5. Synthetic Studies Directed toward the Pseurotins

Part I

Synthesis of Related Furan-3(2*H*)-ones

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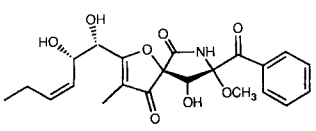
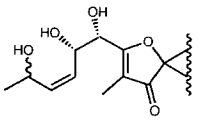
According to a general concept for the total synthesis of pseurotin A (**1**), a secondary metabolite of *Pseudeurotium ovalis* STOLK, 5-[(1*S*,2*S*,*Z*)-1,2-dihydroxyhex-3-enyl]-2,2,4-trimethylfuran-3(2*H*)-one (**17**) was prepared. It is a model substance for the substituted furan-3(2*H*)-one moiety of **1**. The aldol condensation of the aldehyde **26**, derived from D-glucose, and the enolate of ketone **29** served as key reaction.

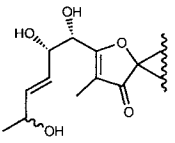
Introduction. – The pseurotins (see **1**–**5**) are a new class of secondary metabolites which have been isolated from cultures of *Pseudeurotium ovalis* STOLK. The isolation, spectral data, and chemical properties as well as biosynthetic studies of pseurotin A (**1**) have been already discussed in [1–3]. **1** possesses a highly substituted 1-oxa-7-azaspiro-[4.4]nonane skeleton and a total of 5 chiral centres. This unusual structure has until now been found only in the pseurotins.



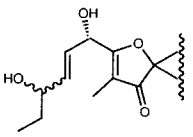
1 pseurotin A



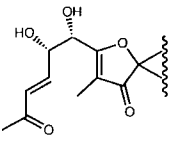
2 pseurotin B



3 pseurotin C



4 pseurotin D

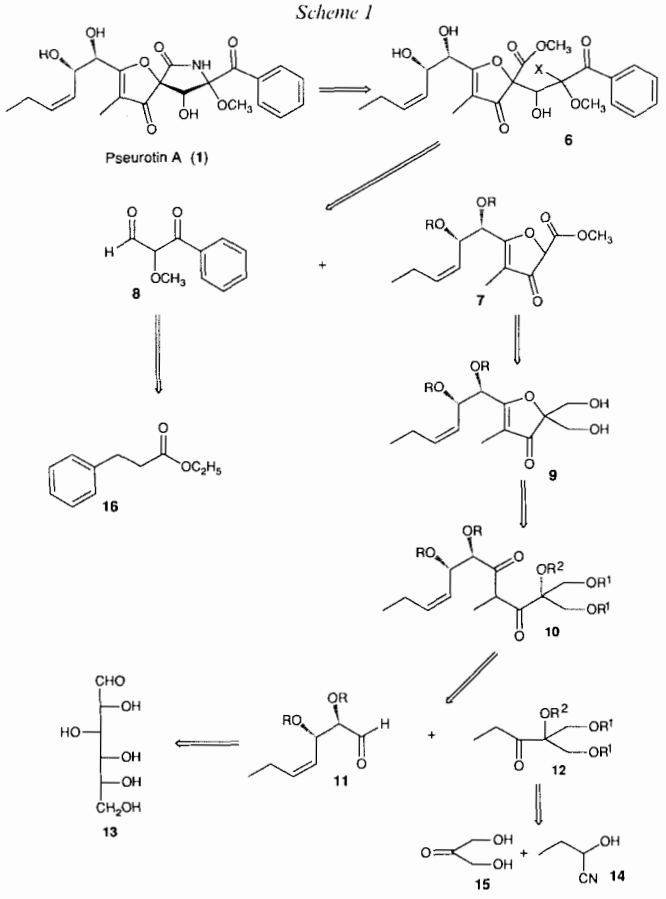


5 pseurotin E

The complicated structure of the pseurotins, which contain a highly functionalized spirocyclic system, exhibits an attractive synthetic challenge. In this and subsequent papers, we wish to report our work directed toward the total synthesis of pseurotin A (**1**). The retrosynthetic analysis of the pseurotin A (**1**) is displayed in *Scheme 1*.

We envisaged pseurotin A (**1**) to be elaborated from the γ-halogeno-ester **6**. The latter could be produced by an aldol condensation of the α-methoxy-β-keto-aldehyde **8** with

Scheme 1

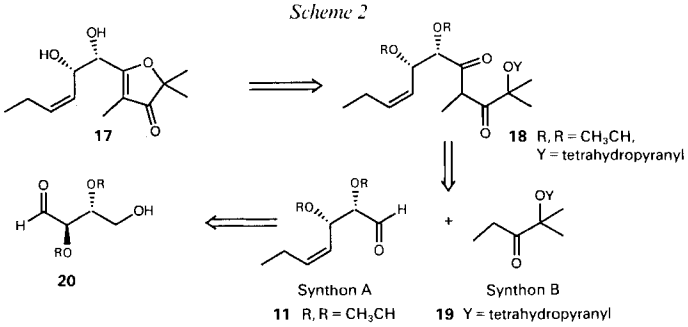


the enolate of the β-keto-ester **7**. The β-keto-ester **7** is formed from the diol **9**. The latter is obtained by ring closure of the open chain β-diketone **10**. The unsaturated side chain is generated from the protected sugar derivative **11** derived from D-glucose **13**. For the formation of the aldehyde **8**, a stereoselective hydroxylation of the protected ester of dihydrocinnamic acid **16** is required.

Results. – Considering the high degree of functionalization of the pseurotins, we started the synthesis with suitably substituted furan-3(2*H*)-ones of type **8** in which all chiral centres possess the correct configuration. In nature, furan-3(2*H*)-ones are relatively rare. They occur as components of fruit flavours and fragrances [4]. The plant products bullatenone [5], geiparvarin [6], jatrophone [7], the eremantholides [8], and lychnophorolide [9] are further examples. The latter four substances possess cytostatic activity. Total syntheses of geiparvarin and jatrophone have been carried out by *Smith et al.* [10].

Our first target molecule which served as a model, was 5-[(1*S*,2*S*,*Z*)-1,2-dihydroxyhex-3-enyl]-2,2,4-trimethylfuran-3(2*H*)-one (**17**). According to a retrograde synthesis *(Scheme 2)*, it was planned to carry out the ring closure of the β-diketone **18** as the final

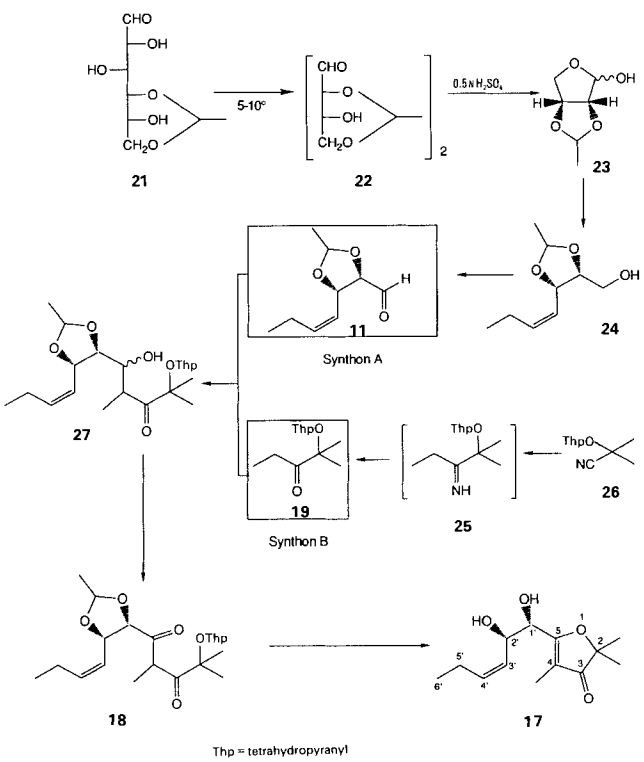
Scheme 2



step. The key reaction is the aldol condensation of the protected aldehyde **11** (synthon **A**) with the enolate of the protected hydroxy-ketone (synthon **B**). Synthon **A** is generated from the aldehyde **20** by a *Wittig* reaction. The latter compound is in fact a protected form of D-erythrose. The planned sequence of reactions was carried out as follows.

D-Glucose (**13**) was converted with paracetaldehyde to the acetate **21** as described in [11] [12]. Glycol cleavage of the latter with $NaIO_4$ led to the protected D-erythrose **22** which proved to be a dimer according to the NMR data. By treatment of **22** with

Scheme 3



H_2SO_4/acetaldehyde, the protecting group was shifted from the 2,4- to the 2,3-position, yielding the D-erythrofuranose **23**. Chain extension with simultaneous introduction of an olefinic double bond was achieved by a *Wittig* reaction. Two equiv. of ylide had to be used, because compound **23** has a free OH group (alcoholate formation). The reaction was carried out according to *Cohen*'s procedure [13] (see *Exper. Part*) and afforded **24** in 90% yield. The ^{1}H-NMR data confirmed the (*Z*)-configuration. Oxidation of **24** according to *Swern*'s procedure [14] led to the desired aldehyde **11** which proved to be unstable during the reaction and storage.

Ketone **19** was produced applying the *Elphimof-Felkin* procedure [15]. A *Grignard* reaction of **26** with EtMgBr allowed the extension of the chain by two C-atoms *via* the imine **25**. The ketone **19** formed was then deprotonated with lithium diisopropylamide (LDA) and condensed with the aldehyde **11**. Subsequent oxidation of the hydroxy-ketone **27** by *Swern* oxidation led to the β-diketone **18**. The final cyclization to the desired furan-3(2*H*)-one derivative **17** was achieved by treatment of **18** with HCl. The yields of all reactions were excellent and the structure of **17** was established by the spectral data.

The IR spectrum of **17** confirmed the presence of the α,β-unsaturated carbonyl system (1680 and 1620 cm^{-1}) and of a free OH group (3400 cm^{-1}). In the ^{1}H-NMR, a *singlet* at 1,73 ppm was assigned to Me–C(4). The signals from both OH groups appeared at *ca.* 2.7 and 3.3–3.6 ppm. In the MS, the molecular ion was found at *m/z* 241. Additional signals at *m/z* 156, 141, 85, 69, and 43 can be interpreted as the corresponding fragments. A comparison of the ^{13}C-NMR data of **17** with those of pseurotin A (**1**) showed excellent agreement *(Table)*. The only significant

Table. *^{13}C-NMR Data of Furan-3(2*H*)-ones* **1** *and* **17**

	1[a])	**17**
C(2)	92.7	86.8
C(3)	197.9	207.9
C(4)	115.6	110.1
C(5)	167.3	181.2
C(1′)	72.8	71.2
C(2′)	69.7	69.3
C(3′)	129.0	125.8
C(4′)	135.9	137.6
C(5′)	21.8	21.3
C(6′)	14.5	14.1
CH_3–C(2)		23.1
CH_3–C(2)		22.9
CH_3–C(4)	5.8	5.6

[a]) The numbering corresponds to that of **17** in order to allow direct comparison.

differences appear for C(3) ($\Delta\delta \approx 10$ ppm) and for C(5) ($\Delta\delta = 14$ ppm). They can be explained by the absence of the spirolactam ring in **17**. The lactam CO of **1** exerts an anisotropic effect, and C(3) is probably located exactly in the range of this shielding. As a result, the resonance of C(3) is shifted to a higher field. The difference in chemical shift of the C-atom of the exocyclic double bond can also be explained by the absence of the spirocyclic lactam in compound **17**. The flexibility of the side chain allows the C(3′) = C(4′) bond to be in close proximity to the lactam moiety in **1** and thus electronic interaction.

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Experimental Part

General. H_2O-Sensitive reactions were carried out in a flamed apparatus under Ar or N_2. All org. extracts were dried (Na_2SO_4) and evaporated at $< 40°$. The anal. samples were dried under high vacuum over night and over P_2O_5 at r.t. TLC: Silica gel *60 F_{254} (Merck)*; detection with UV light, I_2, 10% H_2SO_4 soln. in MeOH or $KMnO_4$ soln. (2.0 g $KMnO_4$, 4.0 g Na_2CO_3, 100 ml H_2O). Column chromatography (CC): Silica gel *60* (0.063–0.200 mm, *Merck* or *Chemische Fabrik Uetikon*). M.p. *Kofler* block; corrected. UV: *Beckman-25*. IR: *Perkin-Elmer-781* grating spectrometer. NMR: *Varian-EM-360* (^{1}H, 60 MHz), *Bruker-WH-90* with *Fourier* transform (^{1}H, 90 MHz; ^{13}C, 22.63 MHz), or *Varian-VXR-400* spectrometer with *Fourier* transform (^{1}H, 400 MHz; ^{13}C, 101 MHz); in $CDCl_3$; chemical shifts in ppm downfield from internal TMS. MS: *VG-70-250* spectrometer; for CI, NH_3. GC/MS: *HP 5790/HP 5970* (EI, 70 eV).

*4,6-(Ethylidenedioxy)-*D*-glucopyranose* (**21**). A soln. of **13** (90.0 g, 0.5 mol), paraacetaldehyde (70 ml), and conc. H_2SO_4 soln. (0.5 ml) was stirred at r.t. for 4 h and then allowed to stand at r.t. for 3 days. Then, abs. EtOH (300 ml) was added. The mixture was neutralized with 1M KOH in EtOH, warmed, treated with 5 g of activated charcoal and filtered. Crystallization from abs. EtOH gave 52.4 g (51%) of **21**. M.p. 175–176°. ^{1}H-NMR (90 MHz): 1.30 (*d*, J = 5, CH_3CH); 3.1–4.2 (*m*, H–C(2), H–(3), H–C(4), H–C(5), CH_2(6)); 4.60 (*q*, J = 5, CH_3CH); 5.10 (*d*, J = 3, H–C(1)).

*2,4-(Ethylidenedioxy)-*D*-erythrose Dimer* (**22**). To a cold (*ca.* 5°) soln. of $NaIO_4$ (22.0 g, 0.10 mol) in H_2O (160 ml), a soln. of **21** (10.0 g, 0.05 mol) in H_2O (50 ml) was added under strong stirring during 1–1.5 h. Simultaneously, a conc. NaOH soln. was added dropwise in order to keep the pH at 4. After 4 h, the pH value was corrected to 6.5 with NaOH and the solvent evaporated. The residue was dried overnight under high vacuum and then extracted with hot AcOEt to give 6.8 g (47%) of **22** as a yellow powder. IR ($CHCl_3$): 3400 (OH), 3000, 2880, 1410, 1140. ^{1}H-NMR (60 MHz): 1.3 (br. *d*, J = 5, 6 H, CH_3CH); 3.1–4.3 (*m*, 10 H, H–C(2), H–C(3), CH_2(4), OH); 4.4–5.0 (*m*, 4 H, CH_3CH, H–C(1)).

*2,3-(Ethylidenedioxy)-*D*-erythrofuranose* (**23**). To a soln. of **22** (5.0 g, 17 mmol) in 0.5N H_2SO_4 (50 ml), acetaldehyde (10 ml) was added. After 3 days, the reaction was completed, the mixture neutralized with conc. NaOH soln., the solvent removed, and the residue extrated with Et_2O. Purification with CC (Et_2O) yielded 4.4 g (88%) of **23** as colourless needles. M.p. 63–65°. IR ($CHCl_3$): 3600 (OH), 3400, 2950, 2880, 1410, 1150, 1100, 1050, 975, 910, 880. ^{1}H-NMR (90 MHz): 1.39 (*d*, J = 5, CH_3CH); 3.08 (br., OH); 4.07 (*d*, J = 2, CH_2(4)); 4.48 (*d*, J = 6, H–C(2)); 4.71, 4.78 (*dd*, J = 2, J = 6, H–C(3)); 5.01 (*q*, J = 5, CH_3CH); 5.46 (*s*, H–C(1)). EI-MS: 145 ([M – 1]$^+$), 131, 102, 85, 71, 65, 64, 45, 43, 29.

*(2*R*,3*S*,*Z*)-2,3-(Ethylidenedioxy)hept-4-en-1-ol* (**24**). A soln. of (propyl)triphenylphosphonium bromide (3.58 g, 9.3 mmol) in abs. THF (30 ml) was cooled to −55°. A soln. of 1.5M BuLi in hexane was added dropwise to the soln. (→ orange) and stirred at −40 to −50° for 30 min. Then, a soln. of 0.68 g (4.6 mmol) of **23** in a little amount of THF was added and stirred for 30 min at −25°. The cooling bath was removed and the soln. stirred for further 1.25 h. Then, H_2O (50 ml) was added and the soln. extracted with Et_2O. The org. layer was washed with brine and evaporated: 0.74 g (94%) of **24**, after CC (5% MeOH/CH_2Cl_2). ^{1}H-NMR (90 MHz): 1.00 (*t*, J = 7, CH_3(7)); 1.43 (*d*, J = 5, CH_3CHO_2); 1.90–2.20 (*m*, CH_2(6)); 3.10 (br., OH); 3.50 (br. *d*, J = 6, CH_2(1)); 4.0–4.2 (*m*, H–C(2)); 4.85 (*t*, J = 7, H–C(3)); 5.07 (*q*, J = 5, CH_3CHO_2); 5.3–5.7 (*m*, H–C(4), H–C(5)). ^{13}C-NMR (22.63 MHz): 14.3 (*q*, C(7)); 20.2 (*q*, CH_3CHO_2); 21.3 (*t*, C(6)); 62.3 (*t*, C(1)); 74.4 (*d*, C(3)); 78.9 (*d*, C(2)); 101.1 (*d*, CH_3CHO_2); 123.9 (*d*, C(4)); 136.9 (*d*, C(5)). EI-MS: 171 ([M – 1]$^+$), 141, 128, 112, 97, 85, 83, 67, 55.

*(2*S*,3*S*,*Z*)-2,3-(Ethylidenedioxy)hept-4-enal* (**11**). A soln. of oxalyl chloride (0.26 ml, 2.8 mmol) in abs. CH_2Cl_2 (6.5 ml) was cooled to −60° and a soln. of DMSO (0.44 ml, 5.7 mmol) in abs. CH_2Cl_2 (1.5 ml) added dropwise. After 5 min, a soln. of **24** (457 mg, 2.6 mmol) in a little amount of abs. CH_2Cl_2 was added slowly and the mixture stirred for 15 min. Then, Et_3N (0.9 ml, 6.0 mmol) was added and stirred at −60° for 15 min. The cooling bath was removed and, after 10 min, H_2O (10 ml) was added. The aq. layer was extracted with CH_2Cl_2 and the org. soln. washed with brine and evaporated: 401 mg (90%) of **11**. Unstable on CC. ^{1}H-NMR (60 MHz): 1.0 (*t*, J = 7, CH_3(7)); 1.5 (*d*, J = 5, CH_3CHO_2); 1.8–2.2 (*m*, CH_2(6)); 4.2 (*dd*, J(1,2) = 4, J(2,3) = 7, H–C(2)); 4.7–5.9 (*m*, H–C(3), CH_3CHO_2, H–C(4), H–C(5)); 9.4 (*d*, J = 4, H–C(1)).

*2-Methyl-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]pentan-3-one* (**19**). To a mixture of Mg chips (1.70 g, 70 mmol) in abs. Et_2O (10 ml), EtBr (7.63 g, 70 mmol) in abs. Et_2O (15 ml) was added and stirred for 15 min. Then, a soln. of **26** (9.73 g, 58.3 mmol) in abs. Et_2O (60 ml) was added. After 3 h, the mixture was poured on ice, and sat. aq. NH_4Cl soln. (50 ml) was added. The mixture was filtered and extracted with Et_2O. The crude product was obtained as a yellow oil which was hydrolyzed in 25 ml of 10% AcOH soln. at r.t. for 45 min. After extraction with Et_2O, washing with 10% aq. Na_2CO_3 soln., evaporation, and CC (Et_2O), 8.41 g (72%) of **19** were obtained. IR (film): 2950, 2860, 1720 (C=O), 1520, 1360, 1170, 1130, 1080, 1040, 990, 870. ^{1}H-NMR (60 MHz): 1.0 (*t*, J = 7, CH_3(5)); 1.3 (*s*,

$CH_3(1)$, $CH_3(2)$); 1.3–1.9 (*m*, 6 H of Thp); 2.7 (*t*, $J = 7$, $CH_2(4)$); 3.2–4.1 (*m*, 2 H of Thp); 4.5–4.7 (*m*, CH–O of Thp).

(6S,7S,Z)-6,7-(Ethylidenedioxy)-5-hydroxy-2,4-dimethyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]undec-8-en-3-one (**27**). BuLi/hexane (1.55 M; 3.87 ml, 6 mmol) was added to a cooled (–10°) soln. of $(i\text{-Pr})_2NH$ (658 mg, 6.5 mmol) in abs. THF (20 ml). The mixture was cooled to –78° and a soln. of **19** (991 mg, 4.9 mmol) in abs. THF (5 ml) added. After 45 min, a soln. of **11** (850 mg, 5 mmol) in abs. THF (5 ml) was added and stirred for 5 min. Then, sat. NH_4Cl soln. (10 ml) was added and the mixture poured into Et_2O (200 ml), washed with brine, and evaporated. CC (Et_2O) yielded 1.640 g (90%) of **27**. IR (film): 3520 (OH), 2950, 2880, 1720 (C=O), 1405, 1380, 1150, 1080, 1030, 990, 900. ^{1}H-NMR (60 MHz): 1.0–1.3 (*m*, CH_3CHO_2, CH_3–C(4), $CH_3(11)$); 1.4 (br., $CH_3(1)$, CH_3–C(2)); 1.4–2.3 (*m*, 6 H of Thp, $CH_2(10)$). ^{1}H-NMR (90 MHz, after cleavage of the Thp group according to [16]): 0.9–1.3 (*m*, CH_3CHO_2, CH_3–C(4), $CH_3(11)$); 1.39 (*s*, $CH_3(1)$, CH_3–C(2)); 1.9–2.3 (*m*, $CH_2(10)$); 2.7 (br., OH); 3.3–4.0 (*m*, H–C(4), H–C(5), H–C(6), OH); 4.9–5.1 (*m*, H–C(7), CH_3CHO_2); 5.4–5.9 (*m*, H–C(8), H–C(9)).

(6S,7S,Z)-6,7-(Ethylidenedioxy)-2,4-dimethyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]undec-8-ene-3,5-dione (**18**). *Swern* oxidation [14] was carried out as for **11**. CC (5% $MeOH/CH_2Cl_2$) yielded 83% of **18** as a light yellow oil. IR (film): 2950, 2880, 1730, 1710 (2 C=O), 1450, 1380, 1150, 1080, 1030, 910.

5-[(1S,2S,Z)-1,2-Dihydroxyhex-3-enyl]-2,2,4-trimethylfuran-3(2H)-one (**17**). A soln. of **18** (324 mg, 0.88 mmol) THF/H_2O/5% HCl 1:1:1 (45 ml) was stirred for 24 h. Then brine (30 ml) was added and the mixture extracted with Et_2O. The aq. layer was washed with sat. $NaHCO_3$ soln., evaporated, and purified by CC (E_2O): 158 mg (75%) of **17** as a yellow oil. IR (film): 3400 (OH), 2980, 2950, 1680 (C=O), 1620 (C=C), 1460, 1380, 1210, 1100, 1030, 960. ^{1}H-NMR (90 MHz): 0.98 (*t*, $J = 7$, $CH_3(6')$); 1.35 (*s*, 2 CH_3–C(2)); 1.73 (*s*, CH_3–C(4)); 2.0–2.2 (*m*, $CH_2(5')$); 2.7 (br., OH); 3.4 (br., OH); 4.6–4.7 (*m*, H–C(1'), H–C(2')); 5.4–5.7 (*m*, H–C(3'), H–C(4')). ^{13}C-NMR (22.63 MHz): *Table*. MS: 241 ($[M + 1]^+$), 156, 141, 85, 69, 67, 57, 43, 41.

REFERENCES

[1] a) P. Bloch, Dissertation, Basel, 1976; b) P. Bloch, Ch. Tamm, P. Bollinger, T. J. Petcher, H. P. Weber, *Helv. Chim. Acta* **1976,** *59,* 133; c) T. J. Petcher, H. P. Weber, P. Bloch, Ch. Tamm, *ibid.* **1976,** *59,* 137; d) P. Bloch, Ch. Tamm, *ibid.* **1981,** *64,* 304.

[2] a) P. Mohr, Ch. Tamm, *Tetrahedron* **1981,** *37,* 201; b) P. Mohr, Dissertation, Basel, 1980.

[3] W. Breitenstein, K. Chexal, P. Mohr, Ch. Tamm, *Helv. Chim. Acta* **1981,** *64,* 379.

[4] G. Ohloff, J. P. Pickenhagen, A. Velluz, *J. Sci. Food Agric.* **1981,** 1132.

[5] T. Brandt, W. I. Taylor, *J. Chem. Soc.* **1954,** 3425.

[6] F. N. Lahey, J. K. Mac Leod, *Aust. J. Chem.* **1967,** *20,* 1943.

[7] R. F. Bryan, R. C. Haltiwanger, S. M. Kupchan, M. J. Matz, J. A. Saenz Renauld, *J. Am. Chem. Soc.* **1970,** *92,* 4476.

[8] T. F. Brennan, P. C. Huang, P. W. Le Quesne, S. B. Levery, R. F. Raffauf, *J. Am. Chem. Soc.* **1975,** *97,* 6884.

[9] T. F. Brennan, K. Donan, C. J. Kelly, P. W. Le Quesne, M. D. Menachery, M. P. Pastore, R. F. Raffauf, C. M. Weeks, *J. Org. Chem.* **1982,** *47,* 1519.

[10] P. J. Jerris, A. B. Smith III, *Tetrahedron Lett.* **1980,** 711; M. A. Guaciaro, T. W. Hall, S. R. Schow, A. B. Smith III, B. H. Toder, *J. Am. Chem. Soc.* **1981,** *103,* 219; P. J. Jerris, P. A. Levenberg, R. M. Scarborough, Jr., A. B. Smith III, P. M. Workulich, *ibid.* **1981,** *103,* 1501.

[11] R. Barker, D. L. MacDonald, *J. Am. Chem. Soc.* **1960,** *82,* 2301.

[12] C. E. Rist, J. W. Van Cleve, *Carbohydr. Res.* **1967,** *4,* 82.

[13] B. L. Banner, N. Cohen, A. A. Liebmann, Y. Liu, R. J. Lopresti, M. Rosenberger, E. Thom, F. Wong, *J. Am. Chem. Soc.* **1983,** *105,* 3661.

[14] S. Huang, A. J. Mancuso, D. Swern, *J. Org. Chem.* **1978,** *43,* 2480.

[15] I. Elphimoff-Felkin, *Bull. Soc. Chim. Fr.* **1955,** 784.

[16] A. Yoshikoshi, M. Miyashita, P. A. Grieco, *J. Org. Chem.* **1977,** *42,* 3772.