

Highly Stereocontrolled Synthesis of the ABCD Ring Fragment of Ciguatoxin CTX3C

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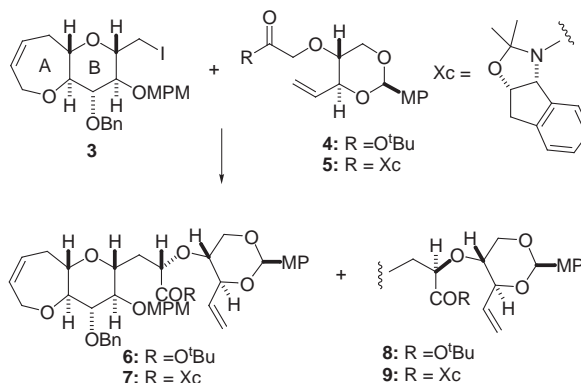
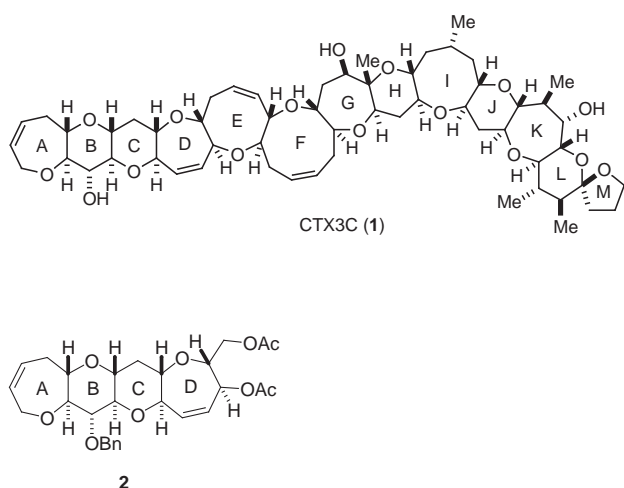
This paper is dedicated to Professor Ryoji Noyori for his outstanding achievements in synthetic organic chemistry.

Abstract: A combination of asymmetric alkylation using (1*R*,2*S*)-1-amino-2-indanol derivative as a chiral auxiliary and the ring-closing metathesis reaction was shown to be an efficient method for synthesizing the ABCD ring fragment of ciguatoxin CTX3C.

Key words: ciguatoxin CTX3C, polycyclic ether, asymmetric alkylation, ring-closing metathesis, multiple asymmetric induction

Ciguatoxin CTX3C (**1**) is one of the causative toxins of ciguatera seafood poisoning prevalent in the tropics and subtropics.² During the course of our synthetic studies directed toward ciguatoxins,^{3,4} we developed a highly convergent strategy for synthesizing polycyclic ethers based on a combination of alkylation and ring-closing metathesis (RCM) reactions,⁵ and have recently succeeded in synthesizing the ABCDE ring fragments of ciguatoxins.⁶ However, stereoselectivity of the alkylation step in the synthesis of the ABCDE fragment of **1** was low and the unnatural type diastereomer even predominated. Therefore, it became necessary to epimerize the epimer at a specific stage, lengthening the synthesis procedure that had only a moderate overall yield.^{6a} In this paper, we describe the efficient synthesis of the ABCD ring fragment (**2**) of **1** through highly stereoselective alkylation and RCM reactions.

Our convergent synthesis of **2** began with the alkylation of *t*-butyl ester **4**⁷ with iodide **3**⁶, corresponding to the AB ring of **1**. As shown in the Table, chemical yield and diastereoselectivity were far from satisfactory (entries 1 and 2). The use of *N,N'*-dimethylpropyleneurea (DMPU) as a co-solvent increased the yield but worsened selectivity. After numerous experiments, an amide **5** possessing an acetonide protected (1*R*,2*S*)-1-amino-2-indanol as a chiral auxiliary⁸ was found to be suitable. The reaction using LDA afforded a 2:1 ratio in favor of a desired **7** (entry 3). The use of butyllithium as a base⁹ remarkably increased the **7**:**9** ratio to 10:1, but the yield was again low, irrespective of the presence or absence of hexamethylphosphoramide (HMPA) (entries 4 and 5). Finally, we found that addition of DMPU dramatically increased the chemical yield (96%) without affecting the selectivity (10:1) (entry 6), while excess **5** was required to attain a high yield of **7** (entries 7 and 8). Thus, a multiple asymmetric induction improved the diastereoselectivity by a factor of 100.¹⁰



Scheme 1

Transformation of **7** to the ABCD ring fragment **2** is shown in Scheme 2. Selective removal of the *p*-methoxybenzylidene acetal of **7** using pyridinium *p*-toluenesulfonate (PPTS) in 1-propanol and the subsequent protection of the resulting 1,3-diol as bis-*t*-butyldiphenylsilyl (bis-TBPS) ether afforded **10** in 75% yield (2 steps). Removal of the MPM group of **10** gave alcohol **11**, which was treated with camphorsulfonic acid (CSA) in toluene at 80 °C to yield lactone **12** (60%). Although addition of

Table Alkylation of **4** and **5** with Iodide **3**^a

entry	base ^b	solvent ^c	4 or 5 (eq) ^d	yield/% ^d	6(7):8(9) ^e
1	LDA	THF-HMPA	4 (2)	23	1:2
2	LDA	THF-DMPU	4 (2)	43	1:10

3	LDA	THF	5 (4)	26	2:1
4	BuLi	THF	5 (4)	25	10:1
5	BuLi	THF-HMPA	5 (4)	26	10:1
6	BuLi	THF-DMPU	5 (4)	96	10:1
7	BuLi	THF-DMPU	5 (2)	73	10:1
8	BuLi	THF-DMPU	5 (1)	26	10:1

^aCarried out at -78 °C to rt.^bOne equivalent of base was added to **4** or **5**.^cRatio of THF-HMPA or THF-DMPU is 10: 1 (v/v).^dBased on iodide **3**.^eDetermined by 500 MHz ¹H NMR.

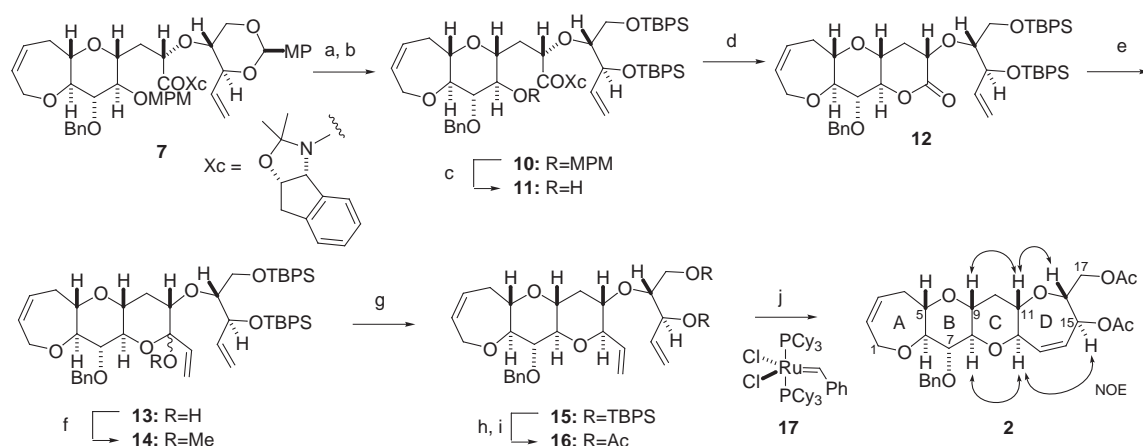
vinylmagnesium bromide resulted in a low yield of **13**, vinyllithium generated from tributyl(vinyl)tin and methyl-lithium reacted with **12** and gave **13** in 98% yield. Conversion of the hemiacetal **13** to the methylacetal **14** as a mixture of diastereomers in a 2:1 ratio and the subsequent reduction with triethylsilane in the presence of BF₃•OEt₂ gave **15**.^{31,3m,5,6} The RCM reaction^{3i-3m,5,11} of the diene **15** using Grubbs catalyst (**17**)¹² was too sluggish, presumably due to steric hindrance of the TBPS groups.^{6a} The bis-TBPS ether **15** was then converted to the less hindered diacetate **16** in two steps (85%). The RCM reaction of **16** proceeded smoothly to afford the ABCD ring fragment (**2**) of **1** in 74% yield.¹³ The stereochemistry of **2** was

unambiguously determined by NOE experiments (Scheme 2).

In conclusion, a highly convergent, efficient and stereoselective synthesis of the ABCD ring fragment **2** of CTX3C (**1**) was achieved. The present asymmetric alkylation and ring-closing metathesis sequence will serve as a powerful tool for the synthesis of polycyclic ether toxins.

References and Notes

- (1) Present address: Department of Chemistry, Graduate School of Science, Osaka University, Osaka 560-0043, Japan
- (2) (a) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380; (b) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975; (c) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hiramata, M.; Harada, N.; Yasumoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11325; (d) Satake, M.; Fukui, M.; Legrand, A. M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197.
- (3) (a) Suzuki, T.; Sato, O.; Hiramata, M.; Yamamoto, Y.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron Lett.* **1991**, *32*, 4505; (b) Oguri, H.; Hishiyama, S.; Oishi, T.; Hiramata, M. *Synlett* **1995**, 1252; (c) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hiramata, M. *Synlett* **1996**, 1165; (d) Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hiramata, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* **1997**, *53*, 3057; (e) Oishi, T.; Shoji, M.; Kumahara, N.; Hiramata, M. *Chem. Lett.* **1997**, 845; (f) Oishi, T.; Maeda, K.; Hiramata, M. *Chem. Commun.* **1997**, 1289; (g) Oishi, T.; Maruyama, M.; Shoji, M.; Maeda, K.; Kumahara, N.; Tanaka, S.; Hiramata, M. *Tetrahedron* **1999**, *55*, 7471; (h) Oguri, H.; Tanaka, S.; Hishiyama, S.; Oishi, T.; Hiramata, M.; Tsumuraya, T.; Tomioka, Y.; Mizugaki, M. *Synthesis* **1999**, 1431; (i) Oishi, T.; Nagumo, Y.; Hiramata, M. *Synlett* **1997**, 980; (j) Oguri, H.; Sasaki, S.; Oishi, T.; Hiramata, M. *Tetrahedron Lett.* **1999**, *40*, 5405; (k) Oguri, H.; Tanaka, S.; Oishi, T.; Hiramata, M. *Tetrahedron Lett.* **2000**, *41*, 975; (l) Oishi, T.; Nagumo, Y.; Shoji, M.; Le Brazidec, J.-Y.; Uehara, H.; Hiramata, M. *Chem. Commun.* **1999**, 2035; (m) Oishi, T.; Uehara, H.; Nagumo, Y.; Shoji, M.; Le Brazidec, J.-Y.; Kosaka, M.; Hiramata, M. *submitted for publication.*



Scheme 2 Reagents and conditions. (a) PPTS, 1-propanol, rt, 5 h, 82%; (b) TBPSCl, imidazole, DMF, 60 °C, 6 h, 92%; (c) DDQ, CH₂Cl₂, H₂O, rt, 1 h, 75%; (d) CSA, toluene, 80 °C, 1 d, 60%; (e) tributyl(vinyl)tin, MeLi, THF, -78 °C, 30 min, 98%; (f) HC(OMe)₃, p-TsOH•H₂O, CH₂Cl₂, rt, 12 h, 70%; (g) Et₃SiH, BF₃•OEt₂, CH₂Cl₂, -30 °C, 2 h, 61%; (h) TBAF, THF, rt, 4 h; (i) Ac₂O, Py, DMAP, rt, 4 h, 85% (2 steps); (j) **17**, CH₂Cl₂, reflux, 12 h, 74%.

- (4) For recent synthetic studies of other groups, see: (a) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1; (b) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21; (c) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 965; (d) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337; (e) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37; (f) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911; (g) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075.
- (5) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041.
- (6) (a) Maruyama, M.; Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Heterocycles* **2001**, *54*, 93; (b) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063.
- (7) Synthesized from D-glucose: (i) *p*-methoxybenzaldehyde dimethylacetal, *p*-toluenesulfonic acid, DMF, 45%; (ii) NaIO₄, MeOH, pH6 acetate buffer; (iii) Ph₃PCH₃Br, *t*-BuOK, THF, 58% (2 steps); (iv) *t*-butyl bromoacetate, NaH, THF, DMF, 84%.
- (8) (a) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771; (b) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673.
- (9) *t*-Butyllithium is also usable and gave a very similar result.
- (10) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
- (11) For the synthetic studies of cyclic polyethers using RCM reported by other groups, see: (a) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565; (b) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335; (c) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123; (d) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127; (e) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310; (f) Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321; (g) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231; (h) Eriksson, L.; Guy, S.; Perlmutter, P. *J. Org. Chem.* **1999**, *64*, 8396; (i) Crimmins, M. T.; Choy, A. *J. Am. Chem. Soc.* **1999**, *121*, 5653; (j) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899. Recent reviews on ring-closing metathesis reactions, see: (k) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371; (l) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (m) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.
- (12) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856; (b) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108; (c) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855.
- (13) Physical data of **2**: [α]_D³⁰ -6.33 (c 0.42, CHCl₃); IR (film) ν 3027, 2932, 1744, 1453, 1369, 1241, 1107, 753, 697 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.61 (1H, q, *J* = 11.5 Hz, H10ax), 2.07 (3H, s, Ac), 2.08 (3H, s, Ac), 2.29-2.38 (2H, m, H4, H10eq), 2.63 (1H, ddd, *J* = 16.5, 8.0, 4.0 Hz, H4), 3.09-3.16 (2H, m, H8, H9), 3.27 (1H, td, *J* = 9.5, 4.0 Hz, H5), 3.34 (1H, t, *J* = 9.5 Hz, H6), 3.36 (1H, ddd, *J* = 11.5, 9.5, 5.0 Hz, H11), 3.47 (1H, t, *J* = 9.5 Hz, H7), 3.79 (1H, ddd, *J* = 9.5, 6.0, 2.5 Hz, H16), 3.94 (1H, dd, *J* = 9.5, 2.0 Hz, H12), 4.01 (1H, dq, *J* = 15.0, 3.0 Hz, H1), 4.04 (1H, dd, *J* = 12.0, 2.5 Hz, H17), 4.09 (1H, dd, *J* = 12.0, 6.0 Hz, H17), 4.29 (1H, dd, *J* = 15.0, 6.0 Hz, H1), 4.83 (1H, d, *J* = 12.0 Hz, OCH₂Ph), 4.88 (1H, d, *J* = 12.0 Hz, OCH₂Ph), 5.44 (1H, dq, *J* = 9.5, 2.0 Hz, H15), 5.52 (1H, dt, *J* = 11.5, 2.0 Hz, H14), 5.74 (1H, dt, *J* = 11.5, 2.0 Hz, H13), 5.77 (1H, ddt, *J* = 12.0, 8.0, 3.0 Hz, H3), 5.86 (1H, ddt, *J* = 12.0, 6.0, 3.0 Hz, H2), 7.24-7.29 (1H, m), 7.33 (2H, t, *J* = 7.5 Hz), 7.39 (2H, d, *J* = 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 20.82, 20.96, 34.59, 36.60, 64.25, 68.40, 71.34, 73.09, 75.15, 76.87, 79.06, 80.05, 80.41, 80.95, 82.06, 87.33, 126.65, 127.43, 127.71, 128.19, 129.97, 131.33, 132.39, 139.12, 169.60, 170.82; MALDI-TOF MS calcd for C₂₈H₃₄O₉ (M+Na)⁺ 537.21, found 537.13.

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