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Practical Total Synthesis of Ciguatoxin CTX3C by Improved Protective Group Strategy

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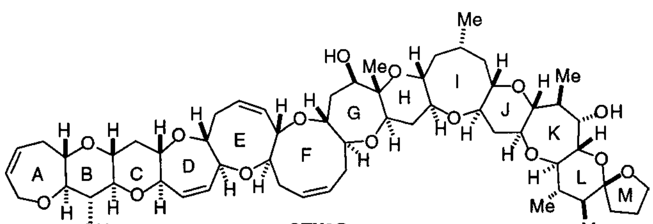
ABSTRACT



Ciguatoxin CTX3C is a representative congener of ciguatoxins, which are known to be the principal causative agents of ciguatera seafood poisoning. The structure of CTX3C spans more than 3 nm and is characterized by 13 ether rings. In this paper, an improved total synthesis of CTX3C is reported. Alteration of the protective group from benzyl ether to 2-naphthylmethyl (NAP) ether drastically increases the yield for final global deprotection and has provided a sufficient amount of sample for further biological studies.

Ciguatera is a major food poisoning in tropical and subtropical regions and often causes long-lasting health problems with diverse symptoms.[1] Causative toxins[2] such as ciguatoxin CTX3C (**1**, Figure 1)[2d] are produced by the marine dinoflagellate *Gambierdiscus toxicus* and accumulate in fish of many species through the food chain.[3] Pharmacological studies have revealed that ciguatoxins exert toxicity through the activation of voltage-sensitive sodium channels (VSSC).[4] However, detailed biological studies at the atomic level as well as the preparation of anti-ciguatoxin antibodies for detecting ciguatoxins prior to consumption[5] have been hampered by the extremely low availability of the causative agents. Chemical synthesis is therefore the only plausible solution.[6,7]

(1) For recent reviews, see: (a) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3. (b) Lewis, R. J. *Toxicon* **2001**, *39*, 97. (c) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (d) Yasumoto, T. *Chem. Rec.* **2001**, *1*, 228.

(2) (a) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc*. **1989**, *111*, 8929. (b) Murata, M.; Legrand, A.-M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc*. **1990**, *112*, 4380. (c) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325. (d) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett*. **1993**, *34*, 1975. (e) Lewis, R. J.; Vernoux, J.-P.; Brereton, I. M. *J. Am. Chem. Soc.* **1998**, *120*, 5914. (f) Yasumoto, T.; Igarashi, T.; Legrand, A.-M.; Cruchet, P.; Chinain, M.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc*. **2000**, *122*, 4988.

(3) Bagnis, R.; Chanteau, S.; Chungue, E.; Hurtel, J. M.; Yasumoto, T.; Inoue, A. *Toxicon* **1980**, *18*, 199.

(4) (a) Lombet, A.; Bidard, J.-N.; Lazdunski, M. *FEBS Lett*. **1987**, *219*, 355. (b) Dechraoui, M.-Y.; Naar, J.; Pauillac, S.; Legrand, A.-M. *Toxicon* **1999**, *37*, 125.

(5) For attempts toward the preparation of anti-CTX antibodies, see: (a) Oguri, H.; Tanaka, S.-i.; Hishiyama, S.; Oishi, T.; Hirama, M.; Tsumuraya, T.; Tomioka, Y.; Mizugaki, M. *Synthesis* **1999**, 1431. (b) Nagumo, Y.; Oguri, H.; Shindo, Y.; Sasaki, S.-y.; Oishi, T.; Hirama, M.; Tomioka, Y.; Mizugaki, M.; Tsumuraya, T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2037. (c) Hokama, Y.; Takenaka, W. E.; Nishimura, K. L.; Ebesu, J. S. M.; Bourke, R.; Sullivan, P. K. *J. AOAC Int.* **1998**, *81*, 727. (d) Pauillac, S.; Sasaki, M.; Inoue, M.; Naar, J.; Branaa, P.; Chinain, M.; Tachibana, K.; Legrand, A.-M. *Toxicon* **2000**, *38*, 669.

(6) For recent synthetic studies from our laboratory, see: (a) Oguri, H.; Sasaki, S.-y.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405. (b) Oguri, H.; Tanaka, S.-i.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 975. (c) Oishi, T.; Tanaka, S.-i.; Ogasawara, Y.; Maeda, K.; Oguri, H.; Hirama, M. *Synlett* **2001**, 952. (d) Imai, H.; Uehara, H.; Inoue, M.; Oguri, H.; Oishi, T.; Hirama, M. *Tetrahedron Lett*. **2001**, *42*, 6219. (e) Maruyama, M.; Inoue, M.; Oishi, T.; Oguri, H.; Ogasawara, Y.; Shindo, Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 1835. (f) Uehara, H.; Oishi, T.; Inoue, M.; Shoji, M.; Nagumo, Y.; Kosaka, M.; Le Brazidec, J.-Y.; Hirama, M. *Tetrahedron* **2002**, *58*, 6493. (g) Inoue, M.; Wang, G. X.; Wang, J.; Hirama, M. *Org. Lett.* **2002**, *4*, 3439.

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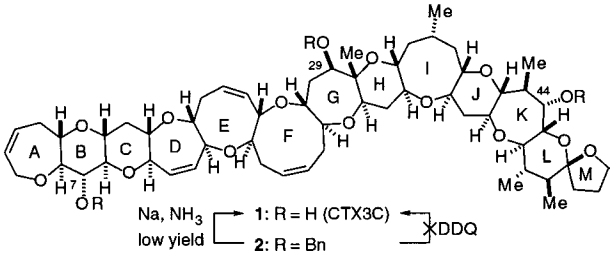
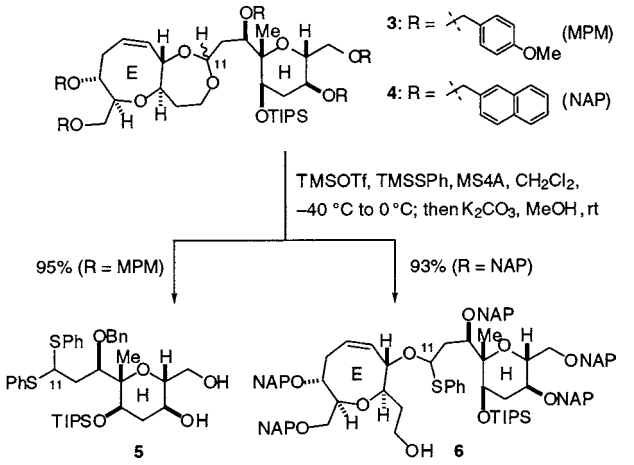


Figure 1. Structure of Ciguatoxin CTX3C (**1**).

In 2001, the total synthesis of CTX3C **1** was achieved in our laboratory.[8] The synthesis relied on the highly convergent and efficient strategy of assembling four structural fragments. To prepare a sufficient amount of **1**, however, the final deprotection of the tris-benzyl CTX3C **2** remained a problem (Figure 1). The reductive cleavage of the benzyl ethers of **2** using sodium in liquid ammonia was complicated by concomitant reduction of the allylic ether in the A ring and was thus low yielding, while DDQ-mediated oxidation of the benzyl groups resulted in decomposition. The problem with the deprotection conditions appeared to be the low reactivity of the pseudoaxial C44-benzyloxy group and competing undesired reactions in particular involving the A ring. Since all attempts to remove the benzyl groups were less than satisfactory, an alternative protective group that can be chemoselectively removed in the highly complex matrix is apparently required.

It is practically important that changes in the overall synthetic strategy should be minimal when the alternative protective group is applied. In this sense, substituted benzyl ethers are considered to be the most favorable, and the *p*-methoxybenzyl (MPM) group was chosen first because it can be readily removed by treatment with DDQ.[9] Due to the lability of MPM to strongly acidic conditions,[10] a model study was performed to assess the suitability of MPM in this context. The conversion of O,O-acetal to O,S-acetal using TMSOTf and TMSSPh[11] in the final stage of the synthesis was likely to be the most acidic step.[6d,8] Therefore, the MPM-protected model compound **3**, which represents the middle portion of **1**, was prepared[12] and subjected to the acetal cleavage reaction as depicted in Scheme 1.[6d,8] However, only the trihydroxy dithioacetal **5** was isolated, demonstrating not only that the MPM groups were removed but that overreaction also occurred. Consequently, a different benzyl-type protective group that is compatible with acidic media should be employed for synthesis. A NAP (2-naphthylmethyl) group has been introduced recently by Spencer[13] and Matta,[14] and its utility in oligosaccharide synthesis has been demonstrated.[14b,c] In favor of our situation, NAP is known to be more acid-stable than MPM, and facile removal can still be achieved using DDQ.[13b,14] Thus, pentakis-NAP ether **4** was synthesized[12] and treated with TMSOTf and TMSSPh to successfully afford the desired O,S-acetal **6** in 93% yield without deprotection.

Scheme 1. Model Study for Acetal Cleavage Reaction



According to the model studies, the NAP group was selected for the new synthetic route to **1** (Scheme 2). The ABCDE ring and the HIJKLM ring segments (**7** and **8**), with hydroxyl groups masked as NAP ethers, were prepared in standard synthetic manipulations from the previously reported intermediates (see Supporting Information).[6e,f] The condensation of **7** and **8** using $Sc(OTf)_3$[15] successfully gave the seven-membered acetal **10** in 69% yield. Unexpectedly, the next

(7) For recent synthetic studies of ciguatoxins from other groups, see: (a) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1090. (b) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. (c) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2771. (d) Fujiwara, K.; Tanaka, H.; Murai, A. *Chem. Lett.* **2000**, 610. (e) Fujiwara, K.; Takaoka, D.; Kusumi, K.; Kawai, K.; Murai, A. *Synlett* **2001**, 691. (f) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821. (g) Takai, S.; Isobe, M. *Org. Lett.* **2002**, *4*, 1183. (h) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875. (i) Eriksson, L.; Guy, S.; Perlmutter, P. *J. Org. Chem.* **1999**, *64*, 8396. (j) Bond, S.; Perlmutter, P. *Tetrahedron* **2002**, *58*, 1779. (k) Leeuwenburgh, M. A.; Kulker, C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1999**, 1945. (l) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372, and references therein.

(8) Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.

(9) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(10) For some examples of acidic removal of MPM, see: (a) Gordon, D. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 659. (b) Hébert, N.; Beck, A.; Lennox, R. B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777. (c) Akiyama, T.; Shima, H.; Ozaki, S. *Synlett* **1992**, 415. (d) Congreve, M. S.; Davison, E. C.; Fuhry, M. A. M.; Holmes, A. B.; Payne, A. N.; Robinson, R. A.; Ward, S. E. *Synlett* **1993**, 663. (e) Yan, L.; Kahne, D. *Synlett* **1995**, 523. (f) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961. (g) Bouzide, A.; Sauvé, G. *Synlett* **1997**, 1153. (h) Onoda, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1997**, *38*, 1443.

(11) Kim, S.; Do, J. Y.; Kim, S. H.; Kim, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2357.

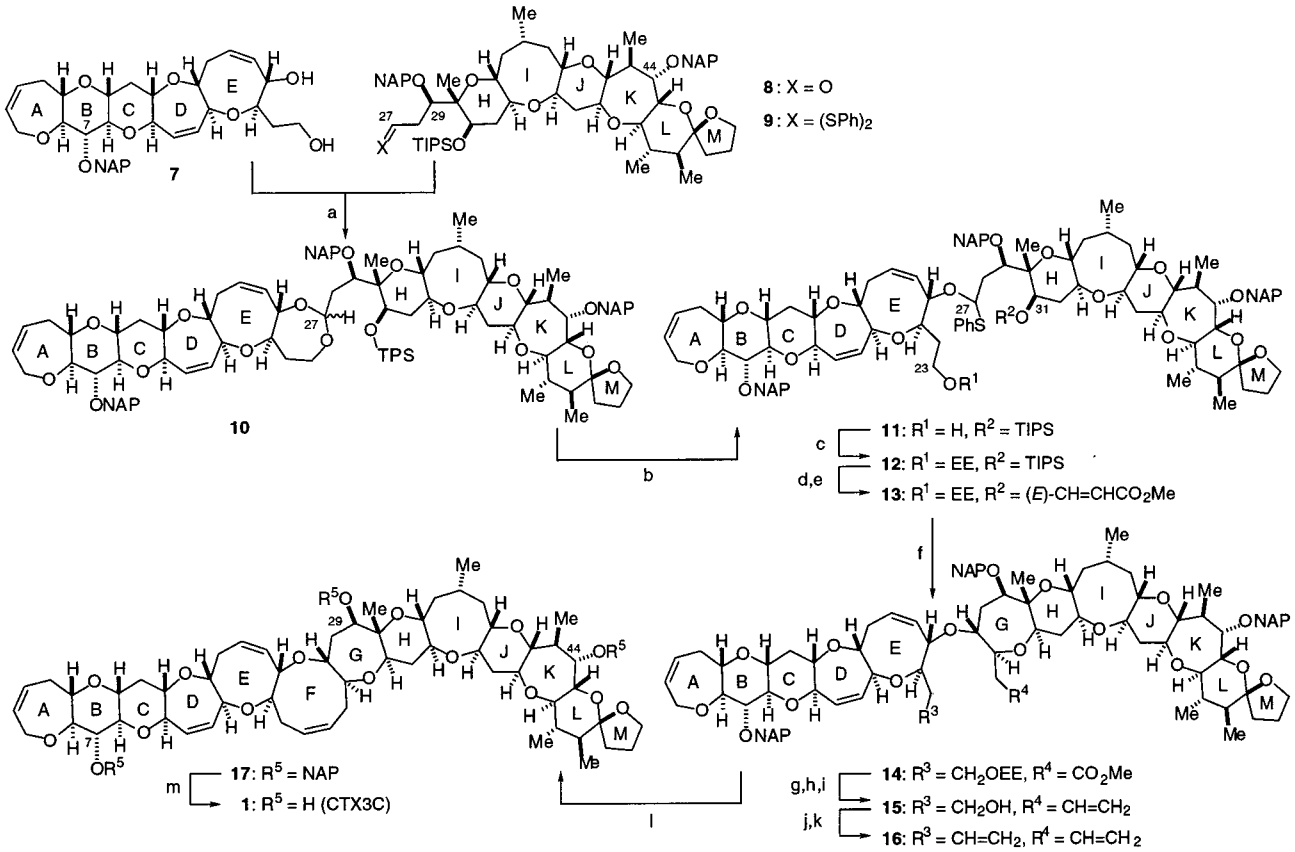
(12) Model compounds were prepared from the previously reported substrate in a standard manner (see ref 6d).

(13) (a) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172. (b) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033.

(14) (a) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169. (b) Liao, W.; Locke, R. D.; Matta, K. L. *Chem. Commun.* **2000**, 369. (c) Xia, J.; Alderfer, J. L.; Piskorz, C. F.; Matta, K. L. *Chem.−Eur. J.* **2001**, *7*, 356.

(15) (a) Fukuzawa, S.-i.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077. (b) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839. (c) Inoue, M.; Sasaki, M.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9416.

Scheme 2. Improved Total Synthesis of CTX3C (**1**)[a]



[a] Reaction conditions: (a) $Sc(OTf)_3$, benzene, rt, 69%. (b) TMSSPh, TMSOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), 4 Å MS, from rt to 35 °C; then K_2CO_3, MeOH, 49% based on recovered **10** (23%). (c) EVE, PPTS, CH_2Cl_2, rt, 73%. (d) TBAF, THF, 40 °C. (e) methyl propiolate, NMM, CH_2Cl_2, rt, 89% (two steps). (f) AIBN, *n*-Bu_3SnH, toluene, 85 °C. (g) DIBAL, CH_2Cl_2, −80 °C. (h) Ph_3PCH_3Br, NaHMDS, THF, 0 °C. (i) CSA, MeOH−THF, rt, 41% (four steps). (j) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, rt. (k) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 100%. (l) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, 40 °C, 90%. (m) DDQ, 20:1 $(CH_2Cl)_2$−H_2O, rt, 63%.

acetal cleavage reaction to form O,S-acetal was proved to be problematic. In trials, S,S-acetal **9** arose from the overreaction of the desired O,S-acetal **11**. After extensive experiments, including model studies, it was speculated that trace amounts of TfOH, probably due to the partial hydrolysis of TMSOTf, catalyzed the conversion of O,S-acetal **11** to S,S-acetal **9**. Thus, it was decided that the reaction was to be performed in the presence of a base that traps proton without inhibiting the Lewis acid-mediated reaction. Reproducibly, **10** was transformed to **11** using TMSOTf and TMSSPh in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) and 4 Å molecular sieves at 35 °C. In this way, **11** was isolated in 49% yield based on recovered **10** (23%) after treatment with K_2CO_3 in MeOH to remove the TMS group on the C23-primary alcohol.

The synthetic operations from **11** to fully protected CTX3C **17** proceeded similarly to the previous synthesis of trisBn-CTX3C **2** (Scheme 2).[8] The primary alcohol of **11** was protected as the ethoxyethyl (EE) ether to give **12** in 73% yield. Removal of the TIPS group from **12**, followed by treatment with methyl propiolate and *N*-methylmorpholine, afforded β-(*E*)-alkoxyacrylate **13** in 89% yield (two steps).[16] Compound **13** was subjected to radical cyclization using *n*-Bu_3SnH and AIBN at 80 °C in toluene, giving rise to the desired oxepane **14** stereoselectively.[6d,17] Prior to construction of the last remaining ring by ring-closing olefin metathesis (RCM),[18] the functional groups needed to be modified. DIBAL reduction of ester **14** to the aldehyde, followed by Wittig methylenation and acidic removal of the EE group, produced primary alcohol **15** in 41% overall yield (four steps). Oxidation of **15** with SO_3·pyridine−DMSO and subsequent Wittig reaction afforded the pentaene **16** in 97% yield (two steps). Then, treatment of **16** with Grubbs catalyst[19] at 40 °C in CH_2Cl_2 provided the NAP-protected CTX3C **17** in 90% yield and set all the rings in place.

(16) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.

(17) (a) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783. (b) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337. (c) Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem.* **2002**, *67*, 3301.

(18) For recent reviews of RCM, see: (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

The stability of NAP ethers has been shown under a variety of reaction conditions as described above. As a final step for the total synthesis, DDQ-mediated removal of the NAP groups of **17** was pursued in the presence of the oxidizable allylic ether of the A ring. A solution of **17** in 20:1 $CH_2Cl_2-H_2O$ was treated with 6 equiv of DDQ (2 equiv per NAP group) at room temperature for 2 h.[13b,14] We were pleased to find that the standard workup and column chromatography afforded synthetic CTX3C **1** in 63% yield.[8] As expected, the NAP groups were smoothly removed at ambient temperature in a short reaction time. The new procedure afforded 1 mg of CTX3C in one batch, already exceeding the amount of **1** isolated from the natural source (0.7 mg).[2d]

In conclusion, the improved total synthesis of CTX3C was achieved using a new protective group strategy and modified acetal cleavage reaction to secure a practical supply of the material. It is particularly noteworthy that the NAP group functions as an easily removable substitute of a benzyl group. Extension of the present method to the synthesis of ciguatoxin congeners and further biological studies related to ciguatoxins are currently under investigation in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds in Scheme 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.