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Synthesis of trans-fused tetrahydrooxepins: stereoselective allylation of sulfur or fluoro-substituted tetrahydrooxepins

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Abstract—An efficient route to the trans-fused tetrahydrooxepin corresponding to the E ring of ciguatoxin was developed. Wide screening of allylation reactions of sulfur or fluoro-substituted tetrahydrooxepin revealed that the optimum method for obtaining the β-allylation product selectively was the use of a combination of allyltrimethylsilane and $TiCl_4$ with 6-fluoro-7-hydroxytetrahydrooxepin.

Keywords: Allylation; Tetrahydrooxepin; Titanium tetrachloride; Ciguatoxin

1. Introduction

During the course of our recent synthetic studies of ciguatoxin (**1**),[1] the principal toxin responsible for ciguatera seafood poisoning, we have continuously worked on the development of an efficient route to trans-fused tetrahydrooxepin, which corresponds to the E ring of **1** (Fig. 1). In particular, by considering the structurally simplified and readily accessible bicyclic model **3** as an alternative to the DE ring, we developed a strategy which ultimately resulted in the first synthesis of the ABCDE ring segment (**2**) of **1**.[2,3]

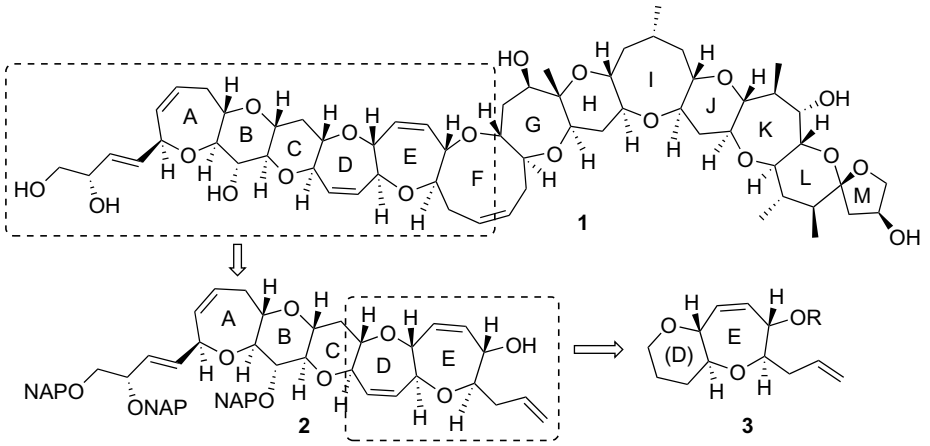

Figure 1. Structures of ciguatoxin (**1**), the ABCDE ring segment (**2**), and the DE ring model (**3**). NAP = 2-naphthylmethyl.

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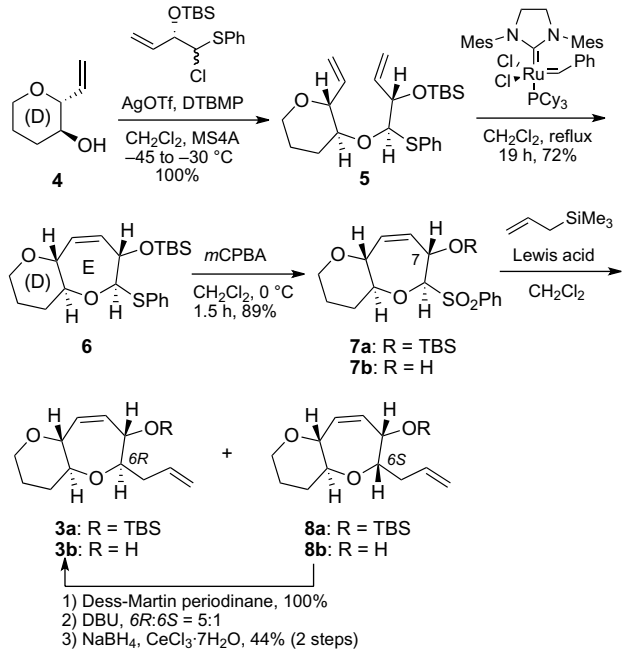

Scheme 1. Strategy for constructing trans-fused tetrahydrooxepin. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TBS = *tert*-butyldimethylsilyl, *m*CPBA = *m*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride.

Our strategy to access **3** involved three key transformations, as shown in Scheme 1: (1) AgOTf-mediated *O*,*S*-acetal formation[4] (**4** to **5**), (2) ring-closing metathesis[5] (**5** to **6**), and (3) Lewis acid-mediated allylation of anomeric sulfone[6] (**7** to **3**). Although this approach is fast and offers a high yield, stereocontrol at the anomeric center has been a formidable challenge, because Lewis acid-mediated substitution normally occurs from the α-side due to the anomeric effect of the ring oxygen. For instance, allylation of **7a** provided the α-adduct **8a** rather than the β-adduct **3a**, regardless of the type of Lewis acid used. In our previous communication, we discovered that the β-adduct **3b** was formed preferentially when $TiCl_4$ was employed with the C-7-hydroxyl derivative **7b**.[2] However, these conditions could not be applied to the highly functionalized ABCDE ring segment **2**, since they were accompanied by side reactions arising from the depressed reactivity of the C-7-hydroxyl sulfone.[2] Therefore, we continued our screening of allylation reactions using other substrates and a variety of activators. Herein, we provide a summary of allylation reactions of sulfur- or fluoro-substituted tetrahydrooxepins and our development of a method for obtaining the β-adduct selectively using 6-fluoro-7-hydroxytetrahydrooxepin.

2. Results and discussion

Our experiments are summarized in Table 1. Direct allylation of TBS-protected phenyl sulfide with NBS/TfOH[7] or NIS/AgOTf[8] activators afforded the α-allylation product **8a** exclusively in moderate yields (entries 1 and 2). Similarly high α-selectivity was observed in the case of sulfoxides, irrespective of the type of C-7-protective group used (entries 3 and 4). To the best of our knowledge, this is the first application of the Tf_2O/DTBMP activation system[9] to a C-nucleophile. As reported previously,[2] allylation of the corresponding sulfone also gave α-product **8a** predominately (entries 5 and 6), while a reversal of α/β selectivity was observed for the C-7-hydroxyl sulfone (entries 7 and 8). In addition to this remarkable β-selectivity, it should be pointed out that addition of the C-nucleophile proceeded in preference to intermolecular O-alkylation (dimerization) even in the presence of free hydroxyl groups. Since the time-consuming processes in entry 8 provoked side reactions when applied to functionalized molecules,[2] we next examined anomeric fluoride, a stable and highly reactive glycosydation precursor.[10] Application of the activators $Cp_2HfCl_2/AgClO_4$ or $Cp_2TiCl_2/AgClO_4$,[11] or the use of $BF_3{\cdot}Et_2O$,[12] generated allylation product **8a** in high yield with α-selectivity (entries 9–11). Since neighboring ester groups and polar solvents have been known to facilitate β-nucleophilic attack by stabilizing the cationic intermediate, we attempted to use C-7-pivalate and CH_3CN (entries 12 and 13). However, only a marginal improvement in selectivity was observed as the reaction time was prolonged (entry 13). Eventually, we again focused our attention on the C-7-hydroxyl substrate. Whereas the application of $Cp_2HfCl_2/AgClO_4$ or $BF_3{\cdot}Et_2O$ activators gave disappointing results due to competition with intermolecular O-alkylation (entry 14), the use of $TiCl_4$ gave rise to the desired β-adduct **3b** in 70% yield with good selectivity (entry 16). Notably, allylation was completed within 10 min even at −100 °C, and α/β selectivity was independent of the C-6-stereochemistry of the starting fluoride.

Since some alkylmagnesium and alkylaluminum reagents can react with glycosyl fluorides in the absence of a Lewis acid,[13,14] we also examined allylation reactions with allylmetal species (entries 17–21). However, the desired isomers (**3a** or **3b**) were not obtained preferentially under any of the conditions examined.[†]

It has been well established in previous studies[15] that formation of the α-product **8a** in the C-8-OTBS series can be rationalized by the anomeric effect, which causes the C-nucleophile to approach from the pseudo-axial side (Fig. 2).[16] In contrast, in the case of the C-7-unprotected alcohol, the cationic intermediate is stabilized by

[†] We expected the formation of **3b** in the reaction of the C-7-hydroxyl substrate with allylmagnesium bromide (entry 20) through an epoxide-like intermediate akin to **11** (see Fig. 2). However, the only product obtained was homoallyl alcohol **9**, which presumably arose from abstraction of the C-7-hydrogen followed by enol-keto tautomerization and allylation to the resulting enone.