Highly Stereocontrolled Synthesis of the ABCD Ring Fragment of Ciguatoxin CTX3C

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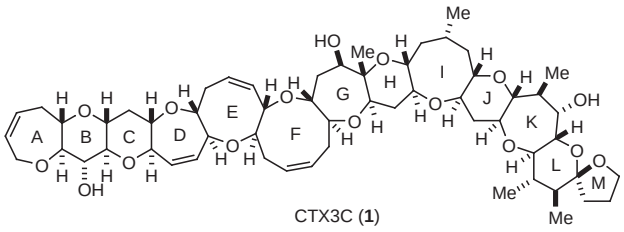
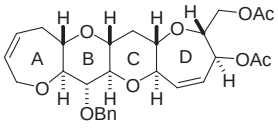
This paper is dedicated to Professor Ryoji Noyori for his outstanding achievements in synthetic organic chemistry.

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

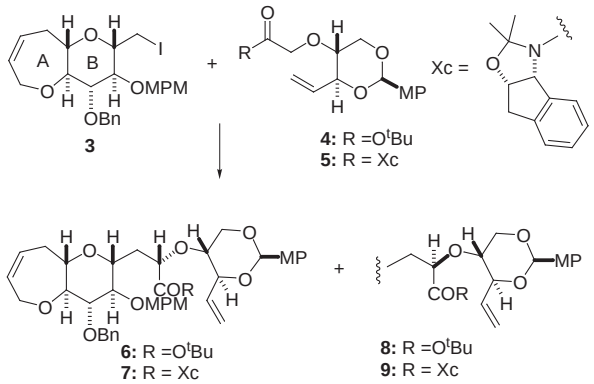
Ciguatoxin CTX3C (**1**) is one of the causative toxins of ciguatera seafood poisoning prevalent in the tropics and subtropics.[2] During the course of our synthetic studies directed toward ciguatoxins,[3,4] we developed a highly convergent strategy for synthesizing polycyclic ethers based on a combination 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.





2

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 auxiliary[8] 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 base[9] 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

[a]Carried out at -78 °C to rt.
[b]One equivalent of base was added to **4** or **5**.
[c]Ratio of THF-HMPA or THF-DMPU is 10: 1 (v/v).
[d]Based on iodide **3**.
[e]Determined by 500 MHz ^{1}H NMR.

vinylmagnesium bromide resulted in a low yield of **13**, vinyllithium generated from tributyl(vinyl)tin and methyllithium 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 BF_3•OEt_2 gave **15**.[3l,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

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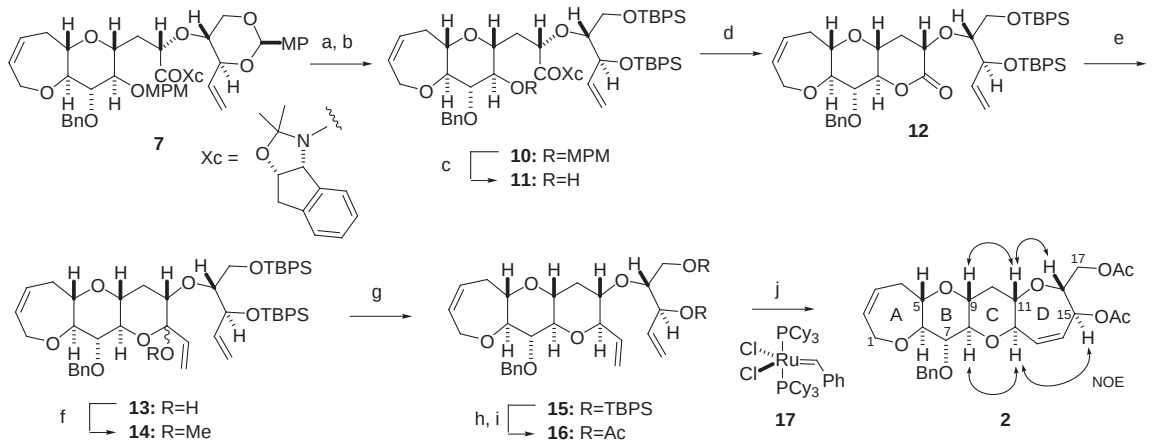

Scheme 2 Reagents and conditions. (a) PPTS, 1-propanol, rt, 5 h, 82%; (b) TBPSCl, imidazole, DMF, 60 °C, 6 h, 92%; (c) DDQ, CH_2Cl_2, H_2O, rt, 1 h, 75%; (d) CSA, toluene, 80 °C, 1 d, 60%; (e) tributyl(vinyl)tin, MeLi, THF, -78 °C, 30 min, 98%; (f) $HC(OMe)_3$, p-TsOH•H_2O, CH_2Cl_2, rt, 12 h, 70%; (g) Et_3SiH, BF_3•OEt_2, CH_2Cl_2, -30 °C, 2 h, 61%; (h) TBAF, THF, rt, 4 h; (i) Ac_2O, Py, DMAP, rt, 4 h, 85% (2 steps); (j) **17**, CH_2Cl_2, reflux, 12 h, 74%.

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(7) Synthesized from D-glucose: (i) *p*-methoxybenzaldehyde dimethylacetal, *p*-toluenesulfonic acid, DMF, 45%; (ii) $NaIO_4$, MeOH, pH6 acetate buffer; (iii) Ph_3PCH_3Br, *t*-BuOK, THF, 58% (2 steps); (iv) *t*-butyl bromoacetate, NaH, THF, DMF, 84%.

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(13) Physical data of **2**: $[\alpha]_D^{30}$ -6.33 (*c* 0.42, $CHCl_3$); IR (film) ν 3027, 2932, 1744, 1453, 1369, 1241, 1107, 753, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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, O*CH*$_2$Ph), 4.88 (1H, d, *J* = 12.0 Hz, O*CH*$_2$Ph), 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{28}H_{34}O_9$ $(M+Na)^+$ 537.21, found 537.13.

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