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PREPARATION AND CHARACTERIZATION OF NATURALLY OCCURRING LONGIPINENE ESTERS

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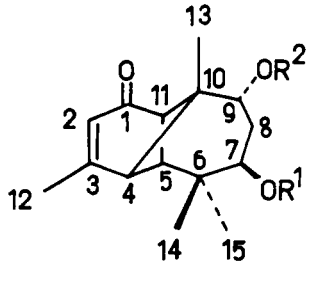
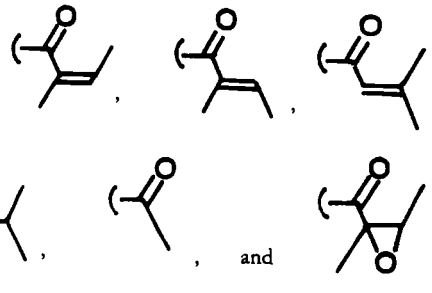
ABSTRACT.—Development of methodology for the introduction of angeloyl, tigloyl, senecioyl, methacryl, and acetyl groups at specific hydroxyl groups of longipin-2-ene-7β,9α-diol-1-one [**36**] allows the preparation of a systematic series of esters, which includes the 25 possible combinations of diesters and the 10 monoesters at C-7 or C-9. The full assignment of their ^{1}H- and ^{13}C-nmr spectra using two-dimensional chemical shift correlation diagrams, ^{1}H-coupled ^{13}C spectra, and selective ^{13}C-^{1}H decoupled spectra, as well as their mp, ir, uv, and optical activity, provide the data to characterize many constituents of the genus *Stevia* which are reported as oils or even in mixtures.

Longipin-2-ene-7β,9α-diol-1-one esters, represented in Figure 1, constitute an important group of naturally occurring substances widely distributed in the genus *Stevia* (1–9). Many of these compounds have been described as oils or only detected in mixtures (1–3). In recent years, we established the stereochemistry (10), absolute configuration (11), and conformation (11) of these structurally complex sesquiterpenes, but a full characterization of such molecules is still needed. Therefore in the present paper we describe the preparation, starting from longipin-2-ene-7β,9α-diol-1-one [**36**], of a systematic series of esters, whose acyl groups are angeloyl, tigloyl, senecioyl, methacryl, and acetyl (Table 1). The products were characterized by the complete assignment of their ^{1}H- and ^{13}C-nmr spectra, as well as by mp, ir, uv, and optical activity.



R^1 and R^2 can be the acyl groups:



and

(see references 1–10)

FIGURE 1. Longipin-2-ene-7β,9α-diol-1-one esters.

RESULTS AND DISCUSSION

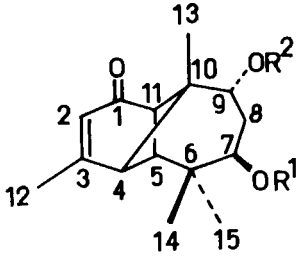
The preparation of the longipinene esters listed in Table 1 required the development of a methodology that allows the introduction of each ester residue at the desired position. For this purpose, we took advantage of the previously noticed difference (11) between the chemical reactivity of both hydroxyl groups of **36** as a consequence of their different orientation (7-eq vs. 9-ax). Thus, esterification of **36** (10) with ca. 1.8 mol equiv of the five acyl chlorides: AngCl (12), TiglCl (13), SenCl, MeacrCl, and AcCl gave, in each case, the diester and the C-7 monoester as the main products and the C-9 monoester in small amounts. In all cases, the reaction products could easily be separated by chromatography, affording the diesters **1** (9), **8**, **15**, **22**, and **29** (10), the C-7 monoesters **6**, **12**, **18**, **24**, and **30**, and the C-9 monoesters **31**, **32**, **33** (9), **34**, and **35**. The mixed diesters having a tiglate, seneciate, methacrylate, or acetate group at C-7 were prepared by esterification of the corresponding monoesters **12**, **18**, **24**, and **30** with the desired acyl chlorides. This procedure provided sixteen diesters **7**, **9–11**, **13**, **14**, **16**, **17**, **19–21**, **23**, and **25–28**. In order to avoid isomerization of angelate residues, a route involving protection of the C-7 hydroxyl group of **36** with *p*-nitrobenzoyl chloride allowed the preparation of the mixed diesters having the angelate group at C-7: **2**, **4**, and **5**. Compound **3** was prepared previously (9). Treatment of the *p*-nitrobenzoate **37** (9) with the acyl chlorides AngCl, TiglCl, MeacrCl, and AcCl, followed by selective hydrolysis of the *p*-nitrobenzoate group, afforded the C-9 monoesters **31**, **32**, **34**, and **35**. Compounds **32**, **34**, and **35** were treated with angeloyl chloride (12) to yield **2**, **4**, and **5**, respectively. Although the preparation of these diesters could be attempted directly from the 7-monoangelate **6**, we preferred to avoid a second esterification step in the presence of an already existing angeloyl group. Furthermore, the route involving the *p*-nitrobenzoate protective group afforded better yields of the C-9 monoesters **31**, **32**, **33** (9), **34**, and **35** than the direct esterification procedure.

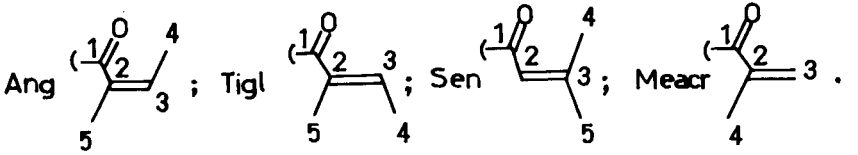
In general, the introduction of angeloyl groups was achieved by treating the corresponding starting materials (Table 1) with angeloyl chloride (12) in CCl_4, CH_2Cl_2, or MeCN at room temperature. While tiglates, seneciates, and acetates were prepared using the corresponding acyl halides (13) essentially under the above reaction conditions, methacrylates were obtained using methacryl chloride in CH_2Cl_2, and in the presence of 4-(*N*,*N*-dimethylamino)-pyridine, triethylamine, and phenothiazine. The use of phenothiazine significantly improved the reaction yields by avoiding polymerization of methacrylate residues.

The structures of the esters were confirmed by ^{1}H- and ^{13}C-nmr measurements; the data are summarized in Tables 2 and 3, respectively. Some assignments of the sesquiterpene moiety (4,10) and of the ester residues (14–17) follow from literature data. However, other signals required further detailed nmr measurements; therefore, the two-dimensional chemical shift correlation diagrams of **6**, **24**, **29**, and **33**, the ^{1}H-coupled ^{13}C spectra of **1**, **29**, **30**, and **35**, and selective ^{13}C-^{1}H decoupled spectra of **1** and **29** were obtained.

The assignment of the proton signals of the H-13 to H-15 methyl groups of the diesters followed (4) from nOe effects. The assignment for **1** is shown in Figure 2a, and therefore, a ^{13}C-^{1}H heteronuclear chemical shift correlation diagram of any diester allows assignment of the signals of these groups in the ^{13}C domain, as exemplified for **29** (Figure 2b). These ^{13}C-nmr assignments were extensive by analogy to all the series including C-7 and C-9 monoesters as shown in Table 3. In contrast, assignments of the ^{1}H-nmr signals of these methyl groups (H-13 to H-15) in the monoesters cannot be made by comparison with those of the diesters, due to a remarkable difference in chemical shifts (Table 2). However, they again follow from the two-dimensional chemical shift correlation diagrams of the C-7 monoester **6** and of the C-9 monoester **33**, as

TABLE 1. Structure, Preparation, Purification, Yield, and mp of Compounds **1**–**37**.





Compound	R^1	R^2	Starting material	Solvent	Acyl chloride	Catalysts	Reaction time (h)	Chromatographic solvent	Yield (%)	mp (°)
1[a–k]	Ang	Ang	**36** (1 g)	MeCN (75 ml)	AngCl (900 mg)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	31[l]	115–117 (prisms)
2[a,j,m]	Ang	Tigl	**32** (400 mg)	CCl_4 (10 ml)	AngCl (500 mg)	none	24	CH_2Cl_2	64	131–134 (needles)
3[a,f,j,k]	Ang	Sen	**33** (410 mg)	CCl_4 (10 ml)	AngCl (600 mg)	none	24	CH_2Cl_2	65	159–161 (needles)
4[a,c,f,j]	Ang	Meacr	**34**[n] (380 mg)	CH_2Cl_2-CCl_4 (2:1) (15 ml)	AngCl (500 mg)	none	24	CH_2Cl_2	69	141–142° (prisms)
5[f,p]	Ang	Ac	**35** (410 mg)	CCl_4 (10 ml)	AngCl (500 mg)	none	24	CH_2Cl_2	75	125–126 (prisms)
6[j,q]	Ang	H	**36** (1 g)	MeCN (100 ml)	AngCl (900 mg)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	25[r]	151–153 (prisms)
7[a,j,m]	Tigl	Ang	**12** (300 mg)	CCl_4 10 (ml)	AngCl (300 mg)	none	24	CH_2Cl_2	75	95–97 (needles)
8[a,j]	Tigl	Tigl	**36** (3 g)	MeCN (150 ml)	TiglCl (2.2 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	32[l]	110–112 (prisms)
9[a,j]	Tigl	Sen	**12** (250 mg)	CH_2Cl_2 (10 ml)	SenCl (250 mg)	none	10	CH_2Cl_2	64	138–139 (prisms)

TABLE 1. Continued

Compound	R^1	R^2	Starting material	Solvent	Acyl chloride	Catalysts	Reaction time (h)	Chromatographic solvent	Yield (%)	mp (°)
10[a,j,s]	Tigl	Meacr	**12** (400 mg)	CH_2Cl_2 (10 ml)	MeacrCl[r] (300 mg)	DMAP[u] (40 mg) Et_3N (0.5 ml)	24	CH_2Cl_2	62	140–142° (needles)
11	Tigl	Ac	**12** (200 mg)	CH_2Cl_2 (10 ml)	AcCl (300 mg)	none	24	CH_2Cl_2	87	121–123 (prisms)
12	Tigl	H	**36** (3 g)	MeCN (150 ml)	Tigl Cl (2.2 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	25[r]	131–132 (needles)
13	Sen	Ang	**18** (300 mg)	CCl_4 (10 ml)	AngCl (300 mg)	none	24	CH_2Cl_2	65	125–127 (needles)
14	Sen	Tigl	**18** (250 mg)	CCl_4 (10 ml)	TiglCl (300 mg)	none	24	CH_2Cl_2	68	122–124 (prisms)
15[a,j]	Sen	Sen	**36** (3 g)	MeCN (150 ml)	SenCl (2.2 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	43[l]	140–142 (prisms)
16	Sen	Meacr	**18** (350 mg)	CH_2Cl_2 (10 ml)	MeacrCl[r] (300 mg)	DMAP[u] (40 mg) Et_3N (0.5 ml)	24	CH_2Cl_2	60	140–142° (prisms)
17	Sen	Ac	**18** (300 mg)	CH_2Cl_2 (15 ml)	AcCl (500 mg)	none	24	CH_2Cl_2	77	138–140 (prisms)
18	Sen	H	**36** (3 g)	MeCN (100 ml)	SenCl (2.2 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	36[r]	137–138 (needles)
19[a–c,f,j]	Meacr	Ang	**24**[n] (400 mg)	CH_2Cl_2-CCl_4 (2:1) (15 ml)	AngCl (400 mg)	none	20	CH_2Cl_2	62	91–93° (needles)
20[a,j]	Meacr	Tigl	**24**[n] (300 mg)	CH_2Cl_2 (10 ml)	TiglCl (300 mg)	none	24	CH_2Cl_2	57	93–95° (prisms)
21[a,j]	Meacr	Sen	**24**[n] (300 mg)	CH_2Cl_2 (10 ml)	SenCl (300 mg)	none	24	CH_2Cl_2	60	126–128° (prisms)
22[a,f,j]	Meacr	Meacr	**36** (3 g)	MeCN (150 ml)	MeacrCl[r] (2.25 g)	DMAP[u] (600 mg) Et_3N (8 ml)	24	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	21[l]	93–95° (prisms)
23	Meacr	Ac	**24**[n] (300 mg)	CH_2Cl_2 (10 ml)	AcCl (500 mg)	none	24	CH_2Cl_2	60	120–123° (prisms)

TABLE 1. Continued

Compound	R^1	R^2	Starting material	Solvent	Acyl chloride	Catalysts	Reaction time (h)	Chromatographic solvent	Yield (%)	mp (°)
24	Meacr	H	**36** (3 g)	MeCN (150 ml)	MeacrCl[t] (2.25 g)	DMAP[u] (600 mg) Et_3N (8 ml)	24	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	17[r]	130–132° (prisms)
25	Ac	Ang	**30** (200 mg)	CCl_4 (15 ml)	AngCl (250 mg)	none	24	CH_2Cl_2	72	125–127 (prisms)
26	Ac	Tigl	**30** (250 mg)	CCl_4 (15 ml)	TiglCl (400 mg)	none	24	CH_2Cl_2	67	138–140 (prisms)
27	Ac	Sen	**30** (230 mg)	CCl_4 (15 ml)	SenCl (300 mg)	none	24	CH_2Cl_2	58	141–143 (powder)
28	Ac	Meacr	**30** (400 mg)	CH_2Cl_2 (10 ml)	MeacrCl[t] (300 mg)	DMAP[u] (40 mg) Et_3N (0.5 ml)	24	CH_2Cl_2	52	120–122° (needles)
29[v]	Ac	Ac	**36** (3 g)	MeCN (150 ml)	AcCl (1.7 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	37[l]	136–138 (needles)
30	Ac	H	**36** (3 g)	MeCN (150 ml)	AcCl (1.7 g)	none	48	1. CH_2Cl_2 2. $CHCl_3$-EtOH (99:1)	29[r]	106–108 (prisms)
31[a–c,j,q]	H	Ang	**37** (400 mg)	(1) CH_2Cl_2-CCl_4 (2:1) (15 ml)	AngCl (400 mg)	none	24	—		
				(2) CH_2Cl_2-MeOH (1:5) (120 ml)	—	KOH[w] (670 mg)	0.5	CH_2Cl_2	75	117–120 (needles)
32	H	Tigl	**37** (800 mg)	(1) CH_2Cl_2 (20 ml)	TiglCl (1 g)	none	0.5	—		
				(2) CH_2Cl_2-MeOH (1:5) (120 ml)	—	KOH[x] (1.34 g)	0.5	CH_2Cl_2	60	115–117 (prisms)
33[a,j,k]	H	Sen	**37** (800 mg)	(1) CH_2Cl_2 (20 ml)	SenCl (1 g)	none	0.5	—		
				(2) CH_2Cl_2-MeOH (1:5) (120 ml)	—	KOH[x] (1.34 g)	0.5	CH_2Cl_2	62	146–148 (needles)
34	H	Meacr	**37** (900 mg)	(1) CH_2Cl_2 (20 ml)	MeacrCl[t] (700 mg)	DMAP[u] (100 mg) Et_3N (1.2 ml)	10	—		
				(2) CH_2Cl_2-MeOH (1:5) (120 ml)	—	KOH[n,x] (1.34 g)	0.5	CH_2Cl_2	45	155–156° (prisms)

TABLE 1. Continued

Compound	R^1	R^2	Starting material	Solvent	Acyl chloride	Catalysts	Reaction time (h)	Chromatographic solvent	Yield (%)	mp (°)
35	H	Ac	**37** (800 mg)	(1) none	AcCl (4 g)	none	0.2[y]	—	—	—
				(2) MeOH (50 ml)	—	KOH[w] (670 mg)	0.1	CH_2Cl_2	70	132–134 (prisms)
36[v]	H	H	—	—	—	—	—	—	—	183–184 (powder)
37[k]	*p*-NO_2Bz	H	—	—	—	—	—	—	—	195–196 (powder)

[a]Natural product from *Stevia polycephala* (2).
[b]From *Stevia mandonii* (3).
[c]From *Stevia boliviensis* (3).
[d]From *Stevia berlandieri* (4).
[e]From *Stevia lemmonia* (4).
[f]From *Stevia salicifolia* (4).
[g]From *Stevia mercedensis* (5).
[h]From *Stevia potrerensis* (6).
[i]From *Stevia aristata* (7).
[j]The stereostructure reported in references prior to 1982 was reassigned in Román *et al.* (10) and in Bohlmann *et al.* (18).
[k]Its preparation is reported in Román *et al.* (9).
[l]The monoesters at C-7 and C-9 are also obtained.
[m]From *Stevia jaliscensis* (1).
[n]Phenothiazine (2 mg) was added to the reaction mixture.
[o]Before recrystallizations, phenothiazine (ca. 0.5 mg) was added.
[p]From *Stevia lucida* (8).
[q]From the partial hydrolysis of the ester mixture from *S. jaliscensis* (1).
[r]The diester and the monoester at C-9 are also obtained.
[s]From *Stevia serrata* (2).
[t]Freshly distilled and stabilized with phenothiazine (500 ppm).
[u]DMAP = 4-(*N*,*N*-dimethylamino)-pyridine.
[v]Its preparation is also reported in Román *et al.* (10).
[w]In H_2O (2 ml).
[x]In H_2O (3 ml).
[y]Under reflux.

TABLE 2. ^{1}H-nmr Data of Compounds **1–36** (300 MHz).[a]

Proton	Compound											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
H-2 (qdd)	5.81	5.81	5.80	5.81	5.81	5.79	5.81	5.81	5.81	5.81	5.81	5.79
H-4 (dd)	2.67	2.66	2.66	2.68	2.64	2.57	2.68	2.66	2.66	2.67	2.64	2.57
H-5 (s)	2.34	2.34	2.32	2.35	2.32	2.29	2.33	2.34	2.32	2.34	2.32	2.28
H-7 (dd)	5.11	5.16	5.12	5.14	5.05	5.10	5.08	5.10	5.08	5.09	5.01	5.06
H-8α (ddd)	2.11	2.05	2.08	2.07	2.13[b]	2.00	2.08	2.04	2.06	2.06	2.07[b]	1.98
H-8β (ddd)	2.24	2.24	2.23	2.25	2.17[b]	2.27	2.23	2.22	2.21	2.23	2.15	2.26
H-9 (dd)	5.13	5.11	5.06	5.12	4.99	3.88[c]	5.13	5.11	5.07	5.12	4.99	3.87[c]
H-11 (dd)	3.17	3.20	3.18	3.18	3.18	3.13	3.15	3.18	3.17	3.17	3.17	3.12
Me-12 (d)	2.06	2.06	2.06	2.07	2.06	2.03	2.07	2.06	2.06	2.06	2.06	2.04
Me-13 (s)	1.02	1.00	0.99	1.01	1.00	1.12	1.01	0.99	0.98	1.01	1.00	1.12
Me-14 (s)	1.08	1.07	1.07	1.08	1.07	1.07	1.09	1.08	1.08	1.09	1.08	1.08
Me-15 (s)	0.93	0.93	0.92	0.93	0.93	0.93	0.91	0.92	0.91	0.92	0.91	0.91
R^1=	Ang	Ang	Ang	Ang	Ang	Ang	Tigl	Tigl	Tigl	Tigl	Tigl	Tigl
H-3 *cis*[d]	—	—	—	—	—	—	6.81	6.81	6.81	6.81	6.82	6.86
H-3 *trans*[d]	6.03	6.02	6.02	6.03	6.05	6.10	—	—	—	—	—	—
H-4	1.95	1.95	1.96	1.95	1.97	2.02	1.78	1.78	1.78	1.78	1.79	1.81
H-5	1.87	1.87	1.87	1.87	1.88	1.90	1.81	1.81	1.82	1.80	1.82	1.84
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
H-2	—	—	5.82	—	2.18	—	—	—	5.81	—	2.18	—
H-3 *cis*[d]	—	6.86	—	6.22	—	—	—	6.95	—	6.22	—	—
H-3 *trans*[d]	6.11	—	—	5.63	—	—	6.13	—	—	5.63	—	—
H-4	2.03	1.83	2.19	2.03	—	—	2.03	1.83	2.18	2.02	—	—
H-5	2.01[b]	1.91	1.93	—	—	—	2.01	1.90	1.92	—	—	—
HO	—	—	—	—	—	1.96	—	—	—	—	—	1.65

TABLE 2. Continued

Proton	Compound											
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
H-2 (qdd)	5.80	5.80	5.79	5.81	5.80	5.78	5.81	5.82	5.81	5.82	5.81	5.79
H-4 (dd)	2.66	2.66	2.65	2.66	2.64	2.58	2.68	2.68	2.68	2.67	2.64	2.58
H-5 (s)	2.32	2.33	2.31	2.33	2.31	2.27	2.34	2.35	2.33	2.34	2.32	2.28
H-7 (dd)	5.07	5.12	5.08	5.09	5.01	5.08	5.08	5.11	5.09	5.09	5.01	5.10
H-8α (ddd)	2.07	2.00	2.04	2.03	2.04	1.96	2.09	2.06	2.08	2.07	2.09[b]	1.99
H-8β (ddd)	2.21	2.22	2.19	2.22	2.14	2.25	2.25	2.25	2.24	2.24	2.16[b]	2.28
H-9 (dd)	5.12	5.11	5.05	5.11	4.98	3.87[c]	5.14	5.13	5.08	5.12	4.99	3.88[c]
H-11 (dd)	3.15	3.19	3.17	3.17	3.17	3.13	3.15	3.19	3.17	3.17	3.17	3.13
Me-12 (d)	2.06	2.06	2.05	2.06	2.05	2.03	2.07	2.07	2.07	2.07	2.06	2.04
Me-13 (s)	1.01	0.99	0.98	1.00	1.00	1.12	1.01	1.00	0.99	1.01	1.00	1.12
Me-14 (s)	1.05	1.05	1.04	1.05	1.04	1.04	1.09	1.09	1.09	1.09	1.08	1.07
Me-15 (s)	0.90	0.91	0.90	0.91	0.90	0.89	0.92	0.93	0.92	0.93	0.92	0.92
R^1=	Sen	Sen	Sen	Sen	Sen	Sen	Meacr	Meacr	Meacr	Meacr	Meacr	Meacr
H-2	5.64	5.64	5.64	5.64	5.64	5.68	—	—	—	—	—	—
H-3 *cis*[d]	—	—	—	—	—	—	6.07	6.07	6.07	6.07	6.07	6.11
H-3 *trans*[d]	—	—	—	—	—	—	5.54	5.55	5.55	5.55	5.56	5.58
H-4	2.13	2.13	2.14	2.13	2.15	2.18	1.93	1.93	1.93	1.93	1.93	1.96
H-5	1.88	1.88	1.88	1.88	1.89	1.91	——	—	—	—	—	—
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
H-2	—	—	5.81	—	2.17	—	—	—	5.81	—	2.18	—
H-3 *cis*[d]	—	6.95	—	6.21	—	—	—	6.96	—	6.22	—	—
H-3 *trans*[d]	6.11	—	—	5.62	—	—	6.14	—	—	5.64	—	—
H-4	2.02[b]	1.83	2.18	2.02	—	—	2.04	1.84	2.19	2.03	—	—
H-5	2.01[b]	1.90	1.92	—	—	—	2.01	1.91	1.93	—	—	—
HO	—	—	—	—	—	2.34	—	—	—	—	—	2.14

TABLE 2. Continued

Proton	Compound											
	25	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
H-2 (qdd)	5.81	5.80	5.79	5.81	5.80	5.79	5.79	5.79	5.79	5.80	5.79	5.78
H-4 (dd)	2.66	2.67	2.64	2.65	2.63	2.56	2.64	2.63	2.62	2.63	2.61	2.56
H-5 (s)	2.32	2.32	2.30	2.33	2.30	2.26	2.33	2.33	2.31	2.33	2.31	2.28
H-7 (dd)	5.02	5.05	5.02	5.03	4.96	5.04	3.83	3.83	3.84	3.83	3.82	3.93
H-8α (ddd)	2.05	2.01	2.04	2.03	2.04	1.92	2.01	2.00	1.97	2.01	1.97	1.91
H-8β (ddd)	2.21	2.20	2.18	2.20	2.14	2.25	2.27	2.25	2.24	2.27	2.23	2.26
H-9 (dd)	5.11	5.09	5.04	5.09	4.96	3.86	5.16	5.10	5.07	5.11	5.05	3.86
H-11 (dd)	3.13	3.17	3.15	3.15	3.15	3.10	3.05	3.09	3.08	3.08	3.07	3.03
Me-12 (d)	2.06	2.06	2.05	2.06	2.05	2.03	2.05	2.05	2.05	2.05	2.05	2.03
Me-13 (s)	1.01	0.99	0.98	1.00	0.99	1.11	0.98	0.97	0.96	0.98	0.96	1.10
Me-14 (s)	1.04	1.04	1.03	1.04	1.03	1.02	0.97	0.97	0.96	0.97	0.96	0.95
Me-15 (s)	0.90	0.91	0.90	0.91	0.90	0.89	1.01	1.02	1.00	1.01	1.00	0.99
R^1=	Ac	Ac	Ac	Ac	Ac	Ac	H	H	H	H	H	H
H-2	2.03	2.02	2.03	2.03	2.04	2.07	—	—	—	—	—	—
HO	—	—	—	—	—	—	1.59	1.51	1.67	1.43	1.64	1.65
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
H-2	—	—	5.79	—	2.15	—	—	—	5.72	—	2.10	—
H-3 *cis*[d]	—	6.94	—	6.21	—	—	—	6.89	—	6.14	—	—
H-3 *trans*[d]	6.13	—	—	5.63	—	—	6.12	—	—	5.61	—	—
H-4	2.03	1.82	2.18	2.01	—	—	2.01	1.81	2.18	1.96	—	—
H-5	1.99	1.89	1.92	—	—	—	1.92	1.85	1.92	—	—	—
HO	—	—	—	—	—	1.72	—	—	—	—	—	1.65

[a] $J_{2,4}=1.5, J_{2,11}=1.5, J_{2,12}=1.5, J_{4,11}=7.0, J_{7,8\alpha}=2.0, J_{7,8\beta}=11.5, J_{8\alpha,8\beta}=15.0, J_{8\alpha,9}=4.0, J_{8\beta,9}=3.0$; Ang $J_{3,4}=7.5, J_{3,5}=1.5, J_{4,5}=1.5$; Tigl $J_{3,4}=7.0, J_{3,5}=1.5, J_{4,5}=1.0$; Sen $J_{2,4}=1.0, J_{2,5}=1.0$; Meacr $J_{3(cis),3(trans)}=1.5, J_{3(cis),4}=1.0, J_{3(trans),4}=1.5$. δ in ppm from internal TMS. Acyl hydrogen numbering is as shown in Table 1.

[b] Complex signal.

[c] Quartet ($J_{9,OH}=3.5$).

[d] With respect to the carbonyl group.

TABLE 3. ^{13}C-nmr Data of Compounds **1–36** (75.4 MHz).[a]

Carbon	Compound											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
C-1	202.93	202.97	203.11	202.77	203.14	203.60	202.97	203.14	203.28	202.95	203.08	203.81
C-2	122.79	122.76	122.77	122.68	122.82	122.83	122.81	122.81	122.81	122.82	122.80	122.74
C-3	170.35	170.38	170.44	170.29	170.37	170.64	170.34	170.40	170.46	170.28	170.35	170.85
C-4	48.41	48.50	48.44	48.47	48.45	48.88	48.42	48.53	48.47	48.50	48.45	48.83
C-5	65.86	65.93	65.87	65.86	65.83	66.10	65.88	65.99	65.92	65.92	65.82	66.08
C-6	37.37	37.43	37.43	37.36	37.29	37.39	37.57	37.63	37.63	37.57	37.46	37.55
C-7	72.25	72.15	72.30	72.12	72.28	72.52	72.47	72.41	72.54	72.35	72.49	72.72
C-8	32.40	32.67	32.51	32.51	32.10	35.72	32.33	32.55	32.42	32.42	31.96	35.61
C-9	74.71	74.75	73.92	75.19	75.16	73.38	74.61	74.76	73.83	75.12	75.13	73.20
C-10	55.86	56.02	55.95	55.86	55.61	57.29	55.91	56.12	56.05	55.96	55.61	57.34
C-11	54.06	53.90	53.85	53.84	53.72	52.96	54.08	53.91	53.87	53.84	53.72	52.93
C-12	23.35	23.32	23.34	23.31	23.37	23.34	23.36	23.35	23.38	23.34	23.34	23.36
C-13	21.36	21.27	21.29	21.26	21.35	21.76	21.37	21.30	21.31	21.30	21.34	21.76
C-14	19.14	19.16	19.23	19.11	19.06	19.19	19.01	19.05	19.11	18.99	18.90	19.06
C-15	26.21	26.23	26.23	26.17	26.14	26.25	26.23	26.26	26.27	26.21	26.15	26.23
R^1=	Ang	Ang	Ang	Ang	Ang	Ang	Tigl	Tigl	Tigl	Tigl	Tigl	Tigl
C-1	166.83	166.83	166.91	166.83	167.08	167.53	166.95	166.99	167.05	167.00	167.15	167.61
C-2	127.98	128.02	128.03	127.98	127.98	128.01	128.85	128.88	128.88	128.84	128.86	128.91
C-3	137.75	137.58	137.64	137.68	137.91	138.36	137.03	137.04	137.03	137.10	137.09	137.25
C-4	15.73	15.70	15.72	15.72	15.77	15.82	14.31	14.31	14.34	14.31	14.32	14.40
C-5	20.63	20.61	20.64	20.61	20.62	20.64	12.08	12.09	12.10	12.08	12.05	12.03
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
C-1	167.28	167.45	166.02	166.79	170.91	—	167.18	167.48	166.07	166.84	170.74	—
C-2	128.11	128.57	116.02	136.28	21.13	—	128.01	128.55	116.00	136.22	21.11	—
C-3	138.29	137.90	157.25	126.02	—	—	138.66	138.07	157.50	126.25	—	—
C-4	15.82	14.45	20.34	18.33	—	—	15.86	14.51	20.41	18.38	—	—
C-5	20.63	12.13	27.47	—	—	—	20.67	12.17	27.56	—	—	—

TABLE 3. Continued

Carbon	Compound											
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
C-1	202.90	203.11	203.28	202.96	203.06	203.86	202.80	203.00	203.19	202.84	203.05	203.69
C-2	122.74	122.77	122.82	122.76	122.76	122.66	122.75	122.78	122.80	122.79	122.78	122.77
C-3	170.41	170.44	170.46	170.37	170.39	171.00	170.34	170.37	170.37	170.28	170.39	170.77
C-4	48.37	48.52	48.51	48.46	48.45	48.82	48.36	48.49	48.49	48.44	48.40	48.85
C-5	65.90	66.03	66.03	65.96	65.89	66.18	65.74	65.87	65.84	65.78	65.70	66.02
C-6	37.28	37.38	37.43	37.30	37.20	37.32	37.50	37.58	37.61	37.51	37.40	37.54
C-7	71.37	71.30	71.48	71.25	71.41	71.63	72.89	72.83	72.99	72.76	72.90	73.17
C-8	32.42	32.73	32.62	32.55	32.14	35.79	32.23	32.45	32.36	32.32	31.85	35.58
C-9	74.74	74.80	73.99	75.23	75.22	73.13	74.53	74.64	73.82	75.04	75.04	73.19
C-10	55.81	56.05	56.03	55.90	55.56	57.36	55.85	56.07	56.00	55.92	55.60	57.33
C-11	54.03	53.90	53.89	53.82	53.71	52.92	54.03	53.87	53.87	53.79	53.66	52.92
C-12	23.32	23.33	23.35	23.33	23.32	23.32	23.34	23.34	23.32	23.35	23.36	23.34
C-13	21.34	21.27	21.30	21.26	21.32	21.74	21.34	21.28	21.29	21.28	21.35	21.76
C-14	18.95	19.02	19.13	18.96	18.87	19.06	18.90	18.95	19.02	18.90	18.80	19.01
C-15	26.12	26.17	26.20	26.10	26.05	26.15	26.19	26.23	26.24	26.18	26.12	26.23
R^1=	Sen	Sen	Sen	Sen	Sen	Sen	Meacr	Meacr	Meacr	Meacr	Meacr	Meacr
C-1	165.50	165.55	165.65	165.56	165.73	166.19	166.24	166.28	166.33	166.30	166.48	166.94
C-2	116.12	116.20	116.23	116.13	116.13	116.26	136.52	136.58	136.62	136.53	136.52	136.64
C-3	156.54	156.46	156.51	156.58	156.66	156.76	125.31	125.29	125.23	125.37	125.38	125.43
C-4	20.19	20.24	20.26	20.25	20.24	20.23	18.31	18.33	18.31	18.33	18.30	18.27
C-5	27.29	27.30	27.34	27.31	27.31	27.37	—	—	—	—	—	—
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
C-1	167.19	167.48	166.11	166.83	170.76	—	167.08	167.41	165.98	166.77	170.77	—
C-2	128.14	128.56	116.09	136.28	21.08	—	127.95	128.52	115.99	136.18	21.10	—
C-3	138.14	137.91	157.26	126.05	—	—	138.67	138.06	157.42	126.26	—	—
C-4	15.80	14.45	20.38	18.34	—	—	15.84	14.50	20.37	18.37	—	—
C-5	20.62	12.13	27.47	—	—	—	20.64	12.16	27.50	—	—	—

TABLE 3. Continued

Carbon	Compound											
	25	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
C-1	202.89	203.04	203.15	202.83	202.87	203.70	203.36	203.70	203.86	203.46	203.66	204.58
C-2	122.74	122.76	122.83	122.80	122.73	122.76	122.74	122.62	122.63	122.68	122.66	122.67
C-3	170.42	170.41	170.37	170.26	170.34	170.78	170.69	171.01	171.11	170.83	171.01	171.70
C-4	48.38	48.45	48.48	48.47	48.38	48.83	48.42	48.45	48.43	48.45	48.42	48.92
C-5	65.70	65.82	65.83	65.79	65.66	66.02	66.22	66.40	66.35	66.33	66.29	66.59
C-6	37.17	37.20	37.27	37.16	37.06	37.27	38.20	38.21	38.19	38.22	38.21	38.23
C-7	72.69	72.58	72.74	72.57	72.64	72.75	70.50	70.22	70.13	70.25	70.06	69.34
C-8	32.27	32.44	32.40	32.34	31.91	35.72	35.81	35.74	35.77	35.72	35.65	38.87
C-9	74.61	74.65	73.38	75.12	75.09	73.19	75.11	75.39	74.31	75.82	75.56	73.72
C-10	55.82	55.97	55.95	55.84	55.47	57.32	55.92	56.03	55.99	55.94	55.76	57.46
C-11	54.01	53.81	53.85	50.80	53.62	52.88	53.92	53.71	53.68	53.66	53.53	52.71
C-12	23.31	23.35	23.35	23.33	23.30	23.34	23.37	23.36	23.37	23.35	23.35	23.42
C-13	21.32	21.28	21.31	21.28	21.28	21.74	21.34	21.27	21.26	21.26	21.25	21.91
C-14	18.73	18.75	18.86	18.71	18.63	18.88	17.69	17.74	17.74	17.74	17.73	17.67
C-15	26.11	26.13	26.17	26.10	26.10	26.17	26.42	26.38	26.38	26.39	26.36	26.49
R^1=	Ac	Ac	Ac	Ac	Ac	Ac	H	H	H	H	H	H
C-1	170.11	170.14	170.19	170.18	170.23	170.80	—	—	—	—	—	—
C-2	21.07	21.11	21.14	21.08	21.10	21.29	—	—	—	—	—	—
R^2=	Ang	Tigl	Sen	Meacr	Ac	H	Ang	Tigl	Sen	Meacr	Ac	H
C-1	167.07	167.36	166.04	166.76	170.59	—	167.05	167.15	165.88	166.57	170.46	—
C-2	127.90	128.46	115.92	136.21	20.98	—	127.76	128.49	115.94	136.18	21.18	—
C-3	138.74	138.06	157.60	126.19	—	—	139.01	138.12	157.80	126.25	—	—
C-4	15.84	14.49	20.41	18.29	—	—	15.98	14.47	20.34	18.34	—	—
C-5	20.54	12.09	27.54	—	—	—	20.72	12.13	27.47	—	—	—

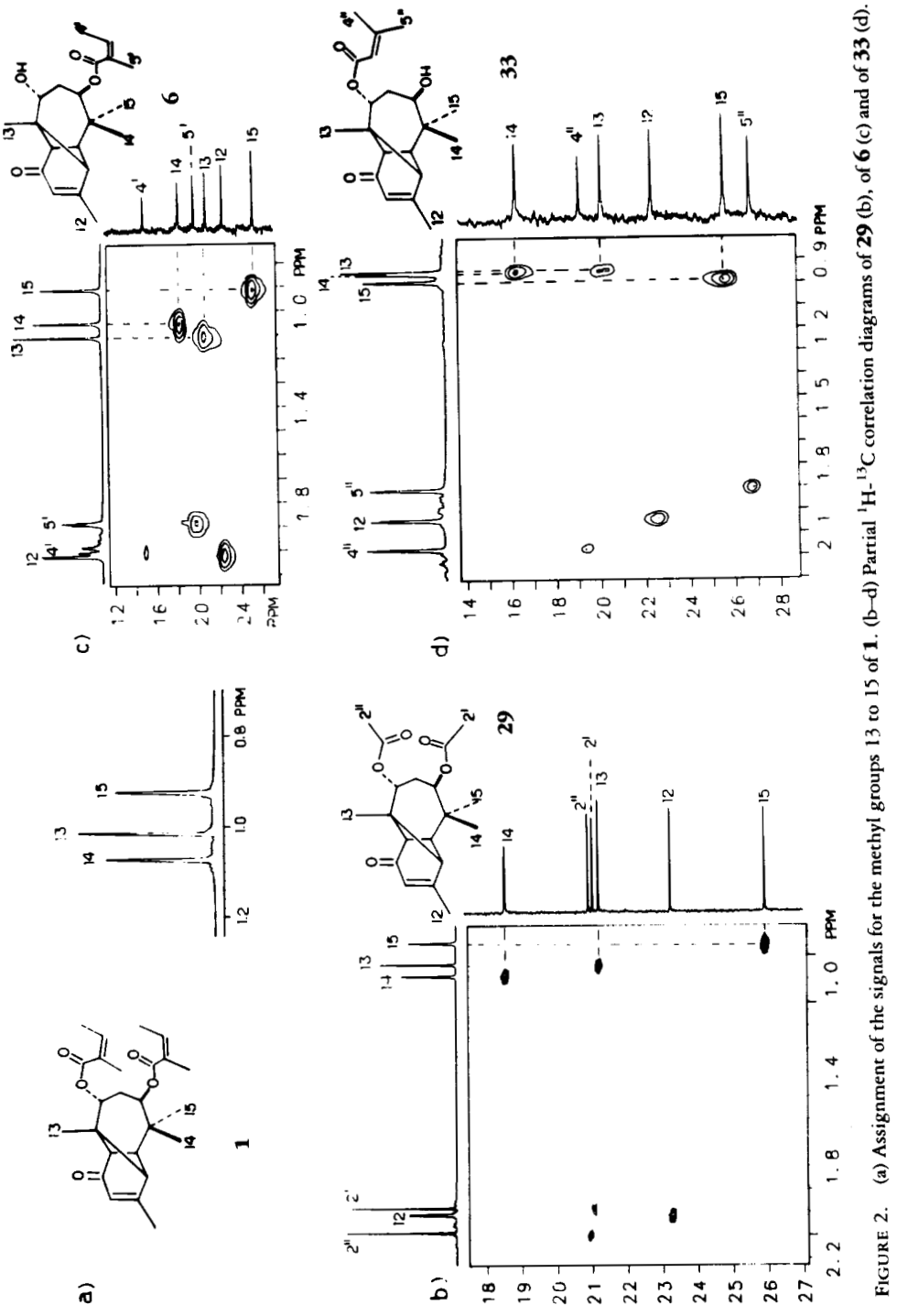


FIGURE 2. (a) Assignment of the signals for the methyl groups 13 to 15 of **1**. (b–d) Partial ^{1}H-^{13}C correlation diagrams of **29** (b), of **6** (c) and of **33** (d).

TABLE 4. Ir, uv, and Optical Activity of Compounds **1–36**.

Compound	ir[a]							
	O-H		R^1		R^2		Unsaturated Ketone	
	Free	Bonded	O=C	C=C	O=C	C=C	O=C	C=C
1	—	—	1710	1649	1710	1649	1672	1619
2	—	—	1706	1650	1706	1650	1672	1618
3	—	—	1711	1653	1711	1653	1672	1617
4	—	—	1712	1651	1712	1638	1672	1617
5	—	—	1713	1650	1724	—	1672	1618
6	3598	3477	1703	1648	—	—	1672	1617
7	—	—	1707	1650	1707	1650	1672	1618
8	—	—	1702	1650	1702	1650	1672	1618
9	—	—	1703	1652	1710	1652	1673	1618
10	—	—	1708	1653	1708	1638	1672	1617
11	—	—	1702	1652	1725	—	1671	1617
12	3597	3486	1697	1653	—	—	1672	1617
13	—	—	1701	1650	1711	1650	1672	1618
14	—	—	1702	1650	1702	1650	1672	1618
15	—	—	1701	1651	1712	1651	1672	1618
16	—	—	1702	1651	1712	1640	1672	1617
17	—	—	1700	1649	1722	—	1671	1617
18	3595	3498	1696	1649	—	—	1671	1617
19	—	—	1711	1638	1711	1648	1673	1618
20	—	—	1709	1638	1709	1653	1672	1617
21	—	—	1712	1639	1712	1651	1672	1618
22	—	—	1712	1637	1712	1637	1672	1617
23	—	—	1714	1637	1724	—	1672	1617
24	3592	3420	1707	1638	—	—	1672	1617
25	—	—	1732	—	1710	1648	1673	1617
26	—	—	1732	—	1702	1651	1672	1617
27	—	—	1733	—	1713	1653	1671	1617
28	—	—	1732	—	1713	1637	1672	1617
29	—	—	1731	—	1731	—	1671	1618
30	3595	3487	1730	—	—	—	1672	1617
31	3620	3486	—	—	1710	1650	1672	1618
32	3609	3480	—	—	1699	1651	1671	1617
33	3610	3470	—	—	1712	1651	1671	1617
34	3604	3511	—	—	1712	1634	1671	1617
35	3605	3458	—	—	1727	—	1671	1615
36	3607	3429	—	—	—	—	1670	1616

[a] ν max in cm^{-1} obtained from $CHCl_3$ solutions in NaCl cells.
[b] λ max in nm from EtOH solutions.
[c] $[\alpha]$ from $CHCl_3$ solutions ($c = 0.1$). All values are positive.

shown in Figures 2c and 2d, respectively. Two-dimensional nmr measurements also allow distinction of the signals owing to C-7 and C-9 when they appear within a very narrow chemical shift range, which is the case of **24** (Table 3), because the signals of H-7 and H-9 have been assigned unambiguously (10).

The ^{1}H-coupled ^{13}C-nmr spectra of **1**, **30**, and **35** allow several signals of quaternary carbons that show small chemical shift differences to be distinguished. For example, although in the spectrum of monoacetate **35** the difference between the resonances of C-3 and the ester carbonyl carbon is ca. 0.5 ppm, their assignment follows from a coupled spectrum in which the signal of C-3 appears as a complex multiplet and that of the COO group as a double quartet.

TABLE 4. Ir, uv, and Optical Activity of Compounds **1–36**.

uv[b]		Optical Activity[c]				
λ_{max} (log ϵ_1)	λ^2_{max} (log ϵ_2)	$[\alpha]_{589}$	$[\alpha]_{578}$	$[\alpha]_{546}$	$[\alpha]_{436}$	$[\alpha]_{365\,nm}$
219 (3.97)	248 (3.57)	57	59	67	134	389
219 (4.14)	248 (3.64)	68	70	80	158	423
220 (4.40)	248 (3.87)	72	75	88	180	495
216 (4.27)	248 (3.97)	57	60	71	146	427
220 (3.96)	248 (3.77)	38	40	48	109	388
220 (3.67)	251 (3.45)	49	51	61	123	433
219 (4.02)	249 (3.57)	58	62	73	155	464
219 (4.35)	250 (3.90)	67	70	81	161	422
221 (4.32)	248 (3.90)	71	74	87	179	483
215 (4.29)	249 (3.86)	66	70	82	168	499
219 (4.02)	248 (3.78)	40	41	48	107	381
219 (4.00)	250 (3.74)	31	33	40	90	377
220 (4.30)	248 (3.77)	50	53	62	140	396
220 (4.29)	248 (3.75)	84	87	101	201	509
221 (4.38)	247 (3.80)	72	78	90	177	457
217 (4.32)	247 (3.93)	56	58	68	138	398
220 (4.21)	248 (3.87)	40	42	49	109	369
221 (4.09)	251 (3.70)	48	50	58	118	407
217 (4.22)	247 (3.97)	62	66	78	163	502
215 (4.45)	248 (4.08)	72	75	88	176	477
217 (4.26)	248 (3.86)	70	74	86	179	495
213 (4.21)	250 (3.94)	52	55	65	139	422
212 (3.71)	249 (3.67)	39	40	48	114	403
210 (3.90)	250 (3.93)	42	44	52	112	427
221 (4.46)	249 (4.31)	76	81	95	203	553
220 (3.96)	248 (3.71)	71	74	86	170	459
221 (3.07)	246 (3.75)	58	60	71	149	411
212 (3.69)	250 (3.64)	69	73	84	173	496
211 (3.15)	250 (3.78)	46	48	57	122	407
216 (3.36)	251 (3.82)	56	60	70	142	484
222 (3.97)	249 (3.74)	50	52	62	134	472
219 (3.98)	250 (3.70)	33	35	41	89	321
220 (4.16)	250 (3.75)	50	54	63	134	430
216 (4.14)	248 (3.88)	43	46	54	119	448
212 (3.27)	251 (3.80)	70	72	84	173	533
214 (3.24)	252 (3.72)	68	71	81	161	574

In those compounds having two like ester residues (**1**, **8**, **15**, **22**, and **29**), the ^{1}H- and ^{13}C-signals for each acyl group can be assigned specifically by comparison with the signals of compounds having unlike esters. For example, in the ^{1}H-nmr spectrum of **29**, both acetate signals are distinguished by comparison with the chemical shifts of the 7-acetate group in **25** and the 9-acetate group in **5** (Table 2). The only exception is the assignment of the carbonyl signals of each acetate group in the ^{13}C-spectrum of **29**, which cannot be achieved by the comparative method because both signals appear in a very narrow chemical shift range of only 0.36 ppm (Table 3). Their distinction is achieved after irradiation of the protons of the acetyl group at C-9 (2.15 ppm) and inspection of the ^{13}C spectrum, whereby the signal at 170.59 ppm changes from a double quartet ($J_{CH_3COOCH} = 3.5$ and $J_{CH_3COOCH} = 7.0$ Hz) to a doublet.

Finally, the mp, ir, uv, and optical activity data, which also can be useful to identify the natural products, are presented in Tables 1 and 4.

From the present series of longipinenes only three (**1**, **3**, and **5**) are reported as solids (4,8) and thirteen (**2**, **4**, **7–10**, **15**, **19–22**, **31**, and **33**) as oils (see sources in Table 1). The ^{1}H-nmr data of the naturally occurring compounds **1**, **3–5**, **10**, **22**, and **31** (1,4,8) are in agreement with the present values, while for the natural products **2**, **7–10**, **15**, **20**, **21**, and **33** only spectra of mixtures, lacking individual assignments, are reported (1–3). Furthermore, the constituents of *Stevia policephala* (2), *Stevia boliviensis* (3), and *Stevia mandonii* (3) should be isolated in pure form since the ^{1}H-nmr data derived from mixtures do not seem to establish the structures unequivocally.

EXPERIMENTAL

GENERAL APPARATUS.—Mp's were determined on a Fisher-Johns apparatus and are uncorrected. All nmr measurements were performed on a Varian Associates XL-300GS spectrometer. The ir spectra were obtained on a Nicolet MX-1-FT spectrophotometer, the uv spectra on a Unicam SP-800 spectrophotometer, and the optical rotations on a Perkin-Elmer 241 polarimeter. Chromatographic separations were made using Alcoa F-20 alumina (80–200 mesh).

GENERAL PROCEDURES FOR THE PREPARATION OF ESTERS.—A solution of the starting material, the acyl chloride, and the catalysts was stored at room temperature unless otherwise stated. After usual workup, the residue was chromatographed. All compounds were recrystallized from CH_2Cl_2/hexane. Treatments involving angeloyl chloride were evaporated by heating the reaction mixture at 60° under an N_2 flow until dryness, followed by chromatography. The detailed reaction conditions are given in Table 1.

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