Synthesis of the bicyclic core of tagetitoxin†

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A synthesis of the 9-oxa-3-thiabicyclo[3.3.1]nonane ring system, which constitutes the core of the RNA polymerase inhibitor tagetitoxin, has been achieved through cyclisation of a thiol onto an electrophilic ketone.

Tagetitoxin is a phytotoxin which was isolated from the plant pathogenic bacterium *Pseudomonas syringae* pv. *tagetis* in 1981.[1] The compound induces chlorosis in the apex of infected plants, an effect which has been traced to inhibition of RNA polymerase in chloroplasts.[2] Furthermore, tagetitoxin inhibits bacterial RNA polymerase,[2] and is the only natural product known to inhibit eukaryotic RNA polymerase III in a specific manner.[3] Recently, a crystal structure of the RNA polymerase from *Thermus thermophilus* with tagetitoxin bound to the active site was published;[4] consideration of this structure led the authors to postulate that tagetitoxin acts by stabilisation of an inactive intermediate in the transcription process.

The structure which was assigned to the compound shortly after its isolation[5] was later rejected in favour of a bicyclic structure based on the 9-oxa-3-thiabicyclo[3.3.1]nonane ring system. Structure **1** was favoured, although the spectroscopic data did not rule out the closely related structure **2** (Fig. 1).[6]

To date, limited work has been published detailing synthetic approaches to tagetitoxin and its analogues,[7] and none has yet been successful in generating the bicyclic ring system. In this communication we describe a synthesis of this bicyclic core structure, starting from a carbohydrate precursor.

Our initial strategy focused on the use of a carbene-mediated ring expansion of 1,3-oxathiolanes.[8] D-Glucose was converted to the bicyclic monothioacetal **3**[9] through displacement of an anomeric bromide and a 6-tosylate with potassium *O*-ethylxanthate (Scheme 1).[10] Ring expansion was then attempted using ethyl diazo(triethylsilyl)acetate and catalytic rhodium(II) acetate;[8] this led not to the anticipated bridged bicycle, but instead to glycal **5**. This product may arise through sulfur ylid formation and heterolytic C–S bond cleavage to give zwitterion **4**; rather than the desired C–C bond formation, this intermediate is presumed to undergo a ring-flip to the more stable conformer followed by proton transfer to afford the observed product.

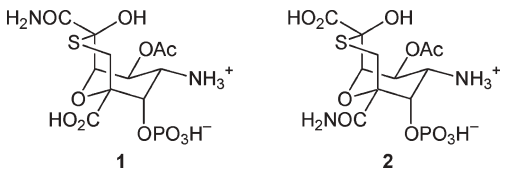
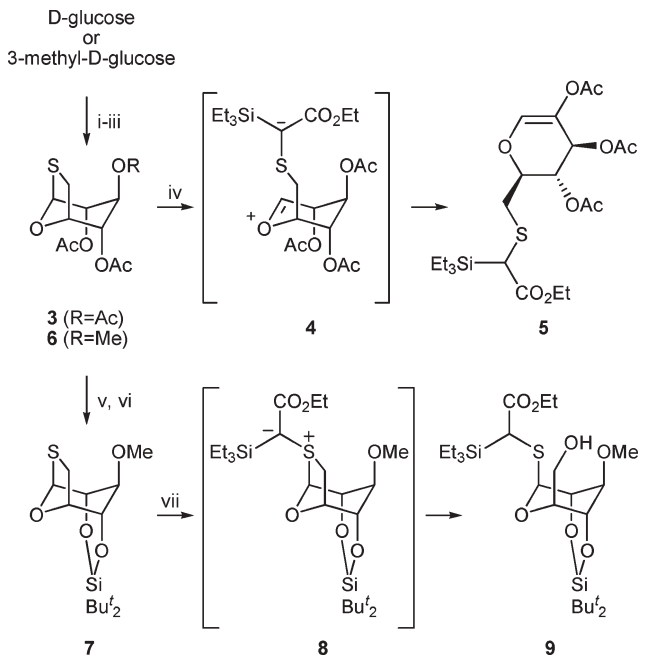


Fig. 1 Proposed structures of tagetitoxin.

To circumvent this difficulty, a conformationally constrained substrate was designed whose derived zwitterion (analogous to **4**) would be incapable of ring-flipping. 3-Methyl-D-glucose was converted to bicycle **6**, then the acetate groups were cleaved and a bridging di-*tert*-butylsilylene protecting group installed. Treatment of the resulting tricycle **7** with ethyl diazo(triethylsilyl)-acetate in the presence of rhodium(II) heptafluorobutyrate gave a low yield of primary alcohol **9** as the only isolable product. In this case, the sulfur ylid **8** forms as required but this, rather than undergoing C–S bond heterolysis and ring expansion, is trapped by adventitious water to give the bicyclic alcohol **9**.

Due to the failure of our initial approach to the tagetitoxin skeleton, a new strategy was adopted in which the 1,4-oxathiane ring of the natural product would be formed by cyclisation of a thiol onto an electron-deficient ketone, rather than through a carbene-mediated ring expansion.



Scheme 1 *Reagents and conditions*: i. TsCl, pyridine; Ac_2O; ii. HBr, AcOH; iii. KSCSOEt, DMF, 50 °C (46% **3** over 3 steps) or KSCSOEt, acetone, reflux (47% **6** over 3 steps); iv. $Et_3SiC(N_2)CO_2Et$, $Rh_2(OAc)_4$, benzene, reflux, 34%; v. NH_3, MeOH, H_2O, 50%; vi. $^tBu_2SiCl_2$, Et_3N, CH_2Cl_2, 86%; vii. $Et_3SiC(N_2)CO_2Et$, $Rh_2(O_2CC_3F_7)_4$, benzene, reflux, 21%.

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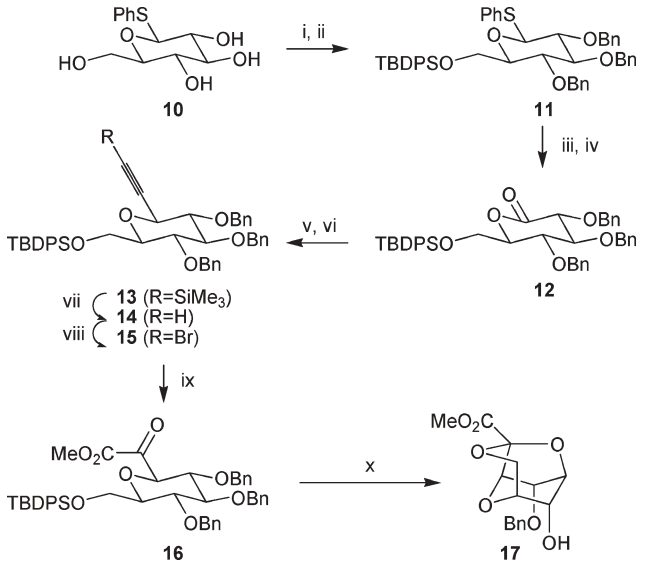
† Electronic supplementary information (ESI) available: HMQC and HMBC spectra for **21**. See DOI: 10.1039/b600819d



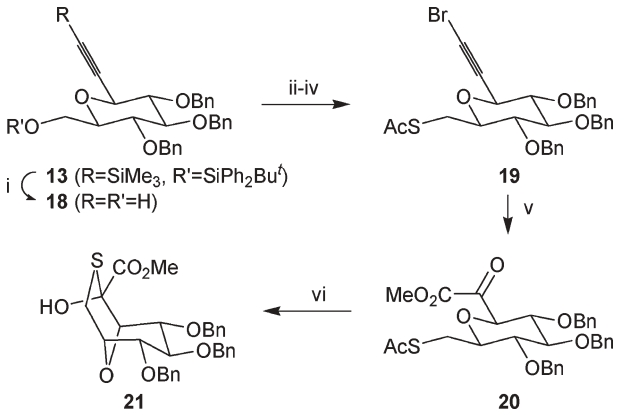
Scheme 2 *Reagents and conditions*: i. TBDPS-Cl, imidazole, DMF, 99%; ii. BnBr, NaH, DMF, 87%; iii. NBS, aq. acetone, 95%; iv. Dess–Martin periodinane, pyridine, CH_2Cl_2, 69%; v. TMSC≡CH, *n*-BuLi, $CeCl_3{\cdot}7H_2O$, THF, −78 °C to rt, 96%; vi. Et_3SiH, TMSOTf, CH_2Cl_2, 74%; vii. NaOH, MeOH, CH_2Cl_2, 100%; viii. NBS, $AgNO_3$, acetone, 98%; ix. $KMnO_4$, $NaHCO_3$, $MgSO_4$, aq. MeOH, 84%; x. HF·py, THF, −78 °C to rt, 77%.

Phenyl 1-thio-β-D-glucopyranoside (**10**) was converted to the fully protected analogue **11**[11] before NBS-promoted hydrolysis of the thioglycoside linkage (Scheme 2). Oxidation to the δ-lactone **12** was accomplished using Dess–Martin periodinane. Cerium-mediated addition of trimethylsilylacetylene followed by deoxygenation and desilylation then afforded terminal alkyne **14**. Bromination to give **15** was followed by oxidation with potassium permanganate in aqueous methanol[12] to yield α-ketoester **16**.

On cleavage of the silyl ether with TBAF, concomitant elimination of the 2-benzyloxy group (glucose numbering) to form an enol ether was observed. However, when silyl ether **16** was treated with HF–pyridine, the sole product was tricyclic acetal **17**, in which not only the silyl ether but also the 3- and 4-benzyl ethers had been cleaved, and an acetal had formed between the ketone and the 3- and 6-OH groups.

Formation of the tricyclic acetal **17** precluded introduction of a sulfur atom at C6, but alteration of the order of steps allowed completion of the synthesis of the tagetitoxin skeleton; thus double desilylation of **13** could be achieved with TBAF to give primary alcohol **18** (Scheme 3). Activation as the mesylate was followed by displacement with potassium thioacetate, and bromination of the alkyne afforded **19**. Oxidation as for compound **15** gave the α-ketoester **20**, and removal of the *S*-acetyl protecting group using hydrazine hydrate in methanol led directly to the bicyclic hemithioacetal **21**.

The structure of **21** was confirmed by mass spectrometry and NMR;‡ in particular, an HMBC correlation was observed between the hemithioacetal carbon at 71.9 ppm and one of the CH_2S protons at 1.57 ppm. Vicinal coupling constants of 9.3 and 9.6 Hz between the pairs of C*H*OBn protons indicated a boat conformation for the tetrahydropyran ring, as depicted in **21**. The hemithioacetal was obtained as a single stereoisomer, although the configuration of this centre was not determined.



Scheme 3 *Reagents and conditions*: i. TBAF, THF, 99%; ii. MsCl, Et_3N, DMAP, CH_2Cl_2, 95%; iii. KSAc, DMF, 99%; iv. NBS, $AgNO_3$, acetone, 98%; v. $KMnO_4$, $NaHCO_3$, $MgSO_4$, aq. MeOH, 71%; vi. $N_2H_4{\cdot}H_2O$, MeOH, 88%.

In conclusion, we have carried out the first synthesis of the tagetitoxin skeleton, by unmasking of a thiol in the presence of an electrophilic α-ketoester, triggering spontaneous cyclisation to a hemithioacetal. Efforts towards synthesis of the fully functionalised tagetitoxin structure are under way and will be reported in due course.

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Notes and references

‡ Data for **21**: $[\alpha]_D^{17}$ +3.1 (*c* 1.07 in EtOH); ν_{max}/cm^{-1} (film) 3445 (OH), 2928 (CH), 1736 (C=O); δ_H (500 MHz, C_6D_6) 7.38–6.99 (15H, m, Ar*H*), 5.01 (1H, d, *J* 11.3), 4.92 (1H, d, *J* 11.3), 4.82 (1H, d, *J* 11.6), 4.75 (1H, d, *J* 11.6) and 4.65 (1H, d, *J* 12.0, 5 of PhCH_2), 4.43 (1H, dd, *J* 9.3, 2.8, *H*-2), 4.39 (1H, *J* 12.0, 1 of PhCH_2), 4.36 (1H, br d, *J* 2.8, *H*-1), 4.22 (1H, t, *J* 9.4, *H*-3), 4.19 (1H, td, *J* 3.6, 1.9, *H*-5), 4.11 (1H, s, O*H*), 4.03 (1H, dd, *J* 9.6, 3.7, *H*-4), 3.30 (1H, dd, *J* 13.4, 3.6, 1 of CH_2S), 3.24 (3H, s, CH_3), 1.57 (1H, br d, *J* 13.4, 1 of CH_2S); δ_C (125 MHz, C_6D_6) 173.4 (*C*=O), 139.1, 138.9 and 138.6 (3 × aromatic *C*), 82.2 (*C*-3), 80.0 (*C*-4), 79.8 (*C*-2), 79.5 (*C*-1), 75.0 (Ph*C*H_2), 73.3 (*C*-5), 73.2 (Ph*C*H_2), 72.4 (Ph*C*H_2), 71.9 (S*C*OH), 52.5 (O*C*H_3), 40.9 (*C*-6), other aromatic carbons obscured by solvent; *m*/*z* (FAB+) 559 (MNa^+, 2%), 326 (21), 199 (26), 176 (100); HRMS (FAB+) found 559.1784; $C_{30}H_{32}O_6SNa$ (MNa^+) requires 559.1766.

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