Stereoselective Synthesis of the LM Ring Moiety of Ciguatoxin: Reagent Control of Asymmetric Dihydroxylation

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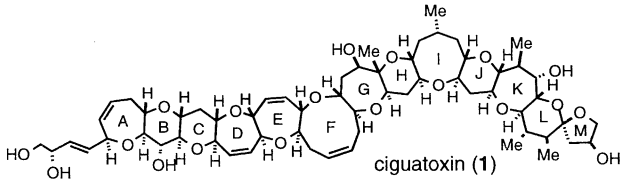
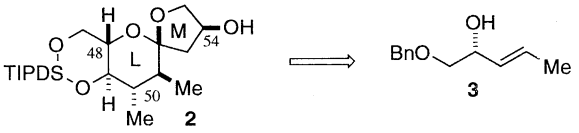
Stereoselective synthesis of the LM ring moiety of ciguatoxin was achieved from (*R*)-(*E*)-1-benzyloxy-2-hydroxy-3-pentene *via* Ireland-Claisen rearrangement, iodolactonization, and reagent-controlled asymmetric dihydroxylation.

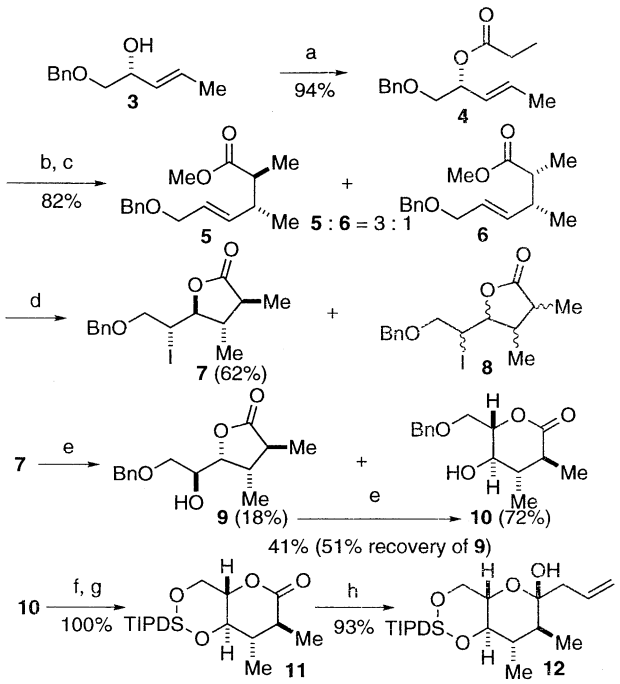
Ciguatoxin **1**[1] is the principal toxin which causes ciguatera poisoning. Although enzyme-linked immunosorbent assay to detect this fish toxin has been required, the very limited availability of **1** has hampered the preparation of its specific monoclonal antibody. The chemical synthesis of **1**[2,3] could be a useful way to solve this problem. In this letter, we report a stereoselective synthesis of **2** which corresponds to the LM ring moiety of **1**. Recent reports on the synthesis of the KLM and LM ring moieties by Tachibana[3a,b] and Murai,[3c] respectively, prompted us to disclose our own strategy.



We planned a versatile route which could provide both enantiomers of **2**,[2] since the absolute configuration of **1** was not determined until recently.[2b,2f,4] Thus, we envisioned the construction of the contiguous stereogenic centers (C48-C52) of the L ring by successive intramolecular reactions starting with enantiomerically pure (*R*)-(*E*)-1-benzyloxy-2-hydroxy-3-pentene **3**.[5] For construction of the M ring, we planned to use an asymmetric dihydroxylation method[6] developed in our laboratory.



Synthesis of the L ring moiety was achieved as shown in Scheme 1. The allylic alcohol **3** was converted to propionate ester **4**, which was subjected to Ireland-Claisen rearrangement[7] in the presence of HMPA to give an inseparable mixture of **5**[8] and **6** (3:1). Iodolactonization[9] of this mixture resulted in the formation of **7** (62%), which has the desired stereochemistry and was easily separated from other diastereomers by silica gel column chromatography. Saponification of **7** to form epoxide[10] followed by treatment with acetic acid at 60 °C gave an equilibrium mixture of γ-lactone **9** (18%) and δ-lactone **10** (72%).[11] Reequilibration of **9** *via* alkaline hydrolysis followed by acid treatment gave **10** in 41% yield (83% based on recovery of **9**). Hydrogenolysis of the benzyl ether **10** followed by protection as TIDPS ether yielded **11**. Treatment of **11** with allylmagnesium bromide resulted in the formation of hemiacetal **12** as a single isomer, which has all



Scheme 1. Reagents and Conditions: (a) propionyl chloride, DMAP, Py; (b) LDA, TMSCl, HMPA, THF, -78 °C-rt; (c) CH_2N_2, AcOEt, Et_2O, 0 °C; (d) I_2, CH_3CN; (e) 5%NaOH, EtOH, rt, then AcOH, 60 °C; (f) H_2, 5%Pd/C, MeOH; (g) $TIDPSCl_2$, Im, DMF; (h) allylmagnesium bromide (1.0 eq), Et_2O, -78 °C.

of the contiguous chiral centers necessary for the L ring.

After completing the synthesis of the L ring system, we next constructed the M ring. Dihydroxylation of olefin **12** using achiral OsO_4-NMO reagents gave **14(*S*)** and **14(*R*)** in a ratio of 1:1.1 (Table1, run 1). Olefin **12** was then treated with chiral OsO_4-(*S*,*S*)-**16** complex in dichloromethane at -78 °C. Asymmetric dihydroxylation of achiral terminal olefins with OsO_4 in the presence of chiral diamine (*S*,*S*)-**16** gave (*S*)-diol in high enantiomeric excess (~90%ee).[6] However, the product was a 1:2.6 diastereomeric mixture of the desired diol **14(*S*)** and undesired **14(*R*)** (run 2). The reaction using Corey ligand (*S*,*S*)-**17**[12] gave a similar selectivity (run 3), contrary to the recent results reported by Tachibana and co-workers.[3b] Dihydroxylation of **12** with OsO_4-(*R*,*R*)-**16** complex gave **14(*R*)** with high selectivity (run 4). Therefore, the stereochemistry of these reactions appeared to be governed mainly by substrate control.[13,14] After considerable experiments, the reagent-controlled, highly diastereoselective reaction was achieved for methyl acetal **13**. Dihydroxylation of **13** with OsO_4-(*S*,*S*)-**16** gave desired **15(*S*)** in high selectivity (run 6). The reaction with OsO_4-(*R*,*R*)-**16** gave **15(*R*)** (run 7). Thus, each diastereomer of **15** was stereospecifically synthesized from

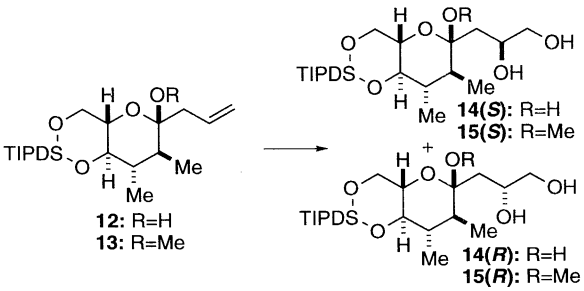
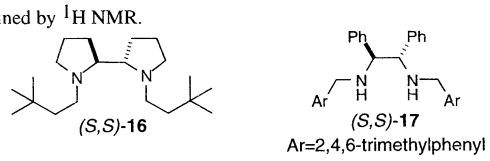


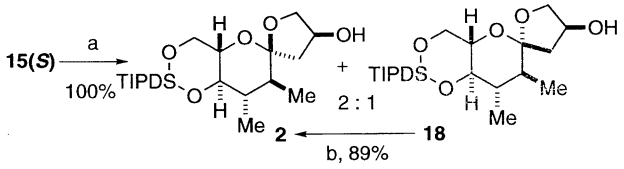
Table 1. Asymmetric dihydroxylation of olefins **12** and **13**[a]

Run	Olefin	Ligand	Ratio[e] (*S*) : (*R*)	Yield/%
1	**12**	-[b]	1 : 1.1	79
2		(*S*,*S*)-**16**[c]	1 : 2.6	72
3		(*S*,*S*)-**17**[d]	1 : 1.4	60
4		(*R*,*R*)-**16**[c]	1 : >10	68
5	**13**	-[b]	1 : 1	76
6		(*S*,*S*)-**16**[c]	>10 : 1	60
7		(*R*,*R*)-**16**[c]	1 : >10	77

[a]1.1 eq OsO_4, 1.2 eq **16** or **17**, CH_2Cl_2, then $Na_2S_2O_5$, aq THF, reflux. [b]0.1 eq OsO_4, 3 eq NMO, ^tBuOH, H_2O, rt. [c]At -78°C. [d]At -90 °C. [e]Determined by ^1H NMR.



13 by the choice of the enantiomer of **16**. Treatment of **15**(*S*) with CSA resulted in the formation of a separable mixture of spiroketal **2** and its diastereomer **18** in 2:1 ratio. Separated **18** was readily converted to **2** in 89% yield by heating with CSA.[15]



Scheme 2. Reagents and Conditions: (a) CSA, benzene, rt. (b) CSA, benzene, 40 °C.

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References and Notes

1 a) M. Murata, A. M. Legrand, Y. Ishibashi, and T. Yasumoto, *J. Am. Chem. Soc.*, **111**, 8929 (1989); b) M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, **112**, 4380 (1990).

2 a) T. Suzuki, O. Sato, and M. Hirama, *Tetrahedron Lett.*, **31**, 4747 (1990); b) T. Suzuki, O. Sato, M. Hirama, Y. Yamamoto, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron Lett.*, **32**, 4505 (1991); c) O. Sato, M. Hirama, *Synlett*, **1992**, 705; d) H. Oguri, S. Hishiyama, T. Oishi, and M. Hirama, *Synlett*, **1995**, 1252; e) T. Oishi, M. Shoji, K. Maeda, N. Kumahara, and M. Hirama, *Synlett*, **1996**, 1165; f) H. Oguri, S. Hishiyama, O. Sato, T. Oishi, M. Hirama, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron*, **53**, 3057 (1997).

3 a) M. Sasaki, A. Hasegawa, and K. Tachibana, *Tetrahedron Lett.*, **34**, 8489 (1993); b) M. Sasaki, M. Inoue, and K. Tachibana, *J. Org. Chem.*, **59**, 715 (1994); c) T. Oka and A. Murai, *Chem. Lett.*, **1994**, 1611.

4 M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hirama, N. Harada, and T. Yasumoto, to be submitted.

5 S. Takano, Y. Sekiguchi, N. Sato, and K. Ogasawara, *Synthesis*, **1987**, 139.

6 a) T. Oishi and M. Hirama, *J. Org. Chem.*, **54**, 5834 (1989); b) T. Oishi, K. Iida, and M. Hirama, *Tetrahedron Lett.*, **34**, 3573 (1993).

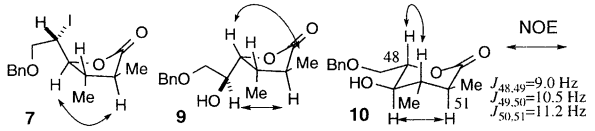
7 R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).

8 The stereochemistry was determined by conversion of **5** into (*S*,*S*)-2,3-dimethylbutane-1,4-diol: G. E. McCasland and S. Proskow, *J. Am. Chem. Soc.*, **78**, 5646 (1956).

9 P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).

10 Intermediary of epoxide was supported by isolation without the subsequent acid treatment.

11 The stereochemistry of **7**, **9**, and **10** was determined by NOE experiments.

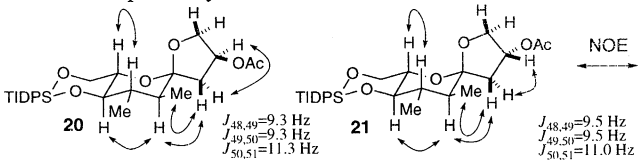


12 E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, and R. D. Connell *J. Am. Chem. Soc.*, **111**, 9243 (1989).

13 S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.* **24**, 1 (1985).

14 The stereoselectivity due to substrate control appears to vary with the size of reagent. Related phenomena have been observed: see ref. 2c and T. Oishi, T. Iwakuma, M. Hirama, and S. Itô, *Synlett*, **1995**, 404.

15 The stereochemistry of C54 of **14** and **15** was determined by ^1H NMR analysis of the corresponding acetates **19** and **20**, respectively.



2: colorless oil; $[\alpha]_D^{22}$ -21.4 (c, 0.81, $CHCl_3$); HRMS(EI, 70eV) calcd for $C_{23}H_{46}O_6Si_2$ 474.2833, found 474.2842; ^{1}HNMR (600MHz, $CDCl_3$) δ 1.01 (3H, d, *J*=6.7 Hz), 1.05 (3H, d, *J*=6.5 Hz), 1.55 (1H, dq, *J*=11.2, 6.7 Hz), 1.65-1.71 (1H, m), 1.95 (1H, ddd, *J*=14.4, 2.2, 1.3 Hz), 2.22 (1H, bs), 2.36 (1H, dd, *J*=14.4, 6.9 Hz), 3.50-3.53 (2H, m), 3.71 (1H, dd, *J*=12.5, 0.9 Hz), 3.78 (1H, bd, *J*=9.8 Hz), 3.93 (1H, dd, *J*=9.8, 4.3 Hz), 4.13 (1H, dd, *J*=12.5, 1.4 Hz), 4.51 (1H, bs), (TIPS group was omitted); ^{13}CNMR (150MHz, $CDCl_3$) δ 13.65, 15.87, 40.56, 41.87, 45.68, 61.96, 70.68, 71.94, 74.40, 109.21, (TIPS group was omitted).