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Oxidative Cyclization of Some γ- and δ-Hydroxy Olefins Induced by Tellurium Dioxide[1]

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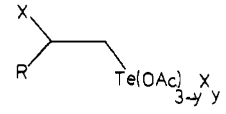
Abstract: TeO_2 reacted with 2 equiv of a γ- or δ-hydroxy olefin in acetic acid containing LiCl. The resulting dialkyltellurium dichlorides are derivatives of furan, tetrahydropyran, and 2,3-dihydrobenzofuran, formed via an internal cyclization. The dialkyltellurium dichlorides were reduced to their corresponding dialkyltellurides with use of $Na_2S_2O_5$ or hydrazine hydrate. A mechanism is postulated involving an electrophilic attack by a solubilized tellurium species followed by an intramolecular nucleophilic attack by a hydroxy group. An analysis of the vicinal proton coupling constants indicated one preferred conformation of the dialkyltellurium dichlorides, where the oxygen atoms of the furan rings are coordinated to tellurium.

Introduction

We have recently reported some stereochemical results concerning the oxidation of alkenes to alkanediol monoacetates and diacetates with tellurium dioxide in acetic acid solution containing a lithium halide.[2a] These results, together with results from the reaction of phenylacetylenes with the system TeO_2/HOAc/LiX,[2b] prompted us to suggest an electrophilic attack as likely to be involved in the first step of the oxidation of alkenes with TeO_2, although a postulated intermediate **1** could never be isolated.



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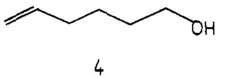
However, we felt that it might be possible to trap an intermediate, if a suitably positioned nucleophilic grouping, e.g., a hydroxy group, was present in the molecule. In this paper we would like to report the reaction of tellurium dioxide with various γ- and δ-hydroxy olefins in acetic acid solution containing lithium chloride.

Results

We have found that tellurium dioxide in acetic acid solution containing LiCl readily adds 2 equiv of a γ- or δ-hydroxy olefin, in a cyclofunctionalization reaction,[3] to yield a dialkyltellurium dichloride. Thus 4-penten-1-ol gave bis(2-tetrahydrofurfuryl)tellurium dichloride (**2**) as a white crystalline material in 58% yield according to Scheme I. A possible isomeric structure **3** of this compound could be excluded by an independent synthesis starting from tetrahydrofurfuryl bromide and sodium telluride (Scheme II). 5-Hexen-1-ol (**4**) likewise gave the tetrahydropyran derivative **5** in 50% yield.



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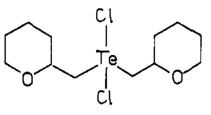

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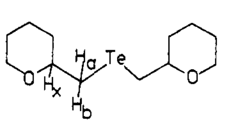

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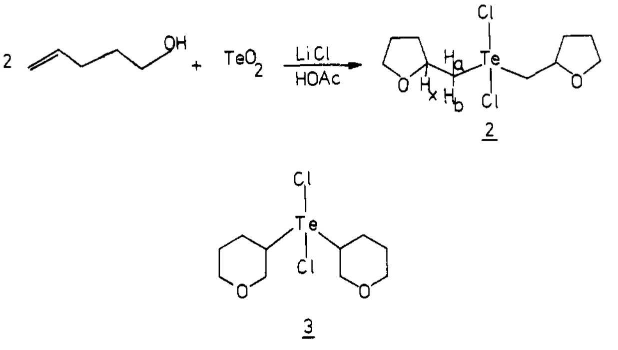
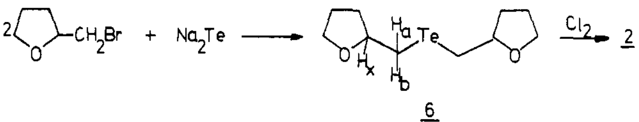
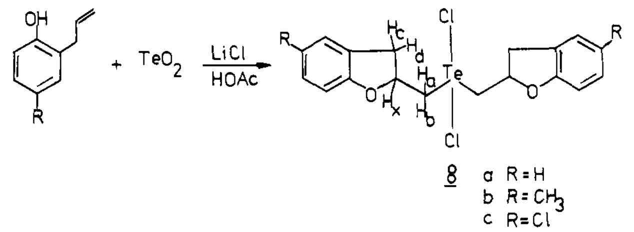
Scheme I



Scheme II



Scheme III



The two dialkyltellurium dichlorides **2** and **5** could easily and in almost quantitative yields be reduced to their corresponding dialkyltellurides **6** and **7**, respectively, by the use of hydrazine hydrate in ethanol.[4]

The 2-allylphenols constitute another class of γ-hydroxy olefins that could be analogously cyclized with TeO_2 in HOAc to give 2,3-dihydrobenzofuran derivatives **8**, according to Scheme III. Similar cyclizations induced by PhSeCl have recently been studied by Clive[5] and Nicolaou.[6] The three compounds **8a–c** crystallized directly from the cooled acetic acid solution in 70–78% yield when TeO_2 was refluxed for 2–4 h with 2 equiv of the appropriate 2-allylphenol in the presence of lithium chloride. Further evidence for the proposed cyclized structure of these products was obtained by Raney nickel (W2) treatment of compound **8a** in ethanol. This yielded a mixture (5:2) of 2-methyl-2,3-dihydrobenzofuran (**9**)

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[1] Part 13 in the series "Tellurium in Organic Synthesis"; for part 12, see: J. Bergman and L. Engman, *J. Am. Chem. Soc.*, **103**, 2715 (1981).

[2] (a) J. Bergman and L. Engman, *J. Organomet. Chem.*, **181**, 335 (1979); (b) *Tetrahedron Lett.*, 1509 (1979); *J. Organomet. Chem.*, **201**, 377 (1980).

[3] D. L. J. Clive, C. G. Russell, G. Chittattu, and A. Singh, *Tetrahedron*, **36**, 1399 (1980).

[4] J. Bergman, *Tetrahedron*, **28**, 3323 (1972).

[5] D. L. J. Clive, G. Chittattu, N. J. Curtis, W. A. Kiel, and C. K. Wong, *J. Chem. Soc., Chem. Commun.*, 725 (1977).

[6] K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.*, **102**, 3784 (1980).

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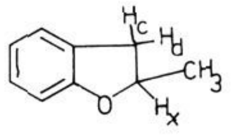
and 2-propylphenol (**10**). A satisfactory conversion of **8a** into



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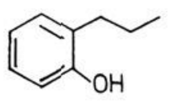

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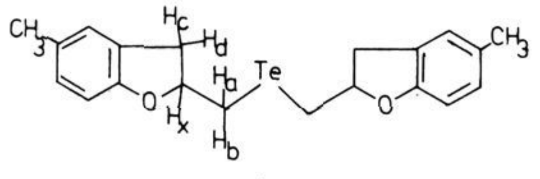
9 could be effected by triphenyltin hydride in refluxing toluene.[7] Sodium borohydride in ethanol was inefficient (cf. ref 8).

Attempted reduction of the dialkyltellurium dichloride **8b** with either hydrazine hydrate or $Na_2S_2O_5$ unexpectedly resulted in formation of two tellurium-containing products. One of them was the a priori expected dialkyl telluride **11**, the other one the corresponding dialkyl ditelluride **12**, apparently formed via rupture of a carbon–tellurium bond. Furthermore, the yield in this reduction process was considerably lower than those obtained in the clean reductions of compounds **2** and **5**.



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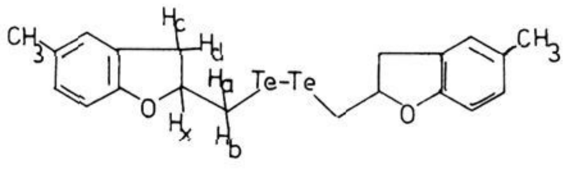

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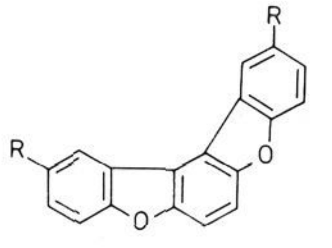
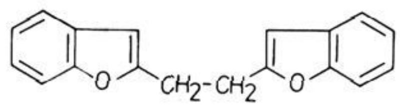
Treatment of **8a** with Pd/C in refluxing 4-methylisopropylbenzene (*p*-cymene) afforded the coupling product **13a** in good yield. This complex benzofuran had earlier been synthesized[9,10] in this laboratory via **13b** (obtained by acid-induced dimerization of *p*-quinone[9]) or by cyclization of 2-(2-oxocyclohexyloxy)dibenzofuran effected by polyphosphoric acid followed by dehydrogenation.[10]

The formation of **13a** from **8a** can be rationalized as follows.



13 a R = H
b R = OH



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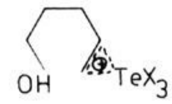
After an initial dehydrogenation the benzylic compound formed would be expected[11] to undergo coupling to **14**, which under the reaction conditions should undergo coupling followed by a final dehydrogenation step yielding **13a**.

Mechanistic Considerations

The "normal" oxidation of alkenes with TeO_2 in acetic acid containing a lithium halide produces 1,2-alkanediol monoacetates and diacetates together with elemental tellurium. When a suitably positioned hydroxy group is introduced in the alkene, apparently no reduction of tellurium occurs, but a stable tellurium(IV) species is formed owing to participation of the hydroxy group. It seems likely that the cyclic products originate from an intramolecular capture of a reactive intermediate like **15**, where X is Cl, OH, or an acetoxy group or a combination of the three. Alternatively a species **16** may be involved. The β chlorine of this molecule is expected to readily undergo a nucleophilic attack (cf. the facile ethanolysis of 8-chloro-4-cyclooctenyltellurium trichloride).[2a]

Figure 1. Acyclic methylene protons H_A/H_B of compound **7**.



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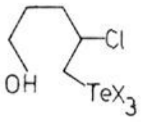

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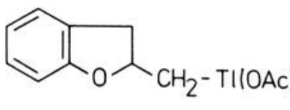
In this connection the results of related cyclofunctionalizations of 2-allylphenol with $Tl(OAc)_3$ and $Hg(OAc)_2$, leading to, e.g., **17** but also to ring-expanded products (chromanes), are of interest.[8]



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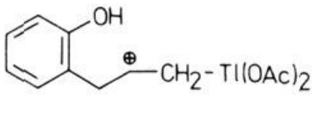

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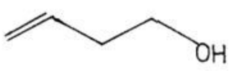
It was concluded that the carbocation formed from the olefin with Hg(II) is longer lived than that formed with Tl(III), which in turn is inconsistent with a representation of the carbocations (e.g., **18**) as "free" ions. More or less interaction of the positive charge on carbon with the neighboring metal atom must be assumed. In the present case involving the more electropositive metal, tellurium, this effect should be even more pronounced, and accordingly no ring-expanded products could be observed.

For the hydroxyalkenes studied in this paper, an exo ring closure is exclusively preferred, although both 5-exo and 6-endo closures are allowed according to the rules for ring closure.[12]

An attempted cyclization of α- and β-hydroxy olefins produced only "normal" oxidation products and no cyclized compounds. Thus treatment of 3-buten-1-ol (**19**) with TeO_2 in HOAc in the presence of LiCl caused separation of elemental tellurium and formation of the triacetate **20**. Allyl alcohol reacted similarly. The reason for this behavior may be a ring opening, e.g., by acetate, of the initially formed strained three- and four-membered rings (that should be kinetically favored), followed by oxidation according to the general, as yet unknown patthway leading to 1,2-alkanediol monoacetates and diacetates.



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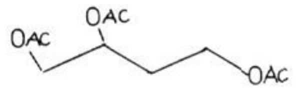

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Conformational Aspects

The tellurium-containing compounds **2**, **5**–**8**, **11**, and **12** all contain two chiral centers, and the products are therefore obtained as mixtures of diastereoisomers. Although no separation of these

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(7) D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. M. Menchen, C. G. Russell, A. Singh, C. K. Wong, and N. J. Curtis, *J. Am. Chem. Soc.*, **102**, 4438 (1980).

(8) A. Lethbridge, R. O. C. Norman, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 2465 (1975).

(9) H. Erdtman and N. E. Stjernström, *Acta Chem. Scand.*, **13**, 653 (1959).

(10) N. E. Stjernström, *Acta Chem. Scand.*, **16**, 553 (1962).

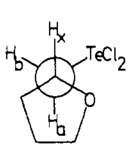
(11) (a) Benzyl tellurides are readily coupled[11b] with degassed Raney nickel as well as with Pd/C (cf. ref 4 and 11c); (b) J. Bergman, unpublished results; (c) S. Uemura, M. Wakasugi, and M. Okano, *J. Organomet. Chem.*, **194**, 277 (1980).

(12) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

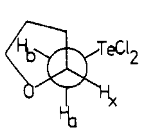
was performed using physical methods, it could be seen from the ^1H NMR spectra (especially from the signals of the acyclic methylene protons H_A/H_B) that equal amounts of the *d,l* pair and the meso form were always present. A maximum separation of the diastereoisomers of 0.03 ppm was recorded for compound **8a** (see Table I). The spectra are further complicated by the presence of two pairs of diastereotopic[13] protons H_A/H_B and H_C/H_D, respectively. Figure 1 shows a nice 16-line pattern of the two diastereotopic protons H_A/H_B of compound **7**, clearly resolved in its diastereoisomers.

Important information concerning the conformation of a molecule in solution can often be obtained by studies of the proton vicinal coupling constants.[14] In the present case the coupling constants J_{AX} and J_{BX} should provide information about the coordination around the tellurium atom while J_{CX} and J_{DX} may give us an idea of the preferred conformation of the five-membered dihydrofuran ring.

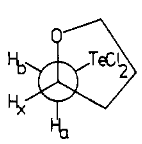
The ^1H NMR spectra of the dialkyltellurium dichlorides **2** and **8a–c** showed one large (J_{AX} = 10.56–11.04 Hz) and one small (J_{BX} = 3.90–4.32 Hz) vicinal coupling constant (Table I). These values are consistent only with a conformation in which H_X is anti to one of the protons H_A or H_B and gauche to the other, e.g., conformers **21a** or **21b**. We have previously shown that an electron-deficient tellurium atom, at least in the solid state, can coordinate an electron-rich ligand like the oxygen of an ethoxy group.[2a] This information urge us to suggest that the dialkyltellurium dichlorides studied in this paper are predominantly in one conformation, viz., **21a**, since this is the only conformer that allows coordination of the furan oxygen to tellurium. On the other hand, it is obvious from Table I that the coupling constant difference, $J_{AX} - J_{BX}$, is significantly decreased when the electron deficiency of tellurium is lowered by reduction to the divalent state. The energy difference between conformers seems to be relatively small for compounds **6–7**, and **11** and **12**.



21a

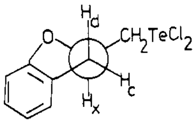


21b

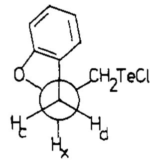


21c

The other vicinal coupling constants of compounds **8**, J_{CX}/J_{DX}, also showed one large (9.03–9.65 Hz) and one small (5.10–5.37 Hz) coupling constant which should be compared with the values[15] 7.87/8.42 Hz obtained for 2-methyl-2,3-dihydrobenzofuran (**9**). This indicates a preference of conformer **22a** over conformer **22b**.



22a



22b

The diastereotopic protons H_A/H_B of compound **6** were found to be accidently equivalent, and the NMR data for compound **5** were omitted in Table I because no reliable interpretation of the complex spectrum could be done.

Stability of the Compounds

The coordination of the tellurium atom in the dichlorides (e.g., **2** and **8a**) to the oxygen atom just demonstrated has a profound influence on the stability, and they can be stored without protection against light, air, and moisture. It was especially noted that

Table I. Chemical Shifts[a] and Coupling Constants for Dialkyltellurium Dichlorides and Dialkyl Tellurides

compd no.	δ														
	H_A	H_B	H_C	H_D	H_X	other cyclic methylene protons	aromatic area	CH_3	$\lvert J_{AB}\rvert$	J_{AX}	J_{BX}	$\lvert J_{CD}\rvert$	J_{CX}	J_{DX}
2	3.54/3.56	3.78/3.79			4.67	1.75 (m, 1 H), 2.00–2.20 (several peaks, 3 H), 3.85 (m, 1 H), 4.06 (m, 1 H)			10.74	10.74	4.05			
6	2.86	2.86			4.07	1.60 (m, 1 H), 1.85–2.15 (several peaks, 3 H), 3.75 (m, 1 H), 3.91 (m, 1 H)				6.20	6.20			
7	2.84/2.85	2.69/2.70			3.97	1.23–1.83 (several peaks, 6 H), 3.37–3.50 (several peaks, 2 H)			11.72	7.07	5.86			
8a	3.79	3.91/3.94	3.05	3.55	5.56		6.85–6.95 (several peaks, 2 H), 7.14–7.26 (several peaks, 2 H)		10.56	10.56	4.32	15.87	5.37	9.03
8b	3.72	3.89/3.91	3.00	3.50	5.51		6.75 (d, 1 H, *J* = 8.10), 6.94–7.00 (several peaks, 2 H)	2.29	10.74	10.74	3.91	15.62	5.24	9.65
8c	3.768/3.772	3.90/3.92	3.03	3.55	5.58		6.79 (dd, 1 H, *J* = 8.30, *J* = 1.96), 7.11–7.17 (several peaks, 2 H)		11.04	11.04	3.90	15.90	5.10	9.15
11	3.02	3.12	2.91	3.34	5.02		6.62 (d, 1 H, *J* = 7.81), 6.88–6.95 (several peaks, 2 H)	2.27	12.20	6.84	5.86	16.01	7.32	9.04
12	3.51/3.52	3.637/3.643	2.93	3.34	4.95		6.64 (d, 1 H, *J* = 8.05), 6.88–6.95 (several peaks, 2 H)	2.27	11.72	7.08	5.86	15.87	6.84	8.79

[a] Measured in $CDCl_3$ relative to Me_4Si.

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[13] W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).

[14] L. M. Jackman and D. P. Kelly, *J. Chem. Soc. B*, 102 (1970); 110 (1970).

[15] (a) In the literature[15b] these coupling constants are reported as $J_{AX} = J_{BX}$ = 8.5 Hz, which is probably due to a measurement on a low-resolution instrument. (b) V. S. Petrosyan, E. A. Karakhanov, L. G. Saginova, E. A. Viktorova and S. V. Lysenko, *Vestn. Mosk. Univ. Khim.*, **28**, 717 (1973).

compound **8a** can be refluxed in xylene (135 °C) for 48 h without any decomposition. It might be added that TeCl$_4$–alkene adducts (cf. ref. 2a) are much more sensitive and should be stored in a refrigerator under dry nitrogen.

When the chlorine atoms in, e.g., **2** and **8a** are stripped off, the insensitivity is lost and the resulting compounds **6** and **11** are as sensitive as normal aliphatic tellurides, and should be accordingly handled (cf. ref 5).

Experimental Section

Elemental analyses were performed by Centrala Analyslaboratoriet, Uppsala, Sweden. NMR spectra were recorded on a Bruker WP 200 instrument. Infrared spectra were obtained using a Perkin-Elmer 257 instrument and mass spectra were recorded with an LKB 9000 mass spectrometer. All melting points are uncorrected. TeO$_2$ was obtained from PCR Research Chemicals Inc. 3-Buten-1-ol and 4-penten-1-ol were purchased from Aldrich Chemical Co. 6-Hexen-1-ol was obtained from Ventron GMBH. 2-Allylphenol,[16] 2-allyl-4-methylphenol,[17] 2-allyl-4-chlorophenol,[18] 2-methyl-2,3-dihydrobenzofuran,[19] and tetrahydrofurfuryl bromide[20] were synthesized according to literature procedures.

Bis(2-tetrahydrofurfuryl)tellurium Dichloride (2). TeO$_2$ (2.0 g, 12.5 mmol), 4-penten-1-ol (2.0 g, 23.3 mmol), and LiCl (1.5 g, 35.4 mmol) were refluxed in HOAc (40 mL) for 15 h. The cooled solution was then poured into ethyl ether (150 mL) and neutralized with NaHCO$_3$ (5% aq). The organic phase was separated, dried (CaCl$_2$), and evaporated to yield a liquid that crystallized upon cooling (−15 °C), yield (**2**) 2.5 g (58%), mp 78–79 °C (ethanol). Anal. Calcd for $C_{10}H_{18}O_2Cl_2Te$: C, 32.57; H, 4.92; Cl, 19.23; Te, 34.60. Found: C, 32.58; H, 5.06; Cl, 19.25; Te, 34.45. Mass spectrum *m/e* (rel intensity, only peeaks stronger than 5% of the base peak above *m/e* 70) 300 (25), 298 (24), 296 (14), 149 (29), 86 (8), 85 (100), 84 (27), 83 (22), 72 (5), 71 (100). IR (KBr): 2970 (m), 2940 (m), 2870 (m), 1460 (w), 1400 (m), 1290 (w), 1180 (w), 1080 (s), 1030 (s), 935 (w), 915 (w), 785 (w).

Bis(2-tetrahydrofurfuryl) Telluride (6). Bis(2-tetrahydrofurfuryl)-tellurium dichloride (0.399 g, 1.08 mmol) and hydrazine hydrate (1.0 g, 20 mmol) were stirred in ethanol (20 mL) at 60 °C for 30 min. The cooled yellowish solution was then poured into water and extracted with ethyl ether. The organic phase was washed with water, dried (CaCl$_2$), and evaporated to yield compound **6** as a yellow oil, 296 mg (92%). The compound could also be independently synthesized according to the following procedure. Tetrahydrofurfuryl bromide (2.0 g, 12.1 mmol) in ethanol (25 mL) was added under N$_2$ to a stirred solution of sodium telluride [prepared from elemental tellurium (0.75 g, 5.9 mmol) and sodium borohydride (0.55 g in water, 25 mL)[21]] kept at 70 °C. After 1 h at this temperature the reaction mixture was poured into water and extracted with ethyl ether. The organic phase was dried (CaCl$_2$) and evaporated to yield 1.4 g (80%) of compound **6**, bp 176 °C (10 mm): IR(neat) 2960 (s), 2860 (s), 1460 (m), 1410 (w), 1350 (m), 1150 (w), 1090 (m), 1050 (s), 920 (m), 865 (w). When Cl$_2$ gas was bubbled through a CCl$_4$ solution of this oil, the dichloride **2** was immediately precipitated, identical in all respects with the compound described above.

Bis(2-tetrahydropyranylmethyl)tellurium Dichloride (5). TeO$_2$ (1.8 g, 11.3 mmol), 5-hexen-1-ol (2.0 g, 20.0 mmol), and LiCl (1.5 g, 35.4 mmol) were refluxed in HOAc (40 mL) for 16 h. The cooled solution was then poured into ethyl ether (150 mL) and neutralized with NaHCO$_3$ (5% aq). The organic phase was separated, dried (CaCl$_2$), and evaporated to yield a liquid that crystallized when dissolved in ethanol (5 mL) and cooled to −15 °C, yield (**5**), 2.0 g (50%), mp 125–30 °C (ethanol). Anal. Calcd for $C_{12}H_{22}O_2Cl_2Te$: C, 36.32; H, 5.59. Found: C, 36.34; H, 5.76. Mass spectrum *m/e* (rel intensity, only peaks stronger than 10% of the base peak above *m/e* 80) 328 (46), 326 (44), 324 (28), 323 (11), 99 (100), 98 (18), 97 (32), 85 (95), 81 (80). IR (KBr): 2930 (s), 2850 (m), 1430 (w), 1400 (m), 1350 (m), 1210 (m), 1170 (w), 1080 (s), 1045 (s), 900 (m). ^{1}H NMR (CDCl$_3$, Me$_4$Si) δ 1.34–2.07 (several peaks, 6H), 3.42–3.57 (several peaks, 2 H), 3.70 (m, 1 H), 3.89–4.09 (several peaks, 2 H).

Bis(2-tetrahydropyranylmethyl) Telluride (7). Bis(2-tetrahydropyranylmethyl)tellurium dichloride (0.225 g, 0.57 mmol) and hydrazine hydrate (0.50 g, 10.0 mmol) were stirred in ethanol (20 mL) at 50 °C for 20 min. The cooled yellowish solution was then poured into water and extracted with ethyl ether. The organic phase was washed with water, dried (CaCl$_2$) and evaporated to yield compound **7** as a yellow oil, 0.171 g (93%): IR (neat) 2930 (s), 2840 (s), 1440 (m), 1370 (w), 1360 (w), 1340 (w), 1275 (w), 1210 (m), 1190 (m), 1080 (s), 1050 (s), 1020 (m), 900 (m).

Bis[2-(2,3-dihydrobenzofuranyl)methyl]tellurium Dichloride (8a). TeO$_2$ (2.4 g, 15.0 mmol), 2-allylphenol (4.0 g, 30.0 mmol), and LiCl (3.0 g, 70.8 mmol) were refluxed in HOAc (50 mL) for 1.5 h. The clear solution was then filtered hot from a small amount of elemental tellurium, and upon cooling (freezing) 5.4 g (78%) of compound **8a** crystallized as a white solid. Purification of the material was achieved by dissolution in a hot 1:1 mixture of ethanol and dichloromethane which was evaporated on a water bath to half its volume and then cooled to precipitate crystals melting at 180–184 °C. Anal. Calcd for $C_{18}H_{18}O_2Cl_2Te$: C, 46.51; H, 3.90. Found: C, 46.38; H, 4.13. Mass spectrum *m/e* (rel intensity, only peaks stronger than 10% of the base peak above *m/e* 100) 396 (19), 394 (16), 392 (10), 263 (30), 261 (28), 259 (18), 134 (26), 133 (48), 132 (80), 131 (100), 119 (22), 105 (30). IR (KBr) 1590 (m), 1475 (s), 1455 (m), 1220 (s), 1160 (s), 1035 (w), 940 (s), 860 (m), 760 (s), 750 (s).

Bis[2-(5-methyl-2,3-dihydrobenzofuranyl)methyl]tellurium Dichloride (8b). TeO$_2$ (1.1 g, 6.9 mmol), 2-allyl-4-methylphenol (2.0 g, 13.5 mmol), and LiCl (1.5 g, 35.4 mmol) were refluxed in HOAc (25 mL) for 3.5 h. The clear solution was then filtered hot from a small amount of elemental tellurium, and upon cooling (freezing) 2.4 g (72%) of compound **8b** crystallized as a white solid. Purification of the material was achieved by dissolution in a hot 1:1 mixture of ethanol and dichloromethane which was evaporated on a water bath to half its volume and then cooled to precipitate crystals melting at 183–86 °C. Anal. Calcd for $C_{20}H_{22}O_2Cl_2Te$: C, 48.78; H, 4.50. Found: C, 47.60; H, 4.57. Mass spectrum *m/e* (rel intensity, only peaks stronger than 10% of the base peak above *m/e* 100) 425 (13), 424 (58), 423 (11), 422 (56), 420 (32), 419 (14), 178 (12), 177 (100), 176 (11), 175 (95), 173 (58), 172 (22), 171 (14), 148 (55), 147 (27), 146 (87), 145 (26), 133 (13). IR (KBr) 2910 (w), 1610 (w), 1490 (s), 1250 (m), 1240 (m), 1190 (m), 1170 (m), 1050 (m), 950 (m), 805 (s).

Bis[2-(5-chloro-2,3-dihydrobenzofuranyl)methyl]tellurium Dichloride (8c). TeO$_2$ (0.95 g, 5.9 mmol) 2-allyl-4-chlorophenol (2.0 g, 11.9 mmol), and LiCl (1.5 g, 35.4 mmol) were refluxed in HOAc (25 mL) for 4 h. The clear solution was then filtered from a small amount of elemental tellurium, and upon cooling (freezing) 2.2 g (70%) of compound **8c** crystallized as a white solid. Purification of the material was achieved in the same way as described for compounds **8a–b** yielding crystals melting at 151–55 °C. Anal. Calcd for $C_{18}H_{16}O_2Cl_4Te$: C, 40.50; H, 3.02. Found: C, 40.64; H, 3.28. Mass spectrum *m/e* (rel intensity, only peaks stronger than 10% of the base peak above *m/e* 100) 464 (12), 462 (10), 297 (31), 295 (26), 293 (15), 170 (14), 169 (16), 168 (80), 167 (57), 166 (100), 165 (76), 153 (20), 133 (33), 132 (26), 131 (39), 125 (19), 115 (13), 105 (20), 103 (43), 102 (13). IR (KBr): 2930 (w), 1470 (s), 1315 (w), 1235 (s), 1195 (w), 1155 (s), 1105 (m), 1060 (w), 1030 (m), 940 (m), 880 (w), 810 (s), 675 (s).

Reduction of 8b with Na$_2$S$_2$O$_5$. Bis[2-(5-methyl-2,3-dihydrobenzofuranyl)methyl]tellurium dichloride (283 mg, 0.57 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and shaken thoroughly with Na$_2$S$_2$O$_5$ (20% aq). The organic phase was separated, washed once with water, dried (CaCl$_2$), and evaporated to yield a semisolid which was filtered through a SiO$_2$ column (CH$_2$Cl$_2$). The material (110 mg) was a mixture of two tellurium-containing products that were separated using a preparative SiO$_2$ TLC plate eluted with CH$_2$Cl$_2$/light petroleum (1:1). The compound with the slightly larger R_f value, bis[2-(5-methyl-2,3-dihydrobenzofuranyl)methyl] ditelluride (**12**), was obtained in 40% yield, mp 97–8 °C (petroleum ether bp 40–60 °C). Anal. Calcd for $C_{50}H_{22}O_2Te_2$: C, 43.70; H, 4.03. Found: C, 43.64; H, 4.16. IR (KBr) 2910 (w), 2880 (w), 1490 (s), 1405 (w), 1325 (w), 1250 (m), 1210 (m), 1115 (m), 1050 (w), 950 (m), 850 (m), 810 (s), 805 (s). The compound with the smaller R_f value, bis[2-(5-methyl-2,3-dihydrobenzofuranyl)methyl] telluride (**11**), was obtained in 20% yield, mp 150–1 °C (petroleum ether bp 40–60 °C). Mass spectrum *m/e* (rel intensity, only relevant peaks above *m/e* 100) 424 (4), 422 (4), 277 (14), 275 (13), 273 (8), 149 (8), 148 (32), 147 (33), 146 (100), 145 (60), 134 (16), 133 (26), 132 (11), 131 (20). IR (KBr): 2910 (m), 1615 (w), 1490 (s), 1415 (m), 1325 (m), 1250 (m), 1240 (m), 1200 (m), 1110 (w), 935 (s), 815 (s), 810 (s).

Oxidation of 3-Buten-1-ol with TeO$_2$. TeO$_2$ (2.0 g, 12.5 mmol), 3-buten-1-ol (2.0 g, 27.8 mmol), and LiCl (1.5 g, 35.4 mmol) were refluxed in HOAc (40 mL) for 16 h. The cooled reaction mixture was then poured into ethyl ether (150 mL) and neutralized with NaHCO$_3$ (5% aq). Drying (CaCl$_2$) of the organic phase and evaporation (including also excess 3-buten-1-ol) yielded 2.4 g (43%) of 1,2,4-trihydroxybutane triacetate (**20**), bp 154 °C (17 mm) (lit.[22] 158 °C (17 mm). The product

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was contaminated by a small amount of a compound that could be acetylated in acetic anhydride to give 1,2,4-trihydroxybutane triacetate. This by-product is probably a 1,2,4-trihydroxybutane diacetate.

Reaction of 8a with Pd/C. Formation of 13a. Compound **8a** (3.94 g) was refluxed with Pd/C (10%, 5.00 g) under N_2 in *p*-cymene (60 mL) for 24 h. The reaction mixture was filtered, concentrated, and treated with light petroleum (60–80 °C). The solid formed recrystallized from acetic acid, yielded **13a**, 1.32 g (49%), mp 142–143 °C (lit.[10] 143–144 °C) which was identical with an authentic sample.[9]

Detelluration of 8a with Triphenyltin Hydride. Compound **8a** (10 mmol) was refluxed with $(C_6H_5)_3SnH$ (50 mmol) under N_2 in toluene (150 mL) for 6 h, whereupon the solvent was removed and the residue distilled yielding 2-methyl-2,3-dihydrobenzofuran (84% yield).

Detelluration of 8a with Raney Nickel (W2). Compound **8a** (10 mmol) was refluxed with Raney nickel (ca. 20 g) under N_2 in dioxane (80 mL) for 6 h; GLC analysis of the reaction mixture revealed the formation of 2-methyl-2,3-dihydrobenzofuran and 2-propylphenol in the ratio 5:2.

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Studies on the Total Synthesis of Chlorothricolide: Stereochemical Aspects of the Intramolecular Diels–Alder Reactions of Methyl Undeca-2,8,10-trienoates

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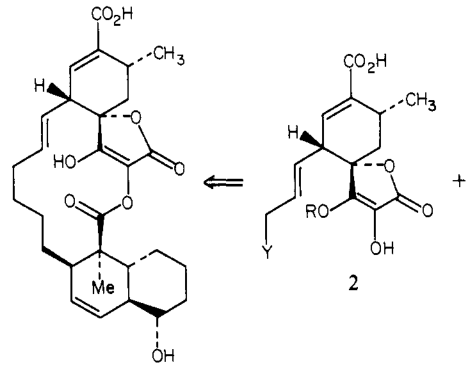
Abstract: The intramolecular Diels–Alder reactions of a series of methyl undeca-2,8,10-trienoates have been examined in connection with a planned synthesis of the bottom half **3** of chlorothricolide (**1**). The intramolecular Diels–Alder reactions of **11**, **18**, **19**, **22**, **23**, and **24** preferentially afford products possessing cis-ring fusions. In each case, the product distribution is independent of dienophile stereochemistry. Product ratios range from 62:38 to 81:19 (cis:trans). Trienes **20** and **21** afford essentially equal mixtures of cis- and trans-fused products. The intramolecular Diels–Alder reaction of trienone **46** shows reversed selectivity for the trans-fused product (65:35 trans:cis), but **47** isomerizes to **49** under the reaction conditions.

Chlorothricolide (**1**) is the aglycone of the antibiotic chlorothricin, which was isolated from *Streptomyces antibioticus* in 1969.[1] Chlorothricin is active against gram-positive bacteria, functioning as an inhibitor of pyruvate carboxylase and maleate dehydrogenase.[2] Chlorothricolide, a hydrolysis product of chlorothricin, retains some of the original activity of chlorothricin itself.[3] Recently, Ireland and Thompson have reported their progress on the total synthesis of chlorothricolide.[4]

Our original plan for the synthesis of **1** involved construction of the bottom half **3** by the intramolecular Diels–Alder reaction of **4**. This strategy was appealing since the cyclization **4** → **3**, an endo Diels–Alder reaction, would introduce each of the stereocenters in the cyclohexene ring in a single step. In addition, some element of stereochemical control of C(1) of **3** would be expected given the proper choice of hydroxyl-protecting group.[5] Of course, the success of such a route would depend on the degree to which the cyclizations of trienes such as **4** follow the endo rule. As a test of this strategy, we chose to attempt the synthesis of compound **5**, a model for the bottom half of chlorothricolide. These efforts led to the discovery of an unexpected reactivity pattern in the intramolecular Diels–Alder reactions of a series of methyl undeca-2,8,10-trienoates. We disclose herein the results of this study.



1

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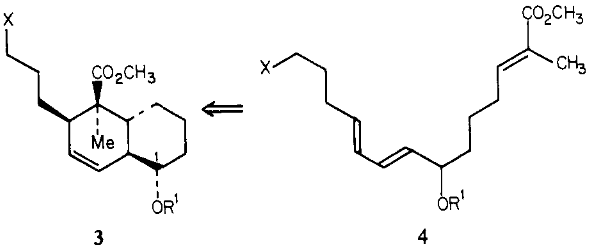

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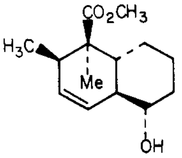
4



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Synthesis and Cyclization of Model Triene 11. Condensation of sorbaldehyde **6** with the Grignard reagent prepared from 4-bromobutyraldehyde diethyl acetal[6] afforded acetal **7** in 93% yield.

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