130. Synthesis of Potential Glucosidase-Inhibitors: D-Xylopyranoside-5-spiro-1'-cyclopropanes[1])

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The synthesis of the D-xylopyranose-5-spiro-1'-cyclopropane **5**, its methyl α-D-glycoside **7** and its benzyl β-D-glycoside **13** from D-glucose is described, and their conformation in solution is discussed. A *Königs-Knorr* glycosidation of **10** reveals the ionic intermediate of a 1,1-(dibromocyclopropyl)carboxonium ion type to be stable against opening of the cyclopropane ring. Very weak inhibition of saccharase was observed for the α-D-configurated methyl glycoside **7**, whereas the β-D-configurated benzyl glycoside **13** did not inhibit emulsin.

1. Introduction. – The potential of glycosidase inhibitors such as inositols [2] and polyhydroxylated piperidines [3] as anticancer and antiviral agents is of current interest [4]. Glycosidase inhibitors are also potentially useful against diabetes [5] and obesity, and for controlling the blood glucose level [4]. The intermediates in the enzymatic cleavage of α- and β-glucosides appear to be enzyme stabilized carboxonium ions possessing a half-chair conformation [6a][7]. *Whiters* and *Street* [8] have identified an α-D-configurated, covalently bound enzyme-glycosyl intermediate in the hydrolysis of 2-deoxy-2-fluoro-β-D-glycopyranosyl fluorides by a β-glucosidase.

Spirocyclopropanes of type **I** (*Scheme 1*) are new glucose derivatives, which still possess the equatorial C(2)–C(4) OH groups of which HO–C(3) and HO–C(4) have been shown to bind to the active site of the enzyme [6]. Such spirocyclopropanes are potential new glucosidase inhibitors. The potential (suicide) inhibition [9] of glucosidases by such spirocyclopropane-glucosides depends upon the opening of the cyclopropane ring in the hypothetical oxonium intermediate of type **II** and the interception of the ensuing intermediates of the allyl-cation type by nucleophilic groups of the glucosidase in question. The opening of the cyclopropane ring may be compared to the reaction of (tosyloxy)- and of halocyclopropanes [10], keeping in mind that a neutral formyl group may be an excellent leaving group. The bisected arrangement of the cyclopropane group and the C(5)–O–C(1) fragment in **II** permits stabilization of the carboxonium ion [11]. The partitioning of intermediates of type **II** towards **III** and **IV** will depend – among other factors – upon the extent to which **II** is stabilized by the enzyme.

Few carbohydrates possessing cyclopropane rings have been prepared[4]) and the recently reported L-2-deoxyarabinose-2-spirocyclopropane is the only known free sugar with a spirocyclopropane group [12].

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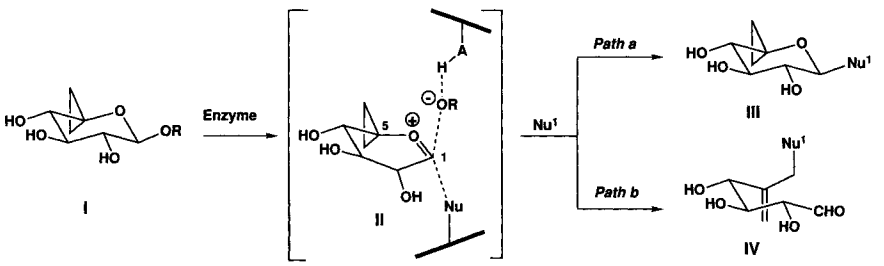
[1]) Taken in part from the thesis of *L.-P. M.* [1].

[2]) Present adress: *Sandoz Technology Ltd.*, Corporate Safety Labs, CH–4002 Basel.

[3]) Present adress: *Ciba-Geigy AG*, Agricultural Division, CH–4002 Basel.

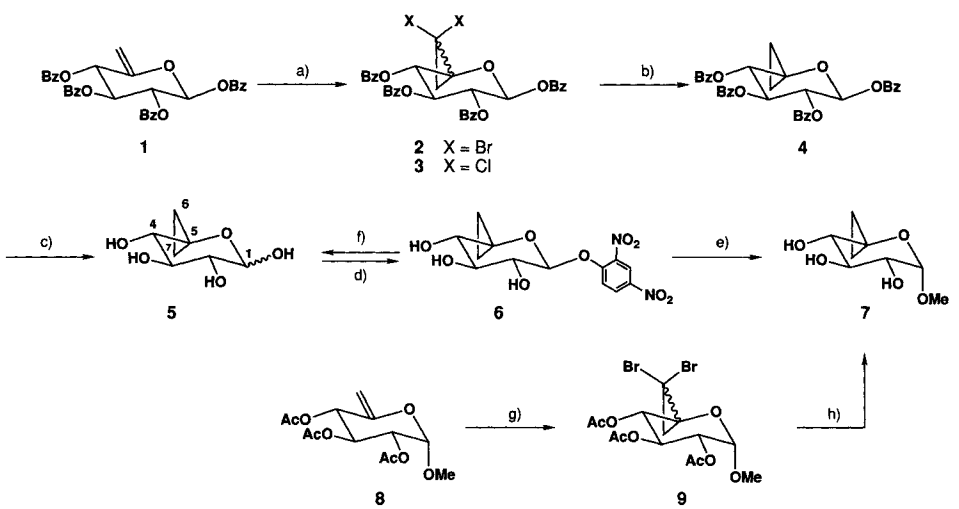
[4]) Spiropyranoses with a spirocyclopropane component at C(2) [12], C(4) [13], or C(5) [14]; a furanose with a cyclopropane group at C(4) [14]. 1,2- [15] or 2,3-Annulated pyranoses [14][16]; 2,3- [17] or 3,4-annulated furanoses [14][18].

Scheme 1



2. Results and Discussion. – 2.1. *Synthesis of the Xylopyranoside-spiro-cyclopropanes* **7** (*Scheme 2*) *and* **13** (*Scheme 3*). The enol ether **1** (*Scheme 2*) was obtained from β-D-glucopyranose pentabenzoate by a slightly modified photobromination (at C(5)), followed by reductive elimination, as described by *Ferrier* and coworkers [19][5]). Cyclopropanation of **1** with Cl_3CCO_2Na or Br_3CCO_2Na under phase-transfer conditions ($BnEt_3NCl$, $CHCl_3$) led, according to the ^1H- and ^{13}C-NMR spectra, to a mixture of the diastereoisomers **2** (72%, **2a/2b** 3.3:1) and **3** (78%, **3a/3b** 3.5:1), which were not separated.

Scheme 2



a) Br_3CCO_2Na, $BnEt_3NCl$, $CHCl_3$, 80°, 4 h, 72% or Cl_3CCO_2Na, $BnEt_3NCl$, $CHCl_3$, 70°, 24 h, 78%. b) Bu_3SnH, AIBN, toluene, reflux, 4 h, 92% from **2** and 40% from **3**. c) MeONa, MeOH, 5 min, r.t., 89% (α and β). d) 2,4-dinitrofluorobenzene, 1,4-diazabicyclo[2.2.2]octane, DMF, –5°, 15 h, 57%. e) MeOH, 50°, 22 h, 47%. f) H_2O, reflux, 30 min, 84%. g) Br_3CCO_2Na, $BnEt_3NCl$, $CHCl_3$, 70°, 2 h, 72%. h) Bu_3SnH, AIBN, toluene, reflux, 90 min; then MeONa, MeOH, 15 min, r.t., 88%.

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[5]) It proved necessary to perform the photobromination in the presence of K_2CO_3; in its absence, we only obtained 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide.

The spirodibromocyclopropanes **2** were reduced with Bu_3SnH and AIBN in good yields (92%) to the spirocyclopropane **4**. A similar treatment of **3** yielded **4** in only 40%. The cyclopropane component of **4** is characterized in the ^{13}C-NMR spectrum (*Table 1*) by two *triplets* at 10.85 and 7.35 ppm and by a *singlet* at 56.82 ppm. In the ^1H-NMR spectrum, the signals of H–C(1) to H–C(4) show coupling constants (*Table 2*) which are slightly larger than the corresponding values observed for β-D-xylopyranose tetrabenzoate ($\Delta J(1,2) = 0.7$, $\Delta J(2,3) = 0.5$, and $\Delta J(3,4) = 0.2$ Hz). This tetrabenzoate is present as a rapidly equilibrating 1:1 mixture of the $^4C_1$- and $^1C_4$-conformers in acetone solution [20]. The J values of **4** (*Table 2*) are consistent with a $^4C_1$:$^1C_4$ equilibrium of 1.7:1[6]) (see the *Fig.*).

Debenzoylation of **4** with NaOMe in MeOH [21] at r.t., chromatography of the product on *Dowex-50 W* (Ca^{2+}-form) [22] and crystallization gave the free D-xylopyranose-5-spiro-1'-cyclopropane **5** (89%). In aqueous solution[7]), **5** is present as a rapidly equilibrating mixture of the α- and β-anomers (α /β = 15 : 85)[8]).

Table 1. *^{13}C-NMR Chemical Shifts* [ppm] *of* D-*Xylopyranose-5-spiro-1'-cyclopropanes*

C-Atom	**4**[a])	**5** (β-anomer)[b])	**6**[c])	**7**[b])	**12**[a])	**13**[c])
C(1)	92.46	96.37	101.53	101.25	98.80	102.44
C(2), C(3), C(4)	70.06	76.03	74.39	71.80	71.61	77.21
	70.97	75.74	76.56	72.31	72.19	75.18
	69.53	70.12	70.29	70.25	69.73	70.46
C(5)	56.82	58.91	59.91	57.19	56.18	58.41
C(6), C(7)	10.85	7.23	7.82	7.37	9.23	7.47
	7.35	6.58	6.34	4.80	7.29	6.67
CH_3O	–	–	–	56.65	–	–
$ArCH_2$	–	–	–	–	70.24	70.77
Arom. C	133.52–		154.87		136.54	138.72
	128.27		141.83		133.15	128.71
			140.32		132.93	128.39
			129.52		129.66–	128.01
			121.72		127.65	
			117.88			
C=O	165.14				165.41	
	164.89				169.99	
	164.65				164.86	
	164.40					

[a]) In $CDCl_3$. [b]) In D_2O. [c]) In $(CD_3)_2CO$.

[6]) Calculated from $J(1,2)$, according to [20]: $J_{obs} = N_{4C1}J(1,2)_{4C1} + N_{1C4}J(1,2)_{1C4}$; $J(1,2)_{4C1} = 8$ Hz; $J(1,2)_{1C4} = 2$ Hz. N = mole fraction of the $^4C_1$- or $^1C_4$-conformer.

[7]) No mutarotation was observed for an aqueous solution (prepared within 10 min) of crystallized **5** .

[8]) The ratios of the α- and β-anomers of D-gluco- and D-xylopyranose in H_2O are 38:62 and 37:63 at the equilibrium, those of D-allopyranose and D-ribopyranose (1,3-diaxial interaction (OH/OH) for the α-D-anomer) are 17:83 and 27:73 [23]. The stronger preference for the β-anomer observed for **5** might be explained by steric interactions between the axial anomeric OH group and the cyclopropane moiety and/or by a weaker anomeric effect. The former rationalization is in keeping with the observation that the vicinal coupling constants $J(2,3)$ and $J(3,4)$ of the α-anomer of **5** (*Table 2*) are 0.2–0.5 Hz smaller than those of α-D-xylopyranose [24] and that the values of the β-anomer of **5** are 0.4–0.6 Hz larger than those of β-xylopyranose [24]. Hence, the (pseudoaxial) CH_2 group ($CH_2(7)$) slightly disfavours a $^4C_1$-conformation in the case of the α-anomer, and favours it in the case of the β-anomer of **5**.

Table 2. *Selected ^{1}H-NMR Chemical Shifts* [ppm] *and Coupling Constants* [Hz] *of* D-*Xylopyranose-5-spiro-1'-cyclopropanes*

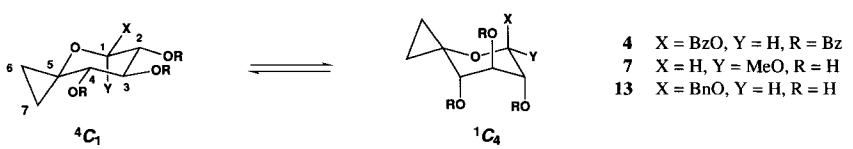
	4	**5** (β-anomer)		**13**	**5** (α-anomer)		**7**	
	$(CD_3)_2CO$	D_2O	CD_3OD	D_2O	D_2O	CD_3OD	$(CD_3)_2CO$	CD_3OD
H–C(1)	6.44	4.65		4.52	5.22		4.62	
H–C(2)	5.83	3.38		3.44	3.68		3.47	
H–C(3)	5.97	3.52		3.49	3.86		3.69	
H–C(4)	5.67	3.87		3.85	3.71		3.58	
J(1,2)	5.8	7.9	7.7	7.6	3.5	3.2	3.6	3.8
J(2,3)	7.2	9.2	9.1	9.1	8.5	7.7	8.3	8.8
J(3,4)	7.1	9.3	9.0	8.9	8.0	7.7	8.3	8.6

The configuration of the anomers of **5** was assigned on the basis of ^{1}H-NMR spectroscopy, the H–C(1) signal occurring at 4.65 ppm (J(1,2) = 7.9 Hz) for the major and at 5.22 ppm (J(1,2) = 3.5 Hz) for the minor isomer, as it is typical for β- and α-D-anomers, respectively. These assignments were confirmed by comparison of the chemical shifts of C(1), C(2), and C(3) in the ^{13}C-NMR spectrum (*Table 1*) with those found for β-D-glucopyranose (96.8, 75.2, and 76.7 ppm [25]) and β-D-xylopyranose (97.6, 75.1, and 76.8 ppm [25]).

Treatment of **5** (*Scheme 2*) with 2,4-dinitrofluorobenzene gave the β-D-glycoside[9]) **6** (57%), which was easily hydrolyzed to **5** (84%). Methanolysis of **6** gave the desired glycoside **7** (47%). This sequence was not optimized, as **7** was obtained in a straightforward way by cyclopropanation (Br_3CCO_2Na) of the easily accessible methyl α-D-hexopyranoside **8** [1][27], followed by dehalogenation (Bu_3SnH) and deacetylation (NaOMe, 74% from **8**).

The ^{1}H-NMR coupling constants of **7** are compiled in *Table 2*. The values are consistent with the assumption of a solvent-dependant equilibrium of the $^4C_1$- and $^1C_4$-conformers (83:17 in $(CD_3)_2CO$; 88:12 in CD_3OD)[10])[11]). The presence of the $^1C_4$-conformer, which is not observed for methyl α-D-xylopyranoside and its acetates, which exclusively adopt a $^4C_1$-conformation under similar conditions [28], might arise from a repulsive interaction of the axial MeO group and the (pseudoaxial) CH_2(7) group (*Scheme 3*).

Scheme 3



4 X = BzO, Y = H, R = Bz
7 X = H, Y = MeO, R = H
13 X = BnO, Y = H, R = H

[9]) Under similiar conditions, but with partially protected sugars, *van Boom* and coworkers [26] obtained exclusively β-D-configurated glycosides, independant of the nature of the participating or not participating group at C(2).

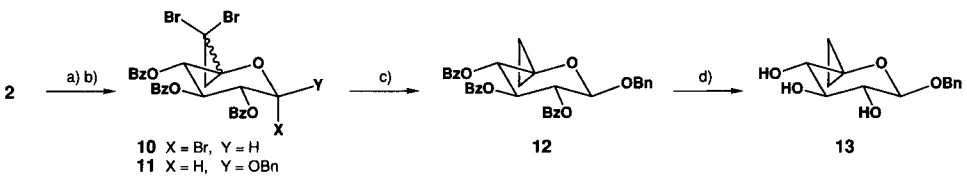
[10]) Calculated from J(2,3) and J(3,4). See [20]. $^4C_1$-Conformer: J(2,3) = 9.8 Hz [28]; J(3,4) = 9.4 Hz [28]; $^1C_4$-Conformer: J(2,3) = J(3,4) = 2 Hz [20].

[11]) AM1 calculations [29] indicate that **7** prefers a slightly flattened $^4C_1$-conformation which is evidenced by the torsion angles Φ(C(1)–C(2)–C(3)–C(4)) = Φ(C(2)–C(3)–C(4)–C(5)) = Φ(C(3)–C(4)–C(5)–O(5)) = Φ(C(4)–C(5)–O(5)–C(1)) = 51±3° for the α-anomer and 54.5±1.5° for the β-anomer of **7**. Both anomers exhibt Φ(C(3)–C(4)–C(5)–C(6)) = 166° and Φ(C(3)–C(4)–C(5)–C(7)) = 95°.

The benzyl β-D-pyranoside **13** (*Scheme 3*), a potential β-glucosidase inhibitor, was obtained by a *Königs-Knorr* glycosidation. The perbenzoylated dibromocyclopropane **2** (*Schemes 2* and *3*) was treated with HBr in AcOH for 4 days at r.t. to yield crystalline **10** (73%, indefinitely stable at r.t.; *Scheme 4*). Glycosidation of **10** with $PhCH_2OH$ in the presence of AgOTf as promoter gave a mixture of the diastereoisomeric benzyl β-D-glycosides **11** (70%), showing that the (solvated) carboxonium ion, presumed as an intermediate, is not reactive enough to suffer opening of the dibromocyclopropane ring. Reduction (→ **12**) and debenzoylation of **12**, similarly as described for **5**, gave **13**.

The coupling constants of H–C(1) to H–C(4) in the ^{1}H-NMR spectrum (*Table 2*) indicate the almost exclusive presence of the $^4C_1$-conformer of **13**[11][12]).

Scheme 4



a) AcOH/HBr, $ClCH_2CH_2Cl$, r.t., 4 d, 73%. b) $PhCH_2OH$, AgOTf, $CaSO_4$, CH_2Cl_2, r.t., 70%. c) Bu_3SnH, AIBN, toluene, reflux, 30 min, 71%. d) MeONa, MeOH, 0°–r.t., 3.5 h, 96%.

2.2. *Enzymatic Tests.* The methyl α-D-glycopyranoside **7** (*Scheme 1*) was almost inactive (33.9 mSIE/mg) in inhibiting the hydrolysis of saccharose by saccharase (isolated from porcine intestine). No inhibition of β-glucosidase from emulsin (*EC 3.2.1.21*) was observed for the benzyl β-D-glycopyranoside **13** using *p*-nitrophenyl β-D-glucopyranoside as substrate.

We thank Dr. *B. Junge*, *Bayer AG*, D–Wuppertal, for inhibition tests with saccharase and the *Swiss National Science Foundation* and *Sandoz AG*, Basel, for generous support.

Experimental Part

General. See [31]. Workup implies extraction (3 ×) with the specified solvent, washing of the org. phase as indicated, drying the org. phase ($MgSO_4$), and evaporation of the solvent below 40° *in vacuo*. TLC: 0.25-mm precoated silica-gel plates (*Merck*, Kieselgel *60*, 0.040–0.063 mm); 1 mm precoated silica gel plates (*Merck* $HF_{254+366}$, activated at 120° for 2 h). Column chromatography (CC): silica gel *Merck 60* (70–230 mesh). Medium-pressure liquid chromatography (MPLC): silica gel *Merck 60* (230-400 mesh). ^{1}H- and ^{13}C-NMR

[12]) The coupling constants $J(1,2)$ = 7.8, $J(2,3)$ = 9.1, $J(3,4)$ = 9.0, and $J(4,5)$ = 10.8 and 5.4 Hz of benzyl β-D-xylopyranoside [30], which adopts a $^4C_1$-conformation (>98%), are almost identical to those of **13** .

spectra: chemical shifts in ppm relative to TMS as internal standard (if not otherwise specified). The chemical shift of (resolved) signals of the minor isomer in diastereoisomeric mixtures are indicated in *italics*. Br_3CCO_2H was finely ground and dried. α,α'-Azo-isobutyronitrile was dried (P_2O_5). AgOTf was freshly prepared [32].

(3RS,5S,6R,7S,8S)-1,1-Dibromo-4-oxaspiro[2.5]octane-5,6,7,8-tetrayl Tetrabenzoate (**2**). A soln. of $BnEt_3NCl$ (15.8 mg, 0.07 mmol) and **1** (2.0 g, 3.46 mmol) in $CHCl_3$ (15 ml) was treated with freshly prepared [33] Br_3CCO_2Na (2.2 g, 6.93 mmol). The suspension was stirred for 3 h at 80°, and additional Br_3CCO_2Na (1.1 g, 3.47 mmol) was added. The mixture was stirred for 1 additional h at 80°, filtered (*Celite*), washed with H_2O, and worked up. Chromatography (Et_2O/hexane 1:1) on silica gel and crystallization ($CHCl_3$/EtOH, 2 ×) gave a highly hygroscopic mixture of **2** (1.88 g, 72%, 3.3:1 according to ^{1}H- and ^{13}C-NMR). R_f (Et_2O/hexane 2:1) 0.45. M.p. 98–101°. $[\alpha]_D^{25}$ = –22.4 (*c* = 1.0). IR: 3080*w*, 3040*w* (br.), 1735*s*, 1608*m*, 1590*w*, 1496*w*, 1460*m*, 1320*m*, 1308*m*, 1185*m*, 1160*w*, 1110*s*, 1100*s*, 1075*s* (sh), 1030*s*, 1010*w*, 985*m* (br.). ^{1}H-NMR (90 MHz, $CDCl_3$): 8.25–7.03 (*m*, 20 arom. H); 6.60 (br. *s*, H–C(5)); 5.94 (*d*, *J* = 3, 0.3 H–C(8)); 5.81 (*d*, *J* = 3, 0.7 H–C(8)); 5.74–5.41 (*m*, H–C(6), H–C(7)); 2.11 (*d*, *J* = 9, 0.7 H, H–C(2)); 1.95 (*d*, *J* = 9, 0.7 H, H–C(2)); 1.95 (*d*, *J* = 9, 0.3 H, H–C(2)); 1.82 (*d*, *J* = 9, 0.3 H, H–C(2)). ^{13}C-NMR (25 MHz, $CDCl_3$): 165.17 (*s*); 164.71 (*s*); 164.44 (*s*); 133,49–128.13 (*s* + *d*); 90.38 (*d*); *67.99* (*d*); 66.90 (*d*); *66.71* (*d*); 66.50 (*d*); 66.32 (*d*); 63.63 (*s*); 63.03 (*s*); *62.83* (*s*); *31.97* (*t*); *30.74* (*s*); 30.39 (*t*). CI-MS: 436 (1), 434 (1), 416 (1), 331 (1), 281 (1), 122 (6), 106 (10), 195 (100). Anal. calc. for $C_{35}H_{26}Br_2O_9 \cdot 0.38\ H_2O$ (756.89): C 55.54, H 3.56; found: C 55.49, H 3.48.

(3RS,5S,6R,7S,8S)-1,1-Dichloro-4-oxaspiro[2.5]octane-5,6,7,8-tetrayl Tetrabenzoate (**3**). Analogous to the preparation of **2**, a mixture of $BnEt_3NCl$ (27.4 mg, 0.12 mmol), **1** (3.0 g, 6.0 mmol) and Cl_3CCO_2Na [33] (11.1 g, 60 mmol) in $CHCl_3$ (36 ml) was stirred for 24 h at 70°. Chromatography (AcOEt/hexane 1:9) on silica gel gave **3** (2.66 g, 78%, 3.5:1 mixture according to ^{1}H- and ^{13}C-NMR). An anal. pure sample was obtained by crystallization from Et_2O/hexane. R_f (hexane/Et_2O/AcOEt 5:3:2) 0.11. M.p. 135°. IR: 3100*w*, 3080*w*, 3040*w*, 3010*w*, 1735*s*, 1610*m*, 1590*w*, 1460*s*, 1325*s*, 1310*s*, 1185*m*, 1165*w*, 1115*s*, 1100*s*, 1075*s* (sh), 1030*s*, 1015*w*, 995*m*, 850*w* (sh). ^{1}H-NMR (90 MHz, $CDCl_3$,): 8.37–6.93 (*m*, 20 arom. H); 6.77 (*d*, *J* ≈ 2, 0.3 H, H–C(5)); 6.70 (br. *s*, 0.7 H, H–C(5)); 5.88 (*d*, *J* ≈ 2, H–C(8)); 5.83–5.40 (*m*, H–C(6), H–C(7)); 2.11 (*d*, *J* = 9, 0.3 H, H–C(2)); 1.98 (*d*, *J* = 9, 0.3 H, H–C(2)); 1.98 (*d*, *J* = 9, 0.7 H, H–C(2)); 1.83 (*d*, *J* = 9, 0.7 H, H–C(2)). ^{13}C-NMR (25 MHz, $CDCl_3$): 165.15 (*s*); *164.92* (*s*); 164.68 (*s*); 164.45 (*s*); *164.17* (*s*); *163.35* (*s*); 133.49–128.26 (*s* + *d*); 90.33 (*d*); *69.66* (*d*); 67.42 (*d*); 66.87 (*d*); 66.43 (*d*); 66.25 (*d*); *64.11* (*s*); 63.60 (*s*); 63.01 (*s*); *33.05* (*t*); 30.37 (*t*). Anal. calc. for $C_{35}H_{26}Cl_2O_9$ (661.50): C 63.55, H 3.96; found: C 63.60, H 3.96.

(5S,6R,7S,8S)-4-Oxaspiro[2.5]octane-5,6,7,8-tetrayl Tetrabenzoate (**4**). a) *From* **2**. A soln. of **2** (1.0 g, 1.33 mmol), Bu_3SnH [34] (1.77 ml, 6.6 mmol), and AIBN (55 mg, 0.3 mmol) in toluene (10 ml) was boiled under reflux under N_2 for 4 h. The concentrated mixture was taken up in MeCN, washed with hexane (4 ×), evaporated, and crystallized ($CHCl_3$/EtOH) to yield **4** (873 mg, 92%) containing 1 equiv. of $CHCl_3$.

b) *From* **3**. See *a*). A soln. of **3** (2 .0 g, 3.0 mmol), Bu_3SnH (8.8 g, 30 mmol) and AIBN (2.98 g, 18 mmol) in toluene (27 ml) was boiled under reflux under N_2 for 4 h. Workup and crystallization ($CHCl_3$/EtOH) yielded **4** (866 mg, 40%) containing 1 equiv. of $CHCl_3$. R_f (AcOEt, $CHCl_3$/hexane 1:1:4) 0.48. M.p. 111–112° (sint. at 60°). $[\alpha]_D^{25}$ = –25.5 (*c* = 1.0). IR: 3090*w*, 3060*w*, 3020*w* (br.), 2950*w* (br.), 1730*s*, 1600*m*, 1585*m*, 1490*w*, 1450*s*, 1365*w*, 1320*s*, 1175*m*, 1160*m*, 1105*s*, 1095*s*, 1070*s*, 1025*s*, 985*m* (sh), 940*w*. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 8.02–7.96 (*m*, 8 arom. H); 7.67–7.55 (*m*, 4 arom. H); 7.49–7.37 (*m*, 8 arom. H); 6.44 (*d*, *J* = 5.8, H–C(5)); 5.97 (*t*, *J* = 7.1, H–C(7)); 5.83 (*dd*, *J* = 7.2, 5.8, H–C(6)); 5.67 (*d*, *J* = 6.8, H–C(8)); 1.16–1.01 (*m*, H–C(1), H–C(2)). ^{13}C-NMR: see *Table 1*. CI-MS: 592.6 (1, M^+), 414(3), 348 (3), 227 (3), 195 (6), 161 (12), 105 (100). Anal. calc. for $C_{35}H_{28}O_9 \cdot CHCl_3$ (711.99): 60.73, H 4.11; found: C 60.82, H 4.16.

(5RS,6R,7S,8S)-4-Oxaspiro[2.5]octane-5,6,7,8-tetrol (**5**). A soln. of **4** (1.43 g, 2 mmol) in MeOH (80 ml) was treated with 0.5M NaOMe in MeOH (0.5 ml). After 5 min at r.t., the mixture was neutralized by addition of *Dowex 50W* (H^+ form, 200–400 mesh), filtered, concentrated to give a brownish oil (338 mg), chromatographed (MeOH) on *Dowex 50* (sat. with Ca^{2+}) [22], and crystallized (AcOEt/MeOH) to give **5** (315 mg, 89%). R_f (CH_3CN/H_2O 4:1) 0.48. M.p. 139–140°. $[\alpha]_D^{25}$ = –25.0 (*c* = 1.0, MeOH); $[\alpha]_D^{25}$ = –28.2 (*c* = 1.0, H_2O). IR (KBr): 3720–3040*s* (br.), 3010*w*, 2920*m*, 2885*w*, 1440*m*, 1405*m*, 1385*w*, 1360*w*, 1315*w*, 1270w, 1230m (br.), 1200*m* (sh), 1170*m*, 1120*s*, 1100*s*, 1060*s*, 1025*s* (br.), 990*m*, 985*m*, 960*w*, 945*w*, 895*w*. ^{1}H-NMR (400 MHz, CD_3OD, from a α/β mixture): α-anomer of **5**: 5.04 (*d*, *J* = 3.2, H–C(5)); 3.79 (*t*, *J* = 7.7, H–C(7)); 3.48 (*d*, *J* = 7.8, H–C(8)); 3.47 (*dd*, *J* = 8.0, 3.3, H–C(6)); 0.9–0.45 (*m*, H–C(1),H–C(2)); β-anomer of **5**: 4.46 (*d*, *J* = 7.7, H–C(5)); 3.70 (*d*, *J* = 9.0, H–C(8)); 3.35 (*t*, *J* = 9.1, H–C(7)); 3.23 (*dd*, *J* = 9.2, 7.7, H–C(6)); 0.9–0.45 (*m*, H–C(1),H–C(2)). ^{13}C-NMR: see *Table 1*. Anal. calc. for $C_7H_{12}O_5$ (176.17): C 47.73, H 6.87; found: C 47.74, H 6.86.

(5S,6R,7S,8S)-6,7,8-Trihydroxy-4-oxaspiro[2.5]oct-5-yl 2,4-Dinitrobenzoate (**6**). A soln. of **5** (200 mg, 1.1 mmol) in DMF (12 ml) was treated at –5° with 1,4-diazabicyclo[2.2.2]octane (395 mg, 3.5 mmol) and 2,4-dinitrofluorobenzene (423 mg, 2.3 mmol). The mixture was stirred for 15 h at –5° and for 2 h at 3°. Chromatography (MeCN/AcOEt 3:1) of the concentrated mixture on silica gel and crystallization (AcOEt/hexane) gave **6** (226 mg). The mother liqour was washed with 1M $NaHCO_3$ and brine, worked up, chromatographed (MeCN/AcOEt 3:1, silica gel), and crystallized. Recrystallization (2 ×) of the two fractions gave slightly yellow **6** (220 mg, 57%). R_f (MeCN/H_2O 9.5:0.5) 0.62. M.p. 164–165°. $[\alpha]_D^{25}$ = –118.1 (*c* = 1.0, MeOH). IR (KBr): 3510*s*, 3470*s*, 3350*s*, 3110*w*, 3020*w*, 2930*w*, 2900*w*, 2880*w*, 1610*s*, 1530*s*, 1520*s*, 1480*m* (sh), 1450*w*, 1420*m*, 1400*w*, 1385*w*, 1350*s*, 1320*m*, 1305*m*, 1288*s*, 1255*s* (sh), 1248*m*, 1212*s*, 1180*w*, 1152*m*, 1130*m*, 1100*m*, 1070*s*, 1020*s*, 1015*s*, 976*m*, 925*w*, 908*m*, 843*m*, 835*m*. ^{1}H-NMR (200 MHz, $(CD_3)_2CO$): 8.72 (*d*, *J* = 3.0, 1 arom. H); 8.51 (*dd*, *J* = 9.0, 3.0, 1 arom. H); 7.56 (*d*, *J* = 9.0, 1 arom. H); 5.39 (*d*, *J* = 7.5, H–C(5)); 4.90 (*d*, *J* = 4.5, 1 H exchanges with D_2O); 4.45 (*d*, *J* = 4.0, 2 H exchange with D_2O); 3.85 (*dd*, *J* = 8.5, 4.0; H–C(8)); 3.76 (*dt*, *J* = 7.5, 4.5, H–C(6)); 3.60 (br. *t*, *J* = 8.0, H–C(7)); 0.89–0.70 (*m*, H–C(1),H–C(2)). ^{13}C-NMR: see *Table 1*. EI-MS: 186 (1), 185 (8), 184 (100), 168 (9), 159.3 (3), 154 (26), 107 (29), 99 (11), 93 (13), 92 (26), 91 (48), 87 (28), 79 (24), 73 (26), 63 (54), 53 (48). Anal. calc. for $C_{13}H_{14}N_2O_9$ (342.26): C 45.62, H 4.12, N 8.18; found: C 45.80, H 4.39, N 8.16.

Solvolysis of **6**. a) *With MeOH*. A soln. of **6** (20 mg, 0.05 mmol) in MeOH (1 ml) was kept for 22 h at 50° and for 4 h at 70°. Prep. TLC (MeCN/H_2O 19:1) gave **7** (5.2 mg, 47%). IR and ^{1}H-NMR identical with the spectra from a sample obtained by an independent synthesis (see **9** and **10**).

b) *With H_2O*. An aq. soln. (1 ml) of **6** (10 mg, 0.03 mmol) was boiled under reflux for 30 min. Prep. TLC (MeCN/H_2O 19:1) gave **5** (4.3 mg, 84%), which was crystallized (AcOEt/MeOH). M.p. and the ^{1}H-NMR spectrum are identical with the data of **5** obtained from **4**.

(3RS,5S,6R,7S,8S)-1,1-Dibromo-5-methoxy-4-oxaspiro[2.5]octane-6,7,8-triyl Triacetate (**9**). According to the preparation of **2**, the mixture of $BnEt_3NCl$ (15 mg, 0.06 mmol), Br_3CCO_2Na (3.16 g, 10 mmol), and **8** (1.0 g, 3.3 mmol) in $CHCl_3$ (20 ml) was stirred for 2 h at 70°. Filtration (*Florisil*, $CHCl_3$), MPLC (hexane/Et_2O/MeOH 8:4:1), and crystallization (CH_2Cl_2/hexane) gave **9** (1.32 g, 84%, 1.3:1 mixture according to ^{1}H-NMR). R_f (hexane/Et$_2$O/MeHO 8:4:1) 0.2. M.p. 166–168°. IR (KBr): 3100*w*, 3015*w*, 3000*w*, 2975*w*, 2950*w*, 2900*w*, 2865*w*, 2840*w*, 1750*s*, 1735*s*, 1458*w*, 1435*w* (br.), 1403*w*, 1385*m*, 1378*m*, 1371*m*, 1310*w*, 1296*w*, 1257*s*, 1239*s*, 1226*s*, 1220*s*, 1159*m* (sh), 1140*m*, 1085*m*, 1076*m*, 1052*s*, 1031*s*, 1019*s*, 1010*m*, 995*m*, 985*m*, 960*m*, 930*w*, 882*m*, 878*m*, 853*w*. ^{1}H-NMR: 5.32–5.03 (*m*, 4 H); 3.60 (*s*, 1.3 H, CH_3); 3.57 (*s*, 1.7 H, CH_3); 2.21 (6*s*, 6 CH_3CO); 2.07 (*d*, *J* = 9.4, 0.4 H, H–C(2)); 1.92 (*d*, *J* = 9.4, 0.4 H, H–C(2)); 1.91 (*d*, *J* = 9.0, 0.6 H, H–C(2)); 1.78 (*d*, *J* = 9.0, 0.6 H, H–C(2)). ^{13}C-NMR: see *Table 1*. CI-MS: 476 ([*M* + 2]$^+$), 474 (M^+), 472 ([*M* –2]$^+$).

(5S,6R,7S,8S)-5-Methoxy-4-oxaspiro[2.5]octane-6,7,8-triol (**7**). Analogous to the preparation of **4**, the soln. of **9** (830 mg, 1.75 mmol), Bu_3SnH (2.32 ml, 8.75 mmol), and AIBN (143 mg, 0.8 mmol) in toluene (12 ml)was hold at reflux under Ar for 90 min. The crude product was taken up in MeOH (50 ml) and treated with 1M NaOMe in MeOH (1 ml). After 5 min at r.t., the mixture was neutralized with *Dowex 50W* (H^+ form, 200–400 mesh), filtered, concentrated (687 mg), and chromatographed (MPLC, AcOEt/hexane/MeOH 4:4:1) to give **7** (293 mg, 88%). R_f (AcOEt/hexane/MeOH) 0.18. $[\alpha]_D^{25}$ = +131.0. IR (KBr): 3495*s* (br.), 3300*s* (br.), 3030*w*, 3020*w*, 2955*m*, 2920*m*, 2855*w*, 1460*m* (sh), 1435*m*, 1405*m*, 1390*m*, 1370*m*, 1340*m*, 1310*m* (br.), 1245*m*, 1230*m*, 1200*m*, 1160*s*, 1115*s*, 1095*s*, 1065*s* (sh), 1040*s*, 1030*s*, 1010*s*, 995*m*, 925*w*, 900*m*, 880*w*. ^{1}H-NMR (200 MHz, $(CD_3)_2CO$ + D_2O): 4.62 (*d*, *J* = 3.6, H–C(5)); 3.69 (*t*, *J* = 8.3, H–C(7)); 3.58 (*d*, *J* = 8.3, H–C(8)); 3.47 (*dd*, *J* = 8.3, 3.6, H–C(6)); 3.33 (*s*, CH_3); 0.93–0.43 (*m*, H–C(1), H–C(2)). ^{13}C-NMR (25 MHz, D_2O): 101.25 (*d*); 72.31 (*d*); 71.80 (*d*); 70.25 (*d*); 57.19 (*s*); 56.65 (*q*), 7.37 (*t*), 4.80 (*t*). CI-MS: 191 (5, [*M* + 1]$^+$), 183 (23), 173 (48), 159 (100), 141 (55), 99 (26), 87 (31), 47 (75). Anal. calc. for $C_8H_{14}O_5$ (190.20): C 50.52, H 7.42; found: C 50.43, H 7.35.

(5R,6R,7S,8S)-1,1,5-Tribromo-4-oxaspiro[2.5]octane-6,7,8-triyl Tribenzoate (**10**). A soln. of **2** (2.5 g, 3.3 mmol) in $ClCH_2CH_2Cl$ (20 ml) was treated with HBr (33% in AcOH) and kept for 4 d at r.t. The mixture was diluted with toluene (40 ml) and concentrated at r.t. This operation was repeated twice. The slightly brown residue was crystallized (Et_2O/hexane) yielding colourless crystals (1.725 g, 73%) of **10**. R_f (Et_2O/hexane 2:1) 0.72. M.p. 150–153°. IR (KBr): 3090*w*, 3060*w*, 3030*w*, 3005*w*, 2980*w*, 2920*w*, 2850*w*, 1742*s*, 1730*s*, 1600*m*, 1585*w*, 1490*w*, 1452*m*, 1415*w* (br.), 1318*m*, 1300*s*, 1275*s*, 1260*s*, 1238*s*, 1179*m*, 1160*w*, 1130*m*, 1110*s*, 1088*s*, 1068*s*, 1028*s*, 1000*w*, 995*w*, 970*w*, 935*w*, 910*w*, 838*w*, 800*w*, 780*w*, 752*w*, 735*w*, 710*s*. ^{1}H-NMR (80 MHz, $CDCl_3$): 8.25–7.00 (*m*, 15 arom. H); 6.14 (*d*, *J* = 3, 0.3 H, H–C(5)); 6.09 (*d*, *J* = 3, 0.7 H, H–C(5)); 5.90–5.65 (*m*, 2 H); 5.50–5.35 (*m*, 1 H); 2.31 (*d*, *J* = 9.5, 0.3 H, H–C(2)); 2.13 (*d*, *J* = 9.9, 0.7 H, H–C(2)); 2.09 (*d*, *J* = 9.5, 0.3 H, H–C(2)); 1.95 (*d*, *J* = 9.9, 0.7 H, H–C(2)).

(5R,6R,7S,8S)-5-(Benzyloxy)-1,1-dibromo-4-oxaspiro[2.5]octane-6,7,8-triyl Tribenzoate (**11**). A suspension of anh. $CaSO_4$ (10 mg, 0.07 mmol), $PhCH_2OH$ (1 ml, 9.6 mmol), and CF_3SO_3Ag [32] (55 mg, 0.2 mmol) in dry CH_2Cl_2 (2 ml) was stirred for 30 min at r.t. in the dark under N_2. After the addition of **10** (100 mg, 0.14 mmol), the mixture was stirred for 3 h. Filtration (*Celite*) and prep. TLC (Et_2O/hexane 2:1) gave **11** (73 mg, 70%) as a mixture of diastereoisomers which were separated by HPLC (*Zorbax-Sil*, 250 × 21.6 mm, Et_2O/hexane 2:1, 400 psi). R_f (Et_2O/hexane 2:1) 0.66. IR: 3095*w*, 3070*w*, 3050*w*, 3020*w* (br.), 2950*w*, 2880*w* (br.), 1735*s*, 1604*m*, 1587*w*, 1493*w*, 1452*m*, 1362*w*, 1318*m*, 1300*m*, 1278*s*, 1261*s*, 1247*s*, 1180*m*, 1107*s*, 1095*s*, 1070*s*, 1057*s*, 1029*s*, 1000*m*.

Major Diastereoisomer: HPLC (conditions see above): k' = 3.5. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.10–7.20 (*m*, 20 arom. H); 5.97 (*d*, *J* = 6.0, H–C(8)); 5.73 (*t*, *J* = 6.0, H–C(7)); 5.57 (*dd*, *J* = 6.0, 4.1, H–C(6)); 5.11 (*d*, *J* = 4.1, H–C(5)); 5.09 (*d*, *J* = 12, PhC*H*); 4.60 (*d*, *J* = 12, PhC*H*); 1.99 (*d*, *J* = 9.0, H–C(2)); 1.75 (*d*, *J* = 9.0, H–C(2)).

Minor Diastereoisomer: HPLC (conditions see above): k' = 4.0. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.10–7.20 (*m*, 20 arom. H); 6.07 (*d*, *J* = 6.2, H–C(8)); 5.72 (*t*, *J* = 6.2, H–C(7)); 5.62 (*dd*, *J* = 6.2, 5.4, H–C(6)); 5.07 (*d*, *J* = 12.0, PhC*H*); 5.04 (*d*, *J* = 5.4, H–C(5)); 4.71 (*d*, *J* = 12.0, PhC*H*); 2.13 (*d*, *J* = 8.5, H–C(2)); 1.91 (*d*, H–C(2)).

(5R,6R,7S,8S)-5-(Benzyloxy)-4-oxaspiro[2.5]octane-6,7,8-triyl Tribenzoate (**12**). Analogous to the preparation of **4**, the soln. of **12** (1.05 g, 1.4 mmol), Bu_3SnH (1.89 ml, 7.1 mmol), and AIBN (100 mg, 0.6 mmol) in toluene (20 ml) was hold at reflux for 30 min under Ar. Workup and chromatography (CH_2Cl_2/hexane 9:1, silica gel) gave **13** (71%, 581 mg) as a foam. R_f (CH_2Cl_2/hexane 9:1) 0.18. $[\alpha]_D^{25}$ = –45.6 (*c* = 1.0). IR: 3095*w*, 3070*w*, 3025*w* (br.), 2960*w*, 2890*w*, 1735*s*, 1606*m*, 1590*w*, 1495*w*, 1455*s*, 1410*w*, 1370*m*, 1320*s*, 1180*s*, 1150*s*, 1110*s*, 1100*s*, 1075*s*, 1060*s*, 1050*s*, 1030*s*, 995*m*, 812*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.96–7.84 (*m*, 5 arom. H); 7.51–7.19 (*m*, 15 arom. H); 5.80 (*t*, *J* = 7.0, H–C(7)); 5.75 (br. *d*, *J* = 7.0, H–C(8)); 5.66 (*dt*, *J* = 7.0, 2.0, H–C(6)); 4.87 (*d*, *J* = 7.0, H–C(5)); 4.84 (*d*, *J* = 12.5, PhC*H*); 4.58 (*d*, *J* = 12.5, PhC*H*); 1.32–0.64 (*m*, H–C(1), H–C(2)). ^{13}C-NMR: see *Table 1*. EI-MS: 578 (0.5, M^+), 487 (2), 414 (2), 401 (3), 400 (7), 281 (21), 230 (11), 229 (19), 228 (11), 217 (13), 215 (11), 161 (62), 147 (71), 107 (11), 106 (95), 105 (95), 104 (24), 92 (56), 91 (99), 77 (100), 65 (26), 51 (36). Anal. calc for $C_{35}H_{30}O_8$ (578.62): C 72.65, H 5.23; found: C 72.79, H 5.10.

(5R,6R,7S,8S)-5-(Benzyloxy)-4-oxaspiro[2.5]octane-6,7,8-triol (**13**). Analogous to the preparation of **5**, the soln. of **12** (335 mg, 0.6 mmol) in MeOH (10 ml) was treated with 1M NaOMe in MeOH (15 ml) and stirred at 0° for 30 min and then at r.t. for 3 h. The mixture was neutralized (*Dowex 50W*), filtered, concentrated, and crystallized (AcOEt/hexane) yielding **13** (147.5 mg, 96%). R_f (AcOEt/Et_2O/MeOH 6:3:1) 0.39. M.p. 115–116° (dec.). $[\alpha]_D^{25}$ = –77.3 (*c* = 1.0). IR (KBr): 3440–3350*s* (br.), 3090*w*, 3060*w*, 3030*w*, 3010*w*, 2940*w*, 2885*m* (br.), 2795*w*, 1497*w*, 1455*m*, 1400*m* (sh), 1355*m* (br.), 1312*m*, 1300*m*, 1270*m* (br.), 1235*m*, 1217*m*, 1197*m*, 1155*s*, 1130*s*, 1115*s*, 1075*s*, 1040*s*, 1028*s*, 982*s*, 955*w*, 940*w*, 915*w*, 890*w*, 752*s*, 730*m*, 700*s*, 690*m*, 680*m*. ^{1}H-NMR (400 MHz, D_2O): 7.51–7.41 (*m*, 5 H); 4.81 (*d*, *J* = 11.8, PhC*H*); 4.70 (*d*, *J* = 11.7, PhC*H*); 4.52 (*d*, *J* = 7.6, H–C(5)); 3.85 (*d*, *J* = 8.8, H–C(8)); 3.49 (*t*, *J* = 8.9, H–C(7)); 3.44 (*dd*, *J* = 9.1, 7.6, H–C(6)); 0.86–0.61 (*m*, H–C(1), H–C(2)). ^{13}C-NMR: see *Table 1*. EI-MS: 248 (1), 207 (2), 191 (1), 189 (5), 158 (8), 157 (11), 148 (9), 147 (72), 105 (14), 104 (39), 99 (25), 92 (95), 91 (100), 89 (16), 87 (14), 83 (15), 73 (55), 65 (56), 61 (41), 43 (64). Anal. calc. for $C_{14}H_{18}O_5$ (266.30): C 63.15, H 6.81; found: C 63.04, H 6.63.

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