

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

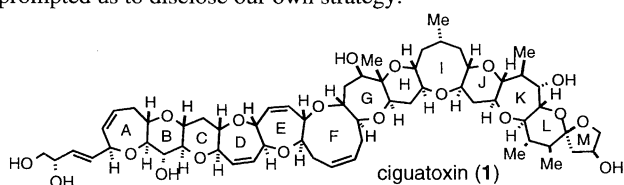
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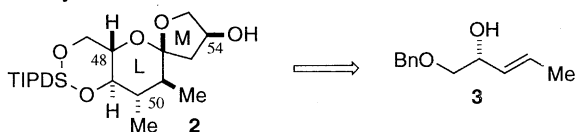
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Stereoselective synthesis of the LM ring moiety of ciguatoxin was achieved from (*R*)-(*E*)-1-benzyloxy-2-hydroxy-3-pentene via Ireland-Claisen rearrangement, iodolactonization, and reagent-controlled asymmetric dihydroxylation.

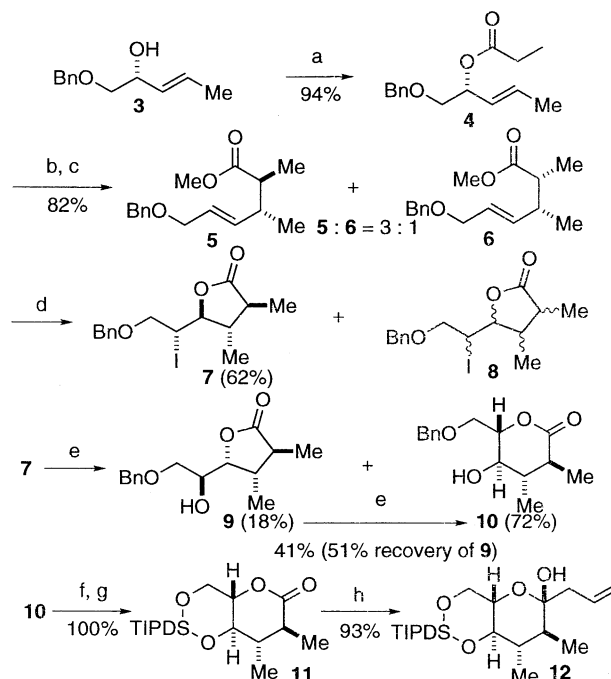
Ciguatoxin **1**¹ is the principal toxin which causes ciguatera poisoning. Although enzyme-linked immunosorbent assay to detect this fish toxin has been required, the very limited availability of **1** has hampered the preparation of its specific monoclonal antibody. The chemical synthesis of **1**^{2,3} 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 method⁶ developed in our laboratory.



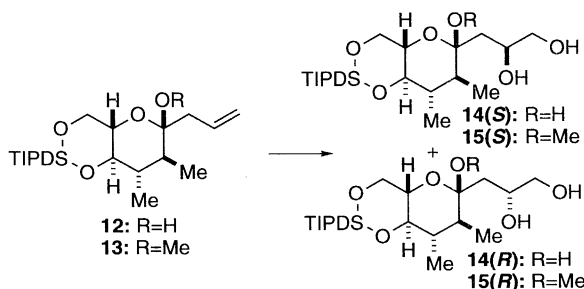
Synthesis of the L ring moiety was achieved as shown in Scheme 1. The allylic alcohol **3** was converted to propionate ester **4**, which was subjected to Ireland-Claisen rearrangement⁷ in the presence of HMPA to give an inseparable mixture of **5**⁸ and **6** (3:1). Iodolactonization⁹ of this mixture 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 epoxide¹⁰ 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



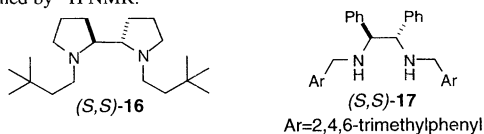
Scheme 1. Reagents and Conditions: (a) propionyl chloride, DMAP, Py; (b) LDA, TMSCl, HMPA, THF, -78 °C-rt; (c) CH₂N₂, AcOEt, Et₂O, 0 °C; (d) I₂, CH₃CN; (e) 5% NaOH, EtOH, rt, then AcOH, 60 °C; (f) H₂, 5% Pd/C, MeOH; (g) TIDPSCl₂, Im, DMF; (h) allylmagnesium bromide (1.0 eq), Et₂O, -78 °C.

of the contiguous chiral centers necessary for the L ring.

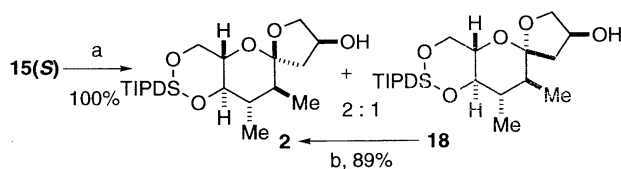
After completing the synthesis of the L ring system, we next constructed the M ring. Dihydroxylation of olefin **12** using achiral OsO₄-NMO reagents gave **14(S)** and **14(R)** in a ratio of 1:1.1 (Table 1, run 1). Olefin **12** was then treated with chiral OsO₄-(*S,S*)-**16** complex in dichloromethane at -78 °C. Asymmetric dihydroxylation of achiral terminal olefins with OsO₄ 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 OsO₄-(*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 OsO₄-(*S,S*)-**16** gave desired **15(S)** in high selectivity (run 6). The reaction with OsO₄-(*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 ^c (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 OsO₄, 1.2 eq **16** or **17**, CH₂Cl₂, then Na₂S₂O₅, aq THF, reflux.^b 0.1 eq OsO₄, 3 eq NMO, ^tBuOH, H₂O, 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

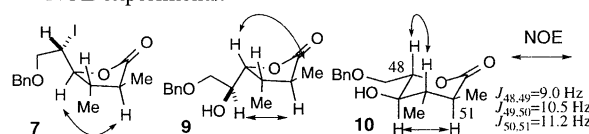
**Scheme 2.** Reagents and Conditions: (a) CSA, benzene, rt. (b) CSA, benzene, 40 °C.

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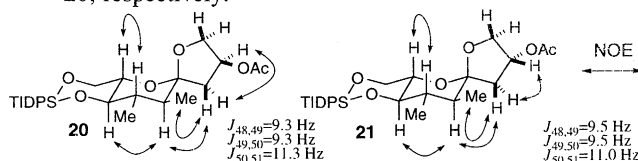
References and Notes

- 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).
- a) T. Suzuki, O. Sato, and M. Hiram, *Tetrahedron Lett.*, **31**, 4747 (1990); b) T. Suzuki, O. Sato, M. Hiram, Y. Yamamoto, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron Lett.*, **32**, 4505 (1991); c) O. Sato, M. Hiram, *Synlett*, **1992**, 705; d) H. Oguri, S. Hishiyama,

- T. Oishi, and M. Hiram, *Synlett*, **1995**, 1252; e) T. Oishi, M. Shoji, K. Maeda, N. Kumahara, and M. Hiram, *Synlett*, **1996**, 1165; f) H. Oguri, S. Hishiyama, O. Sato, T. Oishi, M. Hiram, M. Murata, T. Yasumoto, and N. Harada, *Tetrahedron*, **53**, 3057 (1997).
- 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.
- M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hiram, N. Harada, and T. Yasumoto, to be submitted.
- S. Takano, Y. Sekiguchi, N. Sato, and K. Ogasawara, *Synthesis*, **1987**, 139.
- a) T. Oishi and M. Hiram, *J. Org. Chem.*, **54**, 5834 (1989); b) T. Oishi, K. Iida, and M. Hiram, *Tetrahedron Lett.*, **34**, 3573 (1993).
- R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
- 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).
- P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
- Intermediary of epoxide was supported by isolation without the subsequent acid treatment.
- The stereochemistry of **7**, **9**, and **10** was determined by NOE experiments.



- E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, and R. D. Connell, *J. Am. Chem. Soc.*, **111**, 9243 (1989).
- S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985).
- 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. Hiram, and S. Itô, *Synlett*, **1995**, 404.
- 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, CHCl₃); HRMS(EI, 70eV) calcd for C₂₃H₄₆O₆Si₂ 474.2833, found 474.2842; ¹H NMR (600MHz, CDCl₃) 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); ¹³C NMR (150MHz, CDCl₃) 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).