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Naoya Osato, Hisaaki Onoue, Yoshiki Toma, Kohei Torikai, Makoto Ebine, Masayuki Satake, and Tohru Oishi\*

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## Convergent Syntheses of the WXYZ Ring of Maitotoxin and the HIJK Ring of Brevisulcenal-F

Naoya Osato,<sup>1</sup> Hisaaki Onoue,<sup>1</sup> Yoshiki Toma,<sup>1</sup> Kohei Torikai,<sup>1</sup> Makoto Ebine,<sup>1</sup> Masayuki Satake,<sup>2</sup> and Tohru Oishi\*<sup>1</sup> <sup>1</sup>Department of Chemistry, Faculty and Graduate School of Science, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395 <sup>2</sup>Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

E-mail: oishi@chem.kyushu-univ.jp

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A convergent method to construct the 6/7/6/6tetracyclic ether system possessing contiguous angular methyl groups was developed. The key steps of the 2 3 4 synthesis involve coupling of a lithium acetylide and an 5 aldehyde, cyclodehydration of a hydroxy ketone to form a 6 dihydropyran, ring expansion of a six-membered ring ketone into a seven-membered one, and methylation of a 8 mixed-thioacetal. Based on this strategy, syntheses of the WXYZ ring of maitotoxin and the HIJK ring of brevisulcenal-F were achieved, and the stereochemistry of 10 the HIJK ring of brevisulcenal-F was confirmed. 11

12 Epiphytic dinoflagellates produce highly toxic secondary metabolites, so called ladder-shaped polyethers.<sup>1</sup> 13 Maitotoxin (MTX)<sup>2</sup> and brevisulcenal-F (KBT-F),<sup>3</sup> in 14 15 particular, are outstanding in their large molecular weights. 16 Their unique structures and potent biological activities have 17 attracted much interest in the synthetic community.<sup>4</sup> Despite 18 development of a number of convergent methods to 19 synthesize ladder-shaped polyethers, it is a daunting task to possessing 20 construct polycyclic ether frameworks 21 contiguous angular methyl groups such as the WXYZ ring 22 system of MTX and the HIJK ring system of KBT-F (Figure 23 1) because of the severe steric repulsion existing within 24 them. Thus, there are only three precedents to construct the 25 polycyclic ether system containing the WXYZ ring system of MTX. The WXYZA' ring of MTX was synthesized by 26 Nakata<sup>5</sup> in a linear manner via SmI<sub>2</sub>-induced reductive 27 28 cyclization and 6-endo cyclization of a vinyl epoxide, 29 whereas a convergent synthesis of the WXYZA' ring of 30 MTX was reported by Nicolaou<sup>6</sup> via Takai olefination and 31 ring-closing metathesis. We reported a highly convergent 32 synthesis of the WXYZA'B'C' ring<sup>7</sup> of MTX based on the  $\alpha$ -cyano ether method<sup>8</sup> developed in our laboratory as 33 34 part of a structure-activity relationship study.9



35 Figure 1. Partial structures of the WXYZ ring of MTX, the HIJK ring 36 of KBT-F, and structures of the 6/7/6/6-tetracyclic ethers (1a and 1b).

37 However, there are no reports on the synthesis of the 38 HIJK ring system of KBT-F possessing a β-hydroxy group 39 on the seven-membered ring. Herein, we describe an 40 alternative convergent strategy via two-rings construction<sup>4c</sup> 41 for synthesizing the 6/7/6/6-tetracyclic ether system 42 possessing contiguous angular methyl groups corresponding not only to the WXYZ ring system of MTX (1a) but also the 43 44 HIJK ring system of KBT-F (1b).

45 Our synthetic strategy is shown in Scheme 1. The 46 6/7/6/6-tetracyclic ether system A corresponding to the 47 WXYZ ring of MTX is to be derived from C through the 48 construction of the tetrahydropyran ring via methylation of a mixed-thioacetal reported by Nicolaou<sup>10</sup> in an analogous 49 50 manner as previously reported.<sup>7</sup> The seven-membered ring 51 ketone C could be derived from six-membered D by the 52 ring-expansion reaction reported by Mori,<sup>11</sup> and the cyclic 53 ketone **D** can be traced back to an acyclic saturated ketone **E** 54 via cyclodehydration giving a dihydropyran followed by hydroboration as reported by Crimmins<sup>12</sup> and Nakata.<sup>13</sup> 55 56 Although a related synthetic method of the ketone E was 57 reported by Crimmins via Horner-Wadsworth-Emmons reaction followed by 1,4-reduction,<sup>12</sup> we envisaged that the 58 59 ketone E would be obtained by coupling of a terminal 60 alkyne F and a carbonyl compound G followed by 61 hydrogenation of the alkyne. The 6/7/6/6-tetracyclic ether 62 system **B** corresponding to the HIJK ring of KBT-F is to be 63 synthesized in a similar manner from the common 64 intermediate C, where regio- and stereoselective installation 65 of the hydroxy group of the seven-membered ring is 66 required.



67 Scheme 1. Synthetic strategy for synthesizing the 6/7/6/6-tetracyclic 68 ethers (P = protecting group).

70 Synthesis of the 6/7/6/6-tetracyclic ether 1a via seven-71 membered ring ketone 13 is shown in Scheme 2.



**Scheme 2.** Synthesis of the 6/7/6/6-tetracyclic ether **1a**. (a) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, -78 °C, 3.5 h, then PPh<sub>3</sub>, -78 °C to rt, 3.6 h; (b) MeCOCN<sub>2</sub>PO(OMe)<sub>2</sub>, Cs<sub>2</sub>CO<sub>3</sub>, MeOH, rt, 1.4 h, 83% (two steps); (c) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, *t*-BuOH/H<sub>2</sub>O, rt, 1 h, 90%; (d) Me(OMe)NH·HCl, DCC, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 25.5 h, 97%; (e) **3**, *n*-BuLi, THF, 0 °C, 1 h; then **4**, THF, -78 °C, 1 h, 88%; (f) **3**, *n*-BuLi, THF, 0 °C, 1 h; then **5**, THF, 0 °C to rt, 2 h, 49%; (g) PtO<sub>2</sub>, H<sub>2</sub>, EtOAc, rt, 7.7 h; (h) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.1 h, 87% (two steps); (i) [CuH(PPh<sub>3</sub>)]<sub>6</sub>, phenylsilane, H<sub>2</sub>O, benzene, 0 °C, 2 h, 76%; (j) TBAF, THF, rt, 1 h, **9** (54%), recovery of **8** (40%); (k) Nafion NR-50, MS4A, toluene, reflux, 30 min, 76%; (l) BH<sub>3</sub>·SMe<sub>2</sub>, THF, 0 °C, then H<sub>2</sub>O<sub>2</sub>, NaOH rt, 1.5 h, 98%; (m) TPAP, NMO, MS4A, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.4 h, 97%; (n) TMSCHN<sub>2</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1.9 h; (o) *p*-TsOH·H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, rt, 21.2 h, 63% (two steps); (p) TIPSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1.4 h, 86%; (r) DDQ, pH7 buffer, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 50 min, 85%; (s) EtSH, TfOH, MS4A, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1.6 h; (t) TIPSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 30 min, 74% (two steps); (u) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to -40 °C, 1 h; then Me<sub>3</sub>Al, -40 °C to 0 °C, 1.5 h,

1 Terminal alkyne **3** was prepared from known alkene  $2^{14}$  by 2 ozonolysis followed by treatment with Ohira-Bestmann 3 reagent<sup>15</sup> in the presence of Cs<sub>2</sub>CO<sub>3</sub> in 83% yield for two 4 steps.

5 Alkyne 3 was treated with *n*-BuLi and the resulting lithium acetylide was reacted with known aldehyde  $4^7$  to furnish 6 7 propargylic alcohol 6 in 88% yield as a mixture of 8 diastereomers in a 2.5 : 1 ratio. Hydrogenation of alkyne 6 9 with PtO<sub>2</sub> under a hydrogen atmosphere, followed by Dess-10 Martin oxidation of the resulting saturated alcohol gave 11 ketone 8 in 87% yield over two steps. Although the ketone 8 was alternatively obtained from the Weinreb amide 5 12 13 derived from 4 (87%, two steps) via coupling with 3 (49%) 14 and 1,4-reduction of the resulting ynone 7 with Stryker 15 reagent<sup>16</sup> (76%), the former route (77% for three steps from 16 4) was more practical than the latter one (33% for four steps 17 from 4) both in yield and reagent economy. Removal of the 18 TBS group of 8 with TBAF resulted in the formation of 19 hydroxy ketone 9 in 54% yield as a mixture of its hemiacetal in a 1:1 ratio with 40% recovery of 8 (prolonged 20 21 reaction time resulted in low yield of 9). Treatment of 9 22 with Nafion NR-50<sup>17</sup> in toluene under reflux afforded 23 dihydropyran derivative 10 in 76% yield. Hydroboration of 24 10 with BH3. SMe2 proceeded stereoselectively to vield 25 secondary alcohol 11 in 98% yield as a single isomer. Ley 26 oxidation of alcohol 11 with TPAP and NMO<sup>17</sup> furnished 27 ketone 11 in 97% yield. The next task, ring-expansion of the 28 six-membered ring ketone into the seven-membered one,

29 was carried out as reported by Mori.<sup>10</sup> Thus, treatment of 12 30 with TMSCHN<sub>2</sub> in the presence of BF<sub>3</sub>·OEt<sub>2</sub> resulted in the 31 formation of a seven-membered ring ketone as a mixture 32 with  $\alpha$ -TMS ketone, which was subjected to hydrolytic 33 conditions with p-TsOH in CH2Cl2/MeOH resulting in 34 concomitant removal of the TMS group and benzylidene 35 acetal to afford the diol in 60% yield for two steps. 36 Protection of the resulting diol as TIPS ethers gave 13 37 (64%) with concomitant formation of silvl enol ether 14 38 (34%), which was recovered to form 13 (86%) by treatment 39 with TBAF at -20 °C for 4 min.

40 Having the key intermediate 13 in hand, the WXYZ 41 ring of MTX was synthesized as previously reported but 42 with modification of the mixed-thioacetal formation.<sup>7</sup> After 43 removal of the NAP group of 13 with DDQ giving hydroxy 44 ketone 15 in 85% yield, the mixed-thioacetal formation was 45 examined. As reported,<sup>7</sup> treatment of the hydroxy ketone 46 with EtSH in the presence of Zn(OTf)2 afforded the desired 47 mixed-thioacetal 16 (42%) with concomitant formation of 48 dithioacetal (8%). Recovery of the starting material (42%), 49 and recycling of the recovered 15 gave 16 in 64% total yield. 50 After considerable experimentation with various Lewis 51 acids, such as Sc(OTf)<sub>3</sub> and In(OTf)<sub>3</sub>, we finally found that 52 not metal triflates but TfOH in the presence of MS4A gave better results, and 16 was obtained in 74% yield as a 53 54 mixture of diastereomers ( $\alpha$ : $\beta$  = 4.8:1) after protection of the 55 partially desilylated products. Next, introduction of the 56 angular methyl group was achieved by treatment with



**Scheme 3.** Syntheses of the 6/7/6/6-tetracyclic ether **1b** and **1c**. (a) LHMDS, TMSCl, Et<sub>3</sub>N, THF, -78 °C, 1 h; (b) Pd(OAc)<sub>2</sub>, *p*-benzoquinone, CH<sub>3</sub>CN, rt, 15.5 h, 95% (two steps); (c) B<sub>2</sub>(pin)<sub>2</sub>, CuCl, *n*-Bu<sub>3</sub>P, DMF, rt, 4.5 h; H<sub>2</sub>O<sub>2</sub>, NaOH, rt, 30 min, 84%; (d) DDQ, pH7 buffer, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h, 93%; (e) EtSH, TfOH, MS4A, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h, 74% (a: $\beta$  = 2.9:1); (f) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to -40 °C, 1 h, then Me<sub>3</sub>Al, -40 °C to 0 °C, 1 h, 42%; (g) TBAF, THF, rt, 2.5 h, 87%; (h) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, 0 °C, 20 min, 81%; (i) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h, 87%; (j) TPAP, NMO, MS4A, CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min, 95%; (k) Na[PhSeB(OEt)<sub>3</sub>], AcOH, EtOH, rt, 1.5 h, 90%; (l) DDQ, pH 7 buffer, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, 89%; (m) EtSH, TfOH, MS4A, -40 °C to 0 °C, 1 h; then Me<sub>3</sub>Al, -40 °C to -40 °C, 1 h; then Me<sub>3</sub>Al, -40 °C to -40 °C, 1 h; then Me<sub>3</sub>Al, -40 °C to -40 °C, 1 h; then Me<sub>3</sub>Al, -40 °C to -20 min, 81%; (i) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, 89%; (m) EtSH, TfOH, MS4A, CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min, 95%; (k) Na[PhSeB(OEt)<sub>3</sub>], AcOH, EtOH, rt, 1.5 h, 90%; (l) DDQ, pH 7 buffer, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h, 89%; (m) EtSH, TfOH, MS4A, -40 °C to 0 °C, 3 h, 94%; (p) TBAF, THF, rt, 27 h, 84%.

MCPBA followed by Me<sub>3</sub>Al to afford 17 in 73% yield. 1 2 Although direct methylation of the mixed thioacetal 16 was 3 carried out with Me<sub>2</sub>Zn and Zn(OTf)<sub>2</sub> as reported by Kadota,19 no reaction occurred in CH2Cl2 at room 4 5 temperature, and that in ClCH2CH2Cl under reflux afforded 6 17 with concomitant formation of a enol ether formed via 7 elimination of the ethylthio group as an inseparable mixture 8 in a 1.2 : 1 ratio. Removal of the TIPS group with TBAF 9 furnished the 6/7/6/6-tetracyclic ether 1a corresponding to the WXYZ ring of MTX in 87% yield. 10

11 Next, we moved on to the synthesis of the HIJK ring of 12 KBT-F as shown in Scheme 3. The seven-membered ring 13 ketone 13 was converted to  $\alpha$ .  $\beta$ -unsaturated ketone 18 in 14 95% yield for two steps via silvl enol ether formation by 15 successive treatment with LHMDS, TMSCl, and Et<sub>3</sub>N,<sup>20</sup> followed by the Ito-Saegusa reaction with Pd(OAc)<sub>2</sub> and p-16 benzoquinone.<sup>21</sup> The next crucial step, regio- and 17 18 stereoselective introduction of the  $\beta$ -hydroxy group at the 19 C36 position of KBT-F to form the secondary alcohol 19, was examined using a copper-catalyzed borylation-20 oxidation sequence reported by Hosomi.<sup>22</sup> Thus, treatment 21 22 of the enone 18 with bis-pinacolborane in the presence of 23 CuCl and *n*-Bu<sub>3</sub>P followed by oxidative work-up resulted in 24 the formation of 19 in 84% yield as a single isomer. 25 Unfortunately, the stereochemistry of 19 turned out to be 26 opposite to that of the HIJK ring system of KBT-F.<sup>23</sup> 27 Although attempts to invert the secondary alcohol by 28 Mitsunobu reaction modified by Tsunoda<sup>24</sup> were 29 unsuccessful, producing 18 via  $\beta$ -elimination, we proceeded 30 to the next transformation with the expectation of inverting 31 the stereochemistry after constructing the tetracyclic system. 32 Thus, **19** was converted to **1c** in an analogous sequence with 33 1a: 1) removal of the NAP group (93%); 2) mixed-34 thioacetal formation giving **20** (74%,  $\alpha$ : $\beta$  = 2.9:1); and 3) 35 introduction of the angular methyl group to afford 21  $(42\%)^{23}$  with a byproduct formed via  $\beta$ -elimination of 36

37 ethylthio group (38%). Although the low yield of 21 was 38 considered to be due to the presence of the free hydroxy 39 group, and the reactions were carried out after protecting the 40 alcohol as a TIPS ether, the desired product was obtained as 41 an inseparable mixture with unidentified byproducts. 42 Inversion of the secondary alcohol of 21 was unsuccessful, 43 oxidation of 21 and reduction of the resulting ketone gave 44 21 as a single isomer, and Mitsunobu inversion of 21 did not 45 occur. Finally, removal of the TIPS groups of 21 with 46 TBAF afforded 1c in 87% yield.

47 Since direct introduction of the  $\beta$ -hydroxy group to the 48 enone 18 and inversion of the secondary alcohol of 21 were unsuccessful, we next examined the method applied for the 49 synthesis of gymnocin-A reported by Sasaki.<sup>25</sup> Luche 50 51 reduction<sup>26</sup> of the enone 18 resulted in the formation of an 52 allylic alcohol as a single isomer in 81% yield, which was 53 oxidized with MCPBA to afford  $\beta$ -epoxide 22 in 87% yield 54 as a single isomer. Ley oxidation of the alcohol 22 with 55 TPAP/NMO furnished an epoxy ketone, which was treated 56 with Na[PhSeB(OEt)<sub>3</sub>] developed by Miyashita-Yoshikoshi<sup>27</sup> to afford  $\beta$ -hydroxy ketone **23** in 90% yield. 57 58 Formation of the six-membered ring was achieved in an 59 analogous sequence: 1) removal of the NAP group with 60 DDQ (89%) giving a hydroxyl ketone; 2) mixed-thioacetal formation with EtSH and TfOH to give 24 (69%, 30% 61 62 recovery of the hydroxy ketone); 3) protection of the hydroxyl group as TIPS ether 25 (91%); 4) introduction of 63 the angular methyl group to afford **26** (94%);<sup>23</sup> and 5) 64 removal of the all TIPS groups with TBAF to provide 1b 65 corresponding to the HIJK ring of KBT-F (84%). 66

67 The NMR spectra of **1b** and **1c** were compared with 68 those of KBT-F. The differences in the chemical shifts 69 between KBT-F, **1b** and **1c** are shown in Figure 2: (a) <sup>1</sup>H 70 NMR (600 MHz, C<sub>5</sub>D<sub>5</sub>N), (b) <sup>13</sup>C NMR (150 MHz, C<sub>5</sub>D<sub>5</sub>N). 71 The x- and y-axes represent carbon number and  $\Delta\delta$  ( $\Delta\delta$  =

72  $\delta KBT-F - \delta synthetic 1b$  and 1c in ppm), respectively (The

- carbon numbering of KBT-F is shown in Figure 1). For both 1
- 2 diastereomers, <sup>1</sup>H NMR chemical shifts at both termini
- deviated because the structures are different from the natural 3 4
- product. However, for other parts, chemical shifts of 1b are 5 identical with those of KBT-F, while those of 1c at C33 and
- 6 C38 deviate by 1.03 ppm and 0.68 ppm, respectively.
- Analogously, <sup>13</sup>C NMR chemical shifts at both termini 7
- 8 deviate for both diastereomers, and chemical shifts of 1b for
- 9 other parts are identical with those of KBT-F, while those of
- 10 1c at C33, C34, C104, and C38 deviate by more than 2.0
- ppm. Therefore, the structure of the HIJK ring system of 11
- KBT-F has been confirmed, whereas previously its absolute 12
- configuration was unknown.<sup>3</sup> 13
  - (a) <sup>1</sup>H NMR



Figure 2. Differences in chemical shifts between KBT-F and the 14 15 synthetic fragments 1b and 1c. (a)  ${}^{1}$ H NMR (600 MHz, C<sub>5</sub>D<sub>5</sub>N), (b)  ${}^{13}$ C 16 NMR (150 MHz, C<sub>5</sub>D<sub>5</sub>N). The x- and y-axes represent carbon number 17 18 and  $\Delta\delta$  in ppm. Red and blue bars represent  $\Delta\delta = \delta$  KBT-F –  $\delta$ synthetic 1b and 1c, respectively. 19

20 In conclusion, a convergent method for synthesizing the 6/7/6/6-tetracyclic ether system was developed via 21 22 acetylide-aldehyde coupling, dehydrative cyclization, and 23 ring-expansion as key steps. The advantages of this strategy 24 are its applicability to ring systems possessing contiguous 25 angular methyl groups, and the use of the highly 26 nucleophilic acetylide as a coupling partner, which can be 27 easily recovered after the coupling reaction if an excess 28 amount of the acetylide was used. Based on this strategy, 29 stereoselective syntheses of the WXYZ ring of MTX (1a), 30 the HIJK ring of KBT-F (1b), and its C36 epimer (1c), have been achieved from the key intermediate 13, and the 31 32 stereochemistry of the HIJK ring of KBT-F was confirmed. 33 Applications of this method to synthesize other ladder-34 shaped polyethers are currently underway in our laboratory.

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- 42 Supporting Information available is on http://dx.doi.org/10.1246/cl.\*\*\*\*\*. 43

## **References and Notes**

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- 1 a) Y. Shimizu, Chem. Rev. 1993, 93, 1685. b) T. Yasumoto, M. Murata, Chem. Rev. 1993, 93, 1897.
- 2 a) M. Murata, H. Naoki, T. Iwashita, S. Matsunaga, M. Sasaki, A. Yokoyama, T. Yasumoto, J. Am. Chem. Soc. 1993, 115, 2060. c) M. Murata, H. Naoki, S. Matsunaga, M. Satake, T. Yasumoto, J. Am. Chem. Soc. 1994, 116, 7098.
- 52 53 54 3 a) Y. Hamamoto, K. Tachibana, T. P. Holland, F. Shi, V. Beuzenberg, Y. Itoh, M. Satake, J. Am. Chem. Soc. 2012, 134, 4963. b) D. T. Harwood, F. Shi, M. Satake, P. T. Holland, Toxicon 2014. 84. 19.
- 55 56 57 4 Reviews on the total synthesis of ladder-shaped polyethers, see: 58 a) H. Fuwa, M. Sasaki, Curr. Opin. Drug Discovery Dev. 2007, 59 10, 784. b) T. Nakata, Chem. Rev. 2005, 105, 4314. c) M. Inoue, 60 Chem. Rev. 2005, 105, 4379. d) I. Kadota, Y. Yamamoto, Acc. 61 Chem. Res. 2005, 38, 423. e) M. Sasaki, H. Fuwa, Synlett 2004, 62 1851. f) M. Inoue, Org. Biomol. Chem. 2004, 2, 1811.
  - 5 M. Morita, T. Haketa, H. Koshino, T. Nakata, Org. Lett. 2008, 10, 1679
  - K. C. Nicolaou, T. M. Baker, T. Nakamura, J. Am. Chem. Soc. 6 2011. 133. 220.
  - 7 T. Oishi, F. Hasegawa, K. Torikai, K. Konoki, N. Matsumori, M. Murata, Org. Lett. 2008, 10, 3599.
  - 8 T. Oishi, M. Suzuki, K. Watanabe, M. Murata, Tetrahedron Lett. 2006, 47, 3975.
- 70 71 72 73 74 75 76 77 78 79 80 9 a) K. Konoki, M. Hashimoto, K. Honda, K. Tachibana, R. Tamate, F. Hasegawa, T. Oishi, M. Murata, Heterocycles 2009, 79, 1007. b) M. Kunitake, T. Oshima, M. Ebine, K. Torikai, K. Konoki, M. Murata, T. Oishi J. Org. Chem. 2014, 79, 4948. c) H. Onoue, T. Baba, K. Konoki, K. Torikai, M. Ebine, T. Oishi, Chem. Lett. 2014, 43, 1904.
  - 10 K. C. Nicolaou, C. V. C. Prasad, C.-K. Hwang, M. E. Duggan, C. A. Veale J. Am. Chem. Soc. 1989, 111, 5321.
  - 11 a) T. Sakai, A. Sugimoto, Y. Mori, Org. Lett. 2011, 13, 5850. b) T. Sakai, S. Ito, H. Furuta, Y. Kawahara, Y. Mori, Org. Lett. 2012, 14, 4564.
  - 12 a) M. T. Crimmins, P. J. McDougall, K. A. Emmitte, Org. Lett. 2005, 7, 4033. b) M. T. Crimmins, J. L. Zuccarello, P. A. Clearly, J. D. Parrish, Org. Lett. 2006, 8, 159.
  - 13 T. Saito, T. Takeuchi, M. Matsuhashi, T. Nakata, Heterocycles 2007. 72. 151.
  - 14 a) K. C. Nicolaou, D. A. Nugiel, E. Couladouros, C.-K. Hwang, Tetrahedron 1990, 46, 4517. b) T. Nakashima, T. Baba, H. Onoue, W. Yamashita, K. Torikai, Synthesis 2013, 2417.
  - 15 Ohira, S. Synth. Commun. 1989, 19, 561.
  - 16 W. S. Mahoney, D. M. Brestensky, J. M. Stryker, J. Am. Chem. Soc. 1988, 110, 291.
- 93 17 a) G. A. Olah, P. S. Iyer, G. K. S. Prakash, Synthesis 1986, 513. 94 b) M. Morita, S. Ishiyama, H. Koshino, T. Nakata, Org. Lett. 95 2008, 10, 1675. 96
  - 18 S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, Synthesis 1994 639
  - 19 H. Takamura, S. Kikuchi, Y. Nakamura, Y. Yamagami, T. Kishi, I. Kadota, Y. Yamamoto, Org. Lett. 2009, 11, 2531.
  - 20 C. Tsukano, M. Sasaki, J. Am. Chem. Soc. 2003, 125, 14294.
- 101 21 Y. Ito, T. Hirao, T. Saegusa, J. Org. Chem. 1978, 43, 1011.
- 102 22 H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, Tetrahedron Lett. 103 2000. 41. 6821.
  - 23 The configuration was confirmed by ROESY experiments.
- a) T. Tsunoda, Y. Yamamiya, S. Ito, Tetrahedron 105 24 106 Lett. 1993, 34, 1639. b) T. Tsunoda, J. Otsuka, Y. Yamamiya, S. 107 Ito, Chem. Lett. 1994, 33, 539.
- 108 25 a) C. Tsukano, M. Sasaki, J. Am. Chem. Soc. 2003, 125, 14294. 109 b) C. Tsukano, M. Ebine, M. Sasaki, J. Am. Chem. Soc. 2005, 110 127, 4326.
  - 26 J. L. Luche, J. Am. Chem. Soc. 1978, 100, 2226.
- 112 27 M. Miyashita, T. Suzuki, M. Hoshino, A. Yoshikoshi, Tetrahedron 1997, 53, 12469. 113