Synthesis of Natural and Unnatural Enantiomers of Goniofufurone and Its 7-Epimers from D-Glucose. Application of Palladium(II) - Catalyzed Oxycarbonylation of Unsaturated Polyols[1]

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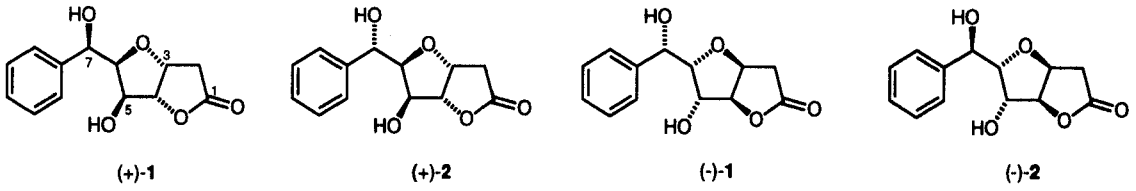
Syntheses of 3,6-anhydro-2-deoxy-7-phenylglyconolactones (+)-**1** and (+)-**2** with D- and L-*glycero*-D-*ido* configuration, respectively, as well as of their enantiomers (-)-**1** and (-)-**2**, from D-glucose are presented. The key steps are, (i) phenylmagnesium bromide additions to C1 or C5 of glucose-derived aldehydes **7** and **10**, respectively, and (ii), palladium(II)-catalyzed oxycarbonylation of intermediate 1-phenyl-D- and -L-5-hexenitols **8/9** or **14/15**. The syntheses proceed in 7 steps with 6 % and 18 % over-all yield for (+)-**1**/ (+)-**2**, and in 6 steps/ 11 % and 16 % for (-)-**1**/ (-)-**2** (from monoacetone glucose). The absolute configurations of goniofufurone (+)-**1** and its 7-epimer (+)-**2** thus established are in accord with those of all suggested biogenetic precursors and allowed, e.g., to propose the absolute configuration of (+)-goniopypyrone, a related cytotoxic, bicyclic styryllactone, and structures of potential biosynthetic intermediates not identified so far.

From the ethanol extract of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae) a number of cytotoxic mono- and bicyclic lactones with dihydroxystyryl fragments has been isolated. Among these, (+)-goniofufurone (+)-**1** and (+)-goniopypyrone (a structural isomer with [3.3.1]-skeleton) showed significant activity in tests with several human tumor cell lines[2] while that of (+)-7-*epi*-goniofufurone (+)-**2** proved insignificant as compared to adriamycin.[3-5]

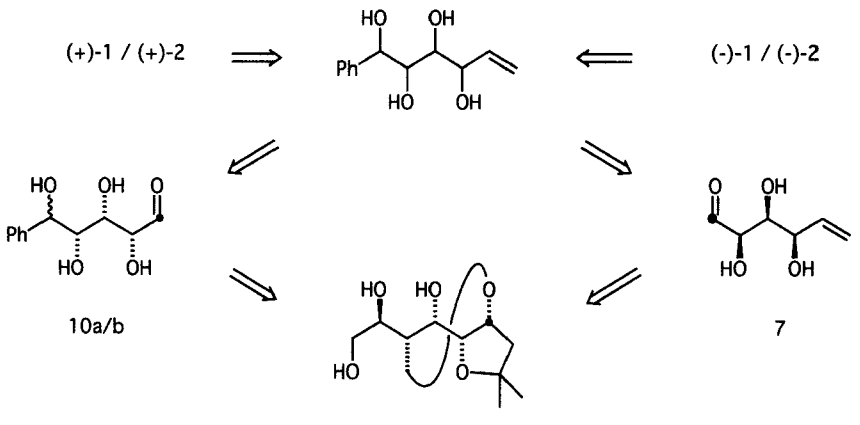
The structure and *relative* configuration of (+)-**1** and (+)-**2** were also deduced by McLaughlin and his group from NMR spectra and crystal structure determinations,[2,3] see Scheme 1. The *absolute* configurations were established independently by Shing *et al.*[6] and ourselves[1] in the course of syntheses of the unnatural enantiomers (-)-**1**[1,6] and (-)-**2**,[1] using glucoheptonolactone[6] and D-glucose,[1] respectively, as chiral starting materials. In the preliminary paper[1] we have also suggested a biogenetic relationship classifying the various styryllactones[2-5] according to the increasing degree of oxygenation. From this comparison pathways for the formation of (+)-goniofufurone and (+)-goniopypyrone from known monocyclic precursors (goniotriols) were proposed, as well as the *absolute* configuration of (+)-goniopypyrone,[1] *vide infra*.

Meanwhile, high attention has been given to this class of compounds, as demonstrated by the rapid development of new total syntheses of goniofufurone (+)-**1**,[7-11] its enantiomer (-)-**1**,[12] of the 7-*epi* compounds (+)-**2**[13] and (-)-**2**,[12] and of (+)-goniopypyrone.[11, 14-17] Most of the strategies applied there involve intramolecular Michael addition to an unsaturated ester/ lactone from *cis*-selective Wittig reactions to build the fully substituted tetrahydrofuran part.[6, 9, 11-14] The other approaches include as a key step a Wittig cyclization[8] or C-glycoside formation of an α-alkoxystannane, derived from D-glucuronolactone.[10]

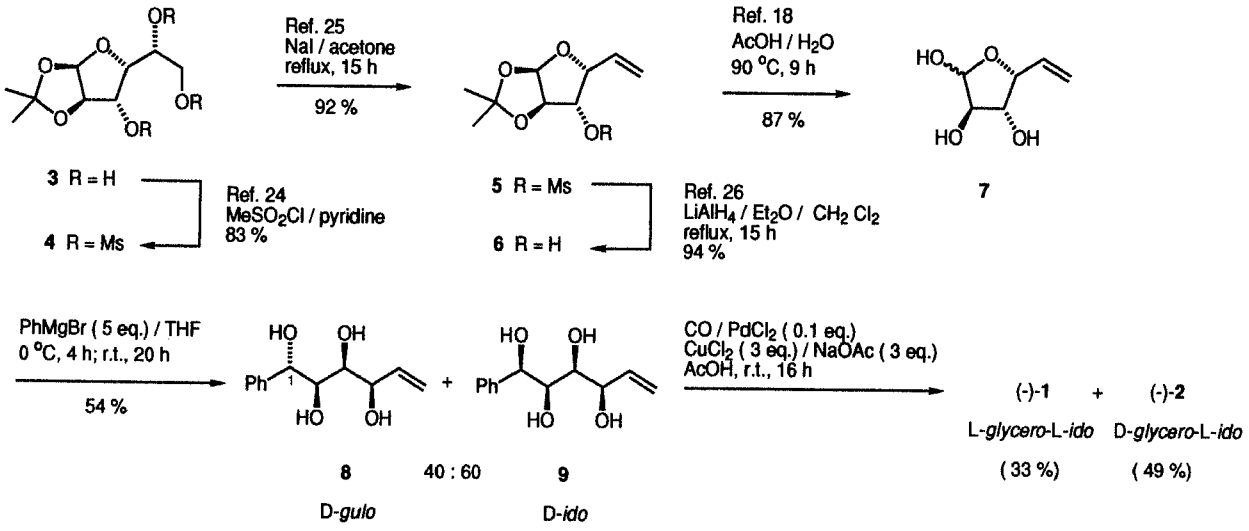
We report herein details of the synthesis of the unnatural enantiomers (-)-**1** and (-)-**2**,[1] and of the natural congeners, (+)-goniofufurone (+)-**1** and the 7-epimer (+)-**2**. The strategy followed is shown in Scheme 2. In both routes the phenyl group is introduced *via* Grignard addition with moderate diastereoselectivity (optimization not studied), at C1 and C5, respectively, of the D-glucose educt, to allow for an entry into *both* series of enantiomers. For the crucial step, bicyclization of respective 1-phenyl-5-hexenitols,[1] advantage is taken of recent progress with Pd(II)-catalyzed carbonylations of unsaturated polyols[18-20] or



Scheme 1. Structures of natural goniofufurone (+)-**1** and 7-*epi*-goniofufurone (+)-**2**, and of unnatural enantiomers (-)-**1** and (-)-**2**. Compounds shown are systematically named and numbered as anhydro-2-deoxyglyconolactones.



Scheme 2. Retrosyntheses for **1** and **2** from monoacetone D-glucose (C1 marked • for clarity)



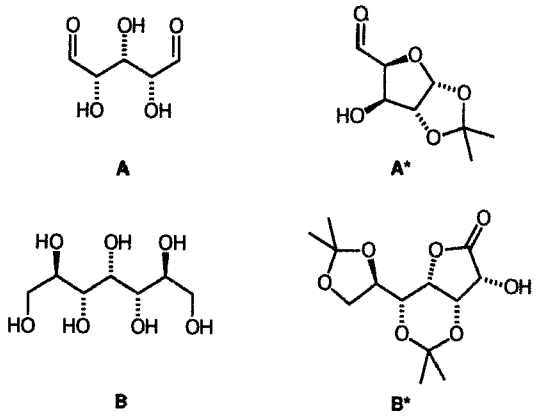
Scheme 3. Synthesis of unnatural goniofufurone (-)-**1** and 7-epimer (-)-**2**.

aminopolyols,[19-22] that have turned out bicyclic lactones/ lactams with high regio-preference and excellent stereoselectivity, without necessity of OH-protection.[23]

The intermediates for the bicyclizing oxycarbonylation, the 1-phenyl-5-hexenitols **8** and **9** with D-*gulo* and D-*ido* configuration, were obtained from commercially available monoacetone D-glucose **3** *via* D-*xylo*-5-hexenose **7**[18] (see Scheme 3) along the route already reported,[18] involving several known steps.[24-26] The Grignard addition to **7** proceeded in moderate yield, with [2:3]-diastereoselectivity. Since separation of **8**/ **9** (D-*gulo*/ D-*ido*) did not occur readily by simple chromatography, the mixture of diastereomers **8**/ **9** was exposed to the CO/ $PdCl_2$/ $CuCl_2$ system. After smooth conversion, at room temperature and atmospheric pressure, a mixture of bicyclic lactones (-)-**1** and (-)-**2** (C7-epimer) resulted which could readily be separated by flash chromatography, cf. Scheme 3.

The compound eluting first was isolated in 33 % yield after crystallization and, according to analytical/ spectroscopic data and specific rotation, was identified as (-)-goniofufurone (-)-**1**.
The chromatographic separation next gave a fraction containing (-)-**1** and (-)-**2** (11 %), and then a fraction with the more polar isomer was recovered, yielding (-)-**2** in 49 % after recrystallization. From ^{1}H NMR data and coupling constants it was concluded that (-)-**2** constituted the 7-epimer of the above goniofufurone (-)-**1**,[1] and this was confirmed when NMR data together with the structural analysis of natural (+)-**2** became available.[3]

Thus, the absolute configurations of natural (+)-goniofufurone (+)-**1** and its 7-epimer (+)-**2** being evident from unambiguous syntheses of the enantiomers,[1, 6] specific routes to the former could be addressed, as done by several groups meanwhile.[7-14] Since the oxycarbonylation had served so well in the first part of our work, access to the L-enantiomers of 1-phenyl-5-hexenitols was defined as the actual problem to be solved. With monoacetone D-glucose again chosen as a suitable starting material, now phenyl had to be introduced at C5, after shortening at this end, and the vinyl group was to be built up from the C1 terminus, see Scheme 2. This "reversal" of events in fact has become a useful strategy in syntheses of *Goniothalamus* lactones, in particular when the first effort did end up with the unnatural enantiomer,[1, 6, 27, 28] *vide supra*. It is based, of course, on the fact that chiral derivatives **A*** of an achiral dialdose like *xylo*-dialdopentose **A** can be elaborated sequentially at either end, see Scheme 4. The same applies to D-*glycero*-D-*gulo*-heptono-γ-lactone **B***, a chiral derivate, so-to-say, of the corresponding achiral heptitol **B** (also, of **A**, with successive glycol cleavages) which has been used in several elegant syntheses by Shing *et al.*[6, 7, 12, 14, 28]

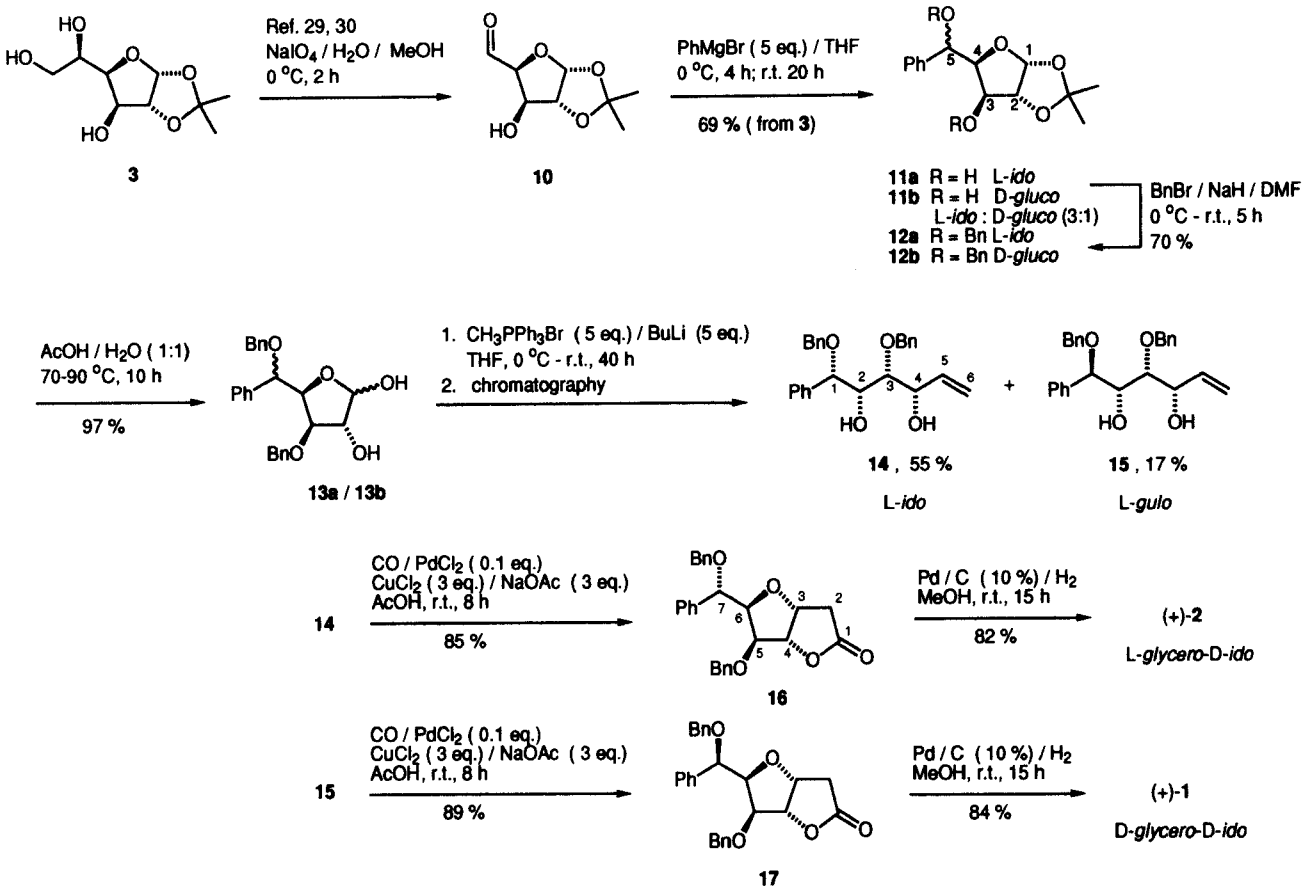


Scheme 4

Monoacetone D-glucose on periodate cleavage gave the *xylo*-dialdofuranoside **10** which without purification was treated with excess phenylmagnesium bromide in THF to afford a ca 3:1 mixture of L-*ido*/ D-*gluco*-pentoses **11a**/ **11b**[29-31] (Scheme 5). Since an increased number of free OH groups present proved detrimental to the success of the Wittig methylenation (*vide infra*), this material was di-O-benzylated (70 % yield). From **12a**/ **12b** on hydrolysis with aqueous acetic acid the furanose **13** was obtained, now a mixture of 4 diastereomers (pairs of β/α-anomers), that were opposed to an excess of Wittig reagent.[32-34] The phenyl-hexenitols of L-*ido* and L-*gluco* configuration, **14** and **15**, respectively, were isolated in 55 and 17 % after chromatographic separation. The oxycarbonylation of these enitol substrates went smoothly, employing the standard conditions[1, 18, 23] (Scheme 5).

The final step, removal of the 7-O-benzyl (with 5-O-benzyl) group seemed critical since O7 itself is located at a (secondary) benzylic position, and reductive cleavage could have been a dead end to this approach. Fortunately, both with **16** and **17** the hydrogenolysis proceeded with high chemoselectivity, when atmospheric pressure of hydrogen/ ca. 5 % palladium catalyst (Pd, 10 % on charcoal) in methanol were employed.[35] Both (+)-7-*epi*-goniofufurone (+)-**2** and (+)-goniofufurone (+)-**1** were produced in high purity and good yield (Scheme 5). The NMR data (see Tables 1, 2), m.p.s, and specific rotations of these samples agree well with the data reported in the literature, see Experimental.

To sum up the synthesis part, both enantiomers of goniofufurone and also of its 7-epimer have been prepared from monoacetone D-glucose in 7 and 6 steps, respectively. The two diastereomers, originating in the



Scheme 5. Synthesis of (+)-1 and (+)-2

moderately selective Grignard addition, were obtained in 6/ 18 and 11/ 17 % yield, respectively, which compares favourably with the other routes proposed so far. The unnatural enantiomers (-)-1 and (-)-2 showed marginal cytotoxicity to human tumor cell cultures,[36] similar in this respect to the natural 7-epimer (+)-2.[3] Concerning future work in this area, routes based on the above oxycarbonylation should lend themselves to efficient introduction of other aryl groups, by Grignard addition, and further to building other bicyclic lactone systems such as the [3.3.1]-structure present in goniopypyrone, the most active compound of this series found so far.[2-4,37]

Table 1. ^{1}H-NMR Data of Compounds **1**, **2**, **8**, **9**, **11**, **12**, **14-17**[a,b,c]

	Chemical Shifts δ [ppm]							
Compound	5-H	4-H	3-H	2-H	1-H			Others
11a	4.98	4.24	3.61	4.46	6.01			1.31, 1.49 (2 CH_3), 7.31-7.57 (C_6H_5)
11b	4.92	4.19	4.29	4.54	5.81			1.31, 1.44 (2 CH_3), 7.31-7.57 (C_6H_5)
12a	4.65	4.28	4.16	4.52	5.78			1.16, 1.31 (2 CH_3), 4.18, 4.30, 4.53, 4.62 (2 CH_2), 7.12-7.38 (C_6H_5)
12b	4.66	4.45	3.30	4.43	5.97			1.22, 1.43 (2 CH_3), 3.98, 4.29, (CH_2), 4.36 (CH_2), 7.12-7.33 (C_6H_5)
	1-H	2-H	3-H	4-H	5-H	6-H_E	6-H_Z	
8	4.75	3.77	3.73	4.22	5.91	5.21	5.35	7.26-7.36 (C_6H_5)
9	4.82	3.14	3.70	4.20	5.76	5.17	5.32	7.32-7.46 (C_6H_5)
14	4.58	3.97	3.20	4.34	5.83	5.16	5.32	2.55, 3.00 (2 OH), 4.27, 4.46, 4.48, 4.71 (2 CH_2), 7.24-7.41 (C_6H_5)
15	4.38	3.82	3.88	4.32	5.87	5.20	5.35	2.45 (2 OH), 4.15, 4.42, 4.56, 4.69 (2 CH_2), 7.25-7.41 (C_6H_5)

Table 1. continued

Compound	Chemical Shifts δ [ppm] 7-H	6-H	5-H	4-H	3-H	2-H_n	2-H_x	Others
16	4.71	4.35	3.71	4.83	5.10	2.76	2.66	4.32, 4.37 (CH_2), 4.42 (CH_2), 7.23-7.36 (C_6H_5)
17	4.85	4.18	4.43	4.69	4.87	2.59	2.47	4.24, 4.38 (CH_2), 4.69 (CH_2), 7.23-7.41 (C_6H_5)
(-)-**1**	4.73	3.86	4.40	4.91	4.86	2.31	2.86	5.47 (7-OH), 5.70 (5-OH), 7.29-7.43 (C_6H_5)
(-)-**2**	4.77	3.85	3.65	4.78	4.94	2.46	2.90	5.13 (7-OH), 5.54 (5-OH), 7.26-7.43 (C_6H_5)
(+)-**1**	4.74	3.87	4.42	4.93	4.86	2.32	2.86	5.52 (7-OH), 5.75 (5-OH), 7.29-7.44 (C_6H_5)
(+)-**2**	4.77	3.84	3.65	4.78	4.93	2.46	2.90	5.28 (7-OH), 5.53 (5-OH), 7.25-7.43 (C_6H_5)

Compound	Coupling Constants J [Hz] $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6E}$	$J_{4,6Z}$	$J_{5,6E}$	$J_{5,6Z}$	$J_{6E,6Z}$	J_{CH_2Ph}
11a	3.7	0.8	2.7	8.4	-	-	-	-	-	-
11b	3.7	0.8	2.6	8.2	-	-	-	-	-	-
12a	3.8	-	2.7	9.2	-	-	-	-	-	10.6, 12.0
12b	3.8	-	3.2	8.5	-	-	-	-	-	11.3, 11.3
8	7.4	2.0	4.0	6.8	1.0	1.1	10.4	17.2	1.9	-
9	7.1	2.0	4.3	6.6	1.0	1.1	10.4	17.2	1.9	-
14	7.1	3.1	4.9	5.9	1.5	1.5	10.5	17.1	1.5	11.3, 11.4
15	8.2	1.6	5.8	6.2	1.5	1.5	10.4	17.2	1.5	11.2, 11.4

Compound	Coupling Constants J [Hz] $J_{2n,2x}$	$J_{2n,3}$	$J_{2x,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{5,OH}$	$J_{7,OH}$	J_{CH_2Ph}
16	18.9	2.1	5.9	5.0	1.6	4.3	6.8	-	-	11.0, 11.5
17	18.8	1.0	5.5	4.4	-[d]	3.2	8.9	-	-	11.3, 11.3
(-)-**1**	18.6	-[d]	6.1	4.1	-[d]	2.6	8.7	3.9	4.9	-
(-)-**2**	18.6	-[d]	6.3	4.6	-[d]	3.1	7.7	4.8	4.7	-
(+)-**1**	18.6	-[d]	6.1	4.1	-[d]	2.6	8.8	4.0	5.0	-
(+)-**2**	18.6	-[d]	6.3	4.6	-[d]	3.2	7.7	4.7	4.6	-

[a] Recorded at 250.1 [(-)-**1**, (+)-**1**, (-)-**2**, (+)-**2** in DMSO-d_6, **8**, **9** in CD_3OD, **16**, **17** in $CDCl_3$) and 300.1 (**11** in CD_3OD, **12**, **14**, **15** in $CDCl_3$).

[b] Assignments of chemical shifts/ couplings of (-)-**1**, (-)-**2** based on H,H-COSY measurements.

[c] The OH signals and the respective spin-spin-splitting were removed by addition of D_2O.

[d] Coupling $J_{2n,3}$ or *trans*-coupling $J_{4,5}$ not resolved.

Table 2. ^{13}C-NMR chemical shifts of compounds **1**, **2**, **8**, **9**, **11**, **12**, **14-17**[a,b,f]

Compound	C-5	C-4	C-3	C-2	C-1	Others
11a	76.4	87.8[c]	74.6[c]	86.9	107.4	24.4, 28.0 [C(<u>C</u>H$_3$)$_2$], 113.7 [<u>C</u>(CH$_3$)$_2$], 129.2, 129.9, 130.2, 143.3 (<u>C</u>$_6$H$_5$)
11b	76.5	87.4[c]	73.1[c]	85.6	107.2	27.4, 28.0 [C(<u>C</u>H$_3$)$_2$], 113.6 [<u>C</u>(CH$_3$)$_2$], 129.0, 129.6, 130.2, 144.6 (<u>C</u>$_6$H$_5$)
12a	78.2	82.9	81.9	82.1	105.0	26.8, 26.3 [C(<u>C</u>H$_3$)$_2$], 70.3, 72.4 (2 OCH$_2$), 111.5 [<u>C</u>(CH$_3$)$_2$], 127.4, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4,137.8, 138.2, 139.3 (3 <u>C</u>$_6$H$_5$)
12b	78.3	82.3	81.1	82.0	104.9	27.1, 26.4 [C(<u>C</u>H$_3$)$_2$], 70.4, 72.6 (2 OCH$_2$), 111.3 [<u>C</u>(CH$_3$)$_2$], 127.5, 127.6, 127.7, 127.8, 128.1, 128.4, 128.5, 137.9, 139.1, 140.0 (3 C$_6$H$_5$)

	C-1	C-2	C-3	C-4	C-5	C-6	
8	76.6[d]	75.9[d]	75.5[d]	74.2[d]	139.3	117.6	127.9, 128.7, 129.4, 144.3 (<u>C</u>$_6$H$_5$)
9	76.8[d]	76.2[d]	75.7[d]	75.3[d]	139.2	117.5	128.5, 128.9, 129.5, 143.3 (<u>C</u>$_6$H$_5$)
14	81.6[d]	80.5[d]	75.7[d]	73.6[d]	137.9	116.5	70.7, 74.2 (2 OCH$_2$), 127.0, 127.6, 127.7, 128.3, 128.4, 128.5, 128.6, 128.7, 137.7, 138.1, 139.0 (3 <u>C</u>$_6$H$_5$)
15	81.6[d]	80.0[d]	75.0[d]	74.6[d]	137.7	117.2	70.44, 75.16 (2 OCH$_2$), 127.7, 127.8, 127.9, 128.0, 128.2, 128.4,128.5, 137.8, 138.3, 140.8 (3 C$_6$H$_5$)

Compound	C-7	C-6	C-5	C-4	C-3	C-2	C-1	Others
16	77.7[d]	84.2[d]	82.6[d]	85.2[d]	82.6[d]	36.2	175.6	70.9, 72.3 (2 OCH$_2$), 127.6, 127.8, 127.9, 128.2, 128.4, 128.5, 128.9, 128.7, 137.2, 138.2, 138.2 (3 <u>C</u>$_6$H$_5$)
17	76.9[d]	85.0[d]	78.2[d]	85.4[c]	81.0[d]	35.9	175.4	70.2, 73.3 (2 OCH$_2$), 127.6, 127.9, 128.0, 128.1, 128.3, 128.5, 128.6, 137.4, 138.0, 139.1 (3 <u>C</u>$_6$H$_5$)
(-)-**1**[f]	75.6	85.5	75.0	89.8	78.7	37.0	178.4	128.3, 128.9, 129.5, 143.9 (<u>C</u>$_6$H$_5$)
(-)-**2**[f]	71.7	85.3	73.4	88.2	77.0	36.2	176.4	127.3, 127.6, 128.5, 142.7 (<u>C</u>$_6$H$_5$)
(+)-**1**[f]	75.8	85.6	75.0	89.8	78.7	37.2	178.7	128.4, 129.0, 129.5, 144.0 (<u>C</u>$_6$H$_5$)
(+)-**2**[f]	71.5	85.1	73.2	88.0	76.8	36.1	176.2	127.1, 127.4, 128.1, 142.6 (<u>C</u>$_6$H$_5$)

[a] Recorded at 75.5 MHz (**11** in CD_3OD, **12**, **14**, **15** in $CDCl_3$) and at 62.9 MHz [(-)-**1**, (+)-**1**, **8**, **9** in CD_3OD, (-)-**2**, (+)-**2** in DMSO, **16**, **17** in $CDCl_3$).

[b] Assignments for chemical shifts of **12**, (-)-**1**, (-)-**2** based on C,H-COSY measurements.

[c] Assignments based on δ changes expected for the change C-C-OH -- C-C-O-C-C, see Ref. 18.

[d] Tentative assignments.

[e] The sequence of chemical shifts of <u>C</u>$_6$H$_5$ in all casis as follow: m-<u>C</u>, p-<u>C</u>, o-<u>C</u> (all d), i-<u>C</u> (s).

[f] Chemical shifts and assignments for **1**, **2** in complete agreement with Lit.[2,3]; cf. Ref. 1.

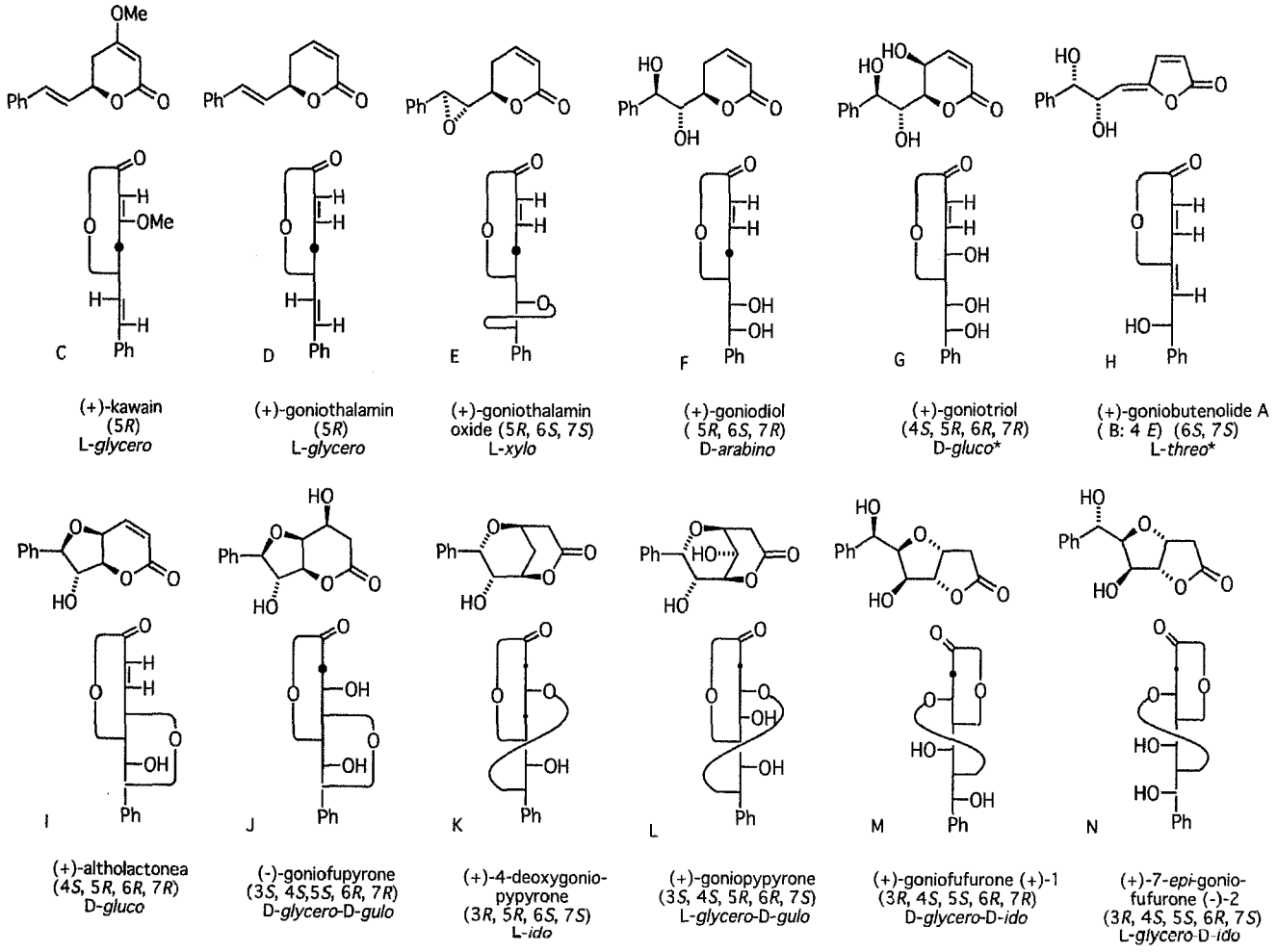
Biogenetic Relationships

The preliminary communications had clarified the absolute configurations[1,6] of the goniofufurones,[2,3] hence subsequent syntheses could be directed to the natural enantiomers (+)-**1** and (+)-**2**.[7-13] Further, the biogenetic formation of (+)-goniopypyrone had been proposed to occur by Michael cyclization of 7-*epi*-goniotriol,[1] and the absolute configuration L-*glycero*-D-*gulo* was deduced on that basis.[1] It has been gratifying to see several reports on successful syntheses of (+)-goniopypyrone along this line meanwhile.[11, 14, 15] The absolute configurations of the bicyclic "goniolactones", if established, now are in complete agreement with the ones known of the related monocyclic lactones from Goniothalamus species. In Scheme 6 an effort is made to group the structures of these styryllactones, **C** - **N**, accompanied by the respective Fischer projection formulas that had facilitated the above conclusions.[1] The order of increasing degree of oxygenation presumably reflects the biogenetic pathway, leading to several comments and conclusions with regard to the configuration at individual stereocentres, to the origin and role of monocyclic precursors, and concerning probable modes of bicycle formation.[38]

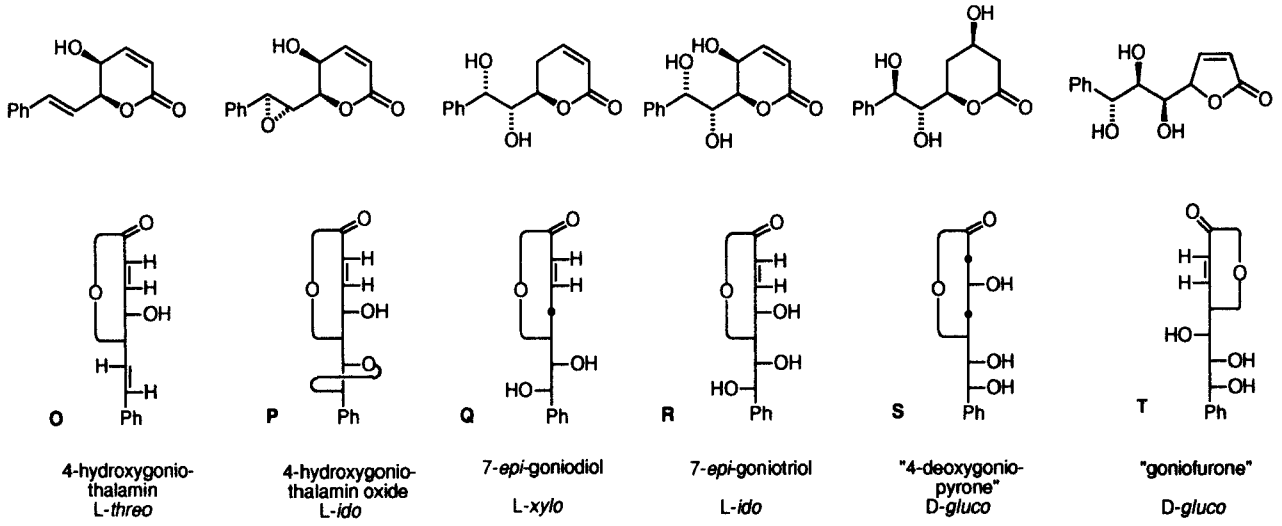
(i) *Absolute configurations*: In all compounds of proven absolute configuration (**C**, **D**, **F**, **G**, **I**, **K** - **N**) the orientation of the oxy-function at C5 is "L"; C4 - oxygenation, first encountered in (+)-goniotriol **G** and met again in **I**, **K** - **N** is "D" throughout; similarly, for C6 in **E**, **G**, **I**, **K** - **N** the "D" arrangement is found. In other terms, with oxygenation at C4/ C5/ C6 the D-*xylo* configuration is present in all cases. As a consequence, the absolute configuration of (+)-goniothalamine oxide **E**[5f] and (-)-goniofupyrone **J**[4c] can safely be predicted as L-*xylo* and D-*glycero*-D-*gulo*, respectively, as presented in Scheme 6. Further, based on the "C6 argument", the unusual 5-membered monocyclic lactones **H**, (+)-goniobutenolide(s) [A: 4*Z*-isomer; B: 4*E*-isomer, not shown] which were recently isolated and shown to have a *threo*-diol group,[4c] should belong to the L-*threo* series, and for the 8-membered lactones (gonioheptolides) isolated recently[4e] the absolute configurations D-*glycero*-D-*talo* are derived similarly.

(ii) *Biogenetic order of monocyclic lactones*: The first member of the styrylpyrone series is (+)-kawain **C**, not isolated from *Goniothalamus* species so far (the directing factor for isolation being brine shrimp lethality tests to find highly cytotoxic or other bioactive compounds[2-4]), with a single sp^3 - stereocentre.[39, 40] Kawain **C** might arise from a cinnamate starter to which two acetate units have been joined;[5e] reduction/ methanol elimination from **C** would lead to (+)-goniothalamine **D**, the simplest "goniolactone" (the parent of all others). The next biogenetic event apparently is epoxidation of the 6,7-double bond, as evidenced by (+)-goniothalamine oxide **E**,[5f] of L-*xylo* configuration, as concluded above. The latter assumption is supported by the structure and proven absolute configuration of (+)-goniodiol **F**,[5a] which would arise by OH-addition at the benzylic C7-position of the epoxide **E** with Walden inversion. In this way the D-*arabino* set at C5/ C6/ C7, met again in several more advanced members of this family (**G**, **I**, **J**, **H**), would arise ("D" - epimer at C7, *vide infra*). The next stage is represented by (+)-goniotriol **G** , formally the 4-hydroxylation product of the diol **F**; this reaction might also occur at the stage of **D** to give **O** (Scheme 7), followed by epoxidation/ hydrolysis as above,[5a] or from **E**, *via* 4-hydroxylation/hydrolysis (epoxide opening). The 4-hydroxy derivative **P** of the epoxide **E** ("4-hydroxygoniothalamine oxide"), not identified up-to-date, would also account for the formation of the bicyclic lactones **I** and **J** through intramolecular epoxide-opening by the 4-OH group.

(iii) *(Monocyclic) Precursors of bicyclic lactones* **I** - **N**: For (+)-altholactone (goniothalenol) **I**, formation from the monocyclic epoxide **P**, as suggested by Sam *et al.*[5f] is the most likely way, and addition of H_2O to **I** would account for the occurrence of (-)-goniofupyrone **J**[4c] (and again answer the question as to the absolute configuration). The following congeners, **K** and **L**, may constitute products of a Michael addition of 7-OH to C3 from monocyclic lactones **Q** and **R**, *i.e.* 7-*epi*-goniodi- and -triol. An alternative way of formation for 4-deoxygoniopypyrone **K** (and goniopypyrone **L**) would be hydration of goniodiol **F** (-triol **G**) to give **S**, an "isogoniotriol", and O-cyclization to C7 with inversion. (+)-Goniofufurone **M** [(+)-**1**] similarly could arise from Michael addition of 6-OH of a "furo-goniotriol" **T**, the butenolide isomer of goniotriol **G** not identified so far. Finally, the formation of 7-*epi*-goniofufurone **N** [(+)-**2**] is conceived to occur by Michael addition of 6-OH of the 7-epimer of **T** ("7-*epi*-furogoniotriol"); an alternative cyclization mode of 3-OH to C6 is less probable since this would require an L-*erythro* (C6/ C7) precursor with "L" - configuration at C6, not seen in any of the "goniolactones" presently known. It is easy to predict that one or the other of the intermediates **O** - **T** will be found in *Goniothalamus* plant extracts when fractions containing less bioactive material are scrutinized.



Scheme 6. Absolute configuration of mono- and bicyclic lactones isolated from *goniothalamus* species (except **C**).
[a]altholactone = goniothalenol[4a, 5d]. An asterisk* denotes absolute configurations now proposed, the other ones having been established earlier



Scheme 7. Potential intermediates in the biosynthesis of styryl-pyranones / -furanones ("gonio-lactones")

Solvents and reagents were purified and dried according to standard procedures. $CuCl_2$ (Aldrich), $PdCl_2$ (Janssen), monoacetone D-glucose (Janssen), 10% Pd/C (Degussa), $LiAlH_4$ (Janssen) were purchased. TLC analyses were carried out with Si60 F_{254}-coated aluminum sheets (E. Merck) using EtOAc/ petroleum ether (bp 30-75 °C) mixtures; detection by UV at 254 nm, phosphomolybdic acid (10 % in EtOH) or sulfuric acid (40 % in H_2O). Silica 32-63 mm (Woelm) was used for flash chromatography, eluents as above. Melting points were determined on a Tottoli apparatus or heat bar (Kofler); they are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter using the Drude method to calculate [a]D from values found for 546 and 579 nm. IR spectra were recorded on a Perkin-Elmer 4120 spectrometer. NMR spectra were obtained from Bruker AC 200 and 250 and Varian VXR 300 spectrometers (^{1}H: 200.1, 250.1, 300.1 MHz; ^{13}C: 50.3, 62.9, 75.45 MHz) with TMS as internal standard (d = 0.00 ppm); evaluation of ^{1}H-NMR spectra according to 1st order interpretation; multiplicity of ^{13}C-NMR signals from broadband-decoupled or DEPT spectra; *endo-* and *exo*-situated H are designated H_n, H_x.

1,2-O-Isopropylidene-3-O-mesyl-α-D-*xylo*-5-hexenofuranose (5) was prepared from monoacetone D-glucose **3** as described.[1, 18, 24, 25]

1,2-O-Isopropylidene-α-D-*xylo*-5-hexenofuranose (6):
Prepared by $LiAlH_4$ reduction of mesylate **5** (6.00 g, 22.7 mmol) according to Lit.[26]; 3.95 g (94 %), mp 58 - 61 °C, $[\alpha]_D^{23}$ -51.4 (*c* = 1.890, $CHCl_3$) {Lit.[41] 81 %, mp 63 °C, $[\alpha]_D^{23}$ -51.5 (*c* = 1.1, $CHCl_3$) after sublimation}.

α/β-D-*xylo*-5-Hexenofuranose (7): Prepared from hexenofuranose acetonide **6** (3.90 g, 20.9 mmol) according to Lit.[18]; yield 2.66 g (87 %), $[\alpha]_D^{23}$ -3.1 (*c* = 1.25, MeOH)
{ Lit.[18] 87 %, $[\alpha]_D^{22}$ -2.9 (*c* = 0.85, MeOH)}.

1-Phenyl-D-*gulo*- and -D-*ido*-5-hexenitol (8) and (9):
At 0 °C under nitrogen a solution of the hexenofuranose **7** (1.30 g, 8.898 mmol) in dry THF (50 mL) was added dropwise during 1 h to a solution of phenylmagnesium bromide (≤ 44.5 mmol, 5 equivv.) in THF (50 mL) freshly prepared from bromobenzene (6.98 g, 4.68 mL, 44.5 mmol) and magnesium (1.08 g, 44.5 mmol),. The mixture was stirred at 0 °C for 4 h, and then at r.t. for 20 h, before quenching with cold, saturated aqueous ammonium chloride (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL). The organic solutions were combined, dried (Na_2SO_4), and filtered. Removal of solvent (20 mbar) gave a mixture of the diastereomers **8** and **9** as a colourless syrup which was purified by passage through a silica-filled column (80 g of silica, column 3.5 cm x 23 cm; eluent EtOAc). Yield 1.078 g (54 %), Rf 0.3 (with EtOAc), $[\alpha]_D^{23}$ -5 (c = 0.52, MeOH).
The product consisted of a 40:60 mixture of D-*gulo* / D-*ido* isomers **8** / **9** (from ^{1}H and ^{13}C-NMR).

$C_{12}H_{16}O_4$	calc.	C64.27	H 7.19
(224.2)	found	63.98	7.33

IR (film): n = 3450 (br s, OH), 2920 (s), 2860, 1562, 1482, 1195, 928 (all m) cm^{-1}.

3,6-Anhydro-2-deoxy-7-phenyl-L-*glycero*-L-*ido*-1,4-heptonolactone [(-)-Goniofufurone] [(-)- 1] and 3,6-Anhydro-2-deoxy-7-phenyl-D-*glycero*-L-*ido*-1,4-heptonolactone [(-)-7-*epi*-Goniofufurone] [(-)- 2]:
A 50 mL-flask, purged with CO and connected to a balloon filled with CO, was charged with $PdCl_2$ (55.3 mg, 0.312 mmol), $CuCl_2$ (anhydrous; 1.258 g, 9.36 mmol), NaOAc (anhydrous; 768 mg, 9.36 mmol), a mixture of the diastereomeric tetrols **8** and **9** (40:60; 700 mg, 3.12 mmol), and AcOH (25 mL). Following the typical procedure lit.,[18] the deep green mixture was stirred at r.t. for 16 h (until coloured yellow to ochre), then filtered through a short tube filled with cellulose (5 g). AcOH was removed by rotary evaporation (20 mbar) and the residue was purified by chromatography (silica gel, 80 g, column 3.5 cm x 23 cm, elution with EtOAc). Fraction 1, goniofufurone (-)-**1**, 258 mg (33 %), colourless crystals (from EtOAc/ n-hexane 1:1), mp 149 - 150 °C, $[\alpha]_D^{20}$ -10.3 (*c* = 0.480, EtOH), Rf 0.41 (with EtOAc) { Lit.[2], data for (+)-**1**: mp 152 - 154 °C, $[\alpha]_D^{22}$ +9 (*c* = 0.5, EtOH); Lit.[12] : mp 152 - 154 °C, $[\alpha]_D^{24}$ -8 (*c* = 0.79, EtOH)}. Fraction 2, 7-*epi*-goniofufurone (-)-**2**, 383 mg (49 %), colourless crystals (from EtOAc/ n-hexane 2:1), mp 189 - 190 °C, $[\alpha]_D^{25}$ -95.7 (*c* = 0.519, DMSO), Rf 0.29 (EtOAc as above) { Lit.[3], data for (+)-**2**: mp 190 - 192 °C, $[\alpha]_D^{22}$ +108 (*c* = 0.2, EtOH); data for (-)-**2**: Lit.[13]: mp 194 - 195 °C, $[\alpha]_D^{22}$ 105.3 (*c* = 0.17, EtOH) [cf. footnote with Ref.13]; Lit.[12]: mp 208 - 209 °C/ sintering at 190 °C, $[\alpha]_D^{24}$ -92.5 (*c* = 1.1, acetone)}. In addition, 86 mg (11 %) of an intermediate fraction containing both (-)-**1** and (-)-**2** was collected (from NMR).

$C_{13}H_{14}O_5$	calc.	C62.39	H 5.64
(205.3)	found (-)-**1**	62.58	5.73
	found (-)-**2**	62.61	5.81

(-)-**1**, IR (KBr): n = 3450 (br s, OH), 1750 (s, CO), 1440 (m), 1185, 1060, 1045 (all s), 900 (w) cm^{-1}.
(-)-**2**, IR (KBr): n = 3450 (br s, OH), 1748 (s, CO), 1445 (w), 1195 (m), 1065, 1045 (all s), 910 (w) cm^{-1}.

1,2-*O*-Isopropylidene-5-*C*-phenyl-β-L-*ido*- (11a) and -α-D-*gluco*-pentofuranose (11b):
Prepared from monoacetone D-glucose **3**, modifying procedures of Inch[29] and Lichtenthaler,[30] respectively. To a solution of **3** (7.997 g, 36.3 mmol) at 0 °C in water/ MeOH (1:2, 200 mL) was added in one portion $NaIO_4$ (15.53 g, 72.6 mmol) and stirring was continued at 0 - 10 °C for 2 h (TLC monitoring). The solvent was removed on a rotavapor (20 mbar, 25 °C), the residue was partitioned between $CHCl_3$ (3 x 50 mL) and water (15 mL), dried ($MgSO_4$), and concentrated to give a colourless oil which was dried (P_2O_5, 0.01 mbar) for 2 h. The crude product of diol cleavage **10** (6.7 g) was dissolved in dry THF (150 mL) and the solution added

dropwise during 2 h at 0 °C to a solution of phenylmagnesium bromide in THF (200 mL), prepared from bromobenzene (28.4 g, 19 mL, 181 mmol) and magnesium (4.40 g, 181 mg-atom). After stirring at 0 °C for 4 h, then at r.t. for 20 h, the mixture was quenched with cold, saturated aqueous NH_4Cl (150 mL) and extracted with CH_2Cl_2 (5 x 100 mL). After drying ($MgSO_4$) and evaporation a yellow oil was obtained, which was purified by flash chromatography (silica gel 150 g, column 3.5 cm x 40 cm; eluent EtOAc). Yield 6.7 g (69 %), colourless crystals, mp 135 - 152 °C, $[\alpha]_D^{21}$ +15.4 (*c* = 1.005, MeOH), Rf 0.5 (with EtOAc). The product consisted of a 3:1 mixture of L-*ido*/ D-*gluco* isomers **11a**/ **11b** as determined by ^{1}H-NMR.

$C_{14}H_{18}O_5$	calc.	C63.15	H 6.81
(266.3)	found	63.25	6.84

IR (KBr): n = 3392 (br m, OH), 2987, 1496 (both w), 1455, 1376, 1316, 1236 (all m), 1216 (s), 1180 (w), 1076, 1008 (both s) cm^{-1}.

3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-phenyl-β-L-*ido*- (12a) and -α-D-*gluco*-pentofuranose (12b):

To sodium hydride [917 mg of a 60 % dispersion in oil, 24.4 mmol, washed with Et_2O (3 x 20 mL)] in dry DMF (2 mL), was added a solution of the mixture **11a**/ **11b** (2.168 g, 8.14 mmol) in DMF (5 mL) at 0 °C. This was followed by the addition of benzyl bromide (4.18 g, 2.90 mL, 24.42 mmol) during 2 min with stirring which was continued at r.t. for 5 h (TLC monitoring). The reaction was quenched with MeOH (10 mL) to destroy excess sodium hydride and concentrated (20 mbar, 30 °C). The residue was treated with brine (20 mL) and extracted with Et_2O (4 x 15 mL); the solutes were dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (silica gel 100 g, column 3.5 cm x 27 cm; eluent EtOAc/ i-hexane 1:1). Yield 2.53 g (70 %), yellow oil, $[\alpha]_D^{21}$ -24.5 (*c* = 1.81, MeOH), Rf 0.6 (with EtOAc/ i-hexane 1:1). The product consisted of a 3:1 mixture of L-*ido*/ D-*gluco* diastereomers **12a**/ **12b** (determined by ^{1}H-NMR).

$C_{28}H_{30}O_5$	calc.	C75.31	H 6.77
(446.5)	found	75.43	6.74

IR ($CHCl_3$): n = 3005 (s), 1498, 1452 (both m), 1375, 1160, 1070, 1035 (all s), 970, 850 (both m) cm^{-1}.

3,5-Di-*O*-benzyl-5-*C*-phenyl-α/β-L-*ido*- and -α/β-D-*gluco*-pentofuranose (13a/ 13b):

The pentofuranose acetonide mixture of **12a**/ **12b** (2.30 g, 5.15 mmol) was dissolved in aqueous AcOH (1:1, 50 mL) and heated to 90 °C for 10 h (TLC monitoring). Removal of solvents *in vacuo* (20 mbar) yielded a yellow oil which was purified by chromatography on silica gel (100 g; column 3.5 cm x 27 cm, eluent EtOAc/ i-hexane 1:1). The furanose **13** was obtained as a yellow, analytically pure oil, consisting of a 3:1 mixture of both diastereomers (by ^{13}C-NMR); yield 2.02 g (97 %), Rf 0.29, 0.26 (with EtOAc/ i-hexane 1:1), $[\alpha]_D^{20}$ +8.8 (*c* = 1.00, MeOH).

$C_{25}H_{26}O_5$	calc.	C73.87	H 6.45
(406.5)	found	73.21	6.39

IR ($CHCl_3$): n = 3440 (br m, OH), 3032, 3008 (all m), 2936 (w), 1496 (m), 1456 (s), 1400 (m), 1216 (s), 1168 (w), 1044 (s), 928, 912 (all m) cm^{-1}.

^{1}H-NMR data were inconclusive because of overlap of signals due to the presence of two anomers of the two diastereomers.

^{13}C-NMR ($CDCl_3$), mixture of 4 isomers: d = 70.21, 70.26, 72.66, 72.78, 71.06, 71.51, 71.70, 74.28 (all t; $\underline{C}H_2$), 73.97, 74.28, 78.56, 79.46, 80.13, 80.42, 81.57, 82.01, 83.43, 83.53, 83.91, 84.39 (all d; C2, C3, C4, C5); 96.66, 96.83 (α - anomers), 103.10, 104.12 (β - anomers) (all d; relative peak intensities 9:58:6:27; C-1), 127.42, 127.59, 127.94, 128.08, 128.15, 128.37, 128.59 (all d; o-, m-, p-$\underline{C}_6H_5$), 131.51, 137.63, 137.87, 138.25 (all s; i-$\underline{C}_6H_5$).

1,3-Di-*O*-benzyl-1-phenyl-L-*ido*- (14) and -L-*gulo*-5-hexenitol (15):

To a stirred solution of methyltriphenylphosphonium bromide (8.345 g, 23.37 mmol, 5 equiv) in dry THF (30 mL) at -5 °C under Ar was added dropwise BuLi (1.6 M in hexane, 14.6 mL, 23.4 mmol, 5 equivv.). After 1 h a solution of the furanose **13** (1.90 g, 4.67 mmol, L-*ido*/ D-*gluco* ca 3:1) in THF (10 mL) was added at -10 °C. The stirred solution was kept for 40 h at r.t., then quenched with cold saturated aqueous ammonium chloride (50 mL), and extracted with Et_2O (5 x 10 mL). The crude mixture of the diastereomers **14** and **15** was purified by chromatography (silica gel 200 g, column 3.5 cm x 55 cm, eluent EtOAc/ i-hexane 2:8); fraction 1: tetrol **15** (L-*gulo*), 315 mg (17 %), colourless oil, $[\alpha]_D^{20}$ -21.3 (*c* = 0.755, MeOH), Rf 0.26 (with EtOAc/ i-hexane 4:6); fraction 2: tetrol **14** (L-*ido*); 1.035 g (55 %), colourless oil, $[\alpha]_D^{20}$ +21.5 (*c* = 1.180, MeOH), Rf 0.22 (with EtOAc/ i-hexane 4:6).

$C_{26}H_{28}O_4$	calc.	C77.20	H 6.98
(404.5)	found **14**	77.12	7.02
	found **15**	77.25	6.96

IR ($CHCl_3$) of **14**: n = 3547 (br m, OH), 3022, 1498 (all m), 1450 (s), 1395, 1344 (all m), 1226, 1202, 1058 (all s), 956, 906, 860 (all w) cm^{-1}.

IR ($CHCl_3$) of **15**: n = 3548 (br m, OH), 3024, 1498 (all m), 1450 (s), 1395, 1342 (all m), 1225, 1200, 1050 (all s), 956, 904, 868 (all w) cm^{-1}.

5,7-Di-*O*-benzyl-3,6-anhydro-2-deoxy-7-phenyl-L-*glycero*-D-*ido*-1,4-heptonolactone [(+)-5,7-Di-*O*-benzyl-7-*epi*-goniofufurone] (16):

Procedure according to the preparation of (-)-**1** and (-)-**2**; tetrol **14** (398 mg, 0.984 mmol), $PdCl_2$ (17 mg, 0.098 mmol), $CuCl_2$ (397 mg, 2.95 mmol), NaOAc (242 mg, 2.95 mmol), and AcOH (20 mL); stirring under CO (balloon) at r.t for 8 h. After work-up the crude product was purified by chromatography (silica , 30 g, column 1.8 cm x 15 cm, elution with EtOAc/ petroleum ether 1:3), and a colourless, analytically pure oil of **16** was obtained; yield 360 mg (85 %), $[\alpha]_D^{15}$ +69 (*c* = 0.40, $CHCl_3$), Rf 0.18 (with EtOAc/ petroleum ether 1:3).

$C_{27}H_{26}O_5$	calc.	C75.33	H 6.09
(430.5)	found	75.27	6.12

IR (Film): n = 3014, 2932 (both m), 1786 (s, CO), 1603 (m), 1497, 1454, 1356 (all s), 1307, 1264 (both m), 1186 (s) cm^{-1}.

5,6-Di-*O*-benzyl-3,6-anhydro-2-deoxy-7-phenyl-D-*glycero*-D-*ido*-1,4-heptonolactone [(+)-5,7-Di-*O*-benzyl-goniofufurone] (17):

Procedure as above; tetrol **15** (232 mg, 0.573 mmol), $PdCl_2$ (10 mg, 0.057 mmol), $CuCl_2$ (231 mg, 1.72 mmol), NaOAc (141 mg, 1.72 mmol) and AcOH (20 mL); stirring under CO (balloon) at r.t. for 8 h. The crude product, a yellow oil, was purified by passage through silica (20 g, column 1.8 cm x 10 cm; EtOAc/ petroleum ether 1:3); yield of **17** as an analytically pure colourless oil 219 mg (89 %), $[\alpha]_D^{18}$ -5.6 (*c* = 0.325, $CHCl_3$) { Lit.[9b], $[\alpha]_D^{25}$ -5.8 (*c* = 1.0, toluene)}, Rf 0.20 (EtOAc/ petroleum ether 1:3).

$C_{27}H_{26}O_5$	calc.	C75.33	H 6.09
(430.5)	found	75.19	6.15

IR (Film): n = 3018, 2932 (all m), 1784 (s, CO), 1604 (m), 1498, 1454, 1356 (all s), 1308, 1266 (both m), 1188 (s) cm^{-1}.

3,6-Anhydro-2-deoxy-7-phenyl-D-*glycero*-D-*ido*-1,4-heptonolactone, [(+)-Goniofufurone] [(+)-1]:

Hydrogenolysis of **17** (150 mg, 0.348 mmol) was done in MeOH (50 mL) with 10 % Pd-C (20 mg), according to the procedure given by Prakash *et al.*.[9] Yield of (+)-**1**: 71 mg (82 %), colourless crystals, mp 148 - 150 °C (from EtOAc/ n-hexane 1:1), $[\alpha]_D^{22}$ +10.4 (*c* = 0.185, EtOH), { Lit.[9]: yield 86 %, mp 149 - 150 °C, $[\alpha]_D^{25}$ +10.5 (*c* = 0.6, EtOH); Lit.[2]: mp 152 - 154 °C, $[\alpha]_D^{22}$ +9 (*c* = 0.5, EtOH)}.

$C_{13}H_{14}O_5$	calc.	C62.39	H 5.64
(205.3)	found	62.32	5.71

IR (KBr): n = 3450 (br s, OH), 1750 (s, CO), 1442 (m), 1185, 1061, 1046 (all s), 903 (w) cm^{-1}, [IR (and NMR) data in agreement with those given in Ref.2].

3,6-Anhydro-2-deoxy-7-phenyl-L-*glycero*-D-*ido*-1,4-heptonolactone [(+)-7-*epi*-Goniofufurone] [(+)-2]:

Prepared as above from **16** (175 mg, 0.40 mmol), 10 % Pd-C (35 mg, 0.05 equiv. of Pd) in MeOH (9 mL) under H_2 (1 atm), with stirring at r.t. for 12 h. Yield 84 mg (84 %), colourless crystals mp 193 - 195 °C (from EtOAc/ n-hexane 2:1), $[\alpha]_D^{22}$ +100 (*c* = 0.46, EtOH) { Lit.[3]: mp 190 - 192 °C, $[\alpha]_D^{22}$ +108 (*c* = 0.2, EtOH)}.

$C_{13}H_{14}O_5$	calc.	C62.39	H 5.64
(205.3)	found	62.51	5.69

IR (KBr): n = 3450 (br s, OH), 1750 (s, CO), 1445, 1325, 1250 (all w), 1067, 1045 (all s), 1015 (m), 912 (w) cm^{-1}.

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(1) Preliminary communication:
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(2) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; Fanwick, P. E.; McLaughlin, J. L. *J. Chem. Soc. Perkin Trans 1* **1990**, 1655 - 1661 [goniofufurone, goniopypyrone, 7-*O*-acetylgoniotriol].

(3) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1991**, *54*, 1034 - 1043 [(+)-7-*epi*-goniofufurone, (+)-4-deoxygoniopypyrone, (+)-goniodiol].

(4) For related structures from Thai *Goniothalamus* species and cytotoxicity tests by McLaughlin's group see, e.g.:
(4a) ElZayat, A. A. E.; Ferrigni, N. R.; McCloud, T. G.; McKenzie, A. T.; Byrn, S. R.; Cassady, J. M.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron Lett.* **1985**, *26*, 955 - 956 [(+)-goniothalenol (altholactone), goniothalamine].
(4b) Alkofahi, A.; Ma, W. W.; McKenzie, A. T.; Byrn, S. R.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 1371 - 1373 [(+)-goniotriol].
(4c) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron* **1991**, *47*, 9751 -9758 [(+)-goniobutenolide A, (-)-goniobutenolide B, (-)-goniofupyrone].
(4d) Reviews: McLaughlin, J. L.; Chang, C.-J.; Smith, D.L. *Studies in Natural Products Chemistry* **1991**, *9*, 383 - 409; McLaughlin, J. L.; Chang, C.-J.; Smith, D.-L. In *Human Medicinal Agents From Plants*; Kinghorn, A. D.; Balandrin, M. F., Eds.; ACS: Washington, DC, 1993; p. 112-137.
(4e) Fang, X.-P.; Anderson, J. E.; Qui, X.-X.; Kozlowski, J. F.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron* **1993**, *47*, 1563 -1570 (gonioheptolides A, B).

(5) See also:
(5a) Hlubucek, J. R.; Robertson, A. V. *Aust. J. Chem.* **1967**, *20*, 2199 - 2208 [(+)-goniothalamin].
(5b) Achenbach, H.; Wittmann, G. *Tetrahedron Lett* **1970**, 3259 - 3262 [(+)-dihydrokawain-5-ol].
(5c) Jewers, K.; Davis, J. B.; Dougan, J.; Manchada, A. H.; Blunden, G.; Aye Kyi; Wetchapinan, S. *Phytochemistry* **1972**, *11*, 2025 - 2030 [(+)-goniothalamin].
(5d) Loder, J. W.; Nearn, R. H. *Heterocycles* **1977**, *7*, 113 -118 [(+)-altholactone].
(5e) Talapatra, S. K.; Basu, D.; Deb, T.; Goswami, S.; Talapatra, B. *Indian J. Chem.* **1985**, *24 B*, 29 - 34 [(+)-goniodiol, (+)-goniotriol].
(5f) Sam, T. W.; Seu-Yeu, C.; Matsjeh, S.; Gan, E. K.; Razak, D.; Mohamed, A. L. *Tetrahedron Lett.* **1987**, *22*, 2541 - 2542 [(+)-goniothalamine and [(+)-goniothalamine oxide].

(6) Shing, T. K. M.; Tsui, H.-C. *J. Chem. Soc., Chem. Commun.* **1992**, 432.

(7) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *J. Chem. Soc., Chem. Commun.* **1992**, 810 - 811.

(8) Murphy, P. J. *J. Chem. Soc., Chem. Commun* **1992**, 1096 - 1097; Murphy, P. J.; Dennison, S. T. *Tetrahedron* **1993**, *49*, 6695 - 6700.

(9) Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505 - 1510.

(10) Ye, J.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007 - 8010.

(11) Tsubuki, M.; Kanai, K; Honda, T. *Synlett* **1993**, 653 - 655.

(12) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *Tetrahedron* **1992**, *48*, 8659 - 666.

(13) Prakash, K. R. C.; Rao, S. P. *Synlett* **1993**, 123 - 124. This paper has some intriguing features: (i) In the title and text a synthesis of "(-)-epigoniofufurone", said a natural product (see Ref. 3), is presented. Actually, from the positive rotation given in a footnote, the (+)-enantiomer was obtained, which was indeed found in nature [not the (-)-enantiomer, see Ref. 3]. (ii) Further, the number of steps and the total yield given there do not agree with the literature cited (actually: 8 steps/ 22 % from D-glucose).

(14) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *Tetrahedron Lett.* **1993**, *34*, 691 - 692.

(15) Zhou, W.-S.; Yang, Z.-C. *Tetrahedron Lett.* **1993**, *34*. 7075 - 7076.

(16) For syntheses of related lactones from *Goniothalamus* species see, e.g.:
Meyer, H. H. *Liebigs Ann. Chem.* **1979**, 484 -491 [(+)- and (-)-goniothalamine];
O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *43*, 5201 - 5202;
Gillard, F.; Heissler, D.; Riehl, J.-J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 291 - 2295 [(+)-goniothalamine].
Tadano, K.-I.; Ueno, Y.; Ogawa, S. *Chem. Lett.* **1988**, 111 -114;
Ueno, Y.; Tadano, K.-I.; Ogawa, S.; McLaughlin, J. L.; Alkofahi, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2328 - 2337; see also Ref. 11 (Tsubuki) (+)-goniothalenol plus stereoisomers].
Gillhouley, J. G.; Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 976 977;
Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 945 - 3948, 3949 - 3952; *Tetrahedron* **1989**, *45*, 2627 - 2639 [(+)- and (-)-goniothalenol].
Shing, T. K. M.; Zhou, Z.-H. *Tetrahedron Lett.* **1992**, *33*, 1234 -1235, 3333 - 3334; see also Ref. 11 (Tsubuki) [(+)- and (-)-goniotriol].

(17) For approaches to the goniofufurone skeleton see:
Prakash, K. R. C.; Rao, S. P. *Tetrahedron Lett.* **1991**, 7473 - 7476;
Saito, S.; Harunari, T.; Shimamura, N.; Asahara, M.; Moriwake, T. *Synlett* **1992**, 325 - 327;
Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans 1* **1992**, 887 - 893.

(18) Gracza, T.; Hasenöhrl, T.; Stahl, U; Jäger, V. *Synthesis* **1991**, 1108 - 1118.

(19) Stahl, U. *Dissertation*, Würzburg 1993.

(20) Hasenöhrl, T. *Dissertation* (projected), Würzburg/ Stuttgart.

(21) Jäger, V.; Hümmer, W. *Angew. Chem.* **1990**, *102*, 1182 - 1183; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1171 - 1173.

(22) Jäger, V.; Gracza, T.; Dubois, E., *manuscript in preparation.*

(23) The prototype of this oxy-carbonylation was first demonstrated with racemic 4-pentene-1,3-diols:
Tamaru, Y.; Kobayashi, T.; Kawamura, S.-I.; Ochiai, H.; Hojo, M.; Yoshida, Z.-I. *Tetrahedron Lett.* **1985**, *26*, 3207 - 3210.
For a literature compilation and survey of known types of such alkene-polyol carbonylations using Pd^{II} see Ref. 18.

(24) Shyluk, W.; Honeyman, J.; Timell, T. E. *Can. J. Chem.* **1955**, *33*, 1202 - 1206.

(25) Jones, J. K. N.; Thomson, J. L. *Can. J. Chem.* **1957**, *35*, 955 - 959.

(26) Pietraszkiewicz, M., Sinaÿ, P. *Tetrahedron Lett.* **1979**, 4741 - 4743.

(27) See, e.g., enantio-divergent syntheses of (-)- and (+)-goniothalenol from D-glucose, Ref. 16 (Gesson) [see also Ref. 16 (Gillhouley)] and of (-)- and (+)-goniotriol, Ref. 16 (Shing); cf. syntheses of related (-)- and (+)-anamarine:
Lichtenthaler, F. W.; Lorenz, K.; Ma, W.-Y. *Tetrahedron Lett.* **1987**, *28*, 47 - 50;
Lorenz, K.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1987**, *28*, 6437 - 6440;
Valverde, S.; Hernandez, A.; Herradon, B.; Rabanal, R. M.; Martin-Lomas, M. *Tetrahedron* **1987**, *43*, 3499 - 3504.

(28) For further examples see, e.g.:
Vasella, A., *Mod. Synth. Meth.*, **1980**, *2*, 173 - 267.
Hanessian, S. *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983.

(29) Inch, T. D. *Carbohydr. Res.* **1967**, *5*, 45 - 52.

(30) Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790 - 712.

(31) Cf. phenyl introduction in the routes of Gesson (Ref. 16), Rao (Ref. 13, 16), Murphy (Ref. 8).
With the 3-*O*-benzyl derivative of **10** higher diastereoselectivity in favour of the L-*ido* isomer is encountered [(12 to 18):1]: see Ref. 29.
See also: Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800 - 1804.

(32) Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G.; Toma, L. *Carbohydr. Res.* **1987**, *171*, 49 - 57.

(33) Redlich, H.; Sudan, W.; Szardenings, A. K.; Vollerthun, R. *Carbohydr. Res.* **1992**, *226*, 57 - 78.

(34) Lancelin, J. M.; Pougny, J. R.; Sinaÿ, P. *Carbohydr. Res.* **1985**, *136*, 369 - 374.

(35) See Ref. 9. Under different conditions — EtOH, ca. 0.23 g-equiv. Pd — a related substrate gave 58 % of the desired and 22 % of the deoxygenated product (Ref. 8).

(36) Personal communication (May 20, 1992) by Prof. J. L. McLaughlin (Purdue University): BSL > 500 (LC_{50}), A-549 > 100, MCF-7 > 100 as ED_{50} (mg/ ml) for both (-)-1 and (-)-2; HT-29 63.17 and 72.11 as ED_{50} (mg/ ml) for (-)-1 and (-)-2, respectively. For details on these tests see Ref. 2 - 4.

(37) So far, adriamycin shows higher activities by ca. 2 orders of magnitude: Ref. 2, 3.

(38) Cf. arguments advanced earlier with respect to goniothalenol formation: Ref. 5f (Sam), Ref. 16 (Gesson); concerning goniodiol: Ref. 5e (Talapatra). See

also scheme given in Ref. 4e.

(39) Snatzke, G.; Hänsel, R. *Tetrahedron Lett.* **1968**, 1797-1799.

(40) A related compounds is (+)-dihydrokawain-"5"-ol, with (4R, 5S)-configuration (L-*threo*): Achenbach, H.; Huth, H. *Tetrahedron Lett.* **1974**, 119 - 120.

(41) Hall, L. D.; Hough, L.; Pritchard, R. A. *J. Chem. Soc.* **1961**, 1537 - 1546.