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1. New Iridoid Glucosides and a Lignan Diglucoside from *Globularia alypum* L.[1])

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Dedicated to Professor *H. Flück* on the occasion of his 80th birthday

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Summary

The four new iridoid glucosides globularicisin (**2**), globularidin (**5**), globularimin (**9**), and globularinin (**13**), the lignan diglucoside liriodendrin (**18**), and syringin (**20**) have been isolated from *Globularia alypum* L. along with the previously reported glucosides globularin (**1**) and catalpol (**4**). Compound **2** is the first report of any cinnamoyl iridoid with a *cis*-configuration at the acyl double bond. Compound **5** is another novel iridoid which lacks the characteristic C(3),C(4) double bond in the aglucone part. Compounds **9** and **13** are diastereomeric and contain highly oxygenated aglucone structures. The isolation of liriodendrin from *Globularia alypum* is the first demonstration of the occurrence of a lignan in the family *Globulariaceae*.

The structures have been elucidated by ^{1}H- and ^{13}C-NMR. spectroscopy as well as by chemical transformations. Taxonomical significance of the cooccurrence of iridoid and lignan glycosides as well as the antileukemic potentiality of the latter are also appraised.

Introduction. - *Globularia alypum* L. is a perennial shrub which is found throughout the mediterranean area [2]. The plant is known for its uses in the indigenous system of medicine for a variety of purposes, *e.g.* laxative [3]. Its glycosidic constituents were previously examined and the isolation and characterization of the major constituents - globularin and catalpol - were reported [4]. In addition the presence of aucubin, catalposide, monotropein and asperuloside in this species was reported by *Wieffering* [5] which was subsequently contradicted by *Balansard et al.* [3]. The latter authors, in addition, isolated a compound, named 'alyposide'. The nature of the compound, however, was not established. The water extract of *Globularia alypum* L. was reported to have moderate antileukemic activity [6]; no attempt was made by the authors to establish the nature of the compound(s) responsible for this activity. In order to resolve the ambiguities about the earlier reports [4] [5], to establish the identity of 'alyposide' [4], and to locate the anti-

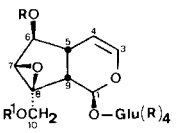
[1]) Part 4 in the series 'Glycosides of Globulariaceae'. For part 3 see [1].

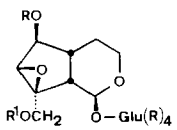
leukemic principle(s) [6] of *Globularia alypum*, we reexamined its water-soluble constituents. We have published two notes [7] [8] describing some of our results, and this paper contains the full details of these investigations.

Results and discussion. – An aqueous extract of the whole plant of *G. alypum* yielded a mixture of at least eight glycosidic constituents which were fractionated by silica gel chromatography followed by preparative and semipreparative scale separation using reversed phase HPLC. Two of them, globularin (**1**) and catalpol (**4**), were known substances and identified by means of physical constants, spectral data, and comparison with authentic samples. On the basis of HPLC. we also sorted out the above mentioned contradictory reports of the other iridoids and established their absence in *G. alypum*. Syringin (**20**; s. below), a widely occurring aryl glucoside was also isolated from this species. A direct comparison of this compound with 'alyposide' [4] proved the identity of the two compounds. The structure elucidation of the remaining five glucosides is described in the following.

Globularicisin (**2**), $C_{24}H_{28}O_{11}$, $[\alpha]_D^{20} = -97.24°$ (MeOH), was obtained as a white amorphous powder. It showed UV. absorptions at 215 and 272 nm and IR. bands for hydroxyl groups, ester carbonyl, enolic double bond and aromatic ring. Acetylation at room temperature of **2** gave the pentaacetate **3**.

The ^{13}C-NMR. spectrum of globularicisin (**2**) exhibited chemical shifts from which straightforward assignment *(Table 1)* could be made. The ^{13}C-NMR. spectra of **1** and **2** were similar, except the C(4″), C(2″)/C(6″) and C(α) signals of their





1 globularin:
R = H; R¹ = *trans*-cinnamoyl

2 globularicisin:
R = H; R¹ = *cis*-cinnamoyl

3 globularicisin pentaacetate:
R = Ac; R¹ = *cis*-cinnamoyl

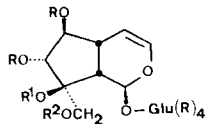
4 catalpol: R = R¹ = H

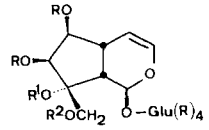
5 globularidin:
R = H; R¹ = *trans*-cinnamoyl

6 globularidin pentaacetate:
R = Ac; R¹ = *trans*-cinnamoyl

7 α,β-dihydroglobularidin = α,β,3,4-tetrahydroglobularin:
R = H; R¹ = phenylpropionyl

8 dihydrocatalpol: R = R¹ = H





9 globularimin:
R = R¹ = H; R² = *trans*-cinnamoyl

10 decinnamoyl-globularimin:
R = R¹ = R² = H

11 globularimin hexaacetate:
R = Ac; R¹ = H; R² = *trans*-cinnamoyl

12 globularimin heptaacetate:
R = R¹ = Ac; R² = *trans*-cinnamoyl

13 globularinin:
R = R¹ = H; R² = *trans*-cinnamoyl

14 decinnamoyl globularinin:
R = R¹ = R² = H

15 globularinin hexaacetate:
R = Ac; R¹ = H; R² = *trans*-cinnamoyl

16 globularinin heptaacetate:
R = R¹ = Ac; R² = *trans*-cinnamoyl

Table 1. *^{13}C-NMR. Spectral Data (CD_3OD) of Iridoid Glucosides from* G. alypum

C-Atom	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**13**	**14**[d])
C(1)	95.41	95.46	95.33	98.05	97.78	93.48	93.34	96.29	95.16
C(3)	141.52	141.53	141.78	62.80	62.89	140.45	140.39	141.61	141.61
C(4)	103.59	103.55	104.03	23.76	23.87	105.84	106.54	106.40	105.27
C(5)	38.63	38.58	39.10[c])	38.09	38.20	38.38	37.32	38.86	37.16
C(6)	79.06	79.06	79.58	73.00	73.23	83.76	83.14	78.63[a])	78.34[a])
C(7)	62.51	62.37	62.55	62.20	62.01	85.38	86.42	78.63[a])	79.34[a])
C(8)	63.40	63.13	66.23	63.27	65.98	80.23	80.33	81.36	81.03
C(9)	43.28	43.20	43.60[c])	43.33	43.47	48.89	48.08	44.59	43.70
C(10)	64.03	63.74	61.60	64.27	61.20	66.41	64.29	69.01	66.37
C(1′)	100.01	100.02	99.74	99.79	99.32	99.68	99.55	100.87	99.20
C(2′)	74.48	74.46	74.82	74.68	74.76	74.44	74.61	74.35	74.61
C(3′)	77.86[a])	77.93[a])	78.54[a])	78.07[a])	78.34[a])	77.59[a])	77.94[a])	77.78[a])	77.99[a])
C(4′)	71.00	71.07	71.74	71.19	71.66	71.07	71.54	70.83	70.39
C(5′)	77.35[a])	77.36[a])	77.70[a])	77.65[a])	77.75[a])	77.59[a])	77.71[a])	77.43[a])	78.34[a])
C(6′)	62.51	62.69	62.90	62.80	62.89	62.45	62.70	62.23	62.42
C(1″)	135.19	135.78	–	135.49	–	135.44	–	135.37	–
C(2″)	129.77[b])	130.68[b])	–	129.94[b])	–	129.77[b])	–	129.86[b])	–
C(3″)	129.12[b])	128.92[b])	–	129.27	–	129.02[b])	–	129.16[b])	–
C(4″)	131.41	129.87	–	131.51	–	131.32	–	131.45	–
C(5″)	129.12[b])	128.92[b])	–	129.27	–	129.02[b])	–	129.16[b])	–
C(6″)	129.77[b])	130.68[b])	–	129.94[b])	–	129.77[b])	–	129.86[b])	–
C(α)	146.48	144.80	–	146.65	–	146.15	–	146.52	–
C(β)	118.23	119.72	–	118.47	–	118.73	–	118.60	–
CO	168.13	167.33	–	168.44	–	168.69	–	169.03	–

[a])[b]) Values with same superscript in the vertical column are interchangeable.
[c]) Confirmed by selective ^{1}H,^{13}C-decoupling.
[d]) A few drops of DMSO-d_6 were added to increase the solubility.

acyl unit. The nearly identical positions of carbon resonances assigned to the iridoid moiety pointed to catalpol (**4**) as the common unit in both acylated glucosides. The placement of the acyloxy unit at C(10) in globularicisin was based on the similarity of the ^{13}C-NMR. spectrum to that of globularin (**1**), and on the expected downfield shift (2.14 ppm) for the signal of the carbon atom in α-position (C(10)) and the high field shift (3.1 ppm) for the signal of the carbon atom in β-position (C(8)) on going from **2** to **4** [9].

The ^{1}H-NMR. spectra of **2** and its pentaacetate **3** were also similar to globularin **1** and its pentaacetate *(Table 2)*. However, a careful study of the ^{1}H-NMR. spectrum of **2** indicated the configuration [10] of the double bond of the acyl unit; the corresponding olefinic protons of **2** were located upfield (observed 7.01 and 5.98 ppm; calculated 7.19 and 6.02 ppm) from the positions of the *trans*-protons of **1** (observed 7.70 and 6.54 ppm; calculated 7.78 and 6.49 ppm). The coupling constant of these protons was also smaller ($J = 13$ Hz) in **2**. The ^{1}H-NMR. spectrum of the pentaacetate **3** showed similar characteristics.

The above facts led us to the conclusion that globularicisin (**2**) has a *cis*-cinnamoyl unit as the acyl function. The small yet diagnostic chemical shift dif-

Table 2. *^{1}H-NMR. Spectral Data (100 MHz) of the Iridoid*

Compound (solvent)	H–C(1)	H–C(3)	H–C(4)	H–C(5)	H–C(6)
1 (CD_3OD)	5.05 *d* (9.2)	6.34 *d*×*d* (6.0 and 1.8)	~5.1[b])	2.30 *m*	3.88 *d* (3.8)
2 (CD_3OD)	5.00 *d* (9.2)	6.34 *d*×*d* (6.0 and 1.8)	~5.0[b])	2.25 *m*	3.85 *s*
3 ($CDCl_3$)	5.2–4.7	6.27[c]) *d*×*d* (6)	5.2–4.7	~2.5 *m*	5.2–4.7
5 (CD_3OD)	4.80[d])[f])	4.15[f])	1.9–1.6[f])	2.10 *m*	3.85[f])
6 ($CDCl_3$)	5.2–4.6	3.9–3.3	1.7–1.2	2.34 *m*	5.2–4.6
7 (CD_3OD)	~4.8[d])	4.2–3.8	1.9–1.6	2.0 *m*	3.83[b])
8 (CD_3OD)	~4.8[d])	4.12	1.9–1.6	2.05 *m*	3.83[b])
9 (CD_3OD)	5.54 *d* (5)	6.22 *d*×*d* (7 and 1.5)	5.08 *d*×*d* (7 and 3)	2.72–2.5	3.74[b])
10 (CD_3OD)	5.48 *d* (4)	6.22 *d*×*d* (6 and 1)	5.1 *d*×*d* (6 and 3)	2.6–2.3	4.0–3.5[b])
11[g])[h]) ($CDCl_3$)	5.45 *d* (2.5)	6.23 *d*×*d* (6 and 3)	5.21 *d*×*d* (6 and 3)	2.66 *m*	4.88 *d*×*d* (6.5 and 4)
12[g]) ($CDCl_3$)	5.98 *d* (2)	6.22 *d*×*d* (6.5 and 2.5)	4.92 *d*×*d* (6.5 and 2.5)	2.82 *m*	4.85 *d*×*d* (2.5 and 2)
13 (CD_3OD)	5.28 *d* (6)	6.31 *d*×*d* (6.5 and 2)[i])	5.12 *d*×*d* (6.5 and 3)	2.84–2.58 *m*	4.0–3.5[b])
14 (CD_3OD)	5.25 *d* (5)	6.27 *d*×*d* (6 and 2)	4.98 *d*×*d* (6 and 2.4)	2.8–2.52 *m*	4.0–3.5[b])
15[g])[j]) ($CDCl_3$)	5.40 *d* (3.7)	6.32 *d*×*d* (6.5 and 2.5)	4.94 *d*×*d* (6.5 and 2.5)	2.75 *m*	5.22 *d*×*d* (4.5 and 4)
16[g]) ($CDCl_3$)	5.57 *d* (1)	6.25 *d*×*d* (6.5 and 2.5)	4.78 *d*×*d*×*d* (6.5, 2.5 and *ca.* 1)[k])	2.71 *m*	5.26 *d*×*d* (4 and 1)

[a]) Values in parenthesis are coupling constants (in Hz). [b]) Signal patterns are unclear due to the overlapping. [c]) Tentative assignment. [d]) Partly merged inside the solvent signal. [e]) Not resolved. [f]) Assign-

Glucosides of G.alypum *and their Derivatives*[a])

H–C(7)	H–C(9)	2 H–C(10)	H–C(α)	H–C(β)	H–C(1′)
3.50[c])	2.66	4.32 and 5.02	7.70	6.54	~4.7[d])
s	*d*×*d* (9.2 and 8.0)	*AB*-Syst. (12.6)	*d* (16)	*d* (16)	
3.35[c])	2.52	4.22 and 4.92	7.01	5.98	~4.7[d])
s	*d*×*d* (9.2 and 8.0)	*AB*-Syst. (13)	*d* (13)	*d* (13)	
3.52	2.5	4.18 and ~4.9	6.96	5.97	5.2–4.7
s	*m*	*AB*-Syst. (13)	*d* (13)	*d* (13)	
3.48[c])	2.42	4.24 and 4.95	7.68	6.50	4.65
s	*d*×*d* (8.8 and 8.0)	*AB*-Syst. (13)	*d* (16)	*d* (16)	*d* (7.2)
3.64	2.34	4.37 and ~5.0	7.66	6.43	5.2–4.6
s	*m*	*AB*-Syst. (13)	*d* (16)	*d* (16)	
3.35[c])	2.32	4.10 and [d])	–	–	4.65
s	*d*×*d* (8.8 and 8.0)	*AB*-Syst. (13)			*d* (7.2)
3.42[c])	2.27	4.05 and 3.75	–	–	4.65
s	*d*×*d* (8.8 and 8.0)	*AB*-Syst. (13)			*d* (7.2)
3.87	2.6–2.3	4.32 and 4.56	7.72	6.52	4.62
d×*d* (6 and < 1)		*AB*-Syst. (13)	*d* (16)	*d* (16)	*d* (7)
4.0–3.5[b])	2.6–2.3	3.81 br. *s*	–	–	4.65 *d* (7.4)
5.19	2.85	4.42 and 4.48	7.72	6.42	4.89
d (6.5)	*d*×*d* (10 and 2.5)	*AB*-Syst. (12.5)	*d* (16)	*d* (16)	*d* (8)
5.62	3.11	5.04 and 4.52	7.64	6.36	4.89
d×*d* (2.5 and 1)	*d*×*d* (9 and 2)	*AB*-Syst. (12.5)	*d* (16)	*d* (16)	*d* (8)
4.0–3.5[b])	2.40	4.55 and 4.34	7.70	6.54	4.65
	d×*d* (10 and 6)	*AB*-Syst. (12)	*d* (16)	*d* (16)	*d* (7)[i])
4.0–3.5[b])	2.41	3.67	–	–	4.65
	d×*d* (9 and 5)	br. *s*			*d* (7)
5.30	2.63	4.41 and 4.31	7.72	6.46	4.91
d (4)	*d*×*d* (9.5 and 3.7)	*AB*-Syst. (12)	*d* (16)	*d* (16)	*d* (7.8)
5.56	3.02	5.07 and 4.50	7.73	6.44	4.89
d (4)	br. *d* (8)	*AB*-Syst. (12)	*d* (16)	*d* (16)	*d* (8.2)

ment is corrected (see [7]). [g]) Measured at 360 MHz. [h]) HO–C(8) at 4.09 ppm. [i]) *J* value is corrected (see [8]). [j]) HO–C(8) at 3.33 ppm. [k]) $J_{4,9} < 1$ Hz, confirmed by double resonance experiment.

ferences in the ^{13}C-NMR. of **2** and **1** were explained by the different configuration of the double bond of the cinnamoyl unit.

Further evidence for the proposed structure was obtained from the alkaline hydrolysis of **2** which afforded cinnamic acid and **4** which was found to be identical with catalpol. The structure of globularicisin was thus established as portrayed in the formula **2**. Globularicisin is the first acyl iridoid glucoside having a *cis*-configuration at the olefinic double bond of the cinnamoyl part.

Globularidin (**5**), $C_{24}H_{30}O_{11}$, $[\alpha]_D^{20} = -57.65°$ (MeOH), had two hydrogen atoms more than **1**. The UV. and the IR. spectra indicated the presence of a cinnamoyl ester chromophore. Acetylation under mild conditions provided the pentaacetate **6** (^{1}H-NMR.).

The ^{1}H-NMR. spectra of **5** and its pentaacetate **6** showed the presence of a *trans*-cinnamoyl moiety but the characteristic iridoid protons due to the H–C(4)=C(3)(O)–H functionality were absent. These data indicated that **5** could have a reduced C(3)=C(4) bond. The ^{13}C-NMR. spectrum of **5** brought further clarity into its structure. As shown in *Table 1*, the chemical shifts of the ^{13}C-NMR. signals of **5** were in good agreement with those of **1** except for the signals arising from C(3), C(4) and C(6). The signals at 62.80 and 23.76 ppm appeared as triplets in the single frequency off resonance decoupled (SFORD) spectrum and could be assigned to C(3) and C(4), respectively. The C(6) in **5** was rather shielded, and it seems that the reduced pyran ring exerts this shielding by assuming a different conformation as compared with the system containing the C(3),C(4) double bond. Comparison of the ^{13}C-NMR. data of **5** with that of **8** *(Table 1)* established the site of the acyloxy group at C(10) [9].

These facts strongly suggested that **5** has a structure similar to that of globularin (**1**) but possesses a reduced C(3)=C(4) bond. This was verified by the finding that the reduction of **1** and **5** separately over 10% Pd/C afforded the same compound **7**, the identity of which was established by spectroscopic methods. Additionally, alkaline hydrolysis of **5** afforded cinnamic acid and **8**, which was found to be identical with dihydrocatalpol. The absolute configuration of all chiral centres in **5** were thus established to be identical with those of **1**. Globularidin is the first iridoid C(1)-glucoside having a reduced C(3)=C(4) double bond[2]).

Globularimin (**9**), $C_{24}H_{30}O_{12}$, $[\alpha]_D^{20} = -105.97°$ (MeOH), showed absorptions in the IR. spectrum at 3400 (br., OH), 1702 (C=O, ester), 1638 (C=C), 1580, 1495 and 1450 cm^{-1} (aromatic ring), and in the UV. spectrum at 217, 223 sh and 278 nm which indicated the presence of a cinnamoyl ester chromophore in the molecule. Alkaline hydrolysis of **9** afforded cinnamic acid and **10**. Acetylation of **9** under mild conditions provided the hexaacetate **11**, in which one hydroxy group remained unaffected. Prolonged acetylation, however, afforded the hexaacetate **12**, indicating the presence of a tertiary hydroxyl group.

The ^{1}H-NMR. spectrum of **9** *(Table 2)* showed, besides the *trans*-cinnamoyl protons, three characteristic signals at 6.22 ($d \times d$), 5.08 ($d \times d$) and 5.54 (d) ppm

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[2]) Other examples include the iridoid C(11)-glucoside villoside [11], the nonglycosidic iridoid allamandin [12], the nonglycosidic secoiridoid xylomollin [13], and the bis-iridoid glucoside sylvestroside IV [14].

attributable to H–C(3), H–C(4) and H–C(1). These data indicated the presence of a proton at C(5) and C(9), and thus C(6), C(7) and C(8) carried oxygen functions. This assumption was also compatible with the ^{13}C-NMR. spectrum of **9** *(Table 1)* which showed, apart from the signals of the *trans*-cinnamoyl residue, signals of fifteen C-atoms. Two absorptions at 140.45 and 105.84 ppm could be assigned to C(3) and C(4), respectively, typical for a C(4) unsubstituted iridoid glucoside without an oxygen function at C(5) [9]. The two signals at 93.48 and 99.68 ppm were attributed to C(1) and C(1'), respectively, on the basis of published values and characteristic coupling constants [9]. Of the remaining eleven C-atoms, nine carried an oxygen function. Five of these could be ascribed to the glucose moiety, and the remaining four to the aglucone moiety, which should then have four oxygenated (1 C, 2 CH and 1 CH_2) and two non-functionalized C-atoms (2 CH) in agreement with structure **9**.

^{13}C-NMR. spectral data of **9** and **10** clearly revealed the site of the acyloxy group at C(10)[3]). On the basis of comparison of the existing data [15] for the coupling constants, we assigned to H–C(1), H–C(5) and H–C(9) the α-, β- and β-configuration, respectively. The configurations at the three hydroxylated centers of the cyclopentane ring will be discussed below.

Globularinin (**13**), $C_{24}H_{30}O_{12}$, $[\alpha]_D^{20} = -84.47°$ (MeOH), was a colourless amorphous powder. The UV. and the IR. spectra of **13** were very similar to those of globularimin (**9**). Alkaline hydrolysis of **13** yielded cinnamic acid and **14**. Acetylation of **13** under mild and drastic conditions afforded the hexa- and heptaacetate **15** and **16**, respectively.

The ^{1}H-NMR. spectra *(Table 2)* of **13** and its decinnamoyl analogue **14** were also very similar to those of **9** and **10**, respectively. This indicated that compound **13** was a diastereomer of **9**. In accord with this assumption, the ^{13}C-NMR. spectrum *(Table 1)* of **13** showed the expected 22 signals arising from 24 C-atoms.

The position of the *trans*-cinnamoyloxy group at C(10) was established, as before, by comparison of the spectra of **13** and **14**. As in **9** (s. above) the α-, β- and β-configuration was attributed to H–C(1), H–C(5) and H–C(9), respectively, of **13**.

Configuration of **9** *and* **13**. The assignment of the configuration of the hydroxylated C-atoms in the cyclopentane ring of **9** and **13** was based on the following arguments. (a) The shielding of the ^{13}C-NMR. signal of the C-atom C(9) caused by the hydroxyl group at a quaternary C(8)-atom is of diagnostic value for the determination of the configuration at C(8) of such compounds [9] [16]. Thus, comparison of the C(9)-signals of **9** and **13** revealed a β- and α-configuration, respectively, for HO–C(8). The chemical shift of H–C(9) in the ^{1}H-NMR. spectrum (360 MHz) of **11** and **12** or **15** and **16** was also in accordance with the above proposal [17].

(b) It is well documented that a *cis*-diol function is associated with a substantial increase in shielding of the hydroxylated C-atoms, as compared with the *trans*-analog [9] [18]. Thus comparison of the ^{13}C-NMR. chemical shifts of C(6)

[3]) No sizeable upfield shift for the C-atom in β (C(8)) was brought about by acylation of C(10)–OH. For a detailed discussion see [9].

and C(7) of **9** and **10** with those of **13** and **14**, respectively, suggested strongly that the former pair has a *trans*-diol and the latter a *cis*-diol function at C(6) and C(7).

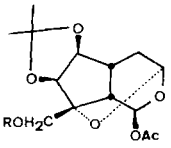
(c) Independent evidence for the configuration at C(6) and C(7) of **9** and **13** came from analyses of the 360-MHz-^{1}H-NMR. spectra *(Table 2)* of **12** and **16**. Irradiation of the multiplet of **12** centered at 2.82 ppm (H–C(5)) simplified both the signals at 4.85 ppm ($d\times d$, $J_{5,6}=2$ and $J_{6,7}=2.5$ Hz, H–C(6)), and at 5.62 ppm ($d\times d$, $J_{5,7}=1$ and $J_{6,7}=2.5$ Hz, H–C(7)) to doublets indicating thereby a W-type coupling between H–C(5) and H–C(7) which demanded a *cis*-relationship between these two protons. $J_{5,6}$ was small (2 Hz) which demanded a dihedral angle close to 90° between H–C(5) and H–C(6), necessitating a *trans*-relationship of these protons [19]. $J_{5,6}$ was also very small (1 Hz) in **16**, and thus these protons were also *trans*.

The above observation thus established the structures **9** and **13** (including the configuration as depicted in the formula) for globularimin and globularinin, respectively.

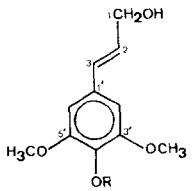
An additional chemical proof for the structure **13** was obtained in the following way. Treatment of **13** with acetone/$HClO_4$ at room temperature (s. exper. part) followed by acetylation gave a tetracyclic compound **17** (the structure was established by ^{1}H- and ^{13}C-NMR. spectra). This established the configuration at C(5), C(6), C(7), C(8) and C(9) of the aglucone moiety. Indeed, the rings of **13** must be *cis*-fused and HO–C(8) α-oriented for the cyclization to proceed [20]. Additionally, formation of an acetonide demonstrated the *cis*-diol function at C(6) and C(7).

Liriodendrin (**18**) *and syringin* (**20**). Liriodendrin was obtained as a crystalline white solid. The molecular formula of **18**, $C_{34}H_{46}O_{18}$, was based on the EI.-MS. [no M^+ peak, *m/z* 418 (aglycone moiety, with a transfer of two protons, 100%)], the number of signals in the ^{13}C-NMR. and the integration of the ^{1}H-NMR. spectra and the FD.-MS. of its peracetate **19** (M^+, 1078).

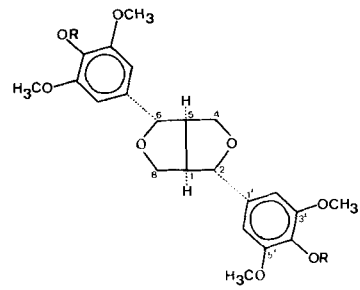
The MS. data clearly indicated **18** to be a lignan of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane skeleton [21]. As expected for structure **18**, the ^{13}C-NMR.



17 R = *trans*-cinnamoyl



20 syringin:
R = β-D-glucose



18 liriodendrin:
R = β-D-glucose

19 liriodendrin octaacetate:
R = tetraacetyl β-D-glucose

spectrum *(Table 3)* showed fourteen signals out of 34 C-atoms. The ^{1}H-NMR. spectra of **18** and its peracetate **19** are given in *Table 4*.

These data suggested that liriodendrin (**18**) belonged to the category of symmetrical bicyclooctane lignans with the aryl groups disposed diequatorially at C(2) and C(6) [22].

Liriodendrin was first isolated from *Liriodendron tulipifera* by *Dickey* [23]. In a subsequent study *Briggs et al.* [24] questioned the configuration of liriodendrin, while working on the nonglycosidic lignans of *Macropiper excelsum*. The diglucoside **18** has recently been isolated from *Acanthophanax cortex* [25]. The configuration, however, was left ambiguous till todate. We have, therefore elucidated the configuration as given in the formula **18**. At this stage, a note [26] appeared on the structure determination of liriodendrin from *Penstemon deustus (Scrophulariaceae)*. The ^{1}H-NMR. data, except those of H_{ax}–C(4) and H_{ax}–C(6), reported by *Jolad et al.* [26] were sufficiently similar to those of our compound to warrant a direct comparison which established the identity in all respect, except melting point. This difference in the melting point could be ascribed to the different solvent used

Table 3. *^{13}C-NMR. Spectral Data of Liriodendrin* (**18**) *and Syringin* (**20**)[a])

C-Atom	**18**	**20**	C-Atom	**18**	**20**
C(1) }	54.03	62.94 (C(1))	OCH_3	57.06	57.19
C(5) }			C(1″)	103.68	103.90
C(4) }	70.11	131.05 (C(2))	C(2″)	74.44	74.54
C(8) }			C(3″)	76.48	76.58
C(2) }	86.49	129.73 (C(3))	C(4″)	70.11	70.21
C(6) }			C(5″)	77.12	77.17
C(1′)	133.73	134.06	C(6″)	61.30	61.42
C(2′) }	104.63	105.24			
C(6′) }					
C(3′) }	153.40	153.39			
C(5′) }					
C(4′)	138.78	135.15			

[a]) The spectra were recorded in D_2O (sparingly soluble) using dioxane as external standard. Chemical shifts in ppm relative to $(CH_3)_4Si$.

Table 4. *^{1}H-NMR. (360 MHz) Spectral Data of Liriodendrin* (**18**) *and its Octaacetate* **19**[a])

Compound (solvent)	H–C(1) H–C(5)	H–C(2) H–C(6)	H_{ax}–C(4) H_{ax}–C(8)	H_{eq}–C(4) H_{eq}–C(8)	H–C(2′) H–C(6′)	OCH_3	H–C(1′)
18 (DMSO-d_6)	*ca.* 3.1[b])	4.67 *d* (3.8)	3.82 *d*×*d* (2.5 and 8.8)	4.20 *d*×*d* (6.5 and 8.8)	6.65 *s*	3.76 *s*	4.88 *d* (7.5)
19 ($CDCl_3$)	3.07 br. *s*	4.73 *d* (3.8)	3.93 *d*×*d* (3.0 and 8.8)	*ca.* 4.25[c]) *m*	6.55 *s*	3.83 *s*	5.05 *d* (7.5)

[a]) Values in parenthesis are coupling constants (in Hz).
[b]) Signal patterns are unclear due to overlapping with glucose protons.
[c]) Overlapping with the glucose H–C(6″).

for crystallization. Our ^{13}C-NMR. spectrum *(Table 3)* in D_2O duplicates that of ref. [26] taken in DMSO-d_6, if the expected minor solvent shifts are taken into consideration. The authors [26] in addition studied *in vivo* antileukemic activity of **18** (T/C 147, 12.5 mg/kg, PS test system). This information helped us to propose that the antileukemic principle of the water extract of *G. alypum* might be liriodendrin (**18**) as our screening of the iridoid constituents of *G. alypum* and related iridoids up to a dose of 100 µg/ml in the PS, LE and KB *in vitro* tumor cell lines[4]) were found to be inactive. *In vitro* studies do not always correlate with *in vivo* studies as for the latter the formation of an active intermediate in the animal body is possible. Our proposal is also supported by the fact that there are only two reports [12] [27] of antitumor iridoids, which contain, furthermore, completely different functionalities. An *in vivo* antitumor screening of the simple iridoids is currently underway.

The recognition of syringin (**20**) as a constituent of *G. alypum* seems to be biosynthetically significant. Indeed, the additional non-iridoid constituent liriodendrin (**18**) is simply a dimer of **20** and thus the first demonstration of a lignan in the family *Globulariaceae*. The occurrence of a lignan in *G. alypum* certainly warrants further search for this class of compounds in other *Globularia* species especially where cinnamoyl iridoids (*i.e.* acylated with a (C_6–C_3)-unit) are present.

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Experimental Part

General. Melting points were determined on a *Mettler* FP5/FP52 apparatus. UV. spectra [λ_{max}(logε)] were determined in MeOH for spectroscopy *(Merck)* on a *Perkin-Elmer* 550 spectrometer. IR. spectra (cm^{-1}) were determined on a *Perkin-Elmer* 257 instrument in KBr pellets, in $CHCl_3$ or in CCl_4. ^{1}H- and ^{13}C-NMR. spectra (δ in ppm, J in Hz) were obtained at 100 MHz using a *Varian* HA-100 spectrometer or at 360 MHz using a *Bruker Spectrospin* instrument and at 25.2 MHz in *Fourier* transform mode using a *Varian* XL-100-12 spectrometer, respectively, with tetramethylsilane as an internal standard. MS. (*m/z*) were recorded with a *Hitachi-Perkin-Elmer* RMU 6M spectrometer. Silica gel 60 (70–230 mesh, *Merck*) and neutral alumina (*Woelm* N, Act. 1) were used for column chromatography and silica gel 60 F_{254} *(Merck)* prepared plates for TLC. Spots were detected by UV. fluorescence and/or spraying with vanillin/H_2SO_4 followed by heating at 100° for 5–10 min. A *Waters Assoc.* HPLC. model ALC 201 was used throughout, together with a *Waters Assoc.* M-6000 pump as the solvent delivery system and a U6K septumless injector. The system was equipped with a *Perkin-Elmer* spectrophotometer (LC 55) with a variable wave length detector. The separation was monitored by a *Spectra Physics*-SP 4000 chromatography data system. For the analytical and the semi-preparative HPLC. work *µBondapak* C_{18} columns (30 cm × 3.9 mm I.D. and 30 cm × 7.8 mm I.D., respectively) were used. For the preparative work a *Waters* Prep. LC/500 System equipped with a

[4]) Obtained from School of Pharmacy, University of Wisconsin, Madison, U.S.A., through Prof. *C.R. Hutchinson*.

reversed phase column and different proportion of MeOH/H_2O was used. Abbreviation: RT. = room temperature.

Extraction and Purification. Dried whole plants of *G. alypum* were obtained from *Siegfried AG*, Zofingen, Switzerland. The milled plant material (500 g) was extracted with MeOH (4 times 1.5 l) at 40°. The MeOH extract was concentrated and extracted with petroleum ether (4 times 1.5 l). The MeOH layer was then concentrated to dryness and the residue was taken up in H_2O. The water-soluble portion was passed through a prewashed (H_2O) column of neutral Al_2O_3 (400 g) eluting with H_2O. The aqueous eluate was concentrated and lyophilized when the crude glycoside fraction[5]) (93.2 g) was obtained. A portion of the mixture (24.4 g) was chromatographed over silica gel (400 g, 65 × 4.3 cm) eluting with CH_2Cl_2/MeOH/H_2O [80:20:2 (2.5 l), 70:30:3 (2 l) and 60:40:4 (2 l)], and five fractions, A (6.4 g), B (2.2 g), C (1.6 g), D (4.4 g) and E (4.2 g), were collected.

Separation of Iridoid Glucosides from Fr. A. The Fr. A (2 times 2 g) was subjected to preparative liquid chromatography [MeOH/H_2O 45:55; flow rate 100 ml/min] and the two major fractions A1 and A2 were collected. MeOH was removed under reduced pressure, the remainder frozen and lyophilized to give 0.32 and 2.2 g, respectively. A part of Fr. A2 (0.5 g) was crystallized from C_2H_5OH to give pure *globularin* (**1**)[6]), m.p. 115–117°, $[\alpha]_D^{20} = -64.85°$ ($c = 0.81$, MeOH). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

The Fr. A1 (0.32 g) was subjected to HPLC. [MeOH/H_2O 30:70, flow rate 3 ml/min] with a semipreparative column. The compounds **13** and **2** eluted from the column were collected separately. After removal of the methanol under reduced pressure these eluates were pooled with the corresponding fractions from earlier runs, frozen and lyophilized to give pure **13** (58 mg) and **2** (132 mg), respectively. *Globularicisin* (**2**): $[\alpha]_D^{20} = -97.2°$ ($c = 0.66$, CH_3OH). – UV. (MeOH): 215 (4.1), 272 (4.4). – IR. (KBr): ~3400 br. (OH), 1710 (C=O, ester), 1655 (C=C), 1575, 1495, 1450 (arom. ring). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

Globularinin (**13**): $[\alpha]_D^{20} = -84.47°$ ($c = 0.64$, MeOH). – UV. (MeOH): 216 (4.11), 222 sh, 278 (4.41). – IR. (KBr): 3410 br. (OH), 1698 (C=O, ester), 1636 (C=C), 1580, 1498, 1450 (arom. ring). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.* – MS. (FD.): 510 (M^+).

Globularicisin pentaacetate (**3**). Acetylation of **2** (83 mg) was effected with acetic anhydride (4 ml) and pyridine (3 ml) at RT. Silica gel chromatography [10 g, $CHCl_3/C_6H_6$/MeOH 3:1:0.1] gave a homogeneous product (88 mg) which crystallized from ethanol/hexane, m.p. 127–129°, $[\alpha]_D^{20} = -90.99°$ ($c = 0.53$, $CHCl_3$). – IR. ($CHCl_3$): ~1735 br. (C=O, ester), ~1635 br. (C=C). – ^{1}H-NMR.: *Table 2.*

Hydrolysis of Globularicisin (**2**). A solution of 100 mg of **2** in 20 ml of methanolic 0.1N NaOH was kept overnight, then neutralized with 0.1N HCl. The solvent was evaporated, and the residue on chromatography over silica gel using CH_2Cl_2/MeOH/H_2O 70:30:3 gave cinnamic acid (TLC., UV.) and catalpol (**4**; 61 mg; TLC., HPLC., ^{13}C-NMR. (s. *Table 1*)).

Globularinin hexaacetate (**15**) was obtained as a foam by acetylation of **13** at RT. for 2 h, $[\alpha]_D^{20} = -97.06°$ ($c = 0.61$, $CHCl_3$). – IR. ($CHCl_3$): 3460 (OH), 1730 br. (C=O, ester), 1632 (C=C). – ^{1}H-NMR.: *Table 2.* – MS.: 762 (< 1, M^+), 745 (< 1, $M^+ - 17$), 702, 642, 415; due to the glucose part at 331 (50), 289, 271 (7), 229, 211, 187, 169 (100), 127, 109 (43); due to the cinnamoyl part at 131 (50), 103 (10), 77 (5).

Globularinin heptaacetate (**16**) was prepared by acetylation (7 days) of either **13** or **15** using acetic anhydride and 4-dimethylaminopyridine. Silica gel chromatography eluting with ether afforded pure **16**, $[\alpha]_D^{20} = -95.03°$ ($c = 0.50$, $CHCl_3$). – IR. (CCl_4): ~1755 br. (C=O, ester), 1638 (C=C). – ^{1}H-NMR.: *Table 2.* – MS.: 804 (< 1, M^+), 745 (< 1, $M^+ - 59$), 684 (< 1, $M^+ - 2 \times 60$), 536, 457, 397; due to the glucose part at 331 (50), 289, 271 (9), 229, 211, 187, 169 (100), 127, 109 (33); due to the cinnamoyl part at 131 (52), 103 (11), 77 (4).

Hydrolysis of Globularinin (**13**) was achieved with methanolic 0.1N NaOH as described for **2**.

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[5]) Antileukemic activity 131 [test/control (T/C)] at 100 mg/kg in the P388 test system. Obtained through NCI, NIH, Bethesda, U.S.A.

[6]) Globularin was isolated from *G. alypum* by several groups [28] and its structure (the position of the ester group was not fully certain) was also determined. *Weinges et al.* [29] isolated a compound, named scutellarioside-1 and proposed the same structure as for globularin. The name globularin has thus priority over scutellarioside-I since we have further proved the site of acylation by ^{13}C-NMR. spectroscopy; consequently, the structure is as proposed in the original work [28].

Lyophilization gave **14** as an amorphous white powder, $[\alpha]_D^{20} = -77.48°$ ($c = 0.56$, MeOH). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

Treatment of Globularinin (**13**) *with acetone/perchloric acid.* Perchloric acid (3 drops) was added to **13** (42 mg) in acetone. After keeping for 45 min at RT., anhydrous K_2CO_3 (*ca.* 200 mg) was added to it. The solution was filtered and evaporated to give a white amorphous solid. The crude mixture was acetylated with acetic anhydride/pyridine for 2 h at RT. Pure **17** was obtained by repeated silica gel chromatography using ether: m.p. 173–176° (C_2H_5OH), Rf 0.44 (ether), $[\alpha]_D^{20} = -34.05°$ ($c = 0.61$, $CHCl_3$). – IR. ($CHCl_3$): 1745 and 1715 (C=O, ester), 1638 (C=C). – ^{1}H-NMR. ($CDCl_3$): 7.62–7.28 (5 arom. H); 7.75 (*d*, $J = 16$, 1 H, H–C(α)); 6.47 (*d*, $J = 16$, 1 H, H–C(β)); 6.54 (*s*, 1 H, H–C(1)); 5.12 (*d*, $J = 3.8$, 1 H, H–C(3)); 4.47 (*s*, 2 H, 2 H–C(10)); 4.44 (unresolved *m*, 2 H, H–C(6) and H–C(7)); ~2.6 (*m*, 2 H, H–C(5) and H–C(9)); 2.11 (*s*, 3 H, CH_3COO); ~1.6 (*m*, 2 H, 2 H–C(4)); 1.42 (*s*, 3 H, CH_3); 1.33 (*s*, 3 H, CH_3). – ^{13}C-NMR. ($CDCl_3$): 91.6 (C(1)), 89.8 (C(3)), 32.6 (C(4)), 34.2 (C(5) or C(9)), 84.6 (C(6) or C(7)), 85.0 (C(7) or C(6)), 81.2 (C(8)), 36.9 (C(9) or C(5)), 65.1 (C(10)), 169.7 (CH_3COO), 21.2 (CH_3COO), 112.2 ($(CH_3)_2CO_2$), 26.0 and 23.9 ($(CH_3)_2CO_2$); due to the *trans*-cinnamoyl part at 134.5 (C(1')), 128.9 (C(2') and C(6') or C(3') and C(5')), 128.2 (C(3') and C(5') or C(2') and C(6')), 130.3 (C(4')), 145.3 (C(α)), 117.7 (C(β)), 166.4 (C(α)–COO).

Separation of Glucosides from Fr. B. The Fr. B (2.2 g) was further chromatographed over silica gel using CH_2Cl_2/MeOH/H_2O 80:80:2 and two major fractions were collected. The earlier eluates enriched with syringin (**20**) gave on semipreparative scale purification [MeOH/H_2O 1:4, flow rate 3 ml/min] 243 mg of **20**. The later eluates showed the presence (HPLC.) of a minor constituent, globularidin (**5**), besides globularinin (**13**) as the major one. This fraction was subjected to HPLC. [MeOH/H_2O 30:70, flow rate 2.5 ml/min, switching to 5 ml/min after the elution of globularinin]. The peaks due to **13** and **5** eluted from the column were collected separately and the usual processing gave a further crop of **13** (113 mg) and **5** (38 mg). *Syringin* (**20**): $[\alpha]_D^{20} = -15.17°$ ($c = 0.5$, MeOH), m.p. 191–192° (MeOH) [30], identified by ^{1}H-NMR. and ^{13}C-NMR. *(Table 3).*

Globularidin (**5**): $[\alpha]_D^{20} = -57.65°$ ($c = 0.51$, MeOH). – UV. (MeOH): 216 (4.02), 221 sh, 278 (4.46). – IR. (KBr): 3410 br. (OH), 1705 (C=O, ester), 1635 (C=C), 1580, 1500 and 1450 (arom. ring). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

Globularidin pentaacetate (**6**). Globularidin (**5**; 13 mg) was acetylated, and the product recrystallized from C_2H_5OH to give needles (6 mg) of m.p. 79–81°, $[\alpha]_D^{20} = -52.24°$ ($c = 0.32$, $CHCl_3$). – IR. (CCl_4): ~1750 br. (C=O, ester), 1635 (C=C). – ^{1}H-NMR.: *Table 2.* – MS.: 704 (2, M^+), 645 (1.5, $M^+ - 59$), 373 (2.5, $M^+ - 331$), 357 (4); due to the glucose part at 331 (28), 289, 271 (5), 229, 211, 187, 169 (70), 127, 109 (35); due to the cinnamoyl part at 131 (100), 103 (17), 77 (5).

Hydrolysis of globularidin (**5**). The hydrolysis was effected with methanolic 0.1N NaOH as described for **2**. Crystallization from C_2H_5OH gave **8** as needles, m.p. 223–224°, $[\alpha]_D^{20} = -99.21°$ ($c = 0.63$, MeOH). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

α,β-Dihydroglobularidin (**7**). A solution of **1** or **5** in C_2H_5OH, was hydrogenated over 10% Pd/C at RT. After the consumption of H_2 was complete, the catalyst was filtered off and the solvent removed. The residue, purified in a semipreparative HPLC. (MeOH/H_2O 2:3, 5 ml/min), afforded pure **7** after usual work-up, $[\alpha]_D^{20} = -60.22°$ ($c = 0.64$, MeOH). – ^{1}H-NMR.: *Table 2.*

Separation of Glucosides from Fr. C. Rechromatography of Fr. C (1.6 g) over silica gel using CH_2Cl_2/MeOH/H_2O 80:20:2 gave two fractions. The residue obtained from the earlier eluates on semipreparative HPLC. [MeOH/H_2O 3:7, flow rate 4 ml/min] afforded pure globularimin (**9**; 172 mg) as an amorphous fluppy substance. The residue obtained from the later eluates was triturated with MeOH, and the MeOH sparingly soluble solid on crystallization from DMSO/MeOH gave pure liriodendrin (**18**; 39 mg). *Globularimin* (**9**): $[\alpha]_D^{20} = -105.97°$ ($c = 0.64$, MeOH). – UV. (CH_3OH): 217 (4.08), 223 sh, 278 (4.38). – IR. (KBr): 3400 br. (OH), 1702 (C=O, ester), 1638 (C=C), 1580, 1495 and 1450 (arom. ring). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.* – MS. (FD.): 510 (M^+).

Liriodendrin (**18**): ^{1}H-NMR.: *Table 4.* – ^{13}C-NMR.: *Table 3.* – MS.: 742 (M^+, no peak), 418 (aglycone, with transfer of two protons, 100), 387 (5), 251 (5), 236 (8), 235 (8), 226 (6), 210 (12), 193 (20), 181 (33), 167 (34), 154 (13).

Globularimin hexaacetate (**11**). Acetylation of **9** as usual afforded **11** as an amorphous powder, $[\alpha]_D^{20} = -81.08°$ ($c = 0.63$, $CHCl_3$). – IR. ($CHCl_3$): ~3430 (OH), ~1740 br. (C=O, ester), 1636 (C=C). – ^{1}H-NMR.: *Table 2.* – MS.: 762 (< 1, M^+) and similar fragmentation peaks as reported for **15**.

Globularimin heptaacetate (**12**). Prolonging the acetylation of **11** to 24 h using 4-dimethylaminopyridine afforded **12** after chromatography. Crystallization gave pure **12**, m.p. 86–88°, $[\alpha]_D^{20} = -81.38°$ ($c = 0.55$, $CHCl_3$). – IR. (CCl_4): ~1730 br. (C=O, ester), 1635 (C=C). – ^{1}H-NMR.: *Table 2.* – MS.: 804 (< 1, M^+) and similar fragment-ion peaks as reported for **16**.

Hydrolysis of Globularimin (**9**). The hydrolysis with methanolic 0.1N NaOH as described for **2** afforded **10**, $[\alpha]_D^{20} = -139.89°$ ($c = 0.64$, MeOH). – ^{1}H-NMR.: *Table 2.* – ^{13}C-NMR.: *Table 1.*

Liriodendrin octaacetate (**19**). Acetylation of **18** with acetic anhydride/pyridine at RT. for 2 h afforded **19** which was crystallized from MeOH, m.p. 122–124°. – ^{1}H-NMR.: *Table 4.* – MS. (FD.): 1078 (M^+), 747 ($M^+ - 331$), 418 ($M^+ - 2 \times 331$).

Purification of catalpol (**4**) *present in Fr. D.* A part (2 g) of Fr. D on prep. liquid chromatography [MeOH/H_2O 1:9; 100 ml/min] gave **4** (1.07 g). – ^{13}C-NMR.: *Table 1.*

The Fr. E contained mainly sugars and was not further worked-up.

REFERENCES

[1] *R. K. Chaudhuri & O. Sticher*, Helv. *63*, 117 (1980).

[2] *R. Hegnauer*, «Chemotaxonomie der Pflanzen», Vol. 4, Birkhäuser Verlag, Basel, Stuttgart 1966, p. 207.

[3] *J. Balansard & J. Delphaut*, Revue de Phytothérapie *12*, 231 (1948).

[4] *P. Bernard, M. Lallemand & G. Balansard*, Plantes médicinales et phytothérapie *8*, 180 (1974) and ref. cit. therein.

[5] *J. H. Wieffering*, Phytochemistry *5*, 1053 (1966).

[6] *G. Caldes, B. Prescott & J. R. King*, Planta medica *27*, 72 (1975).

[7] *R. K. Chaudhuri & O. Sticher*, Helv. *62*, 644 (1979).

[8] *R. K. Chaudhuri, O. Sticher & T. Winkler*, Tetrahedron Lett. *1979*, 3149.

[9] *R. K. Chaudhuri, F. Ü. Afifi-Yazar, O. Sticher & T. Winkler*, Tetrahedron *36*, 2317 (1980), and ref. cit. therein.

[10] *M. Golfier*, in 'Stereochemistry, Fundamentals and Methods', ed. H. B. Kagan, George Thieme Publishers, Stuttgart 1977, p. 55, and ref. cit. therein.

[11] *H. Taguchi, Y. Yokokawa & T. Endo*, Yakugaku Zasshi *93*, 607 (1973).

[12] *S. M. Kupchan, A. L. Dessertine, B. T. Blaylock & R. F. Bryan*, J. Org. Chem. *39*, 2477 (1974).

[13] *M. Nakane, C. R. Hutchinson, D. Van Engen & J. Clardy*, J. Am. Chem. Soc. *100*, 7079 (1978).

[14] *S. R. Jensen, S. E. Lyse-Petersen & B. J. Nielsen*, Phytochemistry *18*, 273 (1979).

[15] *H. Rimpler*, Planta medica *33*, 313 (1978), and ref. cit. therein.

[16] *R. K. Chaudhuri, F. Ü. Afifi-Yazar & O. Sticher*, Helv. *62*, 1603 (1979).

[17] *Y. Takeda, H. Nishimura & H. Inouye*, Phytochemistry *16*, 1401 (1977).

[18] *R. G. S. Ritchie, N. Cyr, B. Korsch, H. J. Koch & A. S. Perlin*, Can. J. Chem. *53*, 1424 (1975).

[19] *P. Eigtved, S. R. Jensen & B. J. Nielsen*, Acta chem. Scand. *B28*, 85 (1974), and ref. cit. therein.

[20] *H. Inouye, S. Ueda, S. Uesato, T. Shingu & P. W. Thies*, Tetrahedron *30*, 2317 (1974).

[21] *A. Pelter*, J. Chem. Soc. (C) *1967*, 1376.

[22] *A. Pelter, R. S. Ward, E. V. Rao & K. V. Sastry*, Tetrahedron *32*, 2783 (1976).

[23] *E. E. Dickey*, J. Org. Chem. *23*, 179 (1958).

[24] *L. H. Briggs, R. C. Cambie & R. A. F. Couch*, J. Chem. Soc. (C) *1968*, 3042.

[25] *H. S. Ro, S. Y. Lee & B. H. Han*, Yakohak Hoe chi *21*, 81 (1977); Chem. Abstr. *88*, 126255x (1978).

[26] *S. D. Jolad, J. J. Hoffmann, J. R. Cole, M. S. Tempesta & R. B. Bates*, J. Org. Chem. *45*, 1327 (1980).

[27] *S. R. Jensen, B. J. Nielsen, C. B. Mikkelsen, J. J. Hoffmann, S. D. Jolad & J. R. Cole*, Tetrahedron Lett. *1979*, 3261.

[28] *J. M. Bobbitt & K.-P. Segebath*, in 'Cyclopentanoid Terpene Derivatives', eds. W. I. Taylor & A. R. Battersby, Marcel Dekker Inc., New York 1969, p. 50.

[29] *K. Weinges, K. Künstler, G. Schilling & H. Jaggy*, Liebigs Ann. Chem. *1975*, 2190.

[30] *T. K. Devon & A. I. Scott*, 'Handbook of Naturally Occurring Compounds', Vol. I, 'Acetogenins, Shikimates, and Carbohydrates', Academic Press, New York, San Francisco, London 1975, p. 30.