Phytochemistry, Vol. 27, No. 9, pp. 2835–2842, 1988.
Printed in Great Britain.

0031-9422/88 $3.00+0.00

THE FIRST 12.8β-GERMACROLIDE AND OTHER CONSTITUENTS FROM BOLIVIAN *STEVIA* SPECIES

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(*Revised received* 27 *November* 1987)

Key Word Index—*Stevia sarensis*; *S. samaipatensis*; *S. yacomensis*; *S. polyphylla*; Compositae; sesquiterpene lactones; germacranolides; 12,8β-germacrolide; guaianolides; fulvene derivative; diterpenes; labdane derivatives; sesquiterpenes; longipinane derivatives.

Abstract—The aerial parts of *Stevia sarensis* afforded several known germacranolides, guaianolides and labdane derivatives while *S. samaipatensis* gave four new guaianolides, one being a fulvene and two new labdane derivatives. From *S. yacomensis* four new longipinene derivatives and a guaianolide were isolated. The aerial parts of *S. polyphylla* afforded in addition to known compounds nine further guaianolides and the first 12.8β-germacrolide. Structures were elucidated by high field NMR spectroscopy and a few chemical transformations.

INTRODUCTION

From the large genus *Stevia* with *ca* 200 species already many interesting constituents have been isolated [1–9]. Most common are longipinene derivatives and guaianolides with a 8β-oxygen function but many other constituents also have been reported. We now have studied four species from Bolivia; our results are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of *S. polyphylla* afforded germacrene D, bicyclogermacrene, the germacrolide **1**, the elemanolides **2** [10] and **3** [11], the eremophilanolides **5b** [12] and **5c** [13], the eudesmanolides **5a**, isoalantolactone and its Δ^4 isomer, the guaianolides **6–13**, **14** [7], **15** [7] and **23**, costic acid and the eremophilenic acids **24** [13] and **25** [13].

From the aerial parts of *S. samaipatensis* germacrene D, bisabolone, and the guaianolides **19–22** as well as the labdane derivatives **30** and **31** were isolated.

The aerial parts of *S. yacomensis* Hieron. afforded germacrene D, α-humulene, *ent*-kaurenic acid and its $\Delta^{9,11}$ dehydro derivative, costunolide, the guaianolides estafiatin and **16** as well as the longipinane derivatives **32** [1] and **35–35**. From the roots in addition to **32** and **33**, **36** was also obtained.

The aerial parts of *S. sarensis* afforded germacrene D, humulene, the germacranolides eupatoriopicrin [14], its 20-desoxy derivative [15] and its 20-tiglate [16] as well as eucannabinolide [17], the guaianolides **17** [18], its $\Delta^{1,10}$ isomer [19] as well as the ketones **14** [7] and **15** [7], 13*Z*-labdenolic acid [9], abienol [20] and its derivatives **27** [21], **28** [22] and **29** [23].

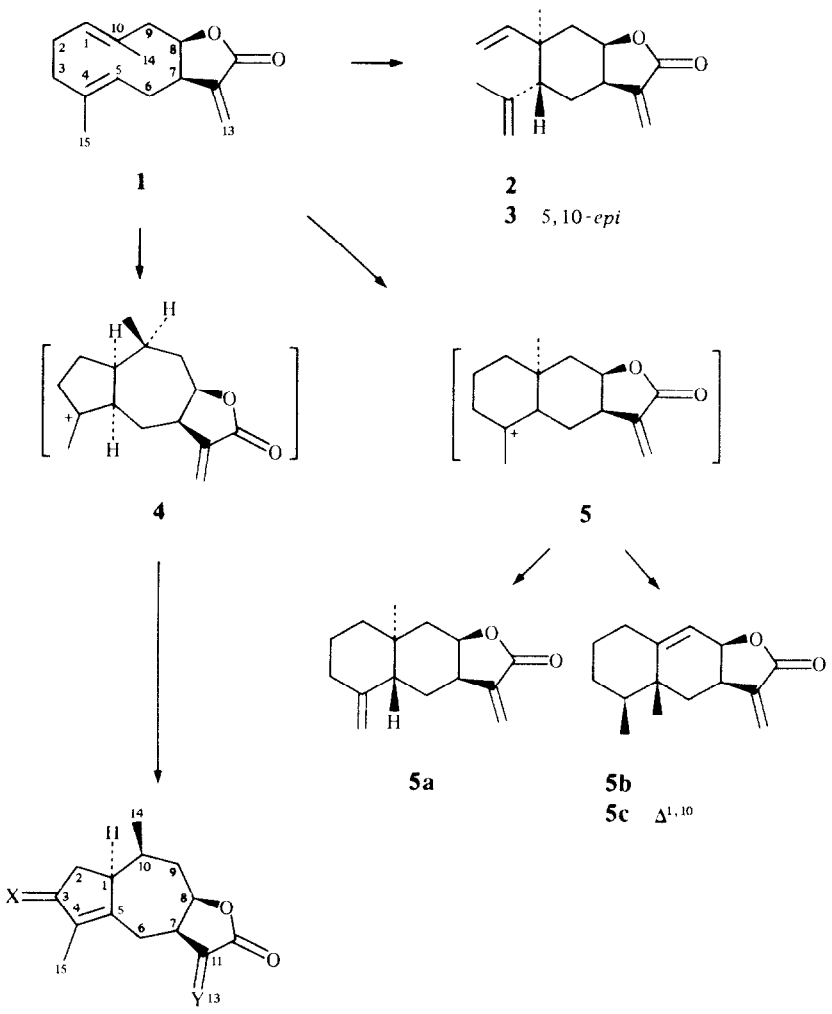
The ^{1}H NMR spectrum of **1** (Table 1) appeared to be a mixture of two compounds. However, no separation of the components was achieved. Accordingly, the presence of two conformers was proposed. Heating to 60° or cooling down to −40° gave no real change. But careful spin decoupling allowed the assignment of nearly all signals and the resulting sequences clearly indicated the presence of two conformers of a germacra-1(10)*E*,4*E*-dien-12.8β-olide. NOE-difference spectroscopy showed that in one of the conformers both methyls were parallel orientated below the plane (**1A**), but not perpendicular to

Table 1. NMR data of **1**($CDCl_3$, 400 MHz, δ-values)

H	A	B	H	A	B
1	4.75	4.81 *br dd*	8	4.90	4.98
2	2.10	2.28, 1.98 *m*	9α	2.92	2.71 *br dd*
3	2.00, 1.80 *m*		9β	2.11	2.00 *dd*
5	4.51 *br d*		13	6.27	6.23 *d*
6α	2.57	2.13 *ddd*	13′	5.51	5.54 *d*
6β	2.71	2.68 *br d*	14	1.30	1.49 *br s*
7	3.39 *m*		15	1.58	1.51 *t*

J[Hz] (in parenthesis of conformer **B**: 1,2 = 5 (6), 1,2′ = 10 (6); 5,6α = 10 (< 2), 5,6β = < 2 (10); 6α,6β = 14; 6α,7 ~ 3 = 7, 13 = 7,13′ ~ 3; 6β,7 = 10; 7,8 = 6 (7); 8,9α = 3,5 (3), 8,9β ~ 2 (10); 9α,9β = 14.

Irradiation	NOE values		
H-14A	H-2 (7%)	H-9α (5%)	H-8 (12%)
H-14B	H-2 (8%)	H-9β (6%)	
H-15A	H-6α (10%)	H-3β (6%)	H-14A (6%)
H-15B	H-6α (8%)		
H-7A/B	H-5B (6%)	H-8 (10%)	
H-8A	H-7 (10%)	H-15 (6%)	
H-8B	H-7 (10%)	H-1 (8%)	
H-1A	H-9β (10%)	H-5 (3%)	
H-1B	H-8 (10%)		



1 **2** **3** 5,10-*epi* **4** **5** **5a** **5b** **5c** $\Delta^{1,10}$

	6	7	8	9	10	11	12	13	14	15
X	αOH,H	αOMe,H	βOH,H	βOMe,H	βOAc,H	H_2	βOH,H	H_2	O	O
Y	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	αMe,H	αMe,H	CH_2	αMe,H

it, H-5 and H-6 forming an angle of *ca* 180°. In this conformation C-5 and C-10 are very near to each other. On heating to 80° in deuteriobenzene the signals of this conformer were highly broadened but on cooling down to room temperature the original spectrum was obtained. While at room temperature no equilibrium of the two conformers could be observed by NOE-difference spectroscopy, at 60° exchange of the methyls of the conformers was obvious. Accordingly, we were dealing with two conformers of **1** which are in a rapid equilibrium only at elevated temperature. Prolonged heating afforded the elemanolide **2** as the main product. Consequently, in the ^{13}C NMR spectrum of **1** nearly all signals were doubled. All data therefore indicated that we were dealing with the first 8.12-*cis*-germacrolide, a compound which most likely is the precursor of many eudesmanolides, eremophilanolides, guaianolides and elemanolides with a 8.12-*cis*-lactone ring. Therefore, it was not surprising that in this species also related lactones like isoalantolactone and its Δ^4 isomer as well as the lactones **2**, **3**, **5a**–**5c** and **6**–**15** were present.

The structure of **5a** followed from its ^1H NMR spectrum (see Experimental) which was close to that of related steiractinolides [24]. This lactone also was obtained from **1** on standing in chloroform containing a trace of hydrochloric acid. Therefore it cannot be excluded that **5a** is an artifact.

The ^1H NMR spectra of **6** and **7** (Table 2) clearly indicated that we were dealing with derivatives of achalensolide (**14**) [7]. The presence of a broadened triplet at δ4.65 and 4.24, respectively, and the upfield shift of several signals showed that the keto group was replaced by hydroxy in the lactone **6** and by methoxy in the lactone **7**. Spin decoupling supported the position at C-3 while the stereochemistry could not be determined from the couplings, However, the ^1H NMR spectrum of **8** (Table 2) clearly indicated that the epimeric alcohol was present. If the spectra of **6** and **8** were compared the most distinct difference was visible in the chemical shift of H-1 which was more downfield in the case of **6**. This was an indication that in the latter a 3α- and in the lactone **8** a 3β-hydroxy group was present. This was supported by

Table 2. ^{1}H NMR spectral data of **6–11**, **16** and **23** (400 MHz, $CDCl_3$, δ-values)

H	6	7	8	9	10	11	16	23
1	2.95 *m*	2.94 *m*	2.64 *br q*	2.62 *br q*	2.70 *br q*	2.76 *br q*	3.33 *br q*	2.02 *m*
2	2.04 *m*	1.86 *ddd*	2.29 *dt*	2.13 *dt*	2.35 *dt*	1.83 *dddd*	—	2.16 *m*
2′	1.69 *ddd*	1.77 *ddd*	1.28 *ddd*	1.34 *ddd*	1.40 *ddd*	1.50 *dddd*	—	2.08 *m*
3	4.65 *br t*	4.24 *br t*	4.50 *br t*	4.09 *br t*	5.50 *br t*	2.27 *br dd* 2.17 *br dd*	6.14 *dq*	5.47 *br s*
5	—	—	—	—	—	—	3.19 *br dd*	—
6	2.56 *br dd*	2.58 *br dd*	2.55 *br dd*	2.55 *br dd*	2.53 *br d*	2.47 *br d*	4.11 *dd*	1.75 *dd*
6′	2.42 *br dd*	2.44 *br dd*	2.49 *br dd*	2.47 *br dd*				1.56 *br d*
7	3.39 *ddddd*	3.38 *ddddd*	3.33 *ddddd*	3.35 *ddddd*	3.34 *ddddd*	3.34 *ddddd*	2.92 *ddddd*	3.51 *ddddd*
8	4.84 *ddd*	4.84 *ddd*	4.82 *ddd*	4.82 *ddd*	4.83 *ddd*	4.81 *ddd*	2.29 *dddd* 1.48 *dddd*	4.63 *ddd*
9	2.04 *m*	2.03 *m*	1.95 *m*	1.95 *m*	1.99 *m*	1.93 *m*	2.53 *ddd*	1.93 *ddd*
9′	1.36 *ddd*	1.37 *ddd*	1.46 *ddd*	1.46 *ddd*	1.46 *ddd*	1.43 *ddd*	2.18 *ddd*	1.81 *ddd*
10	2.04 *m*	2.03 *m*	1.95 *m*	1.96 *m*	1.99 *m*	1.98 *m*	—	2.02 *m*
13	6.32 *d*	6.32 *d*	6.33 *d*	6.31 *d*	6.33 *d*	6.29 *d*	6.28 *d*	6.24 *d*
13′	5.65 *d*	5.65 *d*	5.66 *d*	5.64 *d*	5.66 *d*	5.63 *d*	5.58 *d*	5.67 *d*
14	0.79 *d*	0.79 *d*	0.91 *d*	0.89 *d*	0.87 *d*	0.85 *d*	5.10 *br s* 4.84 *br s*	1.05 *d*
15	1.71 *br s*	1.69 *br s*	1.73 *br s*	1.69 *br s*	1.65 *br s*	1.65 *br s*	2.33 *br s*	1.67 *br s*
OMe	—	3.33 *s*	—	3.30 *s*	—	—	—	—
OAc	—	—	—	—	2.04 *s*	—	—	—

J[Hz]: compounds **6–11**: 6,6′ = 16; 6,7 = 4,5; 6′,7 = 11; 7,8 = 8; 7,13 = 3; 7,13′ = 8,9 = 2.5; 8,9′ = 11; 8,9′ = 12,5; 10,14 = 7; (compounds **6** and **7**: 1,2 = 14; 1,2′ = 7; 2,2′ = 13; 2,3 = 4; 2,3′ = 6,5; compounds **8–11**: 1,2 = 2,3 = 6.5; 1,2′ = 5; 1,10 ~ 6; 2,2′ = 13; 2′,3 = 6) compound **16**: 1,5 = 7; 3,5 = 3,15 ~ 1; 5,6 = 10; 6,7 = 8,5; 7,8 = 4; 7,8′ = 11; 7,13 = 3,5; 7,13′ = 3; 8,9 = 8, 9 = 8′,9 = 4; 8′,9′ = 10; 9,9′ = 13; compound **23**: 6,6′ = 14; 6,7 = 11; 6′,7 ~ 2; 7,8 = 10; 7,13 = 2,5; 7,13′ = 2; 8,9 = 9; 8,9′ = 5; 9,9′ = 13.

boranate reduction of **15** which afforded lactone **12** as the only product. The ^{1}H NMR spectrum of **12** (Table 3) clearly showed that the corresponding 11β.13-dihydro derivative of **8** was present. Inspection of a model showed that reduction of **15** was most likely preferred from the α-face due to the presence of the 10β-methyl group.

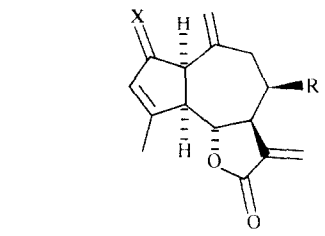
The ^{1}H NMR spectra of **9** and **10** (Table 2) indicated that the methyl ether and the acetate of **8** were present while the spectrum of **11** (Table 2) showed that we were dealing with the corresponding desoxyderivative, the precursor of **6–10**, and **12–15**. The spectrum of **13** (Table 3) was similar to that of **11**. The replacement of the exomethylene lactone by a hydrogenated one followed from the characteristic ^{1}H NMR signals which were close to those of **15**. Accordingly, identical stereochemistry could be proposed.

The ^{1}H NMR spectrum of **23** (Table 2) differed from the isomeric carbinols **6** and **8** by the presence of the signal of an olefinic proton. Furthermore, the H-6 signals were shifted upfield while those of H-2 were shifted downfield. Accordingly, a Δ^3 double bond was very likely. This was supported by spin decoupling which established the whole sequence. The configuration at C-5 followed from the downfield shift of H-7. Most likely the lactone **23** is formed by oxidation of **11** via allylic rearrangement.

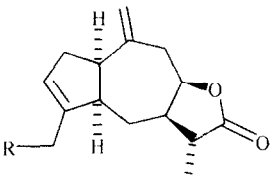
The structure of **16** followed from the ^{1}H NMR spectrum (Table 2) which was similar to that of a 8β-acyloxy derivative from *Trichogonia santosii* [25]. The absence of an ester group caused some shift differences but all signals could be easily assigned by spin decoupling. Lactone **16**, therefore, was an isomer of lidbeckialactone [26].

The ^{1}H NMR spectra of **19–21** (Table 3) indicated that these lactones again were 11.13-dihydro derivatives. The lactones **20** and **21** differed in the nature of the oxygen function which only could be placed at C-15. Spin decoupling allowed the assignment of all signals and the observed NOE's in the case of **21** established the stereochemistry at all chiral centres by clear effects between H-13, H-7 and H-8 as well as between H-5, H-1 and H-7. The spectrum of **19** differed from that of **21** by replacement of the exomethylene signals by an olefinic methyl signal and the absence of an oxygen function followed from the presence of a second olefinic methyl signal. Accordingly, **19** is an isomer of xanthanolide B [20].

The lactone **22** was also a 11.13-dihydro derivative as followed from the ^{1}H NMR spectrum (Table 3). As could be deduced from the molecular formula ($C_{15}H_{18}O_2$) and from the ^{13}C NMR spectrum this lactone had three double bonds which all must be conjugated as UV maxima at 370 and 262 nm were visible. These maxima required the presence of a fulvene. This was supported by the ^{1}H NMR data. A pair of doublets at δ6.37 and 6.29 (J = 5 Hz) required a double bond in a five-membered ring and two olefinic methyl signals indicated two further double bonds. Spin decoupling of the remaining signals showed that a guaianolide was present which must be a dehydro derivative of **19**. The assignment of all signals was possible by NOE-difference spectroscopy. Irradiation at δ2.23 gave NOE's with H-9α (6%) and with the low field proton signal at δ6.37 which, therefore, was due to H-2. Similarly, H-3 and H-15 could be assigned as the latter gave a clear NOE with H-6α and H-3. Furthermore, the presence of a *cis*-lactone followed from the NOE between H-8, H-7 and H-9α. As the signals of H-6,



17

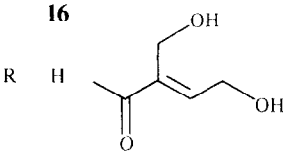


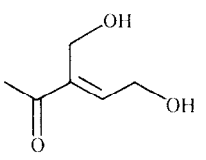
19 **20** **21**

R H OH OAc

$\Delta^{1,10}$

16



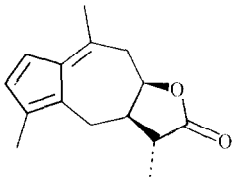


18

R H

X O H_2 H_2

$\Delta^{1,10}$



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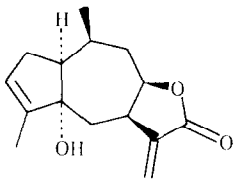
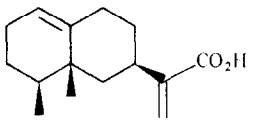
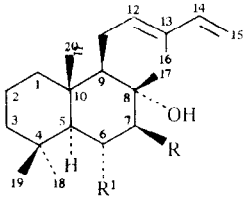


23



24

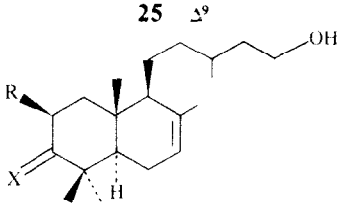
25 Δ^{9}



26 **27** **28** **29**

R H OH OH OH

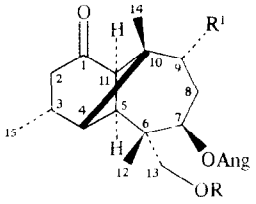
R^1 H H OAng OH



30* **31**

R OH H

X H_2 O



32 **33** **34** **35** **36**

R Ang Ac Ang Ac H

R^1 Ang Ang Ac H Ang

* **30a** is the corresponding diacetate

H-7 and H-11 were overlapped, the configuration at C-11 could not be determined directly. However, in deuteriopyridine the signals of H-7 and H-11 were separated. Clear NOE's between H-13 and H-7 (6%) as well as between H-8 and H-7 (10%) required a 11α-methyl group. Lactone **22** we have named stevisamolide. Two isomeric fulvene lactones recently have been reported from a *Tanacetum* species [27]. Comparing the couplings of H-11 in the related lactones **12**, **13** and **19**–**22** shows that the conformations in part are clearly different. Especially, in the case of **20** and **21** very small vicinal couplings were observed (J = 2.5 Hz).

The ^{1}H NMR spectra of **30**, its acetate **30a** and **31** (Table 4) clearly indicated the presence of labd-7-en-15-ol derivatives. Comparison of the spectra with that of the 2-epimer of **30** [28] showed that the latter was a derivative with an axial hydroxy group at C-2 while **31** was a 3-keto derivative. The observed negative Cotton-effect of the latter allowed the assignment of the absolute configuration, which is identical with that of the corresponding acid [28].

The structures of the longipinane derivatives **33**–**36** directly followed from their ^{1}H NMR spectra (Table 5) which were close to those of related derivatives. If the

Table 3. ^{1}H NMR spectral data of **12**, **13** and **19–22** (400 MHz, $CDCl_3$, δ-values)

H	12	12(C_6D_6)	13	19(C_6D_6)	20	21	22	22(C_6D_6)
1	2.69 *br q*	2.16 *m*	2.76 *m*	—	3.16 *br q*	3.14 *br q*	—	—
2	2.31 *dt*	2.08 *dt*	1.77 *m*	2.91 *br q*	2.55 *br dd*	2.43 *br dd*	6.37 *d*	6.37 *d*
2′	1.10 *ddd*	0.97 *ddd*	1.28 *m*	2.82 *br q*	2.33 *br dd*	2.31 *br dd*		
3	4.55 *br t*	4.34 *br dt*	2.20 *m*	5.35 *br s*	5.66 *br s*	5.71 *br s*	6.29 *d*	6.31 *d*
5	—	—	—	2.68 *br d*	2.71 *m*	2.58 *m*	—	—
6	2.50 *br dd*	2.01 *dd*	2.51 *br dd*	1.78 *m*	1.62 *ddd*	1.58 *ddd*	2.91 *br d*	2.54 *dd*
6′	2.23 *br d*	1.60 *br dd*	2.20 *m*	1.84 *ddd*	1.53 *dt*	1.44 *dt*	2.40 *m*	1.97 *m*
7	2.43 *m*	1.78 *ddddd*	2.39 *m*	1.72 *m*	2.15 *dddd*	2.12 *dddd*	2.38 *m*	1.85 *dddd*
8	4.48 *ddd*	3.95 *ddd*	4.48 *ddd*	4.39 *ddd*	4.69 *ddd*	4.65 *ddd*	4.62 *ddd*	4.14 *ddd*
9	1.53 *ddd*	1.36 *m*	1.56 *ddd*	2.18 *br ddd*	2.70 *dd*	2.69 *dd*	2.93 *dd*	2.45 *br dd*
9′	1.45 *br dd*		1.42 *dd*	2.10 *br d*	2.62 *dd*	2.57 *dd*	2.62 *dd*	2.17 *dd*
10	1.93 *br dd*	1.20 *m*	1.93 *br ddd*	—	—	—	—	—
11	2.43 *m*	2.28 *dq*	2.39 *m*	1.87 *dq*	2.30 *dq*	2.28 *dq*	2.34 *m*	1.97 *dq*
13	1.26 *d*	1.11 *d*	1.26 *d*	1.06 *d*	1.33 *d*	1.32 *d*	1.29 *d*	1.04 *d*
14	0.97 *d*	0.71 *d*	0.96 *d*	1.49 *br s*	4.99 *br s*	4.96 *br s*	2.33 *br s*	1.84 *br s*
14′					4.97 *br s*	4.94 *br s*		
15	1.68 *br s*	1.54 *br s*	1.64 *br s*	1.55 *br s*	4.21 *br d*	4.63 *br d*	1.96 *br s*	1.83 *br s*
					4.16 *br d*	4.54 *br d*	—	—
OH	—	1.66 *br d*	—	—	—	—	—	—
OAc	—	—	—	—	—	2.07 *s*	—	—

J[Hz]: 11,13 = 7; compounds **12** and **13**: 6,7 = 6′,7 = 3; 7,8 = 7; 7,11 = 12; 8,9 = 10; 8,9′ = 4; 9,9′ = 13; (compound **12**: 1,2 = 1,10 = 6.5; 1,2′ = 9; 2,3 = 2′,3 ~ 7; 3,OH = 8; compound **13**: 9,10 = 9); compound **19**: 2,2′ = 20; 2,3 = 3,15 = 5,15 ~ 1.5; 5,6 = 11; 6,7 = 5; 6′,7 = 6,6′ = 12; 7,8 = 7; 7,11 = 8,9 = 11; 8,9′ = 4; 9,9′ = 15; compounds **20** and **21**: 1,2 = 1,2′ = 1,5 ~ 8; 2,2′ = 16; 5,6 = 6,7 = 11; 5,6′ = 6′,7 = 3; 6,6′ = 13; 7,8 = 7; 7,11 = 2.5; 8,9 = 8; 8,9′ = 4; 9,9′ = 13; compound **22**: 2,3 = 5; 6,6′ = 14; 6,7 = 4; 6′,7 = 7,8 = 7,11 = 9; 8,9 = 10; 8,9′ = 2.5; 9,9′ = 15.

chemical shifts of H-13 in the spectra of **32** and **33** were compared the replacement of an unsaturated ester group by an acetate group at C-13 was obvious. Similar, the 9α-position of the acetoxy group in the isomer **34** could be deduced while the changed shifts of H-13 and H-9 in the spectra of **35** and **36**, respectively, indicated the relative position of the hydroxy groups.

Table 4. ^{1}H NMR spectral data of **30**, **30a** and **31** (400 MHz, $CDCl_3$, δ-values)

H	30	30a	31
1α	×	1.28 *m*	×
1β	×	2.17 *dt*	×
2	4.21 *tt*	5.15 *tt*	2.27 *dt* (α)
			2.72 *dt* (β)
3α	×	1.42 *m*	—
3β		1.79 *dt*	—
6	—	2.00 *m*	1.98 *br dd*
			1.92 *br d*
7	5.41 *br s*	5.43 *br s*	5.42 *brs*
15	3.69 *m*	4.10 *m*	3.69 *m*
16	0.94 *d*	0.94 *d*	0.93 *d*
17	1.68 *br s*	1.68 *br s*	1.70 *br s*
18	0.90 *s*	0.91 *s*	1.11 *s*
19	1.13 *s*	1.07 *s*	1.06 *s*
20	1.02 *s*	0.96 *s*	1.00 *s*
OAc	—	2.06, 2.04 *s*	—

×: overlapped multiples

J[Hz]: compounds **30** and **30a**: 1α,2 = 1β,2 = 2,3α = 2,3β = 3; 13,16 = 7; compound **31**: 1α,2 = 1β,2α = 3.5; 1α,2β = 2α,2β = 13; 1β,2β = 4.5; 5,6 = 10; 6,6′ = 15; 13,16 = 7.

The overall picture of the genus *Stevia* still is not very homogeneous. So far we have results on 36 species in our files. From 16 species longipinane derivatives have been isolated, in most cases from the roots. Among the sesquiterpene lactones guaianolides are most widespread, the 6.12-lactones being *trans*- and the 8.12-lactones always *cis*-annellated. However, other types of sesquiterpene lactones also have been reported and from 15 species different types of diterpenes have been isolated. In these cases usually no longipinanes and guaianolides were reported. Further taxonomic investigations may show whether these findings agree with a possible separation within the genus [30].

EXPERIMENTAL

Air-dried plant material was collected in February 1987 in Bolivia, vouchers are deposited in the US National Herbarium. Extraction and sepn was achieved as reported previously [31]. The aerial parts of *S. polyphylla* DC (320 g, voucher RMK 9637, collected in February 1987 between Cochabamba and Santa Cruz (2.700 m) gave by CC (silica gel) four crude fractions (1: petrol, 2: Et_2O–petrol (1:3)–(3:1), 3: Et_2O and 4: Et_2O–MeOH (4:1). Fraction 1 gave by TLC (petrol) 5 mg germacrene D and 3 mg bicyclogermacrene while fraction 2, which contained acids, was first shaken with $NaHCO_3$ soln. The acid fraction was sepd after addition of CH_2N_2 by TLC ($AgNO_3$–silica gel, Et_2O–petrol, 1:3) affording the Me ester of **25** (200 mg), **24** (20 mg) and costic acid (10 mg). The neutral part was sepd by HPLC (MeOH–H_2O (4:1), RP 18, *ca.* 100 bar) affording two mixtures (2/1 and 2/2), 4 mg **2**, 5 mg **3** and 3 mg **13** (R_t 7.7 min.). Fraction 2/1 gave by TLC (Et_2O–petrol (1:3), four developments) 10 mg **1** (R_f 0.65) and 2 mg **5b** (R_f 0.58). Fraction 2/2 gave by TLC (Et_2O–petrol (1:3), two developments) 2 mg **5c**, 1 mg isoalanto lactone, 2 mg of its Δ^4 isomer and 20 mg **11** (R_f

Table 5. ^{1}H NMR spectral data of **33**–**36** (400 MHz, $CDCl_3$, δ-values)

H	33	34	35	36	Multiplicity
2	2.57	2.57	2.54	2.55	*dd*
2β	2.17	2.15	2.11	2.18	*dd*
4	2.20	2.17	2.23	2.16	*br d*
7	5.47	5.38	5.14	5.43	*dd*
9β	5.06	4.91	1.83 *m*	5.05	*t*
11	3.19	3.19	2.78	3.21	*d*
12	1.02	1.07	1.02	0.92	
13	3.98	3.98 *s*	3.92	3.39	*d*
	3.89		3.89	3.27	
14	0.92	0.91	0.88	0.88	*s*
15	1.13	1.13	1.10	1.12	*d*
OAc	2.04	2.17	2.04	–	*s*
OAng	6.14, 6.04	6.11, 6.05	6.09	6.08, 6.06	*q*
	2.05, 1.94	1.99, 1.96	2.00	2.0, 1.93	*dq*
	2.01, 1.86	1.93, 1.87	1.90	1.94, 1.85	*dq*

J[Hz]: 2α,2β = 19; 2α,3 = 8.5; 2β,3 = 5.5; 3,15 = 7; 4,11 = 5; 7α,8α = 1.5; 7α,8β = 12; 8α,9β = 8β,9β = 3; 13,13′ ~ 11; OAng 3,4 = 7; 3,5 = 4,5 = 1.5.

0.5). HPLC of CC fraction 3 (MeOH–H_2O (4:1)) afforded two mixts (3/1 and 3/2). TLC of fraction 3/1 (Et_2O–petrol (1:1)) gave 100 mg **10** (R_f 0.4) and 1 mg **23** (R_f 0.2). TLC of fraction 3/2 [Et_2O–petrol (1:1)] afforded 100 mg **9** (R_f 0.48) and 15 mg **7** (R_f 0.2). TLC of CC fraction 4 [$CHCl_3$–C_6H_6–Et_2O–MeOH (40:40:20:1)] gave 250 mg **15**, 100 mg **14** and a mixture which gave by HPLC (MeOH–H_2O (3:2)) 5 mg **12** (R_t 7.4 min) and a mixture (R_t 4.6 min.) which gave by TLC (Et_2O) 10 mg **8** (R_f 0.63) and 10 mg **6** (R_f 0.48).

The extract of aerial parts of *S. samaipatensis* B.L. Rob. [180 g, voucher RMK 9641, collected in February 1987, 70 km E of bridge at Punata (3.000)] gave four crude CC fractions [1: petrol, 2: Et_2O–petrol (1:1), 3: Et_2O and 4: Et_2O–MeOH (4:1)]. TLC of fraction 1 (petrol) gave 100 mg germacrene D. TLC of fraction 2 [Et_2O–petrol (1:3)] afforded 10 mg bisabola-2,10-dien-1-one and a mixture which gave by HPLC (MeOH–H_2O (4:1)) 2 mg **19** (R_t 7.7 min). TLC of fraction 3 [Et_2O–petrol, (1:1) gave 200 mg **22** (R_f 0.65) and 50 mg **21** (R_f 0.3). TLC of fraction 4 (Et_2O–petrol (3:1)] gave two crude fractions (4/1 and 4/2). HPLC of fraction 4/1 [MeOH–H_2O (4:1)] gave 20 mg **31** (R_t 2 min) and TLC of fraction 4/2 [Et_2O–petrol (3:1)] gave 20 mg **30** (R_f 0.5) and a crude fraction which gave by HPLC [MeOH–H_2O (7:3)] 5 mg **20** (R_t 2.4 min).

The extract of aerial parts of *S. yacomensis* Hieron. [400 g, voucher RMK 9640, collected in February 1987, 60 km E of bridge at Punata (3.000)] gave three crude CC fractions [1: petrol, 2: Et_2O–petrol (1:3), 3: Et_2O and Et_2O-MeOH, (4:1)]. TLC of fraction 1 (petrol) gave 80 mg germacrene D and 20 mg humulene. TLC of fraction 2 (10%) afforded 30 mg *ent*-kaurenic acid containing *ca* 8 mg of its 9,11-dehydro derivative. The fractions obtained by flash chromatography of fraction 3 (silica gel, ϕ 30–60 μm, Et_2O–petrol (1:4)–Et_2O–MeOH (10:1)] were combined to give four crude fractions (3/1–3/4). Fraction 3/1 contained 5 mg costunolide, fraction 3/3 gave 2 g estafiatin and fraction 3/4 afforded 20 mg crystalline **16**. HPLC of fraction 3/2 [MeOH–H_2O (4:1)] gave 20 mg estafiatin (R_t 2.3 min.), 3 mg **32** (R_t 18.5 min.) and a mixture (R_t 8.7 min) which gave by TLC [Et_2O–petrol (1:2), six developments] 2 mg **34** (R_f 0.58), 4 mg **33** (R_f 0.48) and a mixture which gave by repeated TLC (eight developments) 2 mg **35** (R_f 0.55) and 2 mg **33** (R_f 0.50). The extract of roots (65 g) gave by TLC 5 mg germacrene D, 3 mg **32**, 40 mg **33** and 100 mg **36** (R_f 0.40, Et_2O–petrol, 3:1).

The extract of aerial parts of *S. sarensis* B. L. Rob. [100 g, voucher RMK 9655, collected in February 1987, 23 km E of Comarapa (1.700 m)] gave four crude CC fractions [1: petrol, 2: Et_2O–petrol (1:1), 3: Et_2O and 4: Et_2O–MeOH (4:1)]. Fraction 1 gave by TLC 10 mg germacrene D and 10 mg humulene. Fraction 2 contained 50 mg **26** and fraction 3 20 mg **28**. TLC of fraction 4 [$CHCl_3$–C_6H_6–Et_2O (2:2:1)] gave four mixtures (4/1–4/4). TLC of fraction 4/1 (Et_2O) gave 4 mg 20-desoxyeupatoriopicrin (R_f 0.65), 4 mg **27** (R_f 0.5), 1.5 mg **15** (R_f 0.35) and 1 mg **14** (R_f 0.28). HPLC of fraction 4/2 [MeOH–H_2O (7:3)] gave 2 mg eupatoriopicrin (R_t 2.6 min), 10 mg **17** (R_t 3.2 min) and 8 mg **18** (R_t 4 min). TLC of fraction 4/3 [Et_2O–MeOH (49:1)] gave 30 mg 13*Z*-labdenolic acid, 20 mg **29**, 10 mg eucannabinolide and a mixt which gave by HPLC [MeOH–H_2O (7:3)] 5 mg eupatoriopicrin 20-*O*-tiglate (R_t 3.6 min) and 2 mg **18** (R_t 4 min). Fraction 4/4 gave 200 mg eucannabinolide.

Known compounds were identified by comparing the 400 MHz ^{1}H NMR spectra with those of authentic materials.

Germacra-4E,1(10)E-*diene*-12,8β-*olide* (**1**). Colourless gum; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 232.146 [M]$^+$ (26) (calc. for $C_{15}H_{20}O_2$: 232.146), 217 (16), 190 (18), 145 (38), 121 (42), 93 (58), 67 (100), 53 (97); ^{13}C NMR ($CDCl_3$, δ-values): C-1, C-5 131.1, 128.4, 125.6, 123.8 *d*; C-2 26.7, 26.9 *t*; C-3, C-9 43.6, 40.1, 39.9, 38.5 *t*; C-4, C-10 133.4, 132.3, 130.6 *s*; C-6 24.7, 25.7 *t*; C-7 45.7, 43.3 *d*; C-8 81.1, 80.9 *d*; C-11 139.2, 137.3 *s*; C-12 170.5 *s*; C-13 120.2, 119.7 *t*; C-14, C-15 20.0, 17.3, 16.8, 15.6 *q*.

1 (5 mg) in 0.5 ml C_6D_6 were heated for 1 hr at 80°. After cooling down the ^{1}H NMR showed in addition to the spectrum of **1** the typical bands of **2** (*ca* 10%). **1** (3 mg) on standing for 48 hr in 0.5 ml $CDCl_3$ afforded 1 mg **5a** as followed from the typical ^{1}H NMR signals which became present in addition to those of **1**.

5,10-bis-epi-*Isoalantolactone* (**5a**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 232.146 [M]$^+$ (38) (calc. for $C_{15}H_{20}O_2$: 232.146), 217 (41), 204 (100), 187 (22), 171 (23), 159 (26), 145 (34), 121 (86), 93 (70), 68 (68), 76 (47); ^{1}H NMR ($CDCl_3$): δ2.0 (*m*, H-3), 2.33 (*br d*, H-3′), 1.85 (*br d*, H-5), 2.03 and 1.91 (*m*, H-6), 3.29 (*m*, H-7), 4.80 (*ddd*, H-8), 2.00 (*m*, H-9), 1.09 (*dd*, H-9′), 6.31 and 5.54 (*d*, H-13), 0.79 (*s*, H-14), 4.81 and 4.57 (*br s*, H-15) (J [Hz]: 3,3′=14; 5,6=12; 7,8=6.5; 7,13=3.5; 7,13′=3; 8,9=7; 8,9′=10.5; 9,9′=13).

3α-*Hydroxy-desoxo-achalensolide* (**6**). Colourless oil:

IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (28) (calc. for $C_{15}H_{20}O_3$: 248.141), 233 (24), 230 (40), 215 (10), 161 (38), 137 (52), 119 (100), 110 (58), 91 (55); $[\alpha]_D^{24°}$ +167 ($CHCl_3$; *c* 0.65).

3α-*Methoxy-desoxo-achalensolide* (**7**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 262.157 $[M]^+$ (48) (calc. for $C_{16}H_{22}O_3$: 262.157), 247 (100), 230 (18), 151 (76), 137 (42), 124 (64), 119 (63), 91 (48).

3β-*Hydroxy-desoxo-achalensolide* (**8**). Colourless crystals, mp 128 −129° (Et_2O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (20) (calc. for $C_{15}H_{20}O_3$: 248.141), 230 (54), 149 (41), 119 (52), 95 (48), 55 (100); $[\alpha]_D^{24°}$ +116 ($CHCl_3$; *c* 0.50).

3β-*Methoxy-desoxo-achalensolide* (**9**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 262.156 $[M]^+$ (13) (calc. for $C_{16}H_{22}O_3$: 262.157), 247 (17), 230 (14), 137 (100), 123 (48).

3β-*Acetoxy-desoxo-achalensolide* (**10**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone), 1735, 1240 (OAc); MS *m/z* (rel. int.): 290.151 $[M]^+$ (2) (calc. for $C_{17}H_{22}O_4$: 290.152), 248 (100), 230 (28), 203 (63), 145 (84), 119 (79), 105 (67), 91 (68); $[\alpha]_D^{24°}$ +139 ($CHCl_3$; *c* 2.20).

3-*Desoxo-achalensolide* (**11**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1770 (γ-lactone); MS *m/z* (rel. int.): 232.146 $[M]^+$ (68) (calc. for $C_{15}H_{20}O_2$: 232.146), 217 (26), 204 (23), 175 (31), 145 (60), 121 (85), 95 (100), 91 (76), 79 (80); $[\alpha]_D^{24°}$ +162 ($CHCl_3$; *c* 1.55).

3β-*Hydroxy*-11β,13-*dihydro-desoxo-achalensolide* (**12**). Colourless crystals, mp 116° (Et_2O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3630 (OH), 1760 (γ-lactone); MS *m/z* (rel. int.): 250.157 $[M]^+$ (48) (calc. for $C_{15}H_{22}O_3$: 250.156), 232 (82), 217 (5), 177 (39), 159 (48), 122 (56), 119 (100), 96 (57).

To 20 mg **14** in 3 ml MeOH 10 mg $NaBH_4$ were added. After 5 min heating at 70° acid hydrolysis afforded 12 mg **12**, identical with the natural product (mp and ^1H NMR).

11β,13-*Dihydro-desoxo-achalensolide* (**13**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775 (γ-lactone); MS *m/z* (rel. int.): 234.162 $[M]^+$ (100) (calc. for $C_{15}H_{22}O_2$: 234.162), 219 (21), 133 (89), 119 (86), 95 (75), 94 (86).

2-*Oxo-desoxyligustrin* (**16**). Colourless crystals, mp 185°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (γ-lactone), 1690, 1615 (C=CC=O); MS *m/z* (rel. int.): 244.110 $[M]^+$ (100) (calc. for $C_{15}H_{16}O_3$: 244.110), 229 (12), 215 (10), 187 (10), 149 (34), 91 (62); $[\alpha]_D^{24°}$ +250 ($CHCl_3$; *c* 0.62).

11β,13-*Dihydro-desoxo-virginolide* (**19**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone); MS *m/z* (rel. int.): 232.146 $[M]^+$ (61) (calc. for $C_{15}H_{20}O_2$: 232.146), 217 (10), 177 (29), 159 (46), 119 (100), 105 (52), 91 (60).

15-*Hydroxy*-11β,13-*dihydroziniolide* (**20**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1780 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (12) (calc. for $C_{15}H_{20}O_3$: 248.141), 230 (64), 220 (10), 215 (7), 202 (21), 157 (100), 156 (78), 117 (72), 105 (76), 91 (95).

15-*Acetoxy*-11β,13-*dihydroziniolide* (**21**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1775 (γ-lactone), 1740 (OAc); MS *m/z* (rel. int.): 290.152 $[M]^+$ (8) (calc. for $C_{17}H_{22}O_4$: 290.152), 230 (72), 202 (26), 157 (100), 156 (72), 117 (50), 91 (63); $[\alpha]_D$ +125 ($CHCl_3$; *c* 3.6).

Stevisamolide (**22**). Yellow crystals, mp 96–97° (Et_2O–petrol); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1780 (γ-lactone), 1640 (C=C); UV $\lambda_{max}^{Et_2O}$: 370, 262 nm; MS *m/z* (rel. int.): 230.131 $[M]^+$ (66) (calc. for $C_{15}H_{18}O_2$: 230.131), 185 (11), 157 (25), 132 (86), 117 (100), 91 (48); ^{13}C NMR ($CDCl_3$, C-1–C-15): 126.2 *s*, 133.8 *d*, 119.2 *d*, 137.1 *s*, 143.7 *s*, 27.2 *t*, 43.5 *d*, 79.5 *d*, 36.8 *t*, 144.5 *s*, 39.0 *d*, 179.1 *s*, 14.7 *q*, 24.6 *q*, 12.7 *q* (^1H, ^{13}C correlated); $[\alpha]_D^{24°}$ −279 ($CHCl_3$; *c* 0.71).

5α-*Hydroxy*-3,4-*dehydro*-4,5-*dihydro-achalensolide* (**23**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1770 (γ-lactone); MS *m/z* (rel. int.): 248.141 $[M]^+$ (18) (calc. for $C_{15}H_{20}O_3$: 248.141), 230 (11), 215 (4), 119 (22), 96 $[C_6H_8O]^+$ (100).

2β,15-*Dihydroxylabd-7-ene* (**30**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH); MS *m/z* (rel. int.): 308.271 $[M]^+$ (42) (calc. for $C_{20}H_{36}O_2$: 308.271), 290 (32), 275 (34), 232 (32), 230 (42), 207 (60), 159 (51), 119 (83), 95 (84), 93 (81), (100). Acetylation (Ac_2O, 1 hr, 70°) gave the diacetate **30a**, colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1250 (OAc); MS *m/z* (rel. int.): 392.293 $[M]^+$ (1) (calc. for $C_{24}H_{40}O_4$: 392.293), 332 (41), 317 (12), 289 (7), 189 (56), 135 (42), 121 (100), 107 (69), 81 (58); $[\alpha]_D^{24°}$ −12 ($CHCl_3$; *c* 0.66).

3-*Oxo-labd-7-en*-15-*ol* (**31**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 1710 (C=O); MS *m/z* (rel. int.): 306.256 $[M]^+$ (16) (calc. for $C_{20}H_{34}O_2$: 306.256), 291 (12), 205 (41), 119 (76), 81 (100); CD (MeCN): $\Delta\varepsilon_{292}$ −0.4.

13-*Acetoxy*-7β,9-*diangeloyloxy*-3β*H*-*longipinan*-1-*one* (**33**). Colourless crystals, mp 145° (petrol); IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745 (OAc), 1720 (C=CCO_2R, C=O); MS *m/z* (rel. int.): 375.217 [M −OCOR]$^+$ (0.5) (calc. for $C_{22}H_{31}O_5$: 375.217), 315 (7), 215 (6), 83 (100); $[\alpha]_D^{24°}$ −31 ($CHCl_3$; *c* 0.39).

9α-*Acetoxy*-7β,13-*diangeloyloxy*-3β*H*-*longipinan*-1-*one* (**34**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (OAc), 1715 (C=CCO_2R, C=O); MS *m/z* (rel. int.): 414.241 $[M-HOAc]^+$ (0.5) (calc. for $C_{25}H_{34}O_5$: 414.241), 315 (3), 215 (3), 83 (100).

13-*Acetoxy*-7β-*angeloyloxy*-3β*H*-*longipinan*-1-*one* (**35**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745 (OAc), 1715 (C=CCO_2R, C=O); MS *m/z* (rel. int.): 376.225 $[M]^+$ (3) (calc. for $C_{22}H_{32}O_5$: 376.225), 316 (1), 277 (3.5), 276 (4), 234 (3.5), 216 (6), 83 (100).

7β,9α-*Diangeloyloxy*-13-*hydroxy*-3β*H*-*longipinan*-1-*one* (**36**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3610 (OH), 1710 (C=CCO_2R, C=O); MS *m/z* (rel. int.): 432.250 $[M]^+$ (0.1) (calc. for $C_{25}H_{36}O_6$: 432.251), 333 (8), 233 (46), 202 (45), 187 (11), 83 (100); $[\alpha]_D^{24°}$ −21 ($CHCl_3$; *c* 0.92).

Acknowledgement—We thank the Fonds der Chemischen Industrie for financial support.

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