Tetrahedron. Vol. 30, pp 1431 to 1435. Pergamon Press 1974. Printed in Great Britain

FUNGAL EXTRACTIVES—VI[a]

STRUCTURE OF LACTARAL, A NEW SESQUITERPENE FURAN-3-ALDEHYDE FROM *LACTARIUS*, BY SPECTROSCOPIC METHODS[b]

G. MAGNUSSON and S. THORÉN*
Organic Chemistry 2, Chemical Center, The Lund Institute of Technology P.O. Box 740, S-220 07
Lund 7, Sweden

(*Received in the UK* 25 *September* 1973; *Accepted for publication* 12 *December* 1973)

Abstract—The structure of a new sesquiterpene furan-3-aldehyde from *Lactarius vellereus* and *L. pergamenus* has been elucidated by means of IR, UV ^{1}H- and ^{13}C-NMR spectroscopy and computer simulation of the ^{1}H-NMR spectrum.

In a recent publication on the structure of isovelleral[1] **3** we reported the isolation of two further sesquiterpene aldehydes and of two sesquiterpene lactones from *Lactarius vellereus* and *L. pergamenus* (Russulaceae). We have already described structural evidence for the dialdehyde, velleral **4**, and for the two lactones **5**, **6**.[2–4] We now report the structure **1** of the third C_{15}-aldehyde, which we have termed lactaral.

Mass spectrometry ($m/e = 232$, M^+) in combination with ^{13}C-NMR (15 C, 20 H) and ^{1}H-NMR data gave the molecular formula of the aldehyde lactaral as $C_{15}H_{20}O_2$. Analysis of the DNP derivative agreed with this. The IR spectrum suggested a furan ring and a conjugated aldehyde group. The ^{1}H-NMR spectrum showed that the furan ring is disubstituted (signals at $\delta = 7{\cdot}96$ and $7{\cdot}22$ ppm) and that there is one vinyl proton ($\delta = 5{\cdot}20$ ppm). Decoupling experiments showed that the aldehyde group is situated on the furan ring and that the double bond is isolated. Compound **1** has an absorption maximum (EtOH) of low intensity at 257 nm (ϵ 2560) characteristic of substituted furan-3-aldehydes (*cf* furfural: λ_{max} 272 nm; ϵ 13200).[5]

The substitution pattern in the furan ring was determined from the chemical shifts of the furan protons of **1**. Calculated values for the three methylfuran - 3 - aldehyde isomers were obtained using parameters for monosubstituted furans[6,7] with a solvent correction[8] to give values for $CDCl_3$ solution (upfield shift for nonpolar solvents to $CDCl_3$: 0·04 and 0·17 ppm for α and β protons respectively). Compound **1** has the alkyl substituent in position 4 of the furan ring (furan protons at 7·96 and 7·22 ppm; calculated values for 2 - methyl - furan - 3 - aldehyde: 6·76 and 7·29 ppm, 4 - methyl - furan - 3 - aldehyde: 7·89 and 7·23 ppm and 5 - methyl - furan - 3 - aldehyde: 7·85 and 6·48 ppm). The method of calculation was checked with the 3 - methyl- and 4 - methyl - furan - 2 - aldehydes[9] which also give excellent agreement (exp: 6·42, 7·57; calc: 6·49, 7·52 and exp: 7·07, 7·48; calc: 7·10, 7·42 respectively).

To obtain a more stable derivative with a somewhat simpler ^{1}H-spin system, **1** was oxidised to the methyl ester **2** with manganese dioxide.[10] Double irradiation ^{1}H-experiments on **2** showed that the furan protons couple to a methylene group α to the furan ring, that the methyl doublet at 1·01 ppm is coupled to a proton in the allylic region (2·20–3·00 ppm), and that the vinyl proton is coupled to four methylene protons at 2·11 ppm. Further, the ^{1}H-NMR spectrum and the decoupling experiments, strongly suggest that the methylene protons α to the furan ring have vicinal couplings to the proton that splits the methyl signal. Thus, a partial structure, MeOOC(furan)CH_2–$CHCH_3$–C=CH–, can be written for **2**.
|

^{13}C-NMR spectra on **2** showed signals from the furan moiety, and from two further sp^2 carbons, one with one alkyl substituent, one with two. Since the other carbon atoms concerned here are all saturated (*vide infra*), an additional ring must be incorporated to account for the unsaturation number of six given by the molecular formula. The remaining signals showed one quaternary, one methine, three methylene and two methyl carbons (Table 1). Seemingly, there is one carbon atom "missing". As is evident from the ^{1}H-NMR spectrum there are signals from three methyl groups other than the ester methyl. The doublet centered at 1·01 ppm ($J = 6{\cdot}80$ Hz) can be attributed to a methyl group attached to a tertiary carbon atom (*vide supra*) and the two singlets at 1·07 and 1·04 ppm to a *gem* dimethyl group (ν_{max} 1380, 1375 cm^{-1}). In the ^{13}C-NMR spectrum the quartet at 19·1 ppm belongs to the methyl group on the

---

[a] Part V, see Ref 4.

[b] Presented at 4:*e Nordiska Naturproduktskemiska Symposiet*, Koli Finland 16/6 1973.

tertiary carbon and the strong signals centered at 29·8 ppm result from the *two* overlapping quartets of the *gem* dimethyl group. The chemical shifts in ^{13}C-NMR are known to be strongly influenced by environmental changes even at some distance from the carbon atom concerned.[11] Thus these two coincident methyl signals might well indicate the presence of a local symmetry. Two of the methylene carbon atoms also have very similar chemical shifts.

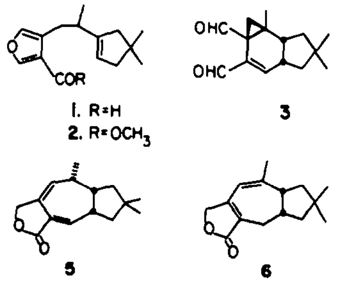
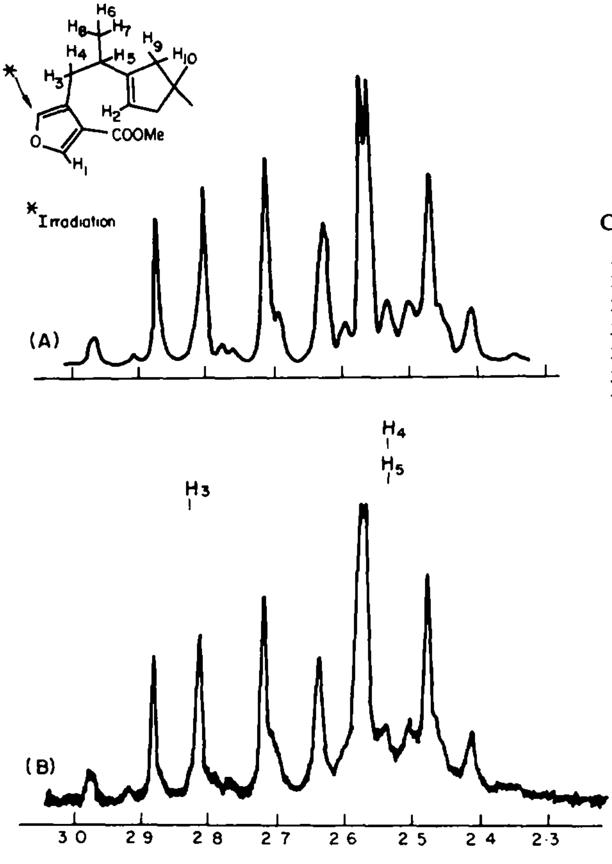


Fig 1.

This spectroscopic evidence suggests that the methyl ester has structure 2. The similarity with the four sesquiterpenoids 3–6 from *L. vellereus* and *L. pergamenus* and with lactarorufin A 7 from *L. rufus*[12] is obvious (Fig 1).

The accidental coincidence of the signals from the two methylene groups of the cyclopentene ring, giving rise to a four proton "singlet", can easily be misleading. Some model substances were therefore prepared (**8–12**, see experimental section). The two methylene groups of all these cyclopentene derivatives appear as more or less broadened "singlets" with a chemical shift close to 2·10 ppm. Another uncertainty in the structure was the aliphatic portion near the furan ring. The structure of this part of the molecule suggested by spectrometric and other information was confirmed by a theoretical simulation of the H$_1$–H$_{10}$ spin system (see Fig 2) using an extension of the UEAITR computer program.[13,14] Successive iterations gave very good agreement between the experimental (furan proton at 7·21 ppm, decoupled) and the theoretical spectra in the 2·30–3·00 ppm region. The magnitudes of all coup-



^{1}H-NMR parameters for the H$_{1-10}$ system

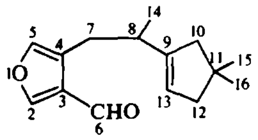
Chemical shifts (ppm)		Coupling constants (Hz)	
H$_1$	7·95	J$_{1-2}$	0·00
H$_2$	5·21	J$_{1-3}$	0·30
H$_3$	2·83	J$_{1-4}$	0·30
H$_4$	2·54	J$_{1-5}$	0·00
H$_5$	2·54	J$_{1-6,7,8}$	0·00
H$_{6,7,8}$	1·01	J$_{1-9,10}$	0·00
H$_{9,10}$	2·11	J$_{2-3}$	0·00
		J$_{2-4}$	0·00
		J$_{2-5}$	− 1·01
		J$_{2-6,7,8}$	0·00
		J$_{2-9,10}$	0·00
		J$_{3-4}$	− 14·27 −
		J$_{3-5}$	6·88
		J$_{3-6,7,8}$	0·00
		J$_{3-9,10}$	0·00
		J$_{4-5}$	7·30
		J$_{4-6,7,8}$	0·00
		J$_{4-9,10}$	0·00
		J$_{5-6,7,8}$	6·80
		J$_{5-9,10}$	0·75
		J$_{6,7,8-9,10}$	0·00

Fig 2. Partial ^{1}H-NMR spectrum (100 MHz) of ester 2. A: simulated spectrum. B: normal spectrum (double resonance).

ling constants in the H_1–H_{10} spin system are in good agreement with the suggested structure **2**. Similar simulation of the 60 MHz spectrum also showed good agreement with the spectrum obtained experimentally (same coupling constants; chemical shifts reduced by the factor 0·6), thereby providing further support for this interpretation of the coupling.

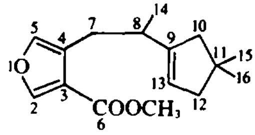
Additional evidence for the presence of the cyclopentene fragment is given by a comparison of the ^{13}C-NMR chemical shifts of the aldehyde **1**, the ester **2** and 4,4 - dimethyl - 1 - isopropyl -

Table 1. ^{13}C-NMR data for aldehyde **1**, methyl ester **2** and 4,4 - dimethyl - 1 - isopropylcyclopentene **12** (25·2 MHz, $CDCl_3$)



1

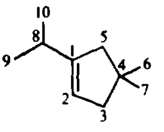
Chemical shift (ppm from TMS)	Signal multiplicity[a]	Group	Assignment (carbon no)
184·9	d	–CHO	6
152·7	d	O–ÇH=C	2
146·9	s	–Ç=C	9
142·2	d	O–ÇH=C	5
127·5	s	–Ç=C	3, 4
122·7	s	–Ç=C	
121·6	d	C=ÇH–	13
47·1	t	$-CH_2-$	10, 12
47·1	t	$-CH_2-$	
38·2	s	–C–	11
35·1	d	–CH–	8
29·9	q	$-CH_3$	15, 16
29·9	q	$-CH_3$	
29·3	t	$-CH_2-$	7
18·9	q	$-CH_3$	14



2

Chemical shift (ppm from TMS)	Signal multiplicity[a]	Group	Assignment (carbon no)
163·4	s	$-ÇOOCH_3$	6
148·5	d	O–ÇH=C	2
147·2	s	–Ç=C	9
141·1	d	O–ÇH=C	5
123·7	s	–Ç=C	4 or 3
121·2	d	C=ÇH–	13
117·9	s	–Ç=C	3 or 4
51·1	q	$COOÇH_3$	17
47·5	t	$-CH_2-$	10, 12
47·3	t	$-CH_2-$	
38·1	s	–C–	11
35·2	d	–CH–	8
29·8	q	$-CH_3$	15, 16
29·8	q	$-CH_3$	
29·5	t	$-CH_2-$	7
19·1	q	$-CH_3$	14

Table 1—*Continued*



12

Chemical shift (ppm from TMS)	Signal multiplicity[a]	Group	Assignment (carbon no)
149·5	s	$-\underline{C}{=}C$	1
119·4	d	$C{=}\underline{C}H-$	2
48·4	t	$-CH_2-$	3, 5
47·7	t	$-CH_2-$	
38·5	s	$-C-$	4
37·3	d	$-CH-$	8
30·1	q	$-CH_3$	6, 7
30·1	q	$-CH_3$	
21·4	q	$-CH_3$	9, 10
21·4	q	$-CH_3$	

[a] s = singlet, d = doublet, t = triplet, q = quartet; obtained by "off-resonance" decoupling.

cyclopentene **12** (Table 1). The close agreement of the chemical shifts for the cyclopentene carbons and the *gem*-dimethyl group carbons confirms structure **1** for lactaral.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian T-60 instrument and on a Varian XL-100 instrument with ^{13}C-NMR capability and Fourier transform equipment. Mass spectra were recorded on an LKB 1100 instrument at an ionisation potential of 70 eV.

A general description of the isolation procedure is given in Ref 2. The column chromatography was easily monitored by TLC, the aldehyde **1** having an R_f value of about 0·70 on silica with methylene chloride as eluent.

Lactaral **1**. $[\alpha]_D^{23}$ $-7{\cdot}6°$ (*c* 1·1 in chloroform); UV (ethanol): λ_{max} 257 nm (ϵ 2560), (hexane): λ_{max} 255 nm (ϵ 2340); IR (neat): ν_{max} 3140 3050 (furan), 2740 1700 (CHO), 1590 1540 (furan), 1385 1380 (*gem* di–Me), 1150, 1050, 875 (furan), 815, 755 cm^{-1}; NMR (CDCl$_3$, TMS): δ 9·93 (1H, d, J = 0·80 Hz; fur-C$\underline{H}$O), 7·96 (1H, d broad, J = 1·60 Hz; fur-$\underline{H}$), 7·22 (1H, sextet broad, J = 0·80 Hz; fur-$\underline{H}$), 5·20 (1H, s broad; C=CH–), 2·35–3·00 (3H, m; fur–C$\underline{H}_2$–C$\underline{H}$CH$_3$–C=CH), 2·07 (4H, s broad; C–C$\underline{H}_2$–C=CH–C$\underline{H}_2$–C), 1·05 1·03 (3H each, s; C–C$\underline{H}_3$), 1·02 (3H, d, J = 6·8 Hz; CH–C$\underline{H}_3$) ppm; for ^{13}C-NMR data see Table 1; MS *m/e*: 232 (M$^+$, 16%)($C_{15}H_{20}O_2$), 214 (15%), 199 (19%), 123 (100%; base peak), 81 (60%). 2,4 - Dinitrophenylhydrazone: M.p. 169–170°. (Found: C, 61·1; H, 6·0; N, 13·3. $C_{21}H_{24}N_4O_5$ requires: C, 61·2; H, 5·9; N, 13·6%).

Methyl ester **2**. Lactaral (162 mg) was oxidised with manganese dioxide according to Corey *et al.*[10] After work-up of the reaction mixture a crude oil was obtained which was chromatographed on a silica gel column. Elution with methylene chloride–carbon tetrachloride (1:4) gave the pure methyl ester **2** (150 mg) (82%) which had: $[\alpha]_D^{22}$ $-12{\cdot}9°$ (*c* 1·13 in methylene chloride); UV (ethanol): λ_{max} 243 nm (ϵ 2300); IR (neat): ν_{max} 3160 3050 (furan), 1735 (ester C=O), 1655 (C=C), 1595 1540 (furan), 1380 1375 (*gem* di-Me), 1310, 1230, 1150, 1100, 1055, 885 (furan) cm^{-1}; NMR (CDCl$_3$, TMS): δ 7·95 (1H, d broad, J = 1·70 Hz; fur-$\underline{H}$), 7·21 (1H, pentet broad, J = 0·90 Hz; fur-$\underline{H}$), 5·21 (1H, s broad; C=C$\underline{H}$–), 3·82 (3H, s; COOC$\underline{H}_3$), 2·30–3·00 (3H, m; for interpretation see Fig 2), 2·11 (4H, s broad; C–C$\underline{H}_2$–C=CH–C$\underline{H}_2$–C), 1·07 1·04 (3H each, s; C–C$\underline{H}_3$, C–C$\underline{H}_3$), 1·01 (3H, d, J = 6·80 Hz; CH–C$\underline{H}_3$) ppm; ^{13}C-NMR (16 C, 22 H) see Table 1; MS *m/e*: 262 (M$^+$, 13%) ($C_{16}H_{22}O_3$), 247 (15%), 230 (12%), 123 (100%; base peak), 81 (55%).

4,4 - *Dimethylcyclopentene* **8**. 4,4 - Dimethylcyclopentene - 1 - carboxaldehyde[15] (500 mg) was added to tris ((triphenylphosphine) chlororhodium[16] (60 mg). The mixture was stirred at room temperature for 1 h to generate the catalytically active carbonyl - bis (diphenyl - phosphine)chlororhodium, and then heated (reflux) at 205°. The evolution of carbon monoxide was measured. After 2·5 h the reaction mixture was distilled to give isomer-free 4,4 - dimethylcyclopentene **8**, b.p. 80° (lit.[17] 74–75°) (120 mg; 76% calc. on reacted aldehyde) and unreacted aldehyde (300 mg). NMR data (^{1}H and ^{13}C) for the olefin were in agreement with the structure (four allylic methylene protons at 2·14 ppm).

1,4,4-*Trimethylcyclopentene* **9**. This compound was prepared from isophorone via 2,4,4 - trimethylcyclopentanone[18] with reduction of its diethyl enol phosphate with lithium in ethylamine.[19] Work up and distillation gave the olefin **9**, which had b.p. 100–102°. NMR data (^{1}H and ^{13}C) of the olefin were in agreement with the structure (four allylic methylene protons at 2·09 ppm).

1 - (4,4 - *Dimethylcyclopentene*) - 1 - *ethanol* **10**. 4,4 - Dimethylcyclopentene - 1 - carboxaldehyde[15] was alkylated by a standard methyl lithium reaction. Alcohol **10** was obtained in 84% yield and had: B.p. 76–77°/12 mm; n_D^{24} 1·4590; IR (neat): ν_{max} 3350, 3060, 1680, 1385, 1370 1065 cm^{-1}; NMR (CDCl$_3$, TMS): δ 5·56 (1H, s broad; C=C$\underline{H}$–), 4·32 (1H, q broad, J = 6·5 Hz; =C–C$\underline{H}$OH–CH$_3$),

2·10 (4H, s; two $\mathrm{C{-}C\underline{H}_2{-}C{=}}$), 1·22 (3H, d, $J = 6·5$ Hz; $\mathrm{CHOH{-}C\underline{H}_3}$), 1·02 (6H, s; two $\mathrm{-CH_3}$) ppm; MS (21 eV) *m/e*: 140 ($\mathrm{M^+}$) ($\mathrm{C_9H_{16}O}$). (Found: C, 77·1; H, 11·3. $\mathrm{C_9H_{16}O}$ requires: C, 77·1; H, 11·5%). p-Nitrobenzoate m.p. 60–62°.

1 - (1 - *Chloroethyl*) - 4,4 - *dimethylcyclopentene* **11**. The allylic alcohol **10** was chlorinated by the triphenyl phosphine–carbon tetrachloride method.[20] The chloride **11** was obtained in 60% yield and had: B.p. 57–58°/11 mm; n_D^{24} 1·4623; IR (neat): ν_{max} 3060, 1680, 1385, 1370, 825 $\mathrm{cm^{-1}}$; NMR ($\mathrm{CDCl_3}$, TMS): δ 5·62 (1H, m; $\mathrm{C{=}C\underline{H}{-}}$), 4·68 (1H, q broad, $J = 6·5$ Hz; $\mathrm{{=}C{-}C\underline{H}Cl{-}CH_3}$), 2·22 (4H, s broad; two $\mathrm{C{-}C\underline{H}_2{-}C{=}}$), 1·63 (3H, d, $J = 6·5$ Hz; $\mathrm{CHCl{-}C\underline{H}_3}$), 1·12 (6H, s; two $\mathrm{-CH_3}$) ppm. (Found: C, 68·1; H, 9·4. $\mathrm{C_9H_{15}Cl}$ requires: C, 68·2; H, 9·5%.)

4,4 - *Dimethyl* - 1 - *isopropylcyclopentene* **12**. Methyl lithium (11 mmol) in ether (13 ml) was added dropwise with stirring to cuprous iodide (0·85 g; 4·6 mmol) in ether (25 ml) at 0° under nitrogen. The chloride **11** (0·67 g; 4·2 mmol) was added to this dimethyl copper–lithium reagent.[21] Stirring was continued for 21 h at 0°. Addition of water, separation of the organic phase, drying and evaporation of the ether through a 30 cm Vigreux column gave a residue which was distilled to give olefin **12** in 77% yield. B.p. 60°/11 mm; n_D^{22} 1·4386; IR (neat): ν_{max} 3060, 3050, 1650, 1385, 1370, 815 $\mathrm{cm^{-1}}$; NMR ($\mathrm{CDCl_3}$, TMS): δ 5·17 (1H, m; $\mathrm{-CH{=}C}$), 2·08 (4H, s broad; two $\mathrm{C{-}C\underline{H}_2{-}C{=}}$), 1·57 (1H, m; $\mathrm{{=}C{-}C\underline{H}(CH_3)_2}$), 1·06 (6H, s; two $\mathrm{C{-}CH_3}$), 0·94 (6H, d, $J = 7·5$ Hz; $\mathrm{CH{-}(C\underline{H}_3)_2}$); MS *m/e*: 138 ($\mathrm{M^+}$, 32%) ($\mathrm{C_{10}H_{18}}$), 123 (100%, base peak), 109 (90%), 95 (68%); ^{13}C-NMR: See Table 1.

Acknowledgements—We thank Prof. B. Wickberg for stimulating discussions, Dr. T. Drakenberg for measurements of NMR spectra, Dr. P. Stilbs for guidance in data techniques and Dr. B. Thomas for helpful linguistic criticism. This work was in part supported by the Swedish Natural Science Research Council.

REFERENCES

[1] G. Magnusson, S. Thorén and B. Wickberg, *Tetrahedron Letters* 1105 (1972)

[2] G. Magnusson, S. Thorén and T. Drakenberg, *Tetrahedron* **29**, 1621 (1973)

[3] G. Magnusson and S. Thoren, *Acta Chem. Scand.* **27**, 1573 (1973)

[4] *Idem, Ibid.* **27**, 2396 (1973)

[5] E. S. Stern and C. J. Timmons, *Gillam and Stern's Introduction to Electronic Absorption Spectroscopy in Organic Chemistry* 3d Ed. p. 166. Edward Arnold Ltd, London (1970)

[6] S. Gronowitz, G. Sörlin, B. Gestblom and R. A. Hoffman, *Arkiv Kemi* **19**, 483 (1963)

[7] R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **39**, 905 (1961)

[8] P. Laszlo, *Bull. Soc. Chim. Fr.* 2658 (1964)

[9] J. P. Kutney, H. W. Hanssen and G. Vijayakumaran Nair, *Tetrahedron* **27**, 3323 (1971)

[10] E. J. Corey, N. W. Gilman and B. E. Ganem, *J. Am. Chem. Soc.* **90**, 5616 (1968)

[11] G. C. Levy and G. L. Nelson, *Carbon*-13 *Nuclear Magnetic Resonance for Organic Chemists*, Wiley-Interscience, New York, London, Sydney, Toronto, (1972)

[12] W. M. Daniewski and M. Kocór, *Bull. Acad. Pol. Sci. Ser. Chim.* **19**, 553 (1971)

[13] R. B. Johannesen, J. A. Feretti and R. K. Harris, *J. Magnetic Resonance* **3**, 84 (1970)

[14] Extension of the program was made by Dr. Peter Stilbs, Physical Chemistry 2, Chemical Center, Lund

[15] G. Magnusson and S. Thorén, *J. Org. Chem.* **38**, 1380 (1973)

[16] J. A. Osborne, F. H. Jardine, J. F. Young and G. Wilkinson, *J. Chem. Soc.* (*A*) 1711 (1966)

[17] H. Kwart and J. A. Ford, *J. Org. Chem.* **24**, 2060 (1959)

[18] G. D. Ryerson, R. L. Wasson and H. O. House in *Organic Syntheses* Coll. Vol. IV, p. 957. Wiley: New York, London (1963)

[19] D. C. Muchmore, *Ibid.* **52**, 109 (1972)

[20] I. M. Downie, J. B. Holmes and J. B. Lee, *Chem and Ind.* 900 (1966)

[21] E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.* **89**, 3911 (1967)