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Synthesis of the Fully Functionalized ABCDE Ring Moiety of Ciguatoxin

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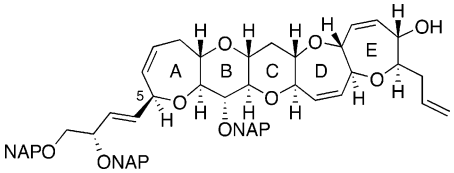
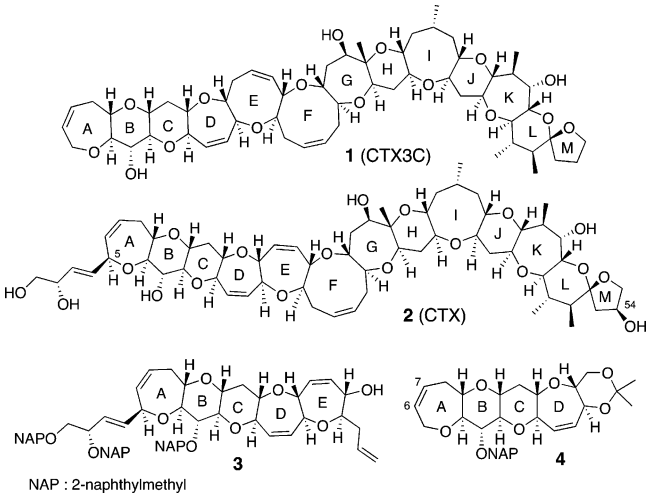
ABSTRACT



A fully functionalized ABCDE ring moiety of ciguatoxin (CTX), the major causative agent of ciguatera poisoning, was synthesized for the first time. The present strategy involves the efficient installation of the C5-dihydroxybutenyl substituent and construction of the tetrahydrooxepin E ring using a novel α-chlorosulfide synthon.

Ciguatoxins (CTXs), the causative agents from epiphytic dinoflagellate (*Gambierdiscus toxicus*),[1] are transferred into more than 100 species of fish through the food chain, causing ciguatera poisoning primarily in tropical and subtropical regions.[2] The extremely low content of toxins in fish has limited the isolation from natural sources and detailed biological studies on the voltage-sensitive sodium channels (VSSC),[3] as well as the preparation of anti-CTX antibodies for detecting CTXs.[4] Chemical synthesis is therefore the only plausible solution. In 2001, our synthetic efforts culminated in the first total synthesis of CTX3C **1**.[5,6] The final stage of the synthesis of **1** involved the coupling of the left and right wings with the concomitant construction of the central FG ring system. This strategy is expected to be applicable to all CTXs due to the common FG ring. In this context, the left wing **3** serves as a key intermediate for synthesizing a biologically more potent and structurally more complex ciguatoxin (CTX, **2**).[7,8] The dihydroxybutenyl substituent embedded in the A ring of **2** poses a greater synthetic challenge. A fully functionalized ABCDE ring moiety such as **3**, therefore, has yet to be achieved, while several methods to construct the AB(C) ring system with the dihydroxybutenyl substituent have been reported.[9,10] Herein, an efficient synthesis of **3** is reported for the first time.



The NAP-protected ABCD ring fragment **4** was selected as a versatile starting material, because a practical, asym-

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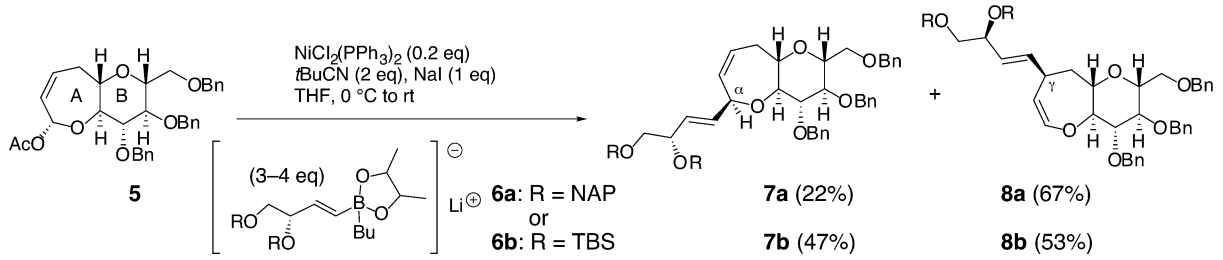
Scheme 1. Ni-Catalyzed Coupling of Alkenyl Borates **6** with the AB Ring Model **5**

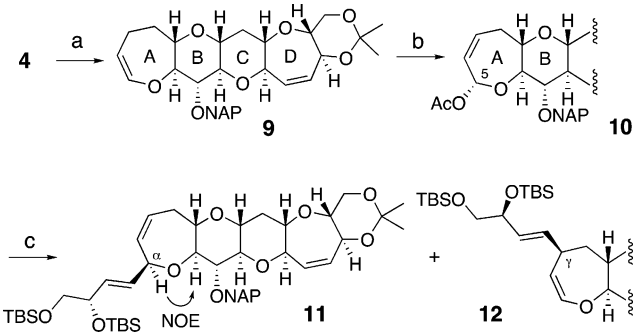


metric route to such an ABCD ring system was recently established[11] and this unit is expected to be a common precursor for the divergent synthesis of the left wings of both **1** and **2**. The required steps for synthesizing **3** include the assembly of the A ring substituent as well as the tetrahydrooxepin E ring. On the other hand, alternative construction of the tetrahydrooxocin E ring system will produce the corresponding left wing of CTX3C **1** as well.

In an effort to adopt the recently developed Ni-catalyzed coupling technology,[9d,12] the effect of dihydroxybutenyl borate protective groups on the regioselectivity was investigated. Since the NAP group proved to be optimal for the total synthesis of **1**,[5b] bis NAP ether **6a** was examined as a coupling agent with the model AB ring fragment **5** (Scheme 1). The α/γ selectivity, however, resulted in a less satisfactory ratio (**7a**:**8a** = 1:3), while the TBS ether **6b** afforded a more acceptable ratio (**7b**:**8b** = 1:1.1).

The allylic acetate **10** of the ABCD ring was stereoselectively synthesized from **4**[11] via enol ether **9** (Scheme 2). Isomerization of the C6,7-double bond of **4** was achieved using Wilkinson catalyst and DBU[13] without affecting the double bond in the D ring. The resulting enol ether **9** was oxidized with $Pb(OAc)_4$[14] at −5 °C in the presence of pyridine, as an acid scavenger yielding a single stereoisomer of unstable **10**. Addition of pyridine to this oxidation reaction was essential to effectively attain **10**. The Ni-catalyzed coupling of **10** with the alkenylborate **6b**[9d,12] proceeded with high stereoselectivity yielding the α-adduct **11** and the γ-adduct **12** with a 42% yield (three steps from **4**) in a 1:1 ratio. The stereochemistry of **11** was established using NOE experiments. Thus, efficient installation of the dihydroxybutenyl substituent into the ABCD ring fragment was achieved with complete stereocontrol.

Scheme 2. Assembly of the Dihydroxybutenyl Substituent in the ABCD Ring System[a]



[a] Reagents and conditions: (a) $(Ph_3P)_3RhCl$ (0.1 equiv), DBU (1 equiv), MeOH−$ClCH_2CH_2Cl$ (1:1), 65 °C, 15 min. (e) $Pb(OAc)_4$ (3 equiv), pyridine (3 equiv), CH_2Cl_2, −18 to −5 °C, 42 h. (f) **6b** (3.3 equiv), $NiCl_2(PPh_3)_2$ (0.3 equiv), *t*BuCN (2.0 equiv), NaI (1.0 equiv), THF, 0 °C to room temperature, 1.7 h, **11** (20%), **12** (22%) (three steps from **4**).

The tetrahydrooxepin E ring was subsequently assembled using a novel synthon, α-chlorosulfide **15**[15] (Scheme 3). After sequential manipulation of the protective groups of **11** and

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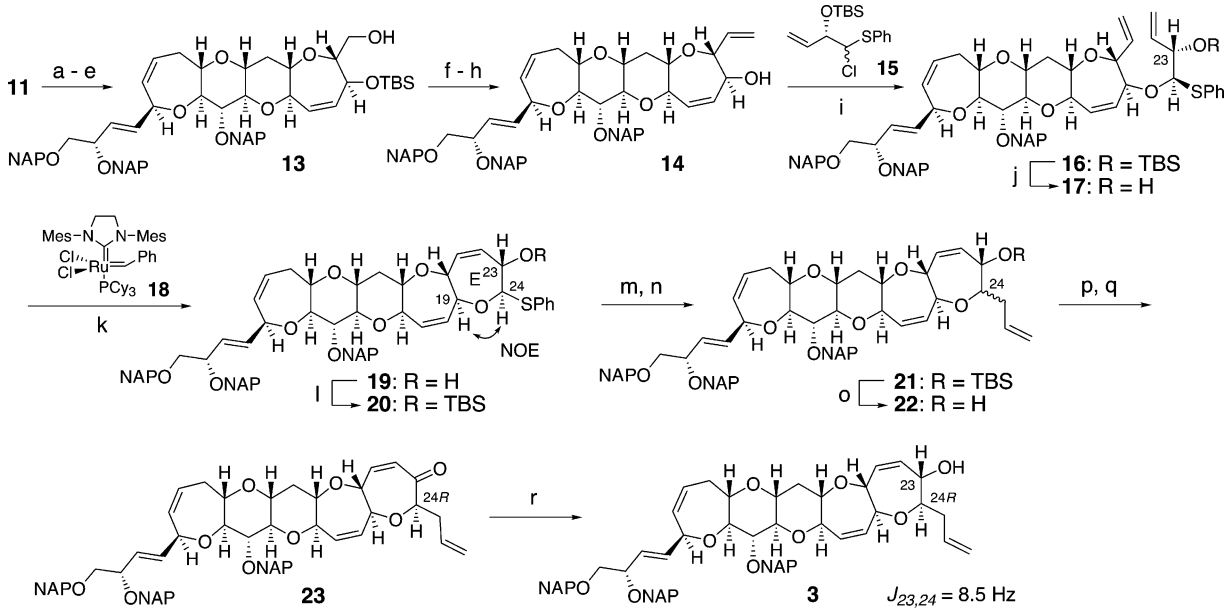
(15) α-Chlorosulfide **15** was synthesized from 2,3-*O*-isopropylideneglyceraldehyde in six steps: (i) Ph_3PCH_3Br, KO*t*Bu, THF, 0 °C; (ii) *p*TsOH·H_2O, THF−MeOH (8:1); (iii) TBSCl, imidazole, DMF; (iv) PPTS, EtOH, 20% in four steps; (v) Bu_3P, $(PhS)_2$, pyridine, 89%; (vi) NCS, CCl_4, 100%.

Scheme 3. Synthesis of the ABCDE Ring Moiety **3** of CTX (**2**)[a]



[a] Reagents and conditions: (a) TBAF, THF, rt, 1 h, 93%. (b) NaH, NAPBr, TBAI, THF−DMF (3:1), 40 °C, 5 h, 89%. (c) 1 N HCl−MeOH−THF (1:5:10), rt, 25 h. (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 72% (two steps). (e) CSA, MeOH−THF (1:1), −5 °C, 69 h, 91%. (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 1 h. (g) Ph_3PCH_3Br, KO*t*Bu, THF, 0 °C to rt, 1 h. (h) TBAF, THF, rt, 1 h, 83% (three steps). (i) **15** (3.0 equiv), AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, MS4A, CH_2Cl_2, −50 to −30 °C, 1 h. (j) TBAF, THF, rt, 30 min, 83% (two steps). (k) **18** (0.05 equiv), CH_2Cl_2 (3 mM), rt, 2 h, 92%. (l) TBSCl, imidazole, DMF, rt, 12 h. (m) *m*CPBA, CH_2Cl_2, −10 °C, 18 h, 71% (two steps). (n) Allyltrimethylsilane, $EtAlCl_2$, CH_2Cl_2, −70 °C, 30 min, 63%, **21** (24*R*:24*S* = 1:3). (o) TBAF, THF, rt, 1 h, 93%. (p) $C_6H_4CO_2I(OAc)_3$, CH_2Cl_2, rt, 1.2 h, 87%. (q) DBU, CH_2Cl_2, rt, 8 h, **23** (24*R*:24*S* = 2.6:1). (r) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2−MeOH (1:1), 0 °C, 10 min, **3** (64%), diastereomers of **3** (24%) (two steps).

Swern oxidation of the primary alcohol **13** followed by Wittig olefination, the resulting alcohol **14** was coupled with **15** using an AgOTf-mediated method[16,17] in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, affording a single stereoisomer of the thioacetal **16**. Whereas ring-closing metathesis (RCM) of the TBS ether **16** using **18**[18] was sluggish, the corresponding alcohol **17** smoothly underwent RCM, yielding **19** in a 92% yield without reacting with other double bonds.

The next step requires the insertion of an allyl group at C24, necessary for the construction of the nine-membered F ring via RCM in the total synthesis of **2**.[5,8,16] Ley's method[19] was examined for the model DE ring system, **24a** and **24b**, under a variety of conditions using allyltrimethylsilane and Lewis acids to elucidate the stereoselectivity. Some of the results are summarized in Table 1. The highest syn/anti ratio was realized when the alcohol **24a** was treated with $TiCl_4$ at −78 °C (entry 3). However, these conditions were not applicable to the ABCDE ring intermediate because they were accompanied by the cleavage of NAP ethers. Careful monitoring of the reaction indicated that deprotection of the NAP groups was slow and could be suppressed if allylation proceeded rapidly. Since the neighboring hydroxyl group was suspected to affect the reaction rate, the alcohol was protected as TBS ether **24b**. In contrast to that observed for **24a**, allylation of **24b** was completed within 1 h, even at low temperatures, with a high yield of the allylated products, **25b** and **26b**, but with a reversed syn/anti ratio (entries 6, 7, and 9). Since the stereochemistry of the allyl group can be readily corrected at the later stage, the protected TBS ether **20** was used (Scheme 3). The sulfide of **20** was carefully oxidized using *m*CPBA (at −10 °C to avoid olefin epoxidation) to give the sulfone. This sulfone was then reacted under the modified allylation conditions. A higher yield was obtained using the less acidic $EtAlCl_2$ (63% yield) than when using $AlCl_3$ (42% yield), leaving the NAP groups untouched. The TBS group was then removed and oxidized to the ketone as a 1:3 mixture of the C24 epimers, which enabled epimerization and provided the more stable isomer **23** in a 2.6:1 ratio. Finally, stereoselective reduction[20] of **23** yielded the ABCDE ring fragment **3** from **22** with an overall yield of 56%. The stereochemistry of **3** was fully assigned from the results of NOE and NOESY experiments.[21]

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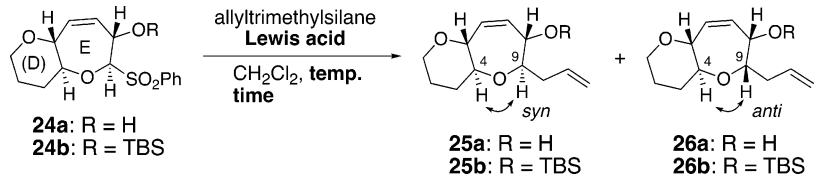
Table 1. Allylation with the DE Ring Model **24**

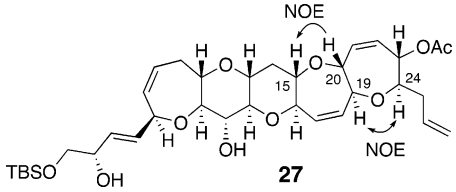


entry	sulfone	Lewis acid[a]	temperature	time (h)	yield (%)[b]	ratio (**25**:**26**)[c]
1	**24a**	$AlCl_3$	−78 to 0 °C	17	81	60:40
2	**24a**	$EtAlCl_2$	−78 °C to rt	10	0	no reaction
3	**24a**	$TiCl_4$	−78 °C	11	62 (78)[d]	84:16
4	**24a**	$TiCl_4$	−78 to −45 °C	10	56	71:29
5	**24a**	$TiCl_2(OiPr)_2$[e]	−78 to −20 °C	10	0	no reaction
6	**24b**	$AlCl_3$	−78 to −45 °C	0.8	89	17:83
7	**24b**	$EtAlCl_2$	−78 to −60 °C	0.8	73	20:80
8	**24b**	Et_2AlCl	−78 °C to rt	9.5	0	no reaction
9	**24b**	$TiCl_4$	−78 °C	0.3	74	31.69

[a] Performed with 3−6 equiv of Lewis acid. [b] Isolated yield. [c] Determined by ^1H NMR analysis (500 MHz, $CDCl_3$). [d] Based on recovery of **24a**. [e] Prepared from $TiCl_4$ and $Ti(OiPr)_4$.

In summary, the fully functionalized ABCDE ring fragment **3** of CTX **2** was synthesized from the readily accessible ABCD ring moiety **4** for the first time. The present synthesis features a short-step installation of the dihydroxybutenyl substituent and efficient construction of the tetrahydrooxepin E ring using the novel synthon **15**. Further investigations directed toward the total synthesis of **2** are currently under way in our laboratory.

(21) NOE and NOESY experiments of **3** were performed after converting to diol **27**: (i) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 5 h, 100%; (ii) DDQ, $CH_2Cl_2-H_2O$ (20:1), rt, 35 min; (iii) CSA, MeOH−THF (1:1), rt, 45 min, 67% (two steps); (iv) TBSCl, Et_3N, DMAP, CH_2Cl_2, 62 h, 100%.



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Supporting Information Available: Experimental procedures and spectroscopic data of all new synthetic products. This material is available free of charge via the Internet at http://pubs.acs.org.

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