COMMUNICATION

Oxidations of 3-alkenyltetronic acids with dimethyldioxirane (DMD) and air: regioselectivity and formation of a spirotricyclic hemiketal endoperoxide lactone

Rainer Schobert,* Sven Siegfried, Jochen Weingärtner and Mark Nieuwenhuyzen

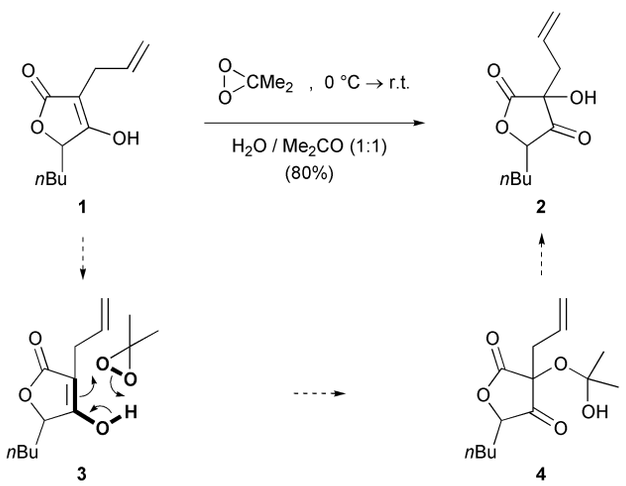
School of Chemistry, The Queen's University of Belfast, 23 Stranmillis Road, Belfast, BT9 5AG, Northern Ireland. E-mail: r.schobert@qub.ac.uk; Fax: +44-28/90 382117

Received (in Cambridge, UK) 15th May 2001, Accepted 13th June 2001
First published as an Advance Article on the web 6th August 2001

The endocyclic C=C bond of 3-allyltetronic acid 1 can be selectively oxidised with dimethyldioxirane to give 3-allyl-3-hydroxydihydrofuran-2,4-dione 2 while 3-*exo*-alkylidene-dihydrofuran-2,4-diones 9 are rapidly autooxidised to furnish the spirotricyclic hemiketal endoperoxide lactones 10.

Natural products featuring a 2,5-dihydrofuran-2,4-dione core are of considerable current interest due to the broad spectrum of bioactivity which many exhibit, such as antibiotic, antiviral, antifungal, antiparasitic, antitumour and growth promoting effects.[1,2] A good deal of them also include a high degree of oxo-functionalization. This was an incentive for us to take a closer look at their reactions with common oxidants.

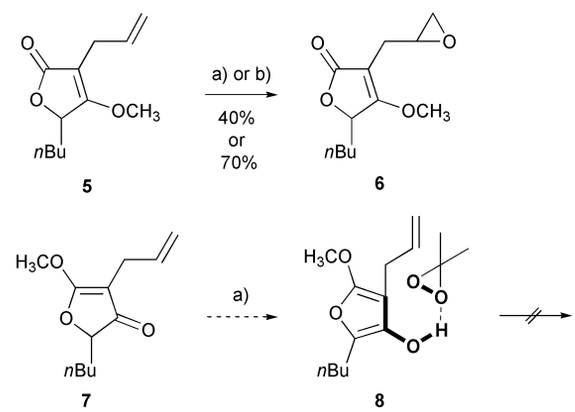
The heterocyclic core of 4-hydroxy-2,5-dihydrofuran-2-ones (tetronic acids) influences the reactivity of certain functional groups in the sidechains at C-3 and C-5. An early hint was the repeated failures to close a five-membered ring by Pd- or Pt-mediated intramolecular addition of the 4-OH group across the exocyclic C=C double bond in 3-allyltetronic acids such as **1**.[3] Analogous cyclizations of similarly acidic phenols are well-known.[4] We have now found that **1** reacts with a solution (1 equiv.) of dimethyldioxirane (DMD)[5] in acetone to give the 3-hydroxydihydrofuran-2,4-dione **2** in 80% yield rather than the anticipated epoxide. † We assume that the mechanism involves a concerted activation of both the DMD and the enolic double bond, not normally accessible for electrophiles, by formation of a six-membered cyclic transition state **3** (Scheme 1). Protonation



Scheme 1 Preferential *endo*-oxidation of 3-allyltetronic acid **1**.

of the DMD by the 4-OH group of the tetronic acid enhances both the nucleophilicity of the formal enolate and the electrophilicity of the second oxygen atom within the DMD and thus facilitates cleavage of the O–O bond. The resulting hemiketal **4** decomposes to give acetone and **2**.

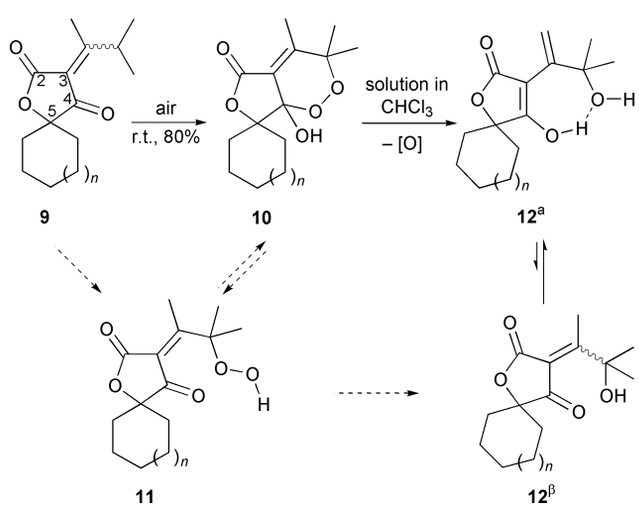
The methyl tetronate **5**, however, reacted with DMD as expected to give the epoxide **6** in 40% yield (Scheme 2). The



Scheme 2 Normal side-chain epoxidation of 3-allyltetronate **5**: a) DMD, −78 °C → rt, 12 h; b) MCPBA, $CHCl_3$, $NaHCO_3$, rt, 12 h.

same compound was obtained in 70% yield upon treating **5** with *m*-chloroperbenzoic acid (MCPBA) in chloroform. ‡ The endocyclic C=C bond proved inert towards both oxidants. Interestingly, and in keeping with the above reasoning, the isomeric 4-allyl-2-*n*-butyl-5-methoxyfuran-3(2*H*)-one **7** did not react with DMD or MCPBA. Like **1**, its aromatic en-3-ol form **8** can interact with the oxidant thus keeping it away from the exocyclic double bond while a concerted mechanism akin to **3** → **4** cannot occur. A similar enolization–aromatization of **5** to give a 2-hydroxyfuran was not observed.

3-*exo*-Alkylidenedihydrofuran-2,4-diones **9**[6] reacted differently (Scheme 3). They are stable only under a protective gas



Scheme 3 Formation and reductive ring opening of endoperoxides **10**.

DOI: 10.1039/b104227k

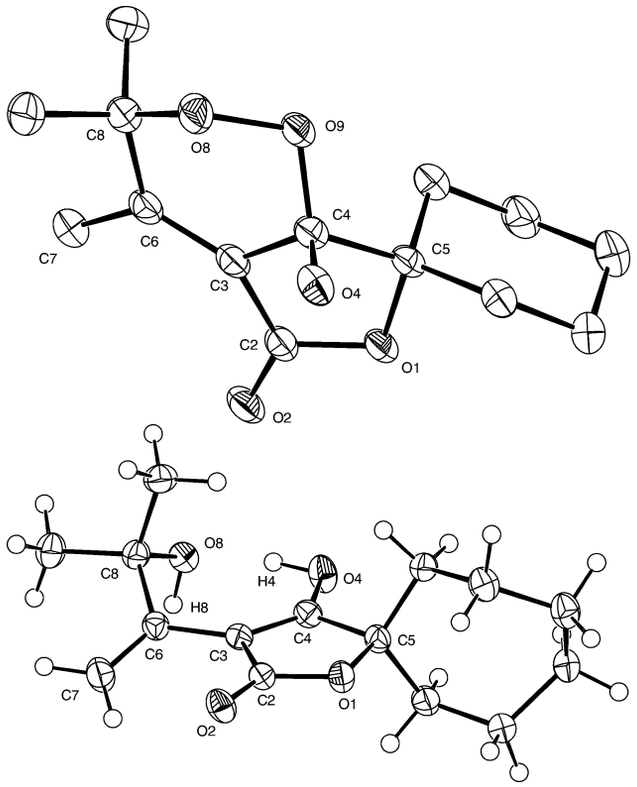


Fig. 1 Molecular structures of **10a** ($n = 1$; top) and **12b**$^{\alpha}$ ($n = 2$; bottom) (ORTEP representations, 50% probability ellipsoids; all H-atoms located). Selected bond lengths (Å): **10a/12b**$^{\alpha}$: C2–O1 1.3287(17)/1.359(3), C2–O2 1.1714(18)/1.219(2), C3–C4 1.523(2)/1.359(3), C4–O4 1.4882(17)/1.321(2), C3–C6 1.3824(19)/1.487(3), C6–C7 1.544(2)/1.324(3), C8–O8 1.5414(19)/1.461(2), O8–O9 1.4436(14)/—, C4–O9 1.3661(17)/—, O8–H8 —/0.95(3), O4–H4 —/0.96(4).

atmosphere. Chromatographic work-up of **9a** ($n = 1$) under ambient atmosphere and natural illumination yielded crops of a crystalline product precipitating from the eluate upon standing. It was shown by X-ray analysis and NMR to be the bicyclic hemiketal endoperoxide **10a** (Fig. 1, top).§ Compounds **10** were produced more efficiently by allowing solutions of **9** in chloroform to slowly evaporate in an open vial. A free-radical autooxidation at the activated tertiary allyl position to give **11** followed by closure of a six-membered endoperoxide ring is a plausible mechanistic assumption.[7] The biosynthesis of the natural antimalarial endoperoxide artemisinin was recently shown to proceed through an analogous allylhydroperoxide.[8] An alternative [4 + 2] cycloaddition of singlet oxygen to the enol tautomer of **9**, as has been proposed for the biosynthesis of a structurally similar metabolite of the Chinese shrub *Baeckea frutescens* (*Myrtaceae*),[9] appears unlikely. Compounds **9** exist exclusively as the keto tautomers shown in Scheme 3, both in solution and in the solid state. With respect to potential antimalarial activity,[10] the stability and the mode of decomposition of **10** are particularly interesting. These compounds are stable in the solid state and in ethereal solvents and methanol (no formation of the full ketal).[11] When dissolved in degassed chloroform, they decomposed in daylight within days to leave the reduced allyl alcohols **12** which exist as mixtures of tautomers (*e.g.* **12b**$^{\alpha}$: **12b**$^{\beta}$ = 3.7 : 1, with **12b**$^{\beta}$ being an unassigned 2 : 1 mixture of *E* and *Z* isomers).¶ The molecular structure of **12b**$^{\alpha}$ (Fig. 1, bottom) features an intramolecular O–H–O bridge in a seven-membered chelate ring. We surmise this formal reduction to proceed *via* hydroperoxide **11**. Of the various conceivable pathways for the decomposition of hydroperoxides the radical-induced homolytic O–O cleavage[12] eventually leading to the formation of alcohols and free oxygen seems to be most likely. The absence of further organic products such as 3-acetyltetronic acids or epoxides also rules out the Haber–Weiss process[13] (hydroperoxide → ketone + alcohol) which is predominant in the artemisinin series.[8]

The parallels in the chemistry of **10** and artemisinin and the readiness with which they lose an 'oxygen' might attract medical interest. Respective biological testing is underway.

Acknowledgements

We acknowledge the generous support from the Fonds der Chemischen Industrie and the EPSRC (grant GR/M97961).

Notes and references

† **2**: oil, bp 132 °C/0.1 Torr (Found: C, 62.14; H, 7.58. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.60%); ν_{max}(film)/cm^{-1} 3420, 1725, 1640, 910; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92 (3 H, t, ^3J 6.86 Hz, CH_3), 1.33–1.46 (4 H, m), 1.68–2.05 (2 H, m), 2.59–2.64 (2 H, m, H_2CC=), 4.41 (1 H, s, OH), 4.77 (1 H, t, ^3J 7.0 Hz, 5-H), 5.15–5.28 (2 H, m, H_2C=), 5.65–5.80 (1 H, m, =CH-C); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.3, 22.1, 27.6, 31.0, 40.1, 72.0, 84.1, 122.3, 128.2, 173.7, 208.0; *m*/*z* (EI) 211 (24%) [M$^+$], 184 (44%), 168 (100%).

‡ Compounds **5** and **7** were obtained by methylation of **1**[3] with CH_2N_2.

§ **10a** ($n = 1$): crystallization from air-saturated chloroform–*n*-pentane solutions of **9a**[6] over a period of five days gave white crystals of **10a** (80%), mp 130–131 °C (Found: C, 62.77; H, 7.56. $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.51%); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 13.1 (=C*C*H$_3$), 21.3, 22.4 (CH_2), 23.6 [C(*C*H$_3$)$_2$], 25.4, 28.0, 32.2 (CH_2), 80.7 (*C*Me$_2$), 87.6 (C-5-spiro), 99.8 (C-4), 122.7 (C-3), 154.3 (=*C*Me), 167.3 (C-2). *Crystal data*: $C_{14}H_{20}O_5$, $M = 268.30$, monoclinic, space group $P21/c$, $a = 12.456(2)$, $b = 8.9927(16)$, $c = 13.549(2)$ Å, $\alpha = 90°$, $\beta = 114.824(3)°$, $\gamma = 90°$, $V = 1377.4(4)$ Å^3, $Z = 4$, ω-scans, range 1.8–31.1°, index ranges $-17 < h < 17$, $-11 < k < 11$, $-16 < l < 16$, $\mu = 0.1$ mm^{-1}; Siemens P4 diffractometer, 3171 unique reflections, 2516 with $I > 2\sigma(I)$, 252 ref. para., final $R_1 = 0.0481$, w$R_2 = 0.1399$. CCDC reference number 158427. See http://www.rsc.org/suppdata/p1/b1/b104227k/ for crystallographic files in .cif or other electronic format

¶ **12b** ($n = 2$): crystallization from degassed solutions of **10b** in chloroform–*n*-pentane gave white crystals of **12b**$^{\alpha}$ (80%), mp 133–134 °C (Found: C, 67.52; H, 8.35. $C_{15}H_{22}O_4$ requires C, 67.64; H, 8.33%); ν_{max}(KBr)/cm^{-1} 3249, 1711, 1634; ^{1}H-NMR [500 MHz, $CDCl_3$; mixture (3.7 : 1) of **12b**$^{\alpha}$ and (*Z* + *E*)-**12b**$^{\beta}$]: δ 1.46 and 1.49 (6 H, each s, C*Me*$_2^{\beta}$, C*Me*$_2^{\alpha}$), 1.59–2.03 (12 H, m, *c*-C_7H_{12}), 2.59 and 2.66 [3 H, each s, *Z*-(=C)C*H*$_3^{\beta}$, *E*-(=C)C*H*$_3^{\beta}$], 4.40 (1 H, s, OH$^{\alpha}$), 5.42 (1 H, s, =C*H*H), 5.80 (1 H, s, =C*H*H); ^{13}C-NMR (125.7 MHz, $CDCl_3$); *major isomer* **12b**$^{\alpha}$: δ 22.9 (CH_2), 27.7 [C(*C*H$_3$)$_2$], 29.4 and 37.0 (CH_2), 74.7 (*C*Me$_2$), 84.5 and 96.2 (C-3, C-5-spiro), 114.9 (=CH_2), 140.7 (*C*=CH_2), 173.3 and 180.0 (C-2, C-4); *minor isomers* **12b**$^{\beta}$ (*Z* + *E*): 14.1 and 19.7/20.4 (CH_3), 22.3/22.4 (CH_2), 27.9 (CH_3), 29.2/29.3 and 36.6/36.8 (CH_2), 75.8/76.3 (*C*Me$_2$), 89.0/92.1 and 116.3/116.9 (C-3, C-5-spiro), 166.9/169.5 (=*C*Me), 193.6/196.0 (C-2), 201.5/204.2 (C-4); *m*/*z* (EI) 266 (9%) [M$^+$], 251 (21%), 223 (34%), 136 (100%). *Crystal data*: $C_{15}H_{22}O_4$, $M = 266.33$, monoclinic, space group $C2/c$, $a = 20.348(2)$, $b = 8.8063(9)$, $c = 18.3387(18)$ Å, $\alpha = 90°$, $\beta = 121.243(2)°$, $\gamma = 90°$, $V = 2809.6(5)$ Å^3, $Z = 8$, ω-scans, range 2.3–28.8°, index ranges $-27 < h < 20$, $-11 < k < 11$, $-18 < l < 23$, $\mu = 0.1$ mm^{-1}; Siemens P4 diffractometer, 3090 unique reflections, 2082 with $I > 2\sigma(I)$; 260 ref. para., final $R_1 = 0.0514$, w$R_2 = 0.1442$. CCDC references number 158428 http://www.rsc.org/suppdata/p1/b1/b104227k/ for crystallographic files in .cif or other electronic format

1 (*a*) G. Pattenden, *Fortschr. Chem. Org. Naturst.*, 1978, **35**, 133; (*b*) S. V. Ley, M. L. Trudell and D. J. Wadsworth, *Tetrahedron*, 1991, **47**, 8285; (*c*) B. J. L. Royles, *Chem. Rev.*, 1995, **95**, 1981.
2 (*a*) B. M. Booth, C. M. J. Fox and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1987, 121; (*b*) K. Rehse and J. Wagenknecht, *Arch. Pharm.*, 1979, **312**, 164; (*c*) B. S. Vanwagenen, *Tetrahedron*, 1986, **42**, 1117; (*d*) B. E. Roggo, F. Petersen, R. Delmondo, H.-B. Jenny and H. H. Roesel, *J. Antibiot.*, 1994, **47**, 143.
3 J. Löffler and R. Schobert, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2799.
4 D. E. Karte, L. S. Hegedus and R. K. Wirth, *J. Org. Chem.*, 1977, **42**, 1329.
5 (*a*) W. Adam and A. K. Smerz, *Bull. Soc. Chim. Belg.*, 1996, **105**, 581; (*b*) W. Adam, R. Paredes, A. K. Smerz and L. A. Veloza, *Liebigs Ann. Chem.*, 1997, 547.
6 R. Schobert, S. Siegfried, G. Gordon, D. Mulholland and M. Nieuwenhuyzen, *Tetrahedron Lett.*, 2001, **42**, 4561.
7 For the reactivity of allylic H-atoms see: D. E. VanSickle, F. R. Mayo, R. M. Arluck and M. G. Syz, *J. Am. Chem. Soc.*, 1967, **89**, 967.
8 L.-K. Sy, G. D. Brown and R. Haynes, *Tetrahedron*, 1998, **54**, 4345.

9 W.-Y. Tsui and G. D. Brown, *Tetrahedron*, 1996, **52**, 9735.
10 (*a*) A. Robert and B. Meunier, *Chem. Soc. Rev.*, 1998, **27**, 273; (*b*) G. H. Posner, H. O'Dowd, P. Ploypradith, J. N. Cumming, S. Xie and T. A. Shapiro, *J. Med. Chem.*, 1998, **41**, 2164.
11 A natural analogue isolated from *Eucalyptus grandis* was found to quickly racemize in methanol at carbon atom C4 *via* ring-opened hydroperoxides similar to **11** without loss of oxygen: W. D. Crow, W. Nicholls and M. Stern, *Tetrahedron Lett.*, 1971, 1353.
12 (*a*) F. R. Mayo, *Acc. Chem. Res.*, 1968, **1**, 193; (*b*) R. Hiatt, J. Clipsham and T. Visser, *Can. J. Chem.*, 1964, **42**, 2754.
13 (*a*) F. Haber and J. Weiss, *Naturwissenschaften*, 1932, **20**, 948; (*b*) F. Haber and J. Weiss, *Proc. R. Soc. London, Ser. A*, 1934, **147**, 332.