

5. Synthetic Studies Directed toward the Pseurotins

Part I

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

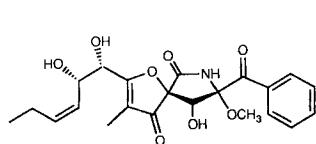
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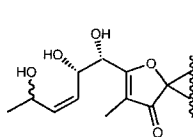
(13.XI.89)

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.

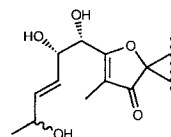
Introduction. – The pseurotins (see **1–5**) are a new class of secondary metabolites which have been isolated from cultures of *Pseudeurotium ovalis* STOLK. The isolation, spectral data, and chemical properties as well as biosynthetic studies of pseurotin A (**1**) have been already discussed in [1–3]. **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.



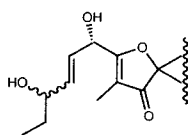
1 pseurotin A



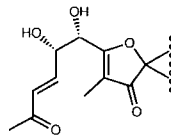
2 pseurotin B



3 pseurotin C



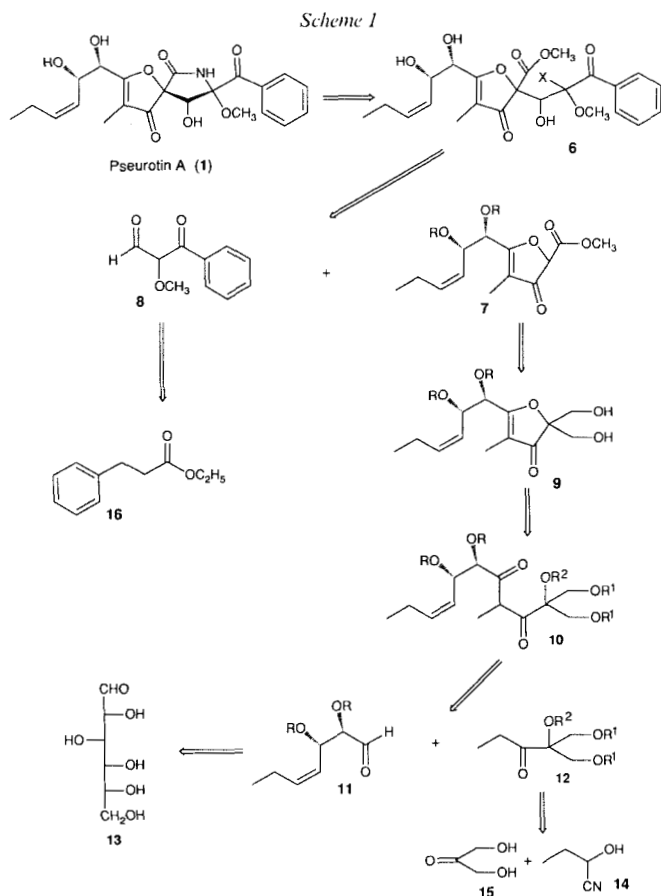
4 pseurotin D



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*.

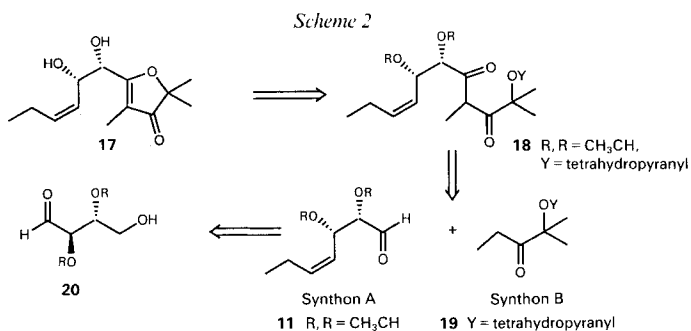
We envisaged pseurotin A (**1**) to be elaborated from the γ -halogeno-ester **6**. The latter could be produced by an aldol condensation of the α -methoxy- β -keto-aldehyde **8** with



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.

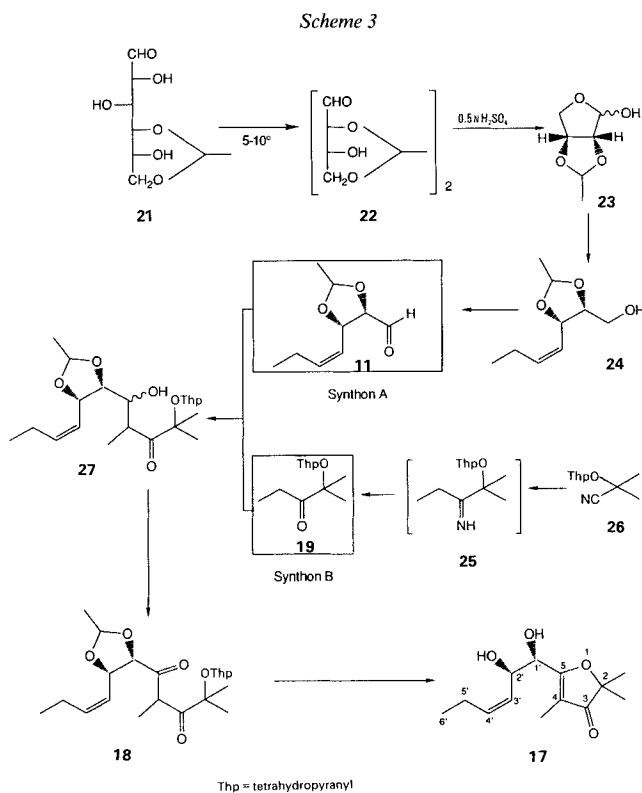
Results. – Considering the high degree of functionalization of the pseurotins, we started the synthesis with suitably substituted furan-3(2*H*)-ones of type **8** in which all chiral centres possess the correct configuration. In nature, furan-3(2*H*)-ones are relatively rare. They occur as components 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



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



H₂SO₄/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 ¹H-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 ¹H-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 ¹³C-NMR data of **17** with those of pseurotin A (**1**) showed excellent agreement (*Table*). The only significant

Table. ¹³C-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 spiro lactam 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.

Financial support of these investigations by the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. H₂O-Sensitive reactions were carried out in a flamed apparatus under Ar or N₂. All org. extracts were dried (Na₂SO₄) and evaporated at < 40°. The anal. samples were dried under high vacuum over night and over P₂O₅ at r.t. TLC: Silica gel 60 F₂₅₄ (Merck); detection with UV light, I₂, 10% H₂SO₄ soln. in MeOH or KMnO₄ soln. (2.0 g KMnO₄, 4.0 g Na₂CO₃, 100 ml H₂O). 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 (¹H, 60 MHz), Bruker-WH-90 with Fourier transform (¹H, 90 MHz; ¹³C, 22.63 MHz), or Varian-VXR-400 spectrometer with Fourier transform (¹H, 400 MHz; ¹³C, 101 MHz); in CDCl₃; chemical shifts in ppm downfield from internal TMS. MS: VG-70-250 spectrometer; for CI, NH₃. 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. H₂SO₄ 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°. ¹H-NMR (90 MHz): 1.30 (*d*, *J* = 5, CH₃CH); 3.1–4.2 (*m*, H–C(2), H–(3), H–C(4), H–C(5), CH₂(6)); 4.60 (*q*, *J* = 5, CH₃CH); 5.10 (*d*, *J* = 3, H–C(1)).

2,4-(Ethylidenedioxy)-D-erythrose Dimer (22). To a cold (*ca.* 5°) soln. of NaIO₄ (22.0 g, 0.10 mol) in H₂O (160 ml), a soln. of **21** (10.0 g, 0.05 mol) in H₂O (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 (CHCl₃): 3400 (OH), 3000, 2880, 1410, 1140. ¹H-NMR (60 MHz): 1.3 (br. *d*, *J* = 5, 6 H, CH₃CH); 3.1–4.3 (*m*, 10 H, H–C(2), H–C(3), CH₂(4), OH); 4.4–5.0 (*m*, 4 H, CH₃CH, H–C(1)).

2,3-(Ethylidenedioxy)-D-erythrofuranose (23). To a soln. of **22** (5.0 g, 17 mmol) in 0.5N H₂SO₄ (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 extracted with Et₂O. Purification with CC (Et₂O) yielded 4.4 g (88%) of **23** as colourless needles. M.p. 63–65°. IR (CHCl₃): 3600 (OH), 3400, 2950, 2880, 1410, 1150, 1100, 1050, 975, 910, 880. ¹H-NMR (90 MHz): 1.39 (*d*, *J* = 5, CH₃CH); 3.08 (br., OH); 4.07 (*d*, *J* = 2, CH₂(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, CH₃CH); 5.46 (*s*, H–C(1)). EI-MS: 145 ([*M* – 1]⁺), 131, 102, 85, 71, 65, 64, 45, 43, 29.

(2R,3S,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, H₂O (50 ml) was added and the soln. extracted with Et₂O. The org. layer was washed with brine and evaporated: 0.74 g (94%) of **24**, after CC (5% MeOH/CH₂Cl₂). ¹H-NMR (90 MHz): 1.00 (*t*, *J* = 7, CH₃(7)); 1.43 (*d*, *J* = 5, CH₃CHO₂); 1.90–2.20 (*m*, CH₂(6)); 3.10 (br., OH); 3.50 (br. *d*, *J* = 6, CH₂(1)); 4.0–4.2 (*m*, H–C(2)); 4.85 (*t*, *J* = 7, H–C(3)); 5.07 (*q*, *J* = 5, CH₃CHO₂); 5.3–5.7 (*m*, H–C(4), H–C(5)). ¹³C-NMR (22.63 MHz): 14.3 (*q*, C(7)); 20.2 (*q*, CH₃CHO₂); 21.3 (*t*, C(6)); 62.3 (*t*, C(1)); 74.4 (*d*, C(3)); 78.9 (*d*, C(2)); 101.1 (*d*, CH₃CHO₂); 123.9 (*d*, C(4)); 136.9 (*d*, C(5)). EI-MS: 171 ([*M* – 1]⁺), 141, 128, 112, 97, 85, 83, 67, 55.

(2S,3S,Z)-2,3-(Ethylidenedioxy)hept-4-enal (11). A soln. of oxalyl chloride (0.26 ml, 2.8 mmol) in abs. CH₂Cl₂ (6.5 ml) was cooled to –60° and a soln. of DMSO (0.44 ml, 5.7 mmol) in abs. CH₂Cl₂ (1.5 ml) added dropwise. After 5 min, a soln. of **24** (457 mg, 2.6 mmol) in a little amount of abs. CH₂Cl₂ was added slowly and the mixture stirred for 15 min. Then, Et₃N (0.9 ml, 6.0 mmol) was added and stirred at –60° for 15 min. The cooling bath was removed and, after 10 min, H₂O (10 ml) was added. The aq. layer was extracted with CH₂Cl₂ and the org. soln. washed with brine and evaporated: 401 mg (90%) of **11**. Unstable on CC. ¹H-NMR (60 MHz): 1.0 (*t*, *J* = 7, CH₃(7)); 1.5 (*d*, *J* = 5, CH₃CHO₂); 1.8–2.2 (*m*, CH₂(6)); 4.2 (*dd*, *J*(1,2) = 4, *J*(2,3) = 7, H–C(2)); 4.7–5.9 (*m*, H–C(3), CH₃CHO₂, H–C(4), H–C(5)); 9.4 (*d*, *J* = 4, H–C(1)).

2-Methyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]pentan-3-one (19). To a mixture of Mg chips (1.70 g, 70 mmol) in abs. Et₂O (10 ml), EtBr (7.63 g, 70 mmol) in abs. Et₂O (15 ml) was added and stirred for 15 min. Then, a soln. of **26** (9.73 g, 58.3 mmol) in abs. Et₂O (60 ml) was added. After 3 h, the mixture was poured on ice, and sat. aq. NH₄Cl soln. (50 ml) was added. The mixture was filtered and extracted with Et₂O. 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 Et₂O, washing with 10% aq. Na₂CO₃ soln., evaporation, and CC (Et₂O), 8.41 g (72%) of **19** were obtained. IR (film): 2950, 2860, 1720 (C=O), 1520, 1360, 1170, 1130, 1080, 1040, 990, 870. ¹H-NMR (60 MHz): 1.0 (*t*, *J* = 7, CH₃(5)); 1.3 (*s*,

CH₃(1), CH₃(2)); 1.3–1.9 (*m*, 6 H of Thp); 2.7 (*t*, *J* = 7, CH₂(4)); 3.2–4.1 (*m*, 2 H of Thp); 4.5–4.7 (*m*, CH–O of Thp).

(6*S*,7*S*,*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*-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. NH₄Cl soln. (10 ml) was added and the mixture poured into Et₂O (200 ml), washed with brine, and evaporated. CC (Et₂O) yielded 1.640 g (90%) of 27. IR (film): 3520 (OH), 2950, 2880, 1720 (C=O), 1405, 1380, 1150, 1080, 1030, 990, 900. ¹H-NMR (60 MHz): 1.0–1.3 (*m*, CH₃CHO₂, CH₃–C(4), CH₃(11)); 1.4 (br., CH₃(1), CH₃–C(2)); 1.4–2.3 (*m*, 6 H of Thp, CH₂(10)). ¹H-NMR (90 MHz, after cleavage of the Thp group according to [16]): 0.9–1.3 (*m*, CH₃CHO₂, CH₃–C(4), CH₃(11)); 1.39 (*s*, CH₃(1), CH₃–C(2)); 1.9–2.3 (*m*, CH₂(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), CH₃CHO₂); 5.4–5.9 (*m*, H–C(8), H–C(9)).

(6*S*,7*S*,*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/CH₂Cl₂) 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-[(1*S*,2*S*,*Z*)-1,2-Dihydroxyhex-3-enyl]-2,2,4-trimethylfuran-3(2*H*)-one (17). A soln. of 18 (324 mg, 0.88 mmol) THF/H₂O/5% HCl 1:1:1 (45 ml) was stirred for 24 h. Then brine (30 ml) was added and the mixture extracted with Et₂O. The aq. layer was washed with sat. NaHCO₃ soln., evaporated, and purified by CC (Et₂O): 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. ¹H-NMR (90 MHz): 0.98 (*t*, *J* = 7, CH₃(6')); 1.35 (*s*, 2 CH₃–C(2)); 1.73 (*s*, CH₃–C(4)); 2.0–2.2 (*m*, CH₂(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')). ¹³C-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. MacLeod, *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. Liebmman, 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.