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Radical Cyclisation onto C-3 of 1,6-Anhydro-β-D-mannopyranose Derivatives. Application to the Formation of the C8a Centre of (-)-Tetrodotoxin

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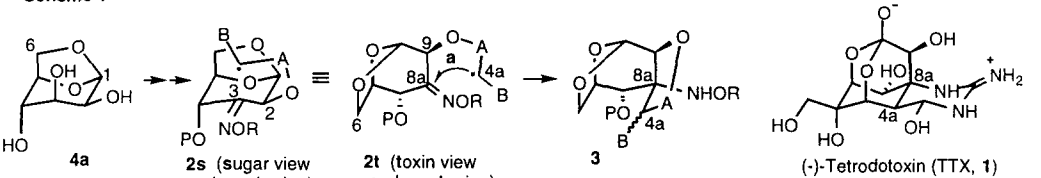
Abstract: Starting from 1,6-anhydro-β-D-mannopyranose, compounds **7a-d**, which have a ketoxime ether at C3 and a carbon radical precursor tethered to the hydroxyl group at position 2, were efficiently prepared. While alkyl π-radicals derived from **7a** and **7b** failed to cyclize, the vinyl σ-radicals derived from **7c** and **7d** underwent the desired 1,5-*exo* cyclization, affording advanced precursors of (-)-tetrodotoxin. This type of transformation should be useful for the formation of sterically crowded nitrogen-bearing carbon centers in carbohydrate-derived substrates. © 1997 Elsevier Science Ltd.

Tetrodotoxin (TTX, **1**, Scheme 1),[1] is a small, highly functionalized molecule of natural origin that binds selectively and with high affinity to voltage-gated sodium channels (transmembrane glycoproteins[2] implicated in the transmission of nerve impulses and consequently, in a large number of other fundamental life processes).[3] By virtue of this property, TTX has played a fundamental role in the investigation of the structural and functional properties of these channels, permitting isolation of some of them and elucidation of the amino acid sequence of their main peptide subunit.[4] The biosynthetic origin of TTX remains a mystery, in spite of significant recent advances spurred by the isolation of new congeners.[5] The biological activity and unique structure of tetrodotoxin make it an attractive and challenging synthetic target.[6] As part of a research programme aimed at the total synthesis of TTX and its analogues, herein we begin by examining the formation of the quaternary center at C8a, reporting preliminary results for a strategy based on the cyclization of carbon centred radicals related to **2t** (Scheme 1).

Scheme 1

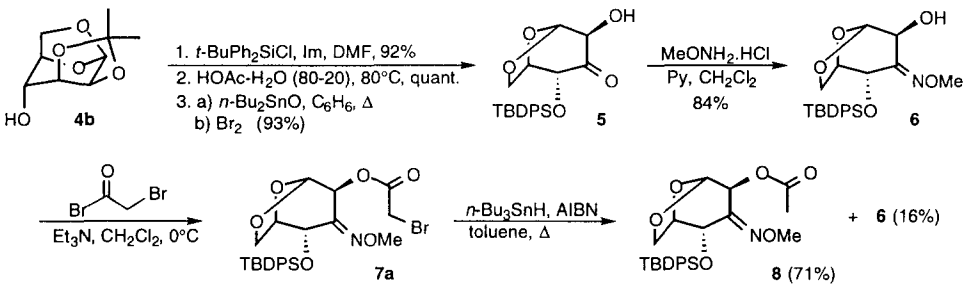


On the basis of the well-documented, strong predilection of the 5-hexenyl radical and related structures for the 5-*exo* over the 6-*endo* mode of cyclization,[7] we reasoned that cyclization of **2t** should proceed through path **a**, affording intermediate **3** with the required C4a-C8a bond. We further reasoned that location of the carbon radical in **2t** in a chain tethered to the hydroxyl group at C9 would guarantee its delivery from the concave face of the bicyclic structure, thus assuring that the new quaternary centre have the same stereochemistry as C8a in tetrodotoxin.

The sugar view of **2** (**2s**, Scheme 1) clearly shows it to be a derivative of 1,6-anhydro-β-D-mannopyranose (**4a**).[8a] Now the radical cyclization can be envisaged as attack on the ketoxime ether at carbon C3 by a carbon radical linked to C2 of the pyranose ring. It is noteworthy that, although aldoxime ethers have been widely used as traps in radical reactions,[9] ketoxime ethers have not.[10] Indeed we know of no previous use of ketoxime ethers in radical reactions of carbohydrate derivatives.

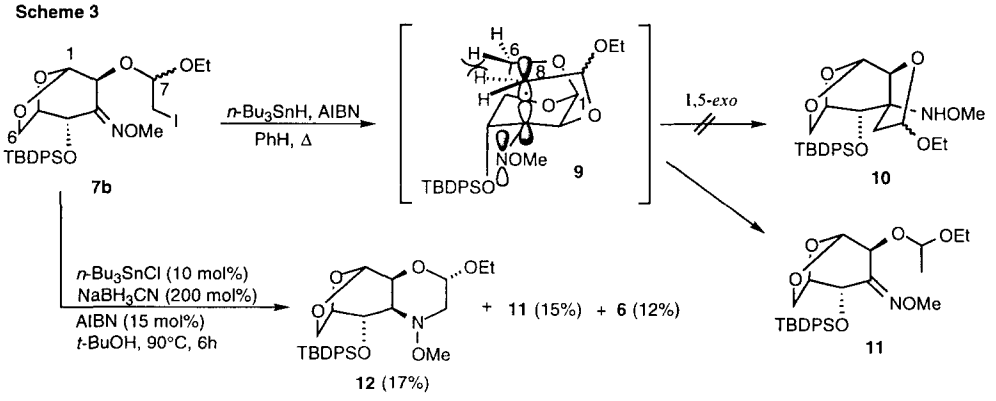
The first radical precursor examined was the α-bromoester **7a**, which was efficiently obtained as shown in Scheme 2.[11] Briefly, treatment of 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose (**4b**)[8b] as detailed afforded crystalline α-hydroxy ketoxime-ether **6**, *via* α-hydroxy-ketone **5**,[6g] in 4 steps and 72% overall yield. Then, reaction of **6** with α-bromoacetylbromide and triethylamine in CH_2Cl_2 at 0°C gave **7a** in 78% yield. Unfortunately, slow addition (2.3 mL/h) of a solution of *n*-Bu_3SnH (0.015 M, 165 mol%) and AIBN (50 mol%) in deoxygenated toluene to a refluxing solution of **7a** in the same solvent (0.005 M) afforded no cyclized product. The major product isolated was acetate **8** - the result of reduction of the intermediate electrophilic α-carbonyl radical by tin hydride. In addition, in spite of the essentially neutral reaction conditions, some cleavage of the ester group took place, giving alcohol **6** (16%).[12]

Scheme 2



The next radical precursor examined was the α-iodoacetal **7b**, which was obtained as a 1:1 mixture of its C7 epimers by treatment of **6** with N-iodosuccinimide and ethyl vinyl ether in THF (-20°C --- > rt, 90% yield). Treatment of **7b** with *n*-Bu_3SnH (slow addition) and AIBN in deoxygenated benzene, gave the reduced derivative **11** as the main product and none of the desired cyclized compound **10** (Scheme 3). On the other hand, treatment of **7b** with *n*-Bu_3SnCl, $NaBH_3CN$ and AIBN in deoxygenated *t*-BuOH,[13] unexpectedly afforded the morpholine derivative **12** (17%) as the only cyclized product.[14] Also isolated were reduced acetal **11** (15%) and alcohol **6** (12%), formed by hydrolysis of the acetal group of **7b** or **11**.[12]

Scheme 3



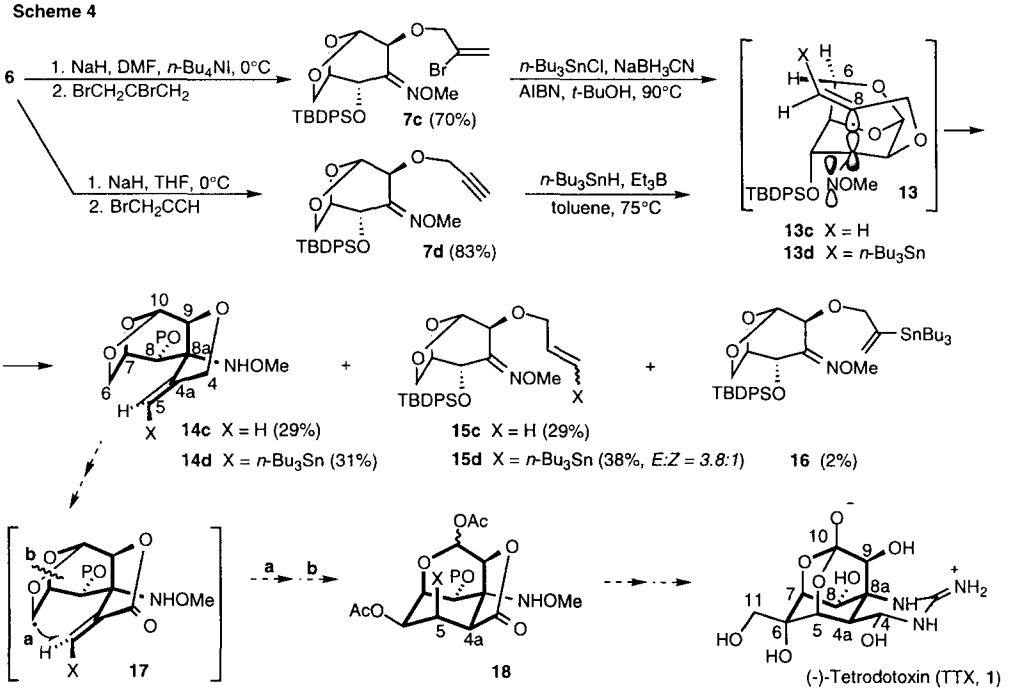
The failure of **7b** to cyclize to **10** could be related to the presence of the 1,6-ether bridge: in the conformation required for 1,5-*exo* cyclization (**9**), this bridge holds the *endo* H atom of C6 in close proximity to one of the C8 hydrogen atoms, thus making 1,5-*exo* cyclization too slow to compite successfully with alternative reaction pathways such as the reduction of the radical intermediate **9** to **11**. This being the case, we reasoned that the 1,5-*exo* cyclization reaction might be favoured by replacing the π-radical **9** with a vinyl σ-radical such as **13** (Scheme 4). The advantage of using a vinyl radical is that the planar geometry of the double bond directs the substituents at the radical centre away from the *endo* H6 atom without interfering with the proper alignment of the orbitals in the 1,5-*exo* cyclization. Additionally, vinyl radicals are known to have high reactivity towards cyclization.[15] These expectations were confirmed by experiments in which both alkene (**7c**) and alkyne (**7d**) precursors of **13** gave similar yields of the expected cyclized products.

Vinyl bromide **7c**, which was prepared in 70% yield by reaction of α-hydroxy ketoxime-ether **6** with 2,3-dibromopropene, was treated under the catalytic tin conditions described for **7b**, affording the desired tetrahydrofuran derivative **14c** in 29% yield, together with a similar yield of the uncyclized reduced product **15c**. Alkyne **7d**, which was prepared in 83% yield by reaction of **6** with 3-bromopropyne, was reacted with tributyltin hydride andEt3B (as radical initiator),[16] affording a 31% yield of the E-isomer of the expected cyclized product, the tri(*n*-butyl)tin-substituted alkene **14d** (assignment of E stereochemistry was supported by the presence of a crosspeak between H5 and H8 (toxin numbering) in the NOESY spectrum), together with a mixture of E and Z isomers of **15d** (38%) and a small amount of **16**.

Compounds **14c** and **14d** can be considered advanced intermediates in the synthesis of tetrodotoxin. As well as the quaternary centre at C8a, both compounds already contain three more of the eight stereocentres present in TTX (C7, C8 and C9), together with a three carbon unit suitable as a precursor of the C4, C4a and C5 centres. Moreover, the functional groups of **14c** and **14d** lend themselves to progress along the synthetic path to tetrodotoxin, particularly the double bond, which appears well disposed for formation of the cyclohexane ring.

The precursors of compounds **14c** and **14d** can be prepared in a few steps and in good overall yields from the readily available sugar D-mannose. Work is currently in progress to improve the overall yields of the cyclized products **14c** and **14d**, either by optimizing the conditions used in the cyclization reaction, or by recycling the allyl ether side products **15c** and **15d** by converting them back to their respective precursors **7c** and **7d** or to the alcohol **6**. In addition, we are examining routes towards tetrodotoxin through species such as **17** and **18**.

Scheme 4



From a more general perspective, this work shows that ketoxime ethers are useful radical traps for the preparation of compounds with nitrogen-bearing quaternary centres by intramolecular cyclization of sugar derivatives. The use of σ-vinyl as opposed to π-radicals appears to offer a two-fold advantage: enhanced radical reactivity and, as occurred in this work, the minimization of unfavourable steric interactions during cyclization. Tethering the chain containing the radical centre to a sugar hydroxyl group lying vicinal to the ketoxime group further enhances the potential utility of this methodology, since it allows stereocontrolled formation of a fused heterocycle on the sugar skeleton. Tethering of this chain *via* other heteroatoms, or the use of all-carbon chains in the radical precursor, should allow access to different fused heterocyclic or carbocyclic sugar derivatives, respectively.

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14. (a) A non radical mechanism for the formation of **12** (i.e. intramolecular N-alkylation of **7b** followed by hydride reduction or *viceversa*), should be operative as this compound is also obtained (39%) by treatment of **7b** with $NaBH_3CN$ in *t*-BuOH in the absence of *n*-Bu_3SnCl and AIBN. We thank a referee for suggesting this last experiment. (b) This idea is further supported by the fact that compound **12** was not formed from **7b** on treatment with *n*-Bu_3SnH and AIBN.
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