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NOVEL 3,4- AND 8,15-POLYETHER ANALOGUES OF MACROCYCLIC TRICHOTHECENES

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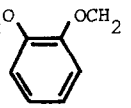
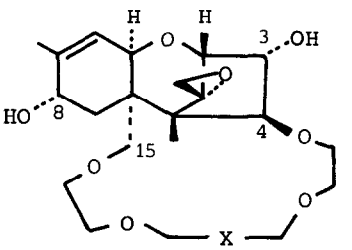
*Protecting group chemistry on derivatives of T-2 toxin (**2**) involving silylation (TBDMS ethers) of the hydroxyl groups at C-3 and C-4, and acetalation (benzylidene acetals) of the C-8 and C-15 hydroxyl groups, has afforded the 3,4- and 8,15-polyether analogues **9-12** and **18** and **19** of macrocyclic trichothecenes.*

The recognition that all naturally-occurring macrocyclic trichothecenes characterised to date are bridged *via* C-4 and C-15 on the sesquiterpenoid skeleton led[1] us to synthesise the 4,15-polyether derivatives **1a**, **1b**, and **1c**, starting from T-2 toxin (**2**) and neosolaniol (**3**). However, in view of the relative ease of preparation of these crown compounds, it was tempting to exploit the hydroxyl functionalities at C-3 and C-8 on the trichothecene nucleus as well. Here, we report some straightforward procedures whereby polyether chains can be introduced between positions 3 and 4, and 8 and 15.

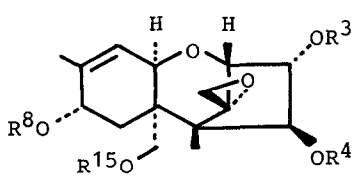
1a X = CH_2OCH_2

1b X = $(CH_2OCH_2)_2$

1c X = 

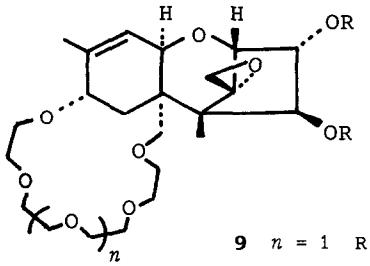


Saponification (NH_4OH/H_2O/MeOH), according to the literature[2] procedure, of T-2 toxin (**2**), obtained microbiologically from *Fusarium tricinctum*, afforded HT-2 (**4**), T-2 triol (**5**), and T-2 tetraol (**6**) in a 10:3:5 ratio, approximately. Preliminary investigations revealed that HT-2 (**4**) was the most suited of these three compounds to the protecting group chemistry[3] necessary to generate the desired diols. Reaction of **4** with TBDMS-Cl/imidazole/DMF *at room temperature for 3 days*[4] gave (>98%) the 3,4-disilyl ether **7**, m.p. 129-133°C, which was deacylated (NaOMe/MeOH/rt) to yield (>98%) the 8,15-diol **8**, m.p. 177°C. Treatment (NaH/THF) of

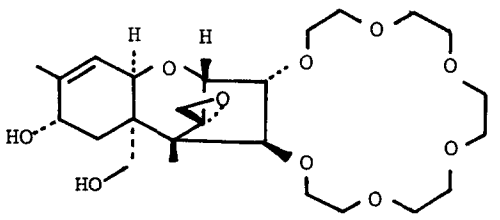


Cpd	R^3	R^4	R^8	R^{15}
2	H	Ac	Val[i]	Ac
3	H	Ac	H	Ac
4	H	H	Val[i]	Ac
5	H	H	Val[i]	H
6	H	H	H	H
7	TBDMS	TBDMS	Val[i]	Ac
8	TBDMS	TBDMS	H	H
13	TBDMS	H	H	H

8 with TEGBT[5] and PEGBT[5] afforded the 17-crown-5 and 20-crown-6 derivatives **9** and **10** as oils in 15 and 18% yields, respectively. Deprotection (Bu_4NF/THF/40°C/3 days)[4] of **9** and **10**, respectively, gave the 3,4-diols **11** (54%, oil) and **12** (58%, oil), which are clearly ideal substrates for building on a second polyether chain to yield bis-crown ether derivatives[6].



9 n = 1 R = TBDMS
10 n = 2 R = TBDMS
11 n = 1 R = H
12 n = 2 R = H



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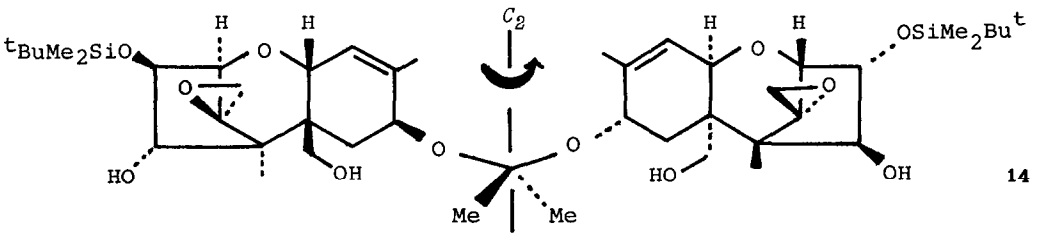
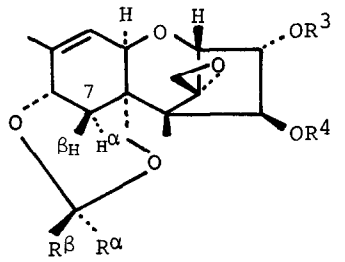
The 3-TBDMS ether **13** of T-2 tetraol (**6**) was prepared from T-2 toxin (**2**) as described[1] previously. Inspection of molecular models indicated that acetal formation is feasible across the 3- and 15-, as well as between the 8- and 15-, positions. In the event, Lewis acid catalysed isopropylidenation [$Me_2C(OMe)_2$/$SnCl_2$/DME] of **13** gave (23%) the acyclic acetal **14**, obtained through bridging of the two C-8 allylic hydroxyl groups of two trichothecene



14

nuclei. Evidence for this unexpected and interesting structure is based on the following observations: (*i*) The low m.p. (80-85°C) compared with that (m.p. 138-141°C)[1] of the parent triol **13**. (*ii*) Chemical ionisation (NH_3 carrier gas) mass spectrometry[7] (c.i.m.s.) which gives *m/e* peaks significantly higher than that (M^+, 453) expected for a monoisopropylidene derivative. (*iii*) The 6H *singlet* present in the ^1H n.m.r. spectrum ($CDCl_3$, 250MHz) at δ2.17 for the isopropylidene methyl protons, indicating that the *two methyl groups are homotopic*. (*iv*) The relative integrated intensities in the ^1H n.m.r spectrum of the isopropylidene methyl singlet and the trichothecene skeleton proton signals indicating the presence of *two* trichothecene nuclei for *each* $>CMe_2$ unit. (*v*) The chemical shifts in the ^1H n.m.r. spectrum ($CDCl_3$) for H-3 (δ4.12), H-4 (δ4.01), H-8 (δ3.85), and H-15 (δ3.44/3.73) indicating (*cf* ref. 1) that, whilst the 4- and 15-positions carry free hydroxyl groups, the 3- and 8-positions are both substituted. By contrast, Lewis acid catalysed benzylidenation (PhCHO/$SnCl_2$/DME) gave (76%) two 8,15-*O*-benzylidene derivatives *(R)*-**15**, m.p. 176-178°C, and *(S)*-**15**, m.p. 125-132°C, after chromatography (SiO_2/$CHCl_3$ containing 3% MeOH), in a *ca.* 24:1 ratio, respectively. The constitutional assignment to *(R)*-**15** and *(S)*-**15** follows from the



Cpd	R^3	R^4	R^α	R^β
(R)-**15**	TBDMS	H	H	Ph
(S)-**15**	TBDMS	H	Ph	H
(R)-**16**	TBDMS	Ac	H	Ph
(R)-**17**	H	H	H	Ph
(R)-**18**	$CH_2(CH_2OCH_2)_4$		H	Ph

observation of a strong M+1 peak (*m/e*, 501) in the mass spectra using chemical ionisation, and the chemical shifts in the ^{1}H n.m.r. spectra ($CDCl_3$) for H-3 (δ_R 4.17 and δ_S 4.14), H-4 (δ_R 3.75 and δ_S 3.47), H-8 (δ_R 4.35 and δ_S 4.03), and H-15 (δ_R 3.42/4.32 and δ_S 3.76/4.26). Additionally, the fact that, on acetylating *(R)*-**15** to produce *(R)*-**16**, m.p. 89-92°C, the resonance for H-4 moves downfield by 1.30 ppm implicates the hydroxyl groups at C-8 and C-15 in acetal formation. The configurational assignment of the major and minor acetals to *(R)*-**15** and *(S)*-**15** respectively has been deduced primarily from the downfield shifts experienced by the signals for H-7α and H-7β relative to their resonances in the triol **13**: δ($CDCl_3$, 250 MHz) 2.02/2.16 (H-7α/7β in **13**), 2.44/2.23 (H-7α/H-7β in *(R)*-**15**), and 2.04/2.10 (H-7α/H-7β in *(S)*-**15**). The larger shifts (+0.42/+0.07 ppm compared with +0.02/-0.06 ppm) can be reasonably attributed to the stereochemical situation present in the major *(R)*-isomer where the phenyl group (R^β = Ph) and the methylene group at C-7 are oriented *syn* with respect to each other within a rigid bicyclic structural fragment. Removal of the silyl protecting group at the 3-position of *(R)*-**16** with fluoride ion gave (93%) the 3,4-diol *(R)*-**17**, m.p. 136-138°C, which was reacted (NaH / THF) with PEGBT[5,8] to afford (15%) the 18-crown-6 derivative *(R)*-**18** as an oil. Deprotection ($SnCl_2$ / TsOH / DME / H_2O) of *(R)*-**18** gave (78%, oil) the 8,15-diol **19**, which is yet another potential precursor for making bis-crown ether derivatives[6].

The complexing abilities and biological activities of the novel macrocyclic trichothecene analogues **9-12** and **18** and **19** are currently under investigation. Together with the 4,15-polyether-bridged trichothecenes[1], these macrocycles are members of a fascinating new class of chiral crown ethers[9].

Acknowledgement. We are grateful for the award of a Research Assistantship (to D.A.L.) from the Ministry of Defence. We thank Mr Peter R. Ashton for obtaining mass spectra on the acetals.

1. D.W. Anderson, R.M. Black, D.A. Leigh, and J.F. Stoddart, *Tetrahedron Lett.*, Preceding communication.

2. R. Wei, F.M. Strong, E.B. Smalley, and H.K. Schnoes, *Biochem. Biophys. Res. Comm.*, 1971, **45**, 396.

3. The compositions of all new compounds were confirmed by either elemental analysis or by high resolution mass spectrometry. The crown compounds **11**, **12**, and **19**, which are oils, were purified by column chromatography (SiO_2) using eluants such as $CHCl_3$, CH_2Cl_2, or Et_2O to which MeOH (5 - 10%) was added. Structural assignments were based upon the results of low resolution mass spectrometry and high field ^{1}H and ^{13}C n.m.r. spectroscopy on either a Bruker AM250 or WH400 spectrometers. In the case of the macrocycles, the signals for H-3, H-4, and H-8, which were masked by the resonances for the OCH_2 protons in the polyether chains, were identified by double resonance difference spectroscopy:

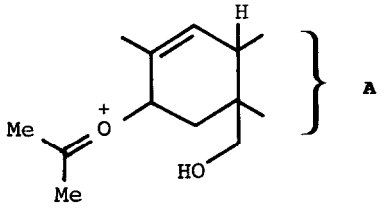
δ ($CDCl_3$, 400 MHz) **9** gives 4.14 (H-3), 3.52 (H-4), 3.61 (H-8); **10** gives 4.14 (H-3), 3.52 (H-4), 3.62 (H-8); **11** gives 4.24 (H-3), 4.40 (H-4), 3.62 (H-8); **12** gives 4.24 (H-3), 4.39 (H-4), 3.62 (H-8); **18** gives 3.97 (H-3), 3.55 (H-4), 4.35 (H-8); **19** gives 3.96 (H-3), 3.55 (H-4), 4.03 (H-8). The range of coupling constants involving these protons in **9** - **12** and **18** and **19** are $J_{2,3}$ 4.8-5.0 Hz, $J_{3,4}$ 2.0-2.4 Hz, $J_{7\beta,8}$ 5.0-5.2 Hz.

4. Both silylation of HT-2 (**4**) to give **7** and desilylation of **9** and **10** to afford **11** and **12**, respectively, require forcing conditions on account of the relatively low reactivities associated with the sterically hindered functional groups at C-4. Work-up of the reaction of **4** with TBDMS-Cl/imidazole/DMF after 1 day at room temperature yielded (94%) the mono-3-TBDMS Ether of HT-2 (**4**), the constitution having been established unambigously by showing that deacylation (NaOMe/MeOH) of the product gave the known (ref. 1) mono-3-TBDMS ether **13** of T-2 tetraol (**6**). Conversely, treatment (n-Bu_4NF/THF/rt/2 h) of the 3,4-disilyl ethers **9** and **10** in the usual manner led exclusively to the formation of the mono-4-TBDMS ethers of the 17-crown-5 and 20-crown-6 derivatives **11** and **12**, respectively.

5. TEGBT and PEGBT are abbreviations (ref. 1) for tetra- and penta-ethyleneglycol bis-tosylates, respectively (J. Dale and P.O. Kristiansen, *Acta. Chem. Scand.*, 1972, **26**, 1471).

6. Presently, we are pursuing the conversion of compounds **11**, **12**, and **19** into bis-crown ethers.

7. The (weak) peak at *m/e* 453 in the c.i.m.s. of **14** can be explained by a fragmentation of the acetal C-O bond to give the fragment ion, **A**. A much stronger peak at *m/e* 395 can be ascribed to the fragment **B** (*M*, 394), which has become protonated. It is significant that this peak is also observed in the c.i.m.s. of **15**. In the case of both acetals, loss of a further 30 mass units (HCHO) accounts for the base peaks observed at *m/e* 365.



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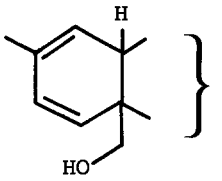

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8. J.F. Stoddart, *Topics Stereochem.*, 1987, **17**, 207.

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