more slowly than the corresponding O- and S-xylosides, studies should be pursued to define their therapeutic index and

Table. In vivo (rat) *Antithrombotic Activity and* in vitro *Association Constant* (K_m) *for Galactosyltransferase 1* (GT-1) *of Carba-xylosides* **5** *and* **6** *and Thio-xylosides* **3**

	Configuration of the xyloside	*in vivo* Activity		*in vitro* Activity
		Dose	Activity[a])	K_m (GT-1)
(±)-**5**	DL	20 mg/kg	28 ± 10%	3.6 mM
(±)-**6**	DL	20 mg/kg	55 ± 10%	0.94 mM
(+)-**6**	D	20 mg/kg	21 ± 10%	[b])
(−)-**6**	L	20 mg/kg	96 ± 3%	0.61 mM
(−)-**3**	D	10 mg/kg	98 ± 2%	0.041 mM
(+)-**3**	L	10 mg/kg	45 ± 10%	[b])

[a]) Inhibition of thrombus formation, see text. [b]) Cannot be evaluated at 5 mM.

cumulative dose/activity ratio in order to establish whether they can be alternative drugs for the treatment of thromboembolic disorders. Our work demonstrates also that thio-β-L- and carba-β-L-xylopyranosides are potential oral antithrombotic agents. Although the thio-β-L-pyranoside (+)-**3** is found to be less active than its enantiomer (−)-**3**, it is striking to observe for the carba-xylosides that the L-*xylo*-configurated derivative (−)-**6** is significantly more active than its D-*xylo*-enantiomer (+)-**6**. Furthermore, it is found that the carba-xylosides with the configuration of L-xylose can be substrates for the galactosyltransferase 1.

Experimental Part

General. See [23]. FC = flash chromatography.

4-Cyanophenyl 5-Thio-β-L-xylopyranoside ((+)-**3**). A suspension of (+)-**27** (260 mg, 0.66 mmol) and 18.8% MeONa in MeOH (60 µl) in MeOH (15 ml) was stirred under N_2 for 90 min. The mixture was then neutralized with resin *Amberlite® 120 IRH*$^+$ and filtered. The filtrate was evaporated and the residue crystallized from MeOH/Et_2O: 90 mg (51%) of (+)-**3**. White crystals. M.p. 180°. $[\alpha]_D^{29} = 70$ ($c = 0.43$, MeOH). ^{1}H-NMR (300 MHz, (D_6)DMSO): 7.80 (d, $J = 9$, 2 H); 7.26 (d, $J = 9$, 2 H); 5.32 (d, $J = 8.7$, 1 H); 3.60 (m, 1 H); 3.51 (m, 1 H); 3.15 (m, 1 H); 2.62 (m, 2 H). ^{13}C-NMR, IR, UV, MS: similar to those reported for the D-*xylo* series. Anal. calc. for $C_{12}H_{13}NO_4S$ (267.31): C 53.91, H 4.90; found: C 53.47, H 5.00.

*(+)-4-Ethyl-7-[(1′*R*,4′*R*,5′*S*,6′*R*)-4′,5′,6′-trihydroxycyclohex-2′-en-1′-yloxy]-2*H*-1-benzopyran-2-one* ((+)-**5**). A mixture of (+)-**18** (0.5 g, 1.13 mmol) and MeOH sat. with NH_3 (30 ml) was stirred at 20° for 48 h. The solvent was evaporated and the residue purified by FC (silica gel, AcOEt/light petroleum ether/MeOH 8:2:1; R_f 0.4): 300 mg (84%) of (+)-**5**. Colorless solid. M.p. 197–198°. $[\alpha]_{589}^{25} = +165$, $[\alpha]_{577}^{25} = +175$, $[\alpha]_{546}^{25} = +201$, $[\alpha]_{435}^{25} = +376$, $[\alpha]_{405}^{25} = +479$ ($c = 0.7$, CH_2Cl_2/MeOH 1:1). UV (MeCN): 214 (14000), 255 (2700). IR (KBr): 3450, 3400, 3340, 3890, 1670, 1610, 1540, 1510, 1425, 1400, 1375, 1290, 1200, 1150, 1110, 1080, 1050, 1020, 1000, 960, 890, 850, 815, 800, 780, 750. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.71 (d, $^3J = 8.9$, H–C(5)); 7.03 (d, $^4J = 2.4$, H–C(8)); 6.99 (dd, $^3J = 8.9$, $^4J = 2.4$, H–C(6)); 6.15 (s, H–C(3)); 5.65 (ddd, $J(2',3') = 10.3$, $J(1',2') = 2.4$, $J(2',4') = 1.7$, H–C(2′)); 5.55 (ddd, $J(2',3') = 10.3$, $J(3',4') = 2.3$, $J(1',3') = 1.9$, H–C(3′)); 5.40–4.80 (br. s, 3 OH); 4.96 (ddd, $J(1',6') = 7.7$, $J(1',2') = 2.4$, $J(1',3') = 1.9$, H–C(1′)); 3.97 (ddd, $J(4',5') = 7.6$, $J(3',4') = 2.3$, $J(2',4') = 1.7$, H–C(4′)); 3.54 (dd, $J(5',6') = 10.2$, $J(1',6') = 7.7$, H–C(6′)); 3.34 (dd, $J(5',6') = 10.2$, $J(4',5') = 7.6$, H–C(5′)); 2.79 (q, $J = 7.4$, MeCH_2); 1.22 (t, $J = 7.4$, *Me*CH_2). ^{13}C-NMR (100.6 MHz, (D_6)DMSO): 161.2 (s, C(2)); 160.4 (s, C(7)); 158.2, 154.8 (2s, C(4a), C(8a)); 133.5 (d, $J = 161$, C(3)); 126.0, 123.7 (2d, $J = 162$, 163, C(2′), C(3′)); 112.3 (s, C(4)); 113.1, 109.2, 102.6 (3d, C(5), C(6), C(8)); 79.3, 75.8, 73.7, 71.2 (4d, $J = 147$, 138, 139, 140, C(1′), C(6′), C(5′), C(4′)); 24.0 (t, $J = 128$, Me*C*H_2); 12.3 (q, $J = 127$, *Me*CH_2). CI-MS (NH_3): 318 (60, M^+), 281 (4), 246 (10), 255 (2), 181 (2), 147 (100), 96 (6). Anal. calc. for $C_{17}H_{18}O_{16}$ (318.33): C 63.64, H 5.74, O 30.62 (with 0.14 H_2O, as titrated by the *Karl-Fisher* technique); found: C 63.19, H 5.78.

Racemate (±)-**5** was prepared from (±)-**18** as above. M.p. 149–151°.

*(+)-4-Ethyl-7-[(1′*R*,2′*R*,3′*S*,4′*R*)-2′,3′,4′-trihydroxycyclohexyloxy]-2*H*-1-benzopyran-2-one* ((+)-**6**). A soln. of 40% aq. HF soln. (0.53 ml) in MeCN (11 ml) was added dropwise to a soln. of (+)-**19** (1.1 g, 1.66 mmol) in

toluene (6 ml) at 20°. After stirring at 20° for 24 h, the solvent was evaporated and the residue purified by FC (silica gel, AcOEt/light petroleum ether/MeOH 8:1:1; R_f 0.4): 498 mg (93%) of (+)-**6**. White solid. M.p. 140–150°. $[\alpha]_{589}^{25} = +8$, $[\alpha]_{577}^{25} = +9$, $[\alpha]_{546}^{25} = +15$, $[\alpha]_{435}^{25} = +21$, $[\alpha]_{405}^{25} = +12$ ($c = 0.9$, CH_2Cl_2/MeOH 1:1). UV (MeCN): 214 (11000), 223 (8300). IR (KBr): 3400 (br.), 3060, 2960, 2940, 2900, 1720, 1610, 1550, 1530, 1500, 1450, 1430, 1370, 1340, 1270, 1200, 1160, 1135, 1080, 1070, 1030, 1000, 940, 880, 850, 820, 800. ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.68 (*d*, *J*(5,6) = 8.9, H–C(5)); 7.04 (*d*, *J*(6,8) = 2.4, H–C(8)); 6.97 (*dd*, *J*(5,6) = 8.9, *J*(6,8) = 2.4, H–C(6)); 6.13 (*s*, H–C(3)); 4.27 (*ddd*, *J*(1′,6′) = 10.1, *J*(1′,2′) = 8.8, *J*(1′,6′) = 4.5, H–C(1′)); 3.29 (*dd*, *J*(2′,3′) = 8.9, *J*(1′,2′) = 8.8, H–C(2′)); 3.25 (*ddd*, *J*(4′,5′) = 10.9, *J*(3′,4′) = 8.8, *J*(4′,5′) = 4.7, H–C(4′)); 3.06 (*dd*, *J*(2′,3′) = 8.9, *J*(3′,4′) = 8.8, H–C(3′)); 2.78 (*q*, *J* = 7.4, Me*C*H_2); 1.95 (*dm*, *J*(1′,6′) = 4.5, H–C(6′)); 1.73 (*dm*, *J*(4′,5′) = 4.7, H–C(5′)); 1.43–1.27 (*m*, H–C(5′), H–C(6′)); 1.22 (*t*, *J* = 7.4, *Me*CH_2). ^{13}C-NMR (100.6 MHz, (D_6)DMSO): 161.6 (*s*, C(2)); 160.5 (*s*, C(7)); 158.3, 154.8 (2*s*, C(4a), C(8a)); 125.8 (*d*, *J* = 162, C(3)); 113.4, 109.0, 102.4 (3*d*, *J* = 164, 170, 163, C(5), C(6), C(8)); 112.0 (*s*, C(4)); 79.3, 77.7, 75.5, 71.5 (4*d*, *J* = 155, 146, 134, C(1′), C(2′), C(3′), C(4′)); 28.4, 25.6 (2*t*, *J* = 130, 131, C(5′), C(6′)); 24.1 (*t*, *J* = 128, Me*C*H_2); 12.4 (*q*, *J* = 127, *Me*CH_2). CI-MS (NH_3): 320 (33, M^+), 190 (100), 162 (29), 147 (14), 112 (15), 83 (21). Anal. calc. for $C_{17}H_{20}O_6$ (320.34): C 62.78, H 6.37, O 30.85 (with 0.27 H_2O, as titrated by the *Karl-Fisher* technique); found: C 62.58, H 6.19.

Enantiomer (–)-**6** was prepared from (–)-**19** (derived from (+)-**14**) as above. White solid. M.p. 142–149°. $[\alpha]_D^{25} = -8$ ($c = 1.0$, CH_2Cl_2/MeOH 1:1).

Racemate (±)-**6** was prepared from (±)-**19** as above. M.p. 157–158°.

*(–)-(1*R,*4*R,*5*R,*6*R*)-5*-exo,*6*-endo-*Bis[[(*tert-*butyl)dimethylsilyl]oxy]-7-oxabicyclo[2.2.1]heptan-2-one* ((–)-**10**). In a *Büchi* bulb oven, (–)-**15** (2.55 g, 4.60 mmol) was heated to 50°/5 min, 100°/5 min, 150°/4 min, 180°/2 min, 190°/5 min, and 200°/6 min under 0.2 Torr. The crude oil obtained was filtered through a pad of silica gel (AcOEt/light petroleum ether 1:9). 1.6 g (94%) of (–)-**10**. Colorless oil. $[\alpha]_D^{25} = -30$ ($c = 2.8$, $CHCl_3$). Other spectral data: see [11].

*(+)-(1*S,*4*S,*5*S,*6*S*)-5*-exo,*6*-endo-*Bis[[(*tert-*butyl)dimethylsilyl]oxy]-7-oxabicyclo[2.2.1]heptan-2-one* ((+)-**10**). As described for (–)-**10**, starting with (+)-**14**. $[\alpha]_D^{25} = +32$ ($c = 2.3$, $CHCl_3$).

*(1*S,*2*S,*4*S,*5*S,*6*S*)-2*-exo-*[[(*S*)-N-*Methyl*-S-*phenylsulfonimidoyl]methyl]-5,6-bis[[(*tert-*butyl)dimethylsilyl]-oxy]-7-oxabicyclo[2.2.1]heptan-2-ol* ((+)-**14**) *and (*1R,*2*R,*4*R,*5*R,*6*R*)-2*-exo-*[[(*S*)-N-*Methyl*-S-*phenylsulfon-imidoyl]methyl]-5,6-bis[[(*tert-*butyl)dimethylsilyl]oxy]-7-oxabicyclo[2.2.1]heptan-2-ol* ((–)-**15**). At –25°, 1.6M BuLi in hexane (6.5 ml, 10.4 mmol) was added dropwise to a stirred soln. of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximide (1.7 g, 10.04 mmol) in anh. THF (88 ml). After stirring at 0° for 10 min, the soln. was cooled to –78°, and ketone (±)-**10** [11] (3.5 g, 9.39 mmol) in anh. THF (18 ml) was added dropwise under stirring. After stirring at –78° for 1 h, the soln. was poured into a sat. aq. NH_4Cl soln. (100 ml). The mixture was extracted with Et_2O (300 ml, 4×), the combined extract dried ($MgSO_4$) and evaporated, and the residue separated and purified by FC (silica gel (5 × 26 cm), AcOEt/light petroleum ether 1:4 (5 l), AcOEt/light petroleum ether 2:3 (1 l), AcOEt/light petroleum ether 1:1 (1 l)): 2.2 g (42%) of (+)-**14** and 2.0 g (39%) of (–)-**15**.

*Data for (+)-***14**: Oil. $[\alpha]_{589}^{25} = +58$, $[\alpha]_{577}^{25} = +59$, $[\alpha]_{546}^{25} = +68$, $[\alpha]_{435}^{25} = +117$, $[\alpha]_{405}^{25} = +144$ ($c = 1.18$, $CHCl_3$). UV (MeCN): 224 (2300), 259 (1200), 265 (1200), 271 (1000). IR (KBr): 3400 (br.), 3250 (br.), 2950, 2930, 2880, 2855, 2800, 1740, 1470, 1460, 1440, 1390, 1250, 1150, 1110, 1080, 1000, 990, 870, 840, 780, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.90–7.88, 7.60–7.26 (*m*, 5 arom. H); 5.67 (*s*, OH); 4.59 (*dd*, *J*(5,6) = 5.1, *J*(1,6) = 2.1, H–C(6)); 4.27 (*dd*, *J*(5,6) = 5.1, *J*(4,5) = 1.7, H–C(5)); 4.16 (*dd*, *J*(3*exo*,4) = 6.0, *J*(4,5) = 1.7, H–C(4)); 3.51, 3.46 (2*d*, ^2J = 14.2, ArCH_2); 3.83 (*d*, *J*(1,6) = 2.1, H–C(1)); 2.99 (*dd*, ^2J = 13.4, *J*(3*exo*,4) = 6.0, H_{exo}–C(3)); 2.67 (*s*, MeN); 1.68 (*d*, ^2J = 13.4, H_{endo}–C(3)); 0.91, 0.89 (2*s*, *t*-BuSi); 0.19, 0.16, 0.08, 0.07 (4*s*, 2 Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 139.7 (*s*, arom. C); 132.6, 129.1, 129.0 (3*d*, *J* = 162, 170, 170, arom. C); 86.0, 84.8, 81.8, 76.8 (4*d*, *J* = 149, 160, 146, 146, C(1), C(4), C(5), C(6)); 80.5 (*s*, C(2)); 64.7 (*t*, *J* = 143, Ar*C*H_2); 43.6 (*t*, *J* = 133, C(3)); 29.3 (*q*, *J* = 137, MeN); 25.7, 25.6 (2*q*, *J* = 125, *Me*$_3$CSi); 17.9, 18.0 (2*s*, 2 Me_3*C*Si); –4.4, –4.8, –4.9, –5.1 (4*q*, *J* = 125, 2 Me_2Si). CI-MS (NH_3): 542 (1, M^+), 484 (2, [M – (*t*-Bu)]$^+$), 315 (1), 231 (7), 154 (10), 125 (28), 73 (100). Anal. calc. for $C_{26}H_{47}NO_5SSi_2$ (541.89): C 57.63, H 8.74; found: C 57.68, H 8.65.

*Data for (–)-***15**: Oil. $[\alpha]_{589}^{25} = -16$, $[\alpha]_{577}^{25} = -17$, $[\alpha]_{546}^{25} = -19$, $[\alpha]_{435}^{25} = -26$, $[\alpha]_{405}^{25} = -26$ ($c = 1.40$, $CHCl_3$). UV (MeCN): 224 (2500), 259 (1200), 265 (1200), 271 (1000). IR (KBr): 3430 (br.), 2930, 2880, 2855, 2800, 1740, 1470, 1460, 1440, 1390, 1370, 1360, 1260, 1150, 1010, 940, 910, 770, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.86–7.83, 7.58–7.26 (*m*, 5 arom. H); 5.40 (*s*, OH); 4.84 (*dd*, *J*(5,6) = 5.2, *J*(1,6) = 1.9, H–C(6)); 4.31 (*dd*, *J*(5,6) = 5.2, *J*(4,5) = 2.1, H–C(5)); 4.14 (*dd*, *J*(3*exo*,4) = 6.6, *J*(4,5) = 2.1, H–C(4)); 3.76 (*d*, *J*(1,6) = 1.9, H–C(1)); 3.73, 3.54 (2*d*, ^2J = 14.9, ArCH_2); 2.02 (*dd*, ^2J = 13.4, *J*(3*exo*,4) = 6.6, H_{exo}–C(3)); 2.62 (*s*, MeN); 1.59

(d, ^2J = 13.4, H_{endo}–C(3)); 0.92, 0.89 (2*s*, *t*-BuSi); 0.25, 0.17, 0.06, 0.05 (4*s*, 2 Me_2Si). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 139.4 (*s*, arom. C); 132.3, 129.3, 128.8 (3*d*, *J* = 161, 165, 165 arom. C); 86.1, 84.2, 82.0, 77.3 (4*d*, *J* = 150, 148, C(1), C(4), C(5), C(6)); 80.8 (*s*, C(2)); 63.4 (*t*, *J* = 138, Ar*C*H_2); 44.3 (*t*, *J* = 140, C(3)); 29.3 (*q*, *J* = 143, MeN); 25.7, 25.6 (2*q*, *J* = 125, 2 *Me*$_3$CSi); 17.9, 17.8 (2*s*, 2 Me$_3$*C*Si); −4.4, −4.8, −5.0, −5.1 (4*q*, *J* = 125, 2 Me_2Si). CI-MS (NH_3): 542 (1, M^+), 484 (5, [*M* − (*t*-Bu)]$^+$), 329 (2), 247 (8), 169 (4), 125 (17), 73 (100). Anal. calc. for $C_{26}H_{47}NO_5SSi_2$ (541.89): C 57.63, H 8.74; found: C 57.74, H 8.67.

*(+)-4-Ethyl-7-{(1′*R*,4′*R*,5′S,6′*S*)-4′,5′,6′-tris{[(*tert*-butyl)dimethylsilyl]oxy}cyclohex-2′-en-1′-yloxy}-2*H*-1-benzopyran-2-one* ((+)-**17**). A soln. of 1,1′-(azodicarbonyl)bispiperidine (516 mg, 2.05 mmol) and $(Bu)_3$P (85%; 500 µl, 1.73 mmol) in anh. THF (15 ml) was added dropwise to a stirred soln. of 4-ethyl-7-hydroxy-2*H*-1-benzopyran-2-one (**16**; 312 mg, 1.64 mmol) [17] in anh. THF (15 ml) at 25°. After stirring at 25° for 15 min, the mixture was cooled to 0° and a 5 : 2 mixture of alcohols (−)-**12** and (−)-**13** [11] (1.0 g, 2.05 mmol) in anh. THF (8 ml) was added and the mixture stirred at 0° for 3 h, then at 20° for 18 h. The solvent was evaporated and the residue purified by FC (silica gel, Et_2O/light petroleum ether 1 : 15; R_f 0.2): 850 mg (63%) of (+)-**17** and 267 mg of (−)-**13**.

Data for (+)-**17**: Colorless oil. $[\alpha]_{589}^{25}$ = + 400, $[\alpha]_{577}^{25}$ = + 420, $[\alpha]_{546}^{25}$ = + 483, $[\alpha]_{435}^{25}$ = + 882, $[\alpha]_{405}^{25}$ = + 1107 (*c* = 2.18, $CHCl_3$). UV (hexane): 317 (7200), 244 (5400). IR (KBr): 2430, 2350, 1720, 1705, 1605, 1500, 1460, 1380, 1300, 1150, 1130, 1060, 870, 830, 770. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.53 (*d*, *J*(5,6) = 8,6, H–C(5)); 6.81 (*dm*, *J*(5,6) = 8.6, H–C(6), H–C(8)); 6.16 (*s*, H–C(3)); 5.90 (*ddd*, *J*(2′,3′) = 10.2, *J*(1′,2′) = 1.7, *J*(2′,4′) = 2.0, H–C(2′)); 5.76 (*ddd*, *J*(2′,3′) = 10.2, *J*(3′,4′) = 1.5, *J*(1′,3′) = 2.0, H–C(3′)); 4.79 (*ddd*, *J*(4′,5′) = 5.8, *J*(3′,4′) = 1.5, *J*(2′,4′) = 2.0, H–C(4′)); 4.18 (*dd*, *J*(5′,6′) = 5.5, *J*(1′,6′) = 4.7, H–C(6′)); 3.96 (*dd*, *J*(4′,5′) = 5.8, *J*(5′,6′) = 5.5, H–C(5′)); 3.79 (*ddd*, *J*(1′,6′) = 4.7, *J*(1′,2′) = 1.7, *J*(1′,3′) = 2.0, H–C(1′)); 2.78 (*q*, *J* = 7.4, MeCH_2); 1.32 (*t*, *J* = 7.4, *Me*CH_2); 0.93–0.83 (*m*, 3 Me_2Si); 0.15–0.10 (*m*, 3 *t*-BuSi). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 161.6 (*s*, C(2)); 160.4 (*s*, C(7)); 157.5, 155.4, (2*s*, C(8a), C(4a)); 132.9 (*d*, *J* = 164, C(3)); 125.2, 124.5 (2*d*, *J* = 161, 164, C(2′), C(3′)); 114.2 (*s*, C(4)); 112.8, 110.0, 102.6 (3*d*, *J* = 161, 169, 163, C(5), C(6), C(8)); 77.7, 76.5, 75.3, 71.7 (4*d*, *J* = 143, 145, 145, 139, C(1′), C(6′), C(5′), C(4′)); 24.7 (*t*, *J* = 125, MeCH_2); 12.1 (*q*, *J* = 128, *Me*CH_2); 26.2, 26.1, 26.0 (3*q*, *J* = 125, *Me*$_3$CSi); 18.2, 18.0 (2*s*, Me$_3$*C*Si); 4.3, 4.2, 3.9, 3.8, 3.5, 3.2 (6*q*, ^1J(C,H) = 120, MeSi). CI-MS (NH_3): 660 (1, M^+), 603 (100), 417 (17), 397 (11), 339 (11), 288 (26), 209 (4), 147 (7), 73 (14). Anal. calc. for $C_{35}H_{60}O_6Si_3$ (661.11): C 63.59, H 9.15, O 14.52, Si 12.74; found: C 63.62, H 9.15, O 14.43, Si 12.78.

Racemate (±)-**17** was prepared following the same procedure starting with a 5 : 2 mixture of (±)-**12** and (±)-**13**. (±)-**17**. Colorless solid, m.p. 129–130°.

*(+)-4-Ethyl-7-[(1′*R*,4′*R*,5′S,6′*S*)-4′,5′,6′-triacetoxycyclohex-2′-en-1′-yloxy]-2*H*-1-benzopyran-2-one* ((+)-**18**). An aq. HF soln. (40%; 240 µl, 5.45 mmol) and MeCN (2 ml) were added to a soln. of (+)-**17** (200 mg, 0.30 mmol) in toluene (1.2 ml). Afer stirring at 20° for 24 h, the solvent was evaporated and the residue dried under high vacuum (4 h). Ac_2O (4 ml), anh. pyridine (440 µl, 5.46 mmol), and 4-(dimethylamino)pyridine (DMAP, 37 mg, 0.30 mmol) were added. After stirring at 20° for 24 h, the solvent was evaporated and the residue purified by FC (silica gel, AcOEt/light petroleum ether 1 : 1; R_f 0.5): 106 mg (79%) of (+)-**18**. White solid. M.p. 158–161°. $[\alpha]_{589}^{25}$ = + 73, $[\alpha]_{577}^{25}$ = + 76, $[\alpha]_{546}^{25}$ = + 87, $[\alpha]_{435}^{25}$ = + 147, $[\alpha]_{405}^{25}$ = + 173 (*c* = 1.10, $CHCl_3$). UV (MeCN): 315 (3100), 259 (1060), 202 (9700). IR (KBr): 3070, 2960, 2940, 2920, 1750, 1710, 1600, 1500, 1420, 1400, 1370, 1340, 1250, 1230, 1160, 1130, 1060, 1040, 1010, 960, 910, 870, 850, 820, 780. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.54 (*d*, *J*(5,6) = 9.5, H–C(5)); 7.06 (*dm*, *J*(5,6) = 9.5, H–C(6), H–C(8)); 6.18 (*d*, *J*(MeCH_2,3) = 1.1, H–C(3)); 5.90 (*ddd*, *J*(2′,3′) = 10.4, *J*(1′,2′) = 1.9, *J*(2′,4′) = 2.0, H–C(2′)); 5.79 (*ddd*, *J*(2′,3′) = 10.4, *J*(3′,4′) = 2.2, *J*(1′,3′) = 2.0, H–C(3′)); 5.65 (*ddd*, *J*(4′,5′) = 7.9, *J*(3′,4′) = 2.2, *J*(2′,4′) = 2.0, H–C(4′)); 5.52 (*dd*, *J*(5′,6′) = 11.1, *J*(1′,6′) = 7.9, H–C(6′)); 5.40 (*dd*, *J*(5′,6′) = 11.1, *J*(4′,5′) = 7.9, H–C(5′)); 5.11 (*ddd*, *J*(1′,6′) = 7.9, *J*(1′,2′) = 1.9, *J*(1′,3′) = 2.0, H–C(1′)); 2.77 (*dq*, *J* = 7.4, *J*(MeCH_2,3) = 1.1, MeCH_2); 2.08, 2.07, 1.96 (3*s*, AcO); 1.32 (*t*, *J* = 7.4, *Me*CH_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 170.2, 169.9, 169.5, (3*s*, 3 AcO); 161.2 (*s*, C(2)); 160.1 (*s*, C(7)); 157.3, 155.2 (2*s*, C(8a), C(4a)); 127.9 (*d*, *J* = 168, C(3)); 126.7, 125.4 (2*d*, *J* = 167, C(3′), C(2′)); 113.8 (*s*, C(4)); 113.3, 110.6, 102.9 (3*d*, *J* = 164, 169, 163, C(5), C(6), C(8)); 76.0, 71.8, 71.6, 71.3 (4*d*, *J* = 153, 148, 150, 152, C(1′), C(6′), C(5′), C(4′)); 24.7 (*t*, *J* = 128, MeCH_2); 20.8, 20.6 (2*q*, *J* = 130, 3 AcO); 12.1 (*q*, *J* = 128, *Me*CH_2). CI-MS (NH_3): 440 (3, M^+), 340 (4), 300 (3), 255 (100), 223 (8), 191 (12), 153 (70), 94 (26). Anal. calc. for $C_{23}H_{24}O_9$ (444.44): C 62.16, H 5.44; found: C 62.23, H 5.53.

Racemate (±)-**18**. As described for (+)-**18**, starting with (±)-**17**. Colorless solid, m.p. 193–195°.

*(+)-4-Ethyl-7-{(1′*R*,2′*S*,3′*S*,4′*R*)-2′,3′,4′-tris{[(*tert*-butyl)dimethylsilyl]oxy}cyclohexyloxy}-2*H*-1-benzopyran-2-one* ((+)-**19**). A degassed mixture of (+)-**17** (0.5 g, 0.76 mmol), AcOEt (20 ml), and 20% $Pd(OH)_2$/C (120 mg) was shaken under H_2 (1 atm) at 20° for 40 min. After consumption of 1 equiv. of H_2, the mixture was degassed, purged with N_2, and filtered. The solvent was evaporated and the residue purified by FC (silica gel, Et_2O/light petroleum ether 1 : 9; R_f 0.3): 462 mg (92%) of (+)-**19**. Colorless oil. $[\alpha]_{589}^{25}$ = + 88, $[\alpha]_{577}^{25}$ = + 91,

$[\alpha]_{546}^{25} = +105$, $[\alpha]_{435}^{25} = +116$. $[\alpha]_{405}^{25} = +81$ ($c = 1.00$, $CHCl_3$). UV (MeCN): 317 (15300), 221 (12500). IR (KBr): 2940, 2920, 2880, 2840, 1720, 1610, 1550, 1500, 1460, 1380, 1250, 1190, 1140, 1080, 1020, 1000, 930, 900, 830, 760, 730, 660. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.62 (*d*, *J*(5,6) = 8.8, H–C(5)); 6.78–6.83 (*dm*, *J*(5,6) = 8.8, H–C(6), H–C(8)); 6.12 (*s*, H–C(3)); 4.48 (*ddd*, *J*(1′,6′) = 6.0, *J*(1′,2′) = 4.0, *J*(1′,6′) = 2.0, H–C(1′)); 3.82 (*dd*, *J*(1′,2′) = 4.0, *J*(2′,3′) = 2.5, H–C(2′)); 3.79 (*dm*, *J*(3′,4′) = 3.5, H–C(4′)); 3.67 (*dd*, *J*(3′,4′) = 3.5, *J*(2′,3′) = 2.5, H–C(3′)); 2.76 (*q*, *J* = 7.2, MeC*H*$_2$); 2.19–2.10 (*m*, H–C(5′)); 1.29–1.45 (*ddm*, *J*(1′,6′) = 6.0, *J*(1′,5′) = 2.0, 2 H–C(6′)); 1.20 (*t*, *J* = 7.2, *Me*CH$_2$); 0.93–0.88 (*m*, 3 Me$_2$Si); 0.09–0.02 (*m*, 3 *t*-BuSi). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 161.8 (*s*, C(2)); 160.9 (*s*, C(7)); 157.6, 155.4 (2*s*, C(4a), C(8a)); 125.0 (*d*, *J* = 160, C(3)); 112.4 (*s*, C(4)); 113.1, 109.6, 102.3 (3*d*, *J* = 162, 169, 162, C(5), C(6), C(8)); 77.7, 75.6, 74.1, 71.0 (4*d*, *J* = 155, 146, 145, 142 C(1′), C(2′), C(3′), C(4′)); 25.9, 25.7 (2*t*, *J* = 125, C(5′), C(6′)); 24.6 (*t*, *J* = 127, Me*C*H$_2$); 12.4 (*q*, *J* = 128, *Me*CH$_2$); 24.2, 24.6 (2*q*, *J* = 125, 3 *Me*$_3$CSi); 19.4, 19.0, 18.1 (3*s*, 3 Me$_3$*C*Si); −4.2, −4.4, −4.6, −4.7, −4.9, −5.0 (6*q*, 3 Me$_2$Si). CI-MS (NH_3): 647 (3), 605 (10), 535 (2), 473 (30), 399 (5), 341 (6), 267 (4), 209 (2). Anal. calc. for $C_{35}H_{63}O_6Si_3$ (663.13): C 63.39, H 9.42; found: C 63.30, H 9.32.

Racemate (±)-**19** was prepared from (±)-**17**. Colorless oil.

*(−)-4-Ethyl-7-[(1′*R*,2′*S*,3′*S*,4′*R*)-2′,3′,4′-triacetoxycyclohexyloxy]-2*H*-benzopyran-2-one* ((−)-**20**). As described for (+)-**17** → (+)-**18**, starting with (+)-**19** (1.2 g, 1.81 mmol): 573 mg (71%) of (−)-**20** after recrystallization from AcOEt/light petroleum ether. Colorless crystals. M.p. 168–170°. $[\alpha]_{589}^{25} = -50$, $[\alpha]_{577}^{25} = -64$, $[\alpha]_{546}^{25} = -64$, $[\alpha]_{435}^{25} = -137$, $[\alpha]_{405}^{25} = -184$ ($c = 1.00$, $CHCl_3$). UV (MeCN): 315 (13800), 220 (12400). IR (KBr): 2960, 2940, 1760, 1740, 1710, 1600, 1500, 1420, 1370, 1240, 1210, 1190, 1150, 1130, 1060, 1030, 1000, 940, 900, 850, 840, 820, 800, 740. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.53 (*d*, *J*(5,6) = 7.7, H–C(5)); 6.85 (*dm*, *J*(5,6) = 7.7, H–C(6), H–C(8)); 6.17 (*d*, *J*(MeC*H*$_2$,3) = 1.1, H–C(3)); 5.27 (*dd*, *J*(1′,2′) = 9.2, *J*(2′,3′) = 2.0, H–C(2′)); 5.17 (*dd*, *J*(3′,4′) = 9.7, *J*(2′,3′) = 2.0, H–C(3′)); 4.95 (*ddd*, *J*(4′,5′) = 11.3, *J*(3′,4′) = 9.7, *J*(4′,5′) = 4.8, H–C(4′)); 4.38 (*ddd*, *J*(1′,6′) = 11.4, *J*(1′,2′) = 9.2, *J*(1′,6′) = 4.6, H–C(1′)); 2.77 (*qd*, *J* = 7.4, *J*(MeC*H*$_2$,3) = 1.1, MeC*H*$_2$); 2.28–2.19 (*ddm*, *J*(5′,6′) = 11.2, *J*(1′,6′) = 4.6, 2 H–C(6′)); 2.1, 2.0, 1.9 (3*s*, 3 AcO); 1.73–1.48 (*ddm*, *J*(5′,6′) = 11.2, *J*(4′,5′) = 4.8, 2 H–C(5′)); 1.32 (*t*, 3 H, *J* = 7.4, *Me*CH$_2$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 170.1, 170.0, 169.7 (3*s*, 3 Me*C*O$_2$); 161.4 (*s*, C(2)); 160.4 (*s*, C(7)); 157.3, 155.2 (2*s*, C(4a), C(8a)); 125.3 (*d*, *J* = 161, C(3)); 113.6 (*s*, C(4)); 113.5, 110.5, 102.9 (3*d*, *J* = 164, 169, 163, C(5), C(6), C(8)); 76.9, 73.9, 72.9, 71.6 (4*d*, *J* = 148, 157, 137, 136 C(1′), C(2′), C(3′), C(4′)); 25.4, 25.3 (2*t*, *J* = 124, 127, C(5′), C(6′)); 24.8 (*t*, *J* = 129, Me*C*H$_2$); 20.9, 20.6 (2*q*, *J* = 130, 3 MeCO$_2$); 12.1 (*q*, *J* = 128, *Me*CH$_2$). CI-MS (NH_3): 446 (21, M^+), 383 (3), 354 (10), 273 (12), 233 (3), 136 (32), 96 (100). Anal. calc. for $C_{23}H_{26}O_9$ (446.45): C 61.88, 5.87; found: C 61.90, H 5.84.

Racemate (±)-**20** was prepared from (±)-**19** as above. M.p. 202–203°.

*(+)-1,2-*O*-Isopropylidene-α-*L*-xylofuranose* ((+)-**21**). A soln. of H_2SO_4 (0.5 ml, *d* 1.83) was added to a suspension of L-xylose (2 g, 13.3 mmol) and molecular sieves *13X* in anh. acetone (30 ml) under N_2. After heating for 4 h at 35°, the mixture was neutralized by successive addition of K_2CO_3 (4.3 g) and H_2O (3 ml). After filtration and solvent evaporation, the residue was dissolved in 1,2-dimethoxyethane under N_2 and heated to 50°. Then 0.25M HCl (0.8 ml) was added and the mixture stirred for 1 h at 50°. It was neutralized with $NaHCO_3$ and concentrated. The residue was dissolved in AcOEt, dried (Na_2SO_4), and purified by FC (silica gel, CH_2Cl_2/MeOH 19:1): 1.39 g (55%) of (+)-**21**. Colorless crystals. M.p. 37–39°. $[\alpha]_D^{24} = +20.4$ ($c = 1.05$, MeOH). ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.80 (*d*, *J*(1,2) = 3.9, H–C(1)); 4.36 (*d*, H–C(2)); 3.95 (*m*, H–C(3), H–C(4)); 3.60 (*t*, $^2J = J(4,5) = 5.7$, H–C(5)); 3.50 (*dd*, $^2J = 5.7$, *J*(4,5′) = 11, H′–C(5)); 1.37 (*s*, Me); 1.22 (*s*, Me). Anal. calc. for $C_8H_{14}O_5 \cdot 0.12\ H_2O$ (192.35): C 49.95, H 7.46; found: C 49.97, H 7.40.

*(+)-1,2-*O*-Isopropylidene-5-*O*-(*p*-tolylsulfonyl)-α-*L*-xylofuranose* ((+)-**22**). A soln. of *p*-toluenesulfonyl chloride (52 g, 0.27 mol) in $CHCl_3$ (120 ml) was added dropwise at 3° to a soln. of (+)-**21** (49 g, 0.26 mol) in pyridine (60 ml) and $CHCl_3$ (250 ml) in 90 min under N_2. After stirring at 20° for 2.5 h, the mixture was poured into ice-water and left overnight. The org. layer was washed successively with 1N HCl, H_2O, aq. $NaHCO_3$ soln., and H_2O and dried (Na_2SO_4). After evaporation, (+)-**22** was obtained by precipitation in $CHCl_3$/(i-Pr)$_2$O as white crystals (54 g, 61%). The filtrate was purified by FC (silica gel, toluene/AcOEt 4:1): 12 g of (+)-**22**. M.p. 138°. $[\alpha]_D^{23} = +10$ ($c = 0.35$, $CHCl_3$). ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): 7.80, 7.50 (2*d*, $^3J = 8.2$, C_6H_4); 5.80 (*d*, *J*(1,2) = 3.6, H–C(1)); 4.35 (*d*, $^3J = 3.6$, H–C(2)); 4.23 (*dd*, $^3J = 10.5, 3$, H–C(5)); 4.10, 3.97 (2*m*); 2.42, 1.33, 1.21 (3*s*, 3 Me). Anal. calc. for $C_{15}H_{20}O_7S$ (344.39): C 52.31, H 5.85; found: C 52.33, H 5.49.

*3-*O*,5-*S*-Diacetyl-1,2-*O*-isopropylidene-5-thio-α-*L*-xylofuranose* ((+)-**23**). AcSK (44 g, 0.39 mol) was added under N_2 to a boiling soln. of (+)-**22** (66 g, 0.20 mol) in 1,2-dimethoxyethane (800 ml). The mixture was heated under reflux for 6 h, then filtered, concentrated, diluted with AcOEt, washed, dried (Na_2SO_4), and evaporated. The residue was purified by FC (silica gel, 4:1 toluene/AcOEt) yielding (+)-**23** (38 g, 63%). Colorless oil. $[\alpha]_D^{23} = +13$ ($c = 0.75$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.90 (*d*, *J*(1,2) = 3.6, H–C(1)); 5.18 (*d*, $^3J = 3.6$,

H–C(2)); 4.50 (*d*, ^3J = 3.6, H–C(3)); 4.35 (*m*, H–C(4)); 3.14 (*dd*, ^2J = 4.5, *J*(3,4) = 6.9, CH_2(5)); 2.34, 2.12 (2*s*, 2 MeCOO); 1.50, 1.30 (2*s*, 2 Me). Anal. calc. for $C_{12}H_{18}O_6S$ (290.34): C 49.64, H 6.25; found: C 49.76, H 6.25.

*1,2-*O*-Isopropylidene-5-thio-α-*L*-xylofuranose* ((+)-**24**). A 18.8% soln. of MeONa in MeOH (43 ml) was added to a cooled soln. of (+)-**23** (37 g, 0.127 mol) in MeOH (350 ml) under N_2. The mixture was stirred for 90 min, then neutralized with cooled AcOH and evaporated. The residue was suspended in $(i\text{-}Pr)_2O$, the mixture filtered, and the filtrate evaporated: 26 g (100%) of (+)-**24**. White solid. M.p. 76°. $[\alpha]_D^{23} = +46$ (c = 0.345, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 5.30 (*d*, ^3J = 2.1, H–C(1)); 4.40 (*d*, ^3J = 2.1, H–C(2)); 4.03 (*m*, H–C(3), H–C(4)); 2.63 (*m*, CH_2(5)); 1.38, 1.23 (2*s*, 2 Me). Anal. calc. for $C_8H_{14}O_4S$ (206.26): C 46.59, H 6.84; found: C 47.02, H 6.45.

*1,2,3,4-Tetra-*O*-acetyl-5-thio-*L*-xylopyranose* ((–)-**25**). A soln. of (+)-**24** (13 g, 63 mmol) in AcOH (26 ml) and H_2O (78 ml) was heated to 60° for 48 h under N_2. After evaporation, the residue was dissolved in H_2O. The by-products were eliminated by extraction with $CHCl_3$. The aq. layer was evaporated to give 5-thio-L-xylopyranose (10.4 g, 100%) which was dissolved in Ac_2O (50 ml) and pyridine (50 ml). The soln. was stirred at 20° overnight under N_2. The mixture was then concentrated and extracted with AcOEt. The org. layer was washed successively with 1N HCl, aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated: 19.9 g (95%) of (–)-**25**. Colorless oil that crystallized. M.p. 92°. $[\alpha]_D^{23} = -176$ (c = 0.45, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.08 (*d*, *J*(1,2) = 9.9, H–C(1) of α-L-anomer); 5.83 (*d*, *J*(1,2) = 9, H–C(1) of β-L-anomer); 5.44 (*dd*, *J*(2,3) = 10.2, *J*(3,4) = 9.9, H–C(3) of α-L-anomer); 5.33 (*t*, ^3J = 9.9, H–C(3) of β-L-anomer); 5.21 (*dd*, *J*(2,3) = 10.2, H–C(2) of α-L-anomer); 5.10 (*m*, H–C(4) of α-L-anomer, H–C(2) and H–C(4) of β-L-anomer); 3.00 (*m*, H–C(5) of both anomers); 2.78 (*m*, H′–C(5) of both anomers); 2.18–2.00 (*m*, 4 MeCOO). Anal. calc. for $C_{13}H_{18}O_8S$ (334.35): C 46.70, H 5.43; found: C 46.74, H 5.35.

*2,3,4-Tri-*O*-acetyl-5-thio-α-*L*-xylopyranosyl Bromide* ((+)-**26**). A soln. of (–)-**25** (19.9 g, 60 mmol) in $CHCl_3$ (100 ml) and 30% HBr in AcOH (40 ml) was stirred at 0° for 1 h. The mixture was then extracted with $CHCl_3$ and ice-cold H_2O. The org. layer was washed with a cooled sat. $NaHCO_3$ soln. and then with iced H_2O, dried ($MgSO_4$), and evaporated. The residue was crystallized from Et_2O: 8.6 g (41%) of white crystals. The filtrate was purified by FC (silica gel, toluene/AcOEt 5:1): 4.3 g of (+)-**26**. Total yield 61%. M.p. 147°. $[\alpha]_D^{24} = +37$ (c = 0.4, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.32 (*t*, ^3J = 9, H–C(2)); 5.12 (*m*, H–C(4)); 5.03 (*t*, ^3J = 9, H–C(3)); 4.70 (*d*, ^3J = 9.9, H–C(1)); 2.89 (*dd*, ^2J = 13.5, ^3J = 4.2, H–C(5)); 2.74 (*dd*, ^2J = 13.5, ^3J = 10.2, H′–C(5)); 2.09–2.04 (*m*, 3 MeCOO). No elemental analysis for instability reasons.

*4-Cyanophenyl 2,3,4-Tri-*O*-acetyl-5-thio-β-*L*-xylopyranoside* ((+)-**27**). A suspension of (+)-**26** (3.6 g, 10 mmol), 4-cyanothiophenol (1 g, 8.3 mol), ZnO (2.5 g, 30.7 mmol), molecular sieves *13X* in toluene (25 ml), and MeCN (25 ml) was heated to 50° overnight under N_2. The mixture was then filtered and extracted with AcOEt. The org. layer was washed successively with 1N HCl, 1N NaOH, and H_2O, dried (Na_2SO_4), and evaporated. The residue was purified by FC (silica gel, toluene/AcOEt 6:1) and then precipitated in Et_2O: 103 mg (2.5%) of (+)-**27**. Colorless crystals. M.p. 140°. $[\alpha]_D^{24} = +22$ (c = 0.25, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.62, 7.10 (2*d*, ^3J = 7.5, 4 arom. H); 5.51 (*t*, ^3J = 8.4, H–C(2)); 5.25 (*d*, ^3J = 8.7, H–C(1)); 5.14 (*m*, H–C(4), H–C(3)); 3.01 (*dd*, ^3J = 3.9, ^2J = 13.5, H–C(5)); 2.71 (*dd*, ^3J = 9.9, ^2J = 13.5, H′–C(5)); 2.06–2.00 (*m*, 3 MeCOO). Anal. calc. for $C_{18}H_{19}NO_7S \cdot 0.19\ H_2O$ (396.83): C 54.48, H 4.92, N 3.53; found: C 54.10, H 5.06, N 3.54.

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REFERENCES

[1] A. N. Teien, U. Abildgaard, M. Höök, *Thromb. Res.* **1976**, *8*, 859.
[2] W. F. Long, F. B. Williamson, G. Kindness, M. Edward, *Thromb. Res.* **1980**, *18*, 493.
[3] M. Okayama, K. Kimata, S. Suzuki, *J. Biochem. (Tokyo)* **1973**, *74*, 1069.
[4] N. B. Schwartz, L. Galligani, P. L. Ho, A. Dorfman, *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 4047; N. B. Schwartz, *J. Biol. Chem.* **1977**, *252*, 6316; K. Mani, B. Havsmark, S. Persson, Y. Kaneda, H. Yamamoto, K. Sakurai, S. Ashikari, H. Habuchi, S. Suzuki, K. Kimata, A. Malmström, G. Westergren-Thorsson, L.-A. Fransson, *Cancer Res.* **1998**, *58*, 1099.
[5] F. Bellamy, V. Barberousse, N. Martin, P. J. Masson, J. Millet, S. Samreth, C. Sepulchre, J. Theveniaux, D. Horton, *Eur. J. Med. Chem.* **1995**, Suppl. to Vol. *30*, 101s.
[6] a) F. Bellamy, D. Horton, F. Millet, F. Picart, S. Samreth, J. B. Chazan, *J. Med. Chem.* **1993**, *36*, 898; b) see also: T. A. Fritz, F. N. Lugemwa, A. K. Sarkar, J. D. Esko, *J. Biol. Chem.* **1994**, *269*, 300; F. N. Lugemwa, A. K. Sarkar, *ibid.* **1996**, *271*, 19159; S. Samreth, V. Barberousse, F. Bellamy, D. Horton, P. Masson,

J. Millet, P. Renaut, C. Sepulchre, J. Theveniaux, 'Pharmacochemistry Library, Trends in Receptor Research', Ed. v. Claassen, Elsevier Science Publ. B. V., Amsterdam, 1993, Vol. 20, p. 41; E. Bozó, S. Borasa, J. Kuszmann, *Carbohydr. Res.* **1997**, *299*, 59; *ibid*. **1997**, *301*, 23.

[7] N. B. Martin, P. J. Masson, C. Sepulchre, J. Theveniaux, J. Millet, F. Bellamy, *Semin. Thromb. Hemost.* **1996**, *22*, 247.

[8] P. J. Masson, D. Coup, J. Millet, N. L. Brown, *J. Biol. Chem.* **1995**, *270*, 2662.

[9] V. Jeanneret, P. Vogel, P. Renaut, J. Millet, J. Theveniaux, V. Barberousse, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1687.

[10] See, *e.g.*, M. Nakajima, I. Tomida, S. Takei, *Chem. Ber.* **1959**, *92*, 163; H. Paulsen, W. Röben, F. R. Heiker, *ibid*. **1981**, *114*, 3242; S. V. Ley, M. Parra, A. J. Redgrave, F. Sternfeld, *Tetrahedron* **1990**, *46*, 4995; H. Seçen, Y. Sütbeyaz, M. Balci, *Tetrahedron Lett*. **1990**, *31*, 1323; Y. Sütbeyaz, H. Seçen, M. Balci, *J. Chem. Soc., Chem. Commun.* **1988**, 1330; H. A. J. Carless, K. Busia, *Tetrahedron Lett*. **1990**, *31*, 16170; T. Hudlicky, J. D. Price, F. Rulin, T. Tsunoda, *J. Am. Chem. Soc*. **1990**, *112*, 9439; T. Hudlicky, H. Luna, H. F. Olivo, C. Andersen, T. Nugent, J. D. Price, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907; T. Hudlicky, M. Mandel, J. Rouden, R. S. Lee, B. Bachmann, T. Dudding, K. J. Yost, S. Merola, *ibid*. **1994**, 1553; T. Hudlicky, J. D. Price, H. F. Olivo, *Synlett* **1991**, 645; C. Jaramillo, R. Fernandez de la Pradilla, M. Martin-Lomas, *Carbohydr. Res.* **1991**, *209*, 296; K.-I. Stao, S. Sakuma, S. Muramatsu, M. Bokura, *Chem. Lett*. **1991**, 1473; T. K. Park, S. J. Danishefsky, *Tetrahedron Lett*. **1994**, *35*, 2667; N. Chida, M. Ohtsuka, K. Nakazawa, S. Ogawa, *J. Chem. Soc., Chem. Commun*. **1989**, 436; N. Chida, M. Ohtsuka, K. Nakazawa, S. Ogawa, *J. Org. Chem*. **1991**, *56*, 2976; D. H. Barton, S. Bath, D. C. Billington, S. D. Gero, B. Quiclet-Sire, M. Samadi, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1551; T. Akiyama, H. Shima, M. Ohnari, T. Okazaki, Ozaki, *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3760; K. Kishta, J. R. Falck, J. Capdevila, *Tetrahedron Lett*. **1993**, *34*, 7869; T. Yoshimitsu, K. Ogasawara, *Synlett* **1995**, 257.

[11] C. Le Drian, J.-P. Vionnet, P. Vogel, *Helv. Chim. Acta* **1990**, *73*, 161.

[12] E. Vieira, P. Vogel, *Helv. Chim. Acta* **1983**, *66*, 1865; J.-L. Reymond, P. Vogel, *Tetrahedron: Asymmetry* **1990**, *1*, 729.

[13] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226; J. L. Luche, A. L. Gemal, *ibid*. **1979**, *101*, 5848.

[14] S. Allemann, P. Vogel, *Tetrahedron* **1994**, *50*, 2469.

[15] C. R. Johnson, J. R. Zeller, *J. Am. Chem. Soc*. **1982**, *104*, 4021.

[16] O. Mitsunobu, *Synthesis* **1981**, 1; T. Tsunoda, Y. Yamamiya, S. Ito, *Tetrahedron Lett*. **1993**, *34*, 1639.

[17] V. K. Akluwalia, Sunita, *Indian J. Chem., Sect. B* **1977**, *15B3*, 240.

[18] a) P. A. Levene, A. L. Raymond, *J. Biol. Chem.* **1933**, *102*, 317; b) D. L. Ingles, R. L. Whistler, *J. Org. Chem.* **1962**, *27*, 3896.

[19] S. Samreth, J. Millet, F. Bellamy, J. Bajgrowicz, V. Barberousse, P. Renaut, Eur. Pat. 365, 397, 1990.

[20] J. Millet, J. Theveniaux, M. Pascal, *Thromb. Res.* **1987**, *45*, 123; J. Millet, J. Theveniaux, N. L. Brown, *Thromb. Haemost.* **1992**, *67*, 176.

[21] S. Wessler, M. Reimer, M. Shap, *J. Appl. Physiol*. **1957**, *14*, 943.

[22] N. B. Schwartz, L. Rodén, *J. Biol. Chem.* **1975**, *250*, 5200.

[23] K. Kraehenbuehl, S. Picasso, P. Vogel, *Helv. Chim. Acta* **1998**, *81*, 1439.

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