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Carbohydrates to densely functionalized carbocycles: 'Armed and disarmed' effects in an approach to tetrodotoxin

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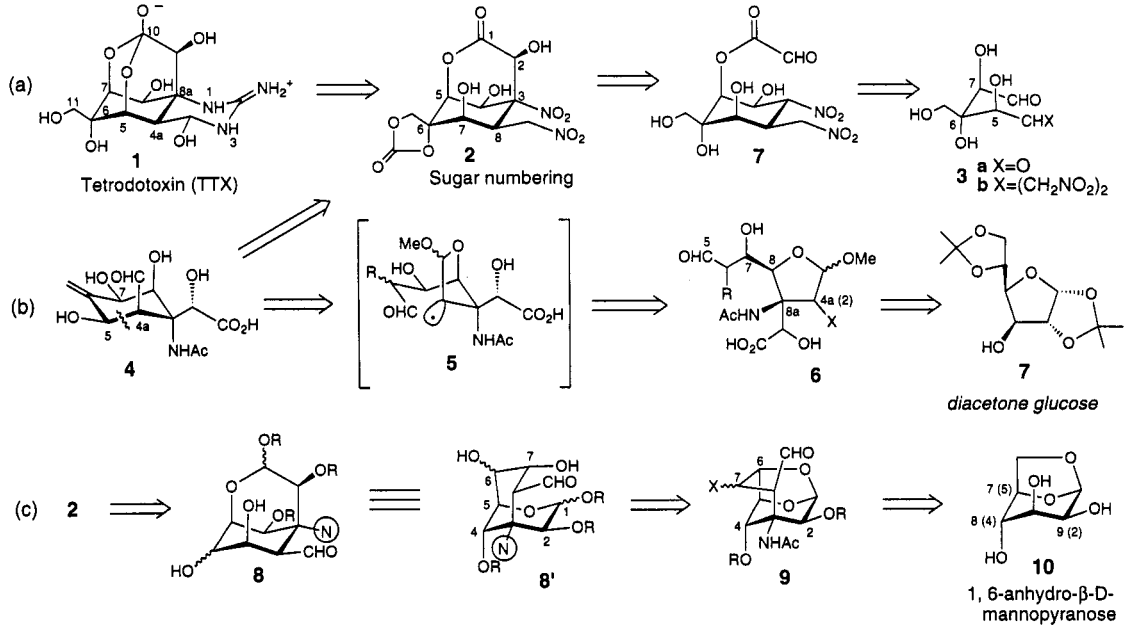
Abstract: A sugar-based approach to tetrodotoxin begins with 1,6-anhydro-β-D-mannopyranose, and exploits the differences between the sugar's various oxygens to effect regio-,chemo-,and stereoselective transformations in achieving an appropriately functionalized advanced intermediate of the target molecule. Free radical reactions are used in key situations, and also the propensity of caged intermediates to undergo adamantyl rearrangement/expansion is incorporated into the synthetic design.

Sugars are densely functionalized natural products, and should be appropriate starting materials for synthetic routes to families of other densely functionalized natural products. Indeed a pioneering example of this concept is the retrosynthetic correlation between tetrodotoxin (TTX),[1] **1** and the apiose derivative, **3**, depicted in Scheme 1a, which is based upon approaches in the laboratories of Woodward[2] and Yoshimura.[3] However the trade-off between functionalization of starting material and target may be difficult to optimize, as is attested by the problems with these[2,3] or other more recent sugar-based approaches[4] to this intriguing molecule. Indeed the only successful route to **1** remains the 1972 triumph of Kishi/Goto where the target's dense functionalities were installed incrementally, beginning with comparatively unfunctionalized starting materials.[5]

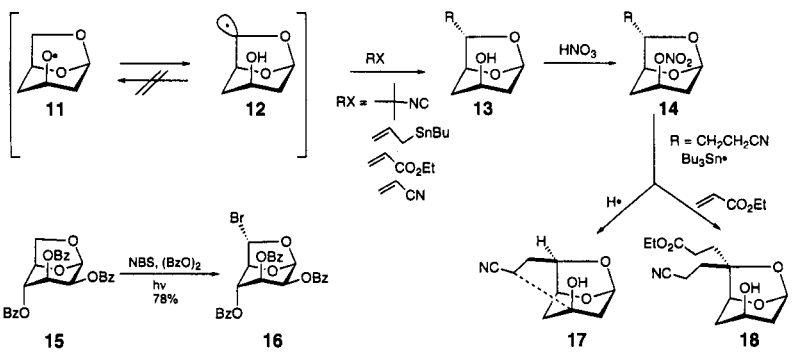
Scheme 1



The elegant conceptions of Woodward[2] and Yoshimura[3] were, in a sense, ahead of their time because much of the available science was incompatible with sugar-derived substrates. In the last two decades free-radical methods have been shown to be highly tolerant of a wide variety of functional groups.[6] We therefore embarked upon a synthetic plan for tetrodotoxin which would rely heavily upon free radical chemistry for the key transformations. In this lecture we will give an account of some of our progress in this undertaking.

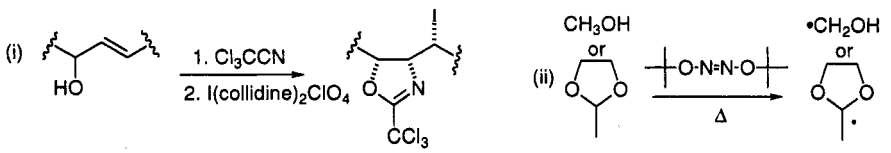
An alternative to Woodward's retrosynthetic plan[2] led us to the hydroxy aldehyde **4** (Scheme 1b), which could be bridged into a furanoside, the carbocyclic ring of which could be achieved *via* retron **5** through the radical-aldehyde cyclization procedure developed in our laboratory.[7] A plausible precursor could be **6** which would originate from "diacetone glucose" **7**. However realization of this task proved elusive. An alternative disconnection of hydroxy lactone **2** (Scheme 1c) led to **8**, represented alternatively as the bridged pyranoside **8'**, and thence to the caged tricycle **9**. "Visual dialogue"[8] with the C2 and C4-OH groups of the latter implicate 1,6-anhydromannose **10** as a compatible precursor.

Scheme 2



Synthon **9** requires a 2-carbon bridge between C3 and C6 which, in turn, necessitated appropriate adjustment of the oxidation states at these centers, and in keeping with the above-stated commitment, we turned to free radical methods. We showed that a C3 oxygen-centered radical, (e.g. **11**, Scheme 2), could be used for site-specific H-abstraction at C6 of 1,6-anhydro sugars. The resulting C-centered radical,(e.g. **12**), could be trapped stereospecifically to give a monoalkylated derivative such as **13** or, by another H-abstraction, the 6-epi counterpart **17**. Alternatively, a second alkylation could be effected to give **18** stereoselectively.

A more direct method, developed by Ferrier and Furneaux,[10] involved photobromination such as **15** to **16**. Monoalkyl derivatives such as **17** opened the possibility of the 2-carbon bridge to C3 required by synthon **9.** With regard to the required oxidation change at C3, Hanessian and David[11] had shown that with stannylene acetals such as **19**, the axial site would be selectively oxidized. A ready route to **20a** and thence **20b** (Scheme 3) was thereby opened.

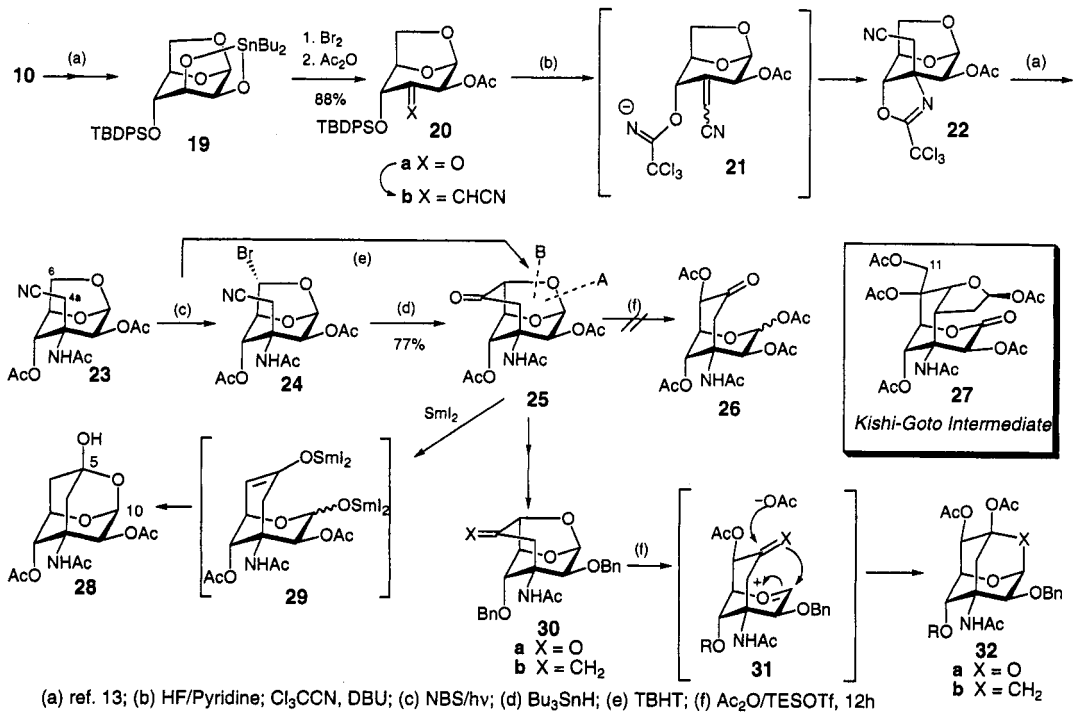


But the availability of **20b** provided a different avenue to the 2-carbon bridge. Thus we envisaged that the angular nitrogen could be introduced through the *cis* oxyamination protocol, equation (i), developed in these laboratories.[12] The procedure is usually driven by an electrophile, but in the case at hand the intermediate imidate anion **21** underwent spontaneous conjugate addition to afford the crystalline oxazoline **22** in 97% yield. Three steps, which turned out to be unexpectedly difficult, then afforded compound **23**.[13]

The foregoing reaction was pivotal in that it simultaneously introduced the angular nitrogen, and presented the 2-carbon entity to C6 for bridge formation.

The choice of nitrile as functional group in **20b** was designed to take advantage of Clive's procedure for converting δ hydroxy nitriles into cyclopentanones[14] which we have utilized successfully elsewhere.[15] Although cyclohexanone formation was unprecedented, we believed that the proximity of the reacting sites, enforced by the 1,6-anhydro scaffold, augured well for success. Indeed the 6-bromo derivative **24** reacted smoothly with tributyltin hydride to give **25** in 77% yield.

Scheme 3



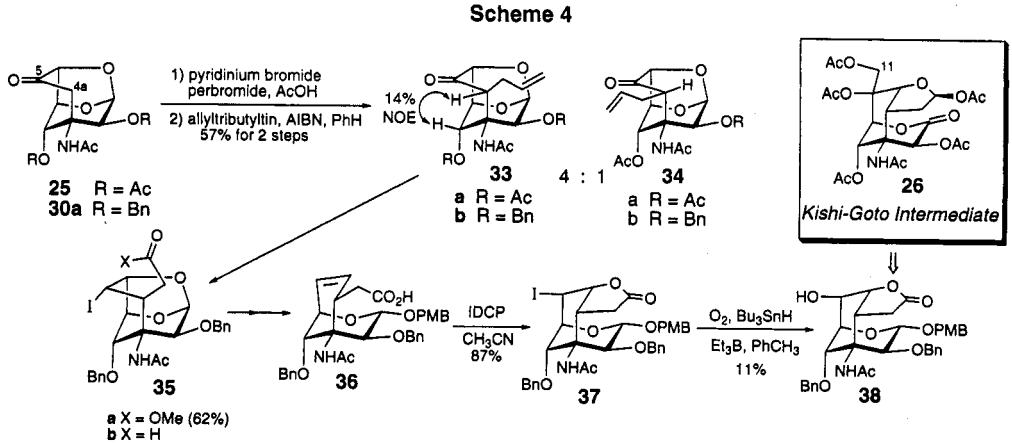
(a) ref. 13; (b) HF/Pyridine; Cl_3CCN, DBU; (c) NBS/hv; (d) Bu_3SnH; (e) TBHT; (f) Ac_2O/TESOTf, 12h

The use of di-tert-butylhyponitrite for generating α-alkoxy carbinyl radicals, e.g. equation (ii)[16] has been explored in our laboratory. It was therefore exciting to find that compound **23** could be converted directly into **25** in 84% yield (based on recovered **23**) by use of di-tert butylhyponitrite in refluxing tert-butanol. Nevertheless the two steps involving bromide **24** turned out to be more practical for the preparation of **25.**

Creation of the carbocyclic moiety in **25** was clearly an important plateau. It was considered judicious to connect up with a late-stage intermediate from the Kishi-Goto synthesis, and lactone **27** seemed an interesting possibility. This would require cleavage of the internal acetal (i.e. 1,6-anhydro ring) sometime in the future, but it is known that hydrolysis at site A can be difficult.[17] However our studies on the 'armed/disarmed strategy' for oligosaccharide synthesis has sensitized us to the dramatic influence that protecting groups can have on glycoside activation.[18] Accordingly it was found that whereas diester **25** gave no evidence of acid catalyzed acetolysis after 24 h, the corresponding dibenzyl ether **30a** reacted in 12 h.[19]

The salutary effect of the benzyl group was therefore apparent. However it was notable that the product was not a glycosyl acetate such as **26**, but the dioxaadamantane **32a** whose formation can be rationalised by the Prins-like process depicted in **31**.[19] Clearly acid catalysed procedures would be problematic, but reductive elimination at site B of **25** was an alternative. Interestingly, treatment with samarium(II) iodide gave acetal **28,** presumably *via* the samarium enolate **29**.[20] Not surprisingly, **28** proved to be completely refractory to reducing agents.

Scheme 4



The ready formation of the dioxadamantane core in **28** and **32a**, was of immense tactical interest in view of the presence of this motif in TTX. The ease of adamantyl expansion was also seen with the Wittig product **30b**, which required only 1 hour to be converted into **32b**. It was therefore seen as a challenge to try and make creative use of the propensity of these caged systems, e.g. **30**, for adamantyl expansion.

But before exploring this possibility ketone **25** presented an opportune stage at which to further functionalize the cyclohexyl core. A free-radical procedure seemed appropriate and so the Keck reaction[21] was applied to the α-bromo derivative of **25**, by which a 4:1 mixture of stereoisomers **33a** and **34** was produced (Scheme 4). This product distribution was fortuitous in view of the fact that molecular mechanics calculations using MM3* force field in MacroModel on the O-benzyl structures showed that steric energy of **33b** was higher than **34b** by ~ 0.45 kcal/mol, making it improbable that based catalyzed epimerization could be used to our advantage.

The allyl group of **33** provided an attractive implement for the furanosyl moiety of **27**, but the results in Scheme 3 indicated that neither acid-catalyzed procedures nor SmI_2 reduction were suitable for these caged systems. With this limitation in mind, the benzyl protected ketone **33b** was subjected to three steps, including Schrieber ozonolysis[22] which led to a preponderance of ester **35a**, and only minor amounts of the corresponding aldehyde, **35b**. The iodoalkoxy moiety permitted cleavage of the internal acetal by reductive elimination rather than hydrolysis, and the resulting γ,δ-unsaturated acid,**36**, was subjected to iodolactonization to give **37**.

The impetus for the approach being pursued came from the hope that radical oxygenation could be effected to convert **37** into **38**. Initial efforts using TEMPO[23] were unavailing. A procedure reported by Nakamura and coworkers[24a] was investigated, but even after the modification shown in Scheme 4, we obtained only 11% of **38**. Variations in the procedure introduced more recently[24b,25] may prove more rewarding.

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