

## Convergent Total Synthesis of (+)-Ophiobolin A\*\*

Kazuhiro Tsuna, Naoyoshi Noguchi, and Masahisa Nakada\*

In 1958, (+)-ophiobolin A (**1**; Figure 1) was isolated from the culture broth of the pathogenic plant fungus *Ophiobolus miyabeanus* as the first naturally occurring sesterterpene.<sup>[1]</sup> In 1965, the absolute structure of **1** was elucidated by X-ray crystallographic analysis of its derivative,<sup>[2]</sup> and a number of congeners of **1** have been isolated to date.<sup>[3]</sup> Compound **1** exhibits a wide spectrum of bioactivity against nematodes, fungi, and bacteria.<sup>[4]</sup> Moreover, **1** inhibits calmodulin-activated cyclic nucleotide phosphodiesterase.<sup>[5]</sup> It has also been reported to induce apoptotic cell death in the L1210 cell line,<sup>[6]</sup> and to show potent cytotoxicity against the cancer cell lines A-549, Mel-20, and P-335 with low IC<sub>50</sub> values, which range from 62.5 to 125 nM.<sup>[7]</sup> Furthermore, the C6-epi congeners of **1** show enhanced cytotoxicity;<sup>[3g,i]</sup> hence, the structure–activity relationships and mode of action of **1** have attracted the attention of researchers.

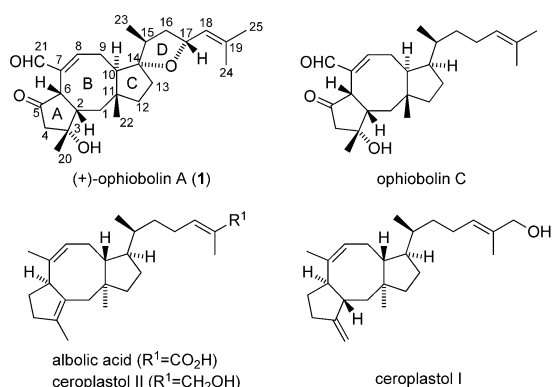
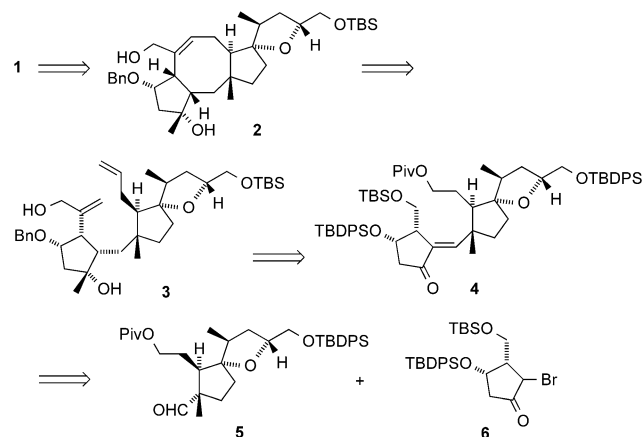


Figure 1. Structures of (+)-ophiobolin (**1**) and congeners.

The potent bioactivity of **1** as well as its complex structure have made it an attractive synthetic target, and a number of synthetic studies on ophiobolins<sup>[8]</sup> and total syntheses of congeners of **1** (Figure 1) have been reported.<sup>[9]</sup> However, the total synthesis of ophiobolins has been limited to only one

example, that of (+)-ophiobolin C by Kishi and co-workers.<sup>[9c]</sup> Herein, we report the first enantioselective total synthesis of **1**.

Our retrosynthetic analysis of **1** is briefly outlined in Scheme 1. We envisioned that the carbonyl group on the



Scheme 1. Retrosynthetic analysis of (+)-ophiobolin A (**1**). Bn = benzyl, Piv = pivaloyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

A ring and the 2,2-dimethylethenyl group on the D ring should be installed in the later stages of this synthesis because of their high reactivity. Therefore, we set the intermediate **2** for further elaboration toward **1**. The B ring was surmised to be constructed by the ring-closing metathesis (RCM) of **3**; this reaction was challenging because the B ring is a barely accessible eight-membered carbocyclic ring. The C2 and C3 stereogenic centers were thought to be generated by the stereoselective hydrogenation of **4** and the subsequent addition of a methyl lithium to the A-ring ketone; this addition would occur from the less-hindered  $\beta$  side. Enone **4** could be prepared by the coupling of **5** and **6**. Substituents on the cyclopentane ring of **6** were rationally set for the stereoselective construction of the C2 and C3 stereogenic centers as well as for the regioselective coupling with **5**.

We reported the enantioselective synthesis of the C,D-ring fragment **7** (Scheme 2).<sup>[10]</sup> Therefore, preparation of **5** commenced with the hydroboration of **7** with 9-BBN. The subsequent reaction with pivaloyl chloride, the removal of the methoxymethyl group, and the oxidation with Dess–Martin periodinane provided aldehyde **5** (94 %).

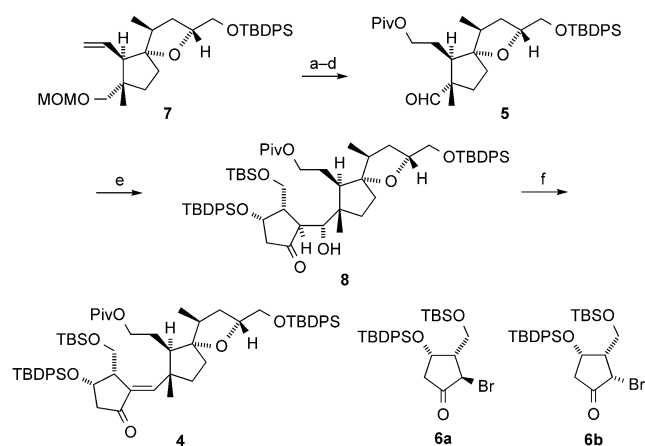
As fragments **6a** and **6b** were easily prepared,<sup>[11]</sup> we next investigated the coupling reaction of **5** and **6**. To the best of our knowledge, the coupling reaction reported by Utimoto and co-workers<sup>[12]</sup> has never been utilized for natural product synthesis; however, we decided to employ it because the

[\*] K. Tsuna, N. Noguchi, Prof. Dr. M. Nakada  
Department of Chemistry and Biochemistry  
Faculty of Science and Engineering, Waseda University  
3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555 (Japan)  
E-mail: mnakada@waseda.jp  
Homepage: <http://www.chem.waseda.ac.jp/nakada/>

[\*\*] This work was financially supported in part by a Waseda University Grant for Special Research Projects, a Grant-in-Aid for Scientific Research on Innovative Areas (No. 21106009), Young Scientists (No. 19890231), and the Global COE program “Center for Practical Chemical Wisdom” by MEXT.



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201104447>.

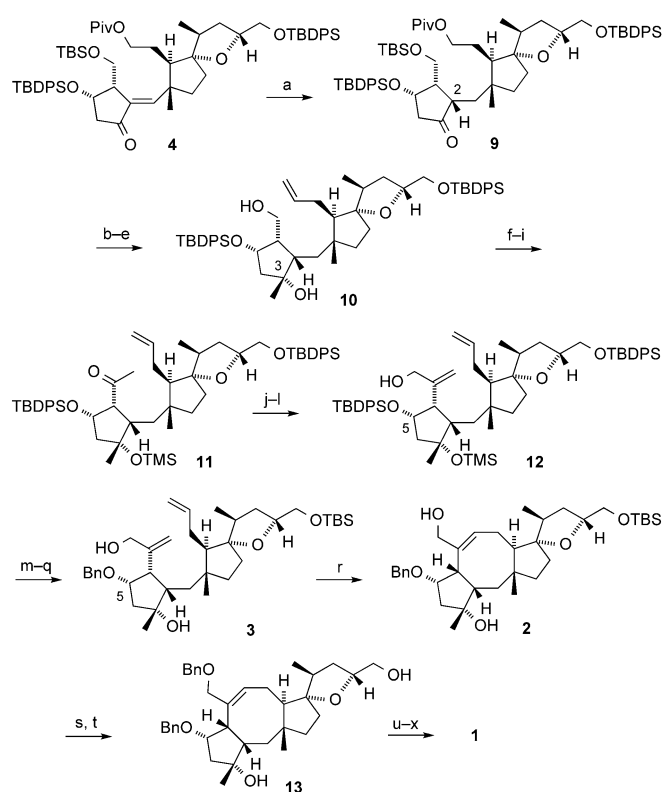


**Scheme 2.** Preparation of **4**. a) 9-BBN, THF, RT; then 3 M NaOH, 30% aqueous  $\text{H}_2\text{O}_2$ , RT, 100%; b) PivCl, py, DMAP,  $\text{CH}_2\text{Cl}_2$ , RT, 100%; c)  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{Me}_2\text{S}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-30^\circ\text{C}$ , 92%; d) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , RT, 94%; e) **6a** or **6b** (2.0 equiv),  $\text{Ph}_3\text{SnH}$ ,  $\text{Et}_3\text{B}$ , benzene, RT, 90% (from **6a**), 83% (from **6b**); f) Burgess reagent, benzene, RT, 92%. 9-BBN = 9-borabicyclo[3.3.1]nonane, DMAP = 4-dimethylamino-pyridine, MOM = methoxymethyl, py = pyridine.

reaction of the involved boron enolate with a bulky aldehyde proceeds efficiently under mild conditions to afford the coupling products. Indeed, the reaction of **5** and **6a** with triphenyltin hydride and triethyl borane in benzene was carried out at room temperature to afford **8** as the single product (90%). The reaction of **5** with **6b** under the same conditions also provided **8** (83%) as the single product. It should be noted that this coupling reaction proceeded without the  $\beta$ -elimination reaction of the silyloxy group, a reaction that often occurs in such a cyclopentenone system. The dehydration of **8** with the Burgess reagent<sup>[13]</sup> successfully afforded the desired enone **4** in 92% yield.

Considerable attention has been given to the formation of eight-membered carbocyclic rings by RCM because of its potential utility.<sup>[14]</sup> However, to the best of our knowledge, the number of natural product syntheses that employ RCM to form an eight-membered carbocyclic ring is limited.<sup>[14a,c,d,i]</sup> We also found that there are only two natural product syntheses that utilize RCM to form a trisubstituted double bond in an eight-membered carbocyclic ring.<sup>[14a,c]</sup> Moreover, the construction of the ophiobolin skeleton by RCM has not been reported to date. Nonetheless, among the various preparation methods for eight-membered carbocyclic rings, RCM is the most straightforward approach. Therefore, we decided to examine the RCM of **12**, which was prepared from **4** (Scheme 3).

Hydrogenation of **4** with Raney Ni in a mixed solvent (MeOH/THF = 1:1) afforded **9** with high selectivity and yield.<sup>[15]</sup> The reaction of methyllithium with ketone **9** occurred as predicted from the less-hindered  $\beta$  face with concomitant removal of the pivaloyl group to afford the desired diol as the single isomer. The subsequent Swern oxidation, Wittig reaction, and removal of the TBS group afforded **10**. Unfortunately, the Swern oxidation of **10** caused dehydration of the tertiary alcohol. However, the oxidation with IBX<sup>[16]</sup> proceeded without dehydration to afford the lactol, which was



**Scheme 3.** Total synthesis of (+)-ophiobolin A (**1**). a)  $\text{H}_2$ , Raney Ni, MeOH/THF = 1:1, RT, 82%, d.r. = 41:1; b) MeLi,  $\text{Et}_2\text{O}$ ,  $-78$  to  $0^\circ\text{C}$ , 98%, d.r. = 1:0; c)  $(\text{COCl})_2$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; then  $\text{Et}_3\text{N}$ , RT, 98%; d)  $\text{Ph}_3\text{P}^+\text{MeBr}^-$ ,  $t\text{BuOK}$ , THF,  $0^\circ\text{C}$ , 99%; e) PPTS, EtOH, RT, quant.; f) IBX, DMSO, RT; g) MeLi,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ ; h) Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , RT, 78% (over 3 steps); i) TMSCl, imidazole, DMF, RT, quant.; j) Comins reagent, KHMDS, THF,  $-78^\circ\text{C}$ ; k)  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Et}_3\text{N}$ , CO (1 atm), MeOH/toluene = 20:1,  $50^\circ\text{C}$ ; l) DIBAL-H, hexane,  $-78^\circ\text{C}$ , 47% (over 3 steps); m) PivCl, py, DMAP,  $\text{CH}_2\text{Cl}_2$ , RT; n) TBAF, THF, RT; o) TBSCl, DIPEA, DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; p) BnBr, NaH, DMF,  $0^\circ\text{C}$ ; q) DIBAL-H, hexane,  $-78^\circ\text{C}$ , 76% (over 5 steps); r) Hoveyda–Grubbs II, 1,4-benzoquinone, toluene,  $110^\circ\text{C}$ ; s) BnBr, NaH,  $0^\circ\text{C}$ ; t) PPTS, EtOH, RT, 68% (over 3 steps); u)  $(\text{COCl})_2$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; then  $\text{Et}_3\text{N}$ , RT; v)  $(\text{CH}_3)_2\text{CHPPh}_3^+\text{I}^-$ ,  $n\text{BuLi}$ , RT; w) Li, naphthalene, THF,  $-30^\circ\text{C}$ ; x)  $(\text{COCl})_2$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; then  $\text{Et}_3\text{N}$ , RT, 49% (over 4 steps). DIBAL-H = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, DMF = *N,N*-dimethylformamide, DMSO = dimethyl sulfoxide, IBX = *ortho*-iodoxybenzoic acid, KHMDS = potassium hexamethyldisilazide, PPTS = pyridinium *para*-toluenesulfonate, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl.

then subjected to the reaction with methyllithium, followed by oxidation with Dess–Martin periodinane, and the reaction of the products with TMSCl to afford ketone **11**. The reaction of **11** with Comins reagent<sup>[17]</sup> afforded the enol triflate, the following palladium-mediated carbonylation and the reduction with DIBAL-H gave **12**.

The RCM of **12** was first attempted with Grubbs II catalyst<sup>[18]</sup> in toluene or dichloroethane under reflux; however, the desired product was not obtained. Use of the Hoveyda–Grubbs II catalyst<sup>[18]</sup> or the modified Grubbs II catalyst<sup>[19]</sup> which was reported to be effective for hindered alkenes, gave the same results. We found that in all RCM reactions most of the starting material remained and a small

amount of styrene derivatives was formed. These compounds could be derived from the metathesis reaction of the terminal alkene with the catalyst.

We expected that the ring-closing step would suffer from the steric hindrance of the bulky TBDPS group at the C5 hydroxy group. Consequently, we decided to examine the RCM of compound **3**, which has a benzyl group in place of the TBDPS group. After the protection of the primary hydroxy group of **12** by a pivaloyl group, all the silyl groups were removed to afford the triol. The selective protection of the primary hydroxy group as the TBS ether and the secondary hydroxy group as the benzyl ether was followed by the removal of the pivaloyl group by DIBAL-H to afford **3**.

The RCM of **3** was carried out with Hoveyda–Grubbs II catalyst in toluene. Although the RCM did not proceed at room temperature, the desired compound **2** was successfully obtained upon heating. It should be noted that the dehydration of the tertiary hydroxy group of compound **3** occurs easily under acidic conditions but dehydrated products were not obtained in the RCM.

The primary hydroxy group of **2** was selectively protected as a benzyl ether, and subsequent removal of the TBS group afforded compound **13**. Swern oxidation of **13**, Wittig reaction, removal of the benzyl group with lithium naphthalenide, and another Swern oxidation finally afforded **1**. The product proved to be identical to naturally occurring (+)-ophiobolin A in all respects ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR, MS, and  $[\alpha]_D^{25}$ ),<sup>[11]</sup> thus confirming the first enantioselective total synthesis of (+)-ophiobolin A (**1**).

In summary, the total synthesis of (+)-ophiobolin A has been achieved in a convergent approach. This synthesis was straightforward and the assembly of the A-ring fragment with the C, D-ring fragment was efficiently carried out by following the reaction reported by Utimoto and co-workers. To the best of our knowledge, this application of the above-mentioned reaction is the first in natural product synthesis. The construction of the ophiobolin carbocyclic skeleton by RCM is also highlighted, but was sensitive to the substrate structure, and use of a less bulky protective group, such as benzyl ether, was crucial. Based on the results of this total synthesis, new synthetic studies for congeners of (+)-ophiobolin A are in progress.

Received: June 27, 2011

Published online: September 13, 2011

**Keywords:** cross-coupling · natural products · ring-closing metathesis · sesterterpenes · total synthesis

- [1] K. Ishibashi, R. Nakamura, *J. Agric. Chem. Soc. Jpn.* **1958**, *32*, 739–744.
- [2] S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Tokahashi, S. Tamura, K. Ishibashi, M. Shirasaka, *J. Am. Chem. Soc.* **1965**, *87*, 4968–4970.
- [3] a) L. Canonica, A. Fricchi, U. Galli Kienle, A. Scala, *Tetrahedron Lett.* **1966**, *7*, 1329–1333; b) S. Nozoe, K. Hirai, K. Tsuda, *Tetrahedron Lett.* **1966**, *7*, 2211–2216; c) A. Itai, S. Nozoe, K. Tsuda, S. Okuda, Y. Iitaka, Y. Nakayama, *Tetrahedron Lett.* **1967**, *8*, 4111–4112; d) S. Nozoe, A. Itai, K. Tsuda, S. Okuda, *Tetrahedron Lett.* **1967**, *8*, 4113–4117; e) S. Nozoe, K. Morisaki, K. Fukushima, S. Okuda, *Tetrahedron Lett.* **1968**, *9*, 4457–4458; f) H. G. Culter, F. G. Crumley, R. H. Cox, J. P. Springer, R. F. Arrendale, R. J. Cole, P. D. Cole, *J. Agric. Food Chem.* **1984**, *32*, 778–782; g) F. Sugawara, G. Strobel, R. N. Strange, J. N. Siedow, G. D. V. Duyne, J. Clardy, *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 3081–3085; h) F. Sugawara, N. Takahashi, G. Strobel, C. Yun, G. Gray, Y. Fu, J. Clardy, *J. Org. Chem.* **1988**, *53*, 2170–2172; i) S. B. Singh, J. L. Smith, G. S. Sabnis, A. W. Dombrowski, J. M. Schaeffer, M. A. Goetz, G. F. Bills, *Tetrahedron* **1991**, *47*, 6931–6938; j) E. Li, A. M. Clark, D. P. Rotella, C. D. Hufford, *J. Nat. Prod.* **1995**, *58*, 74–81; k) A. Tsiouras, A. A. Adefarati, J. S. Tkacz, E. G. Frazier, S. P. Rohrer, E. Birzin, A. Rosegay, D. L. Zink, M. A. Goetz, S. B. Singh, J. M. Schaeffer, *Bioorg. Med. Chem.* **1996**, *4*, 531–536; l) H. Wei, T. Itoh, M. Kinoshita, Y. Nakai, M. Kurotaki, M. Kobayashi, *Tetrahedron* **2004**, *60*, 6015–6019; m) A. Evidente, A. Andolfi, A. Cimmino, M. Vurro, M. Fracchiolla, R. Charudattan, A. Motta, *Phytochemistry* **2006**, *67*, 2281–2287.
- [4] T. K. Au, W. S. H. Chick, P. C. Leung, *Life Sci.* **2000**, *67*, 733–742.
- [5] H. Fujiwara, K. Matsunaga, H. Kumagai, M. Ishizuka, Y. Ohizumi, *Pharm. Pharmacol. Commun.* **2000**, *6*, 427–431.
- [6] P. C. Leung, W. A. Taylor, J. H. Wang, C. L. Tipton, *J. Biol. Chem.* **1984**, *259*, 2742–2747.
- [7] X. Shen, S. B. Krasnoff, S.-W. Lu, C. D. Dunbar, J. O'Neal, B. G. Turgeon, O. C. Yoder, D. M. Gibson, M. T. Hamann, *J. Nat. Prod.* **1999**, *62*, 895–897.
- [8] For synthetic studies on ophiobolins, see: a) W. G. Dauben, D. J. Hart, *J. Org. Chem.* **1977**, *42*, 922–923; b) T. K. Das, P. C. Dutta, G. Kartha, J. M. Bernassau, *J. Chem. Soc. Perkin Trans. 1* **1977**, 1287–1295; c) R. K. Boeckman, Jr., J. P. Bershas, J. Clardy, B. Solheim, *J. Org. Chem.* **1977**, *42*, 3630–3633; d) L. A. Paquette, D. R. Andrews, J. P. Springer, *J. Org. Chem.* **1983**, *48*, 1147–1149; e) L. A. Paquette, J. A. Colapret, D. R. Andrews, *J. Org. Chem.* **1985**, *50*, 201–205; f) R. M. Coates, J. W. Muskopf, P. A. Senter, *J. Org. Chem.* **1985**, *50*, 3541–3557; g) G. Mehta, N. Krishnamurthy, *J. Chem. Soc. Chem. Commun.* **1986**, 1319–1321; h) M. Umehara, S. Hishida, S. Okumoto, S. Ohba, M. Ito, Y. Saito, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4474–4476; i) J. H. Rigby, C. Senanayake, *J. Org. Chem.* **1987**, *52*, 4634–4635; j) M. Rowley, Y. Kishi, *Tetrahedron Lett.* **1988**, *29*, 4909–4912; k) W. G. Dauben, A. M. Warshawsky, *J. Org. Chem.* **1990**, *55*, 3075–3087; l) L. A. Paquette, S. Liang, P. Galatsis, *Synlett* **1990**, 663–665; m) B. B. Snider, K. Yang, *J. Org. Chem.* **1992**, *57*, 3615–3626; n) J. H. Rigby, T. McGuire, C. Senanayake, K. Khemani, *J. Chem. Soc. Perkin Trans. 1* **1994**, 3449–3457; o) L. A. Paquette, S. Liang, H.-L. Wang, *J. Org. Chem.* **1996**, *61*, 3268–3279; p) A. J. Blake, A. J. Highton, T. N. Majid, N. S. Simpkins, *Org. Lett.* **1999**, *1*, 1787–1789; q) K. F. McGee, Jr., T. H. Al-Tel, S. M. Sieburth, *Synthesis* **2001**, 1185–1196; r) P. K. Ruprah, J.-P. Cros, J. E. Pease, W. G. Whittingham, J. M. J. Williams, *Eur. J. Org. Chem.* **2002**, 3145–3152; s) B. Salem, J. Suffert, *Angew. Chem.* **2004**, *116*, 2886–2890; *Angew. Chem. Int. Ed.* **2004**, *43*, 2826–2830; t) K. Michalak, M. Michalak, J. Wicha, *Molecules* **2005**, *10*, 1084–1100; u) C. Bour, G. Blond, B. Salem, J. Suffert, *Tetrahedron* **2006**, *62*, 10567–10581.
- [9] For the total synthesis of (+)-alcoholic acid and (+)-ceroplastol II, see: a) N. Kato, H. Kataoka, S. Ohbuchi, S. Tanaka, H. Takeshita, *J. Chem. Soc. Chem. Commun.* **1988**, 354–356; b) N. Kato, H. Takeshita, H. Kataoka, S. Ohbuchi, S. Tanaka, *J. Chem. Soc. Perkin Trans. 1* **1989**, 165–174; for (+)-ophiobolin C, see: c) M. Rowley, M. Tsukamoto, Y. Kishi, *J. Am. Chem. Soc.* **1989**, *111*, 2735–2737; for (±)-ceroplastol I, see: d) R. K. Boeckman, Jr., A. Arvanitis, M. E. Voss, *J. Am. Chem. Soc.* **1989**, *111*, 2737–2739; for (+)-ceroplastol I, see: e) L. A. Paquette, T. Z. Wang, N. H. Vo, *J. Am. Chem. Soc.* **1993**, *115*, 1676–1683.

- [10] N. Noguchi, M. Nakada, *Org. Lett.* **2006**, *8*, 2039–2042. Optimization of the cyclization conditions increased the yield from 45 % to 68 %; details will be reported in due course.
- [11] See the Supporting Information.
- [12] The classic Reformatsky reaction of **5** with **6** gave no products; a) K. Nozaki, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1988**, *29*, 1041–1044; b) K. Nozaki, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403–409.
- [13] a) E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Am. Chem. Soc.* **1970**, *92*, 5224–5226; b) E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26–31. Reactions with  $\text{TiF}_4$ ,  $\text{Ac}_2\text{O}$ , and Martin's sulfurane gave no products. The reaction with  $\text{MsCl}$  was low-yielding (28 %) and the use of  $\text{SOCl}_2$  caused decomposition of the starting material.
- [14] a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746–8749; b) S. D. Edwards, T. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4267–4270; c) L. A. Paquette, J. Tae, M. P. Arrington, A. H. Sadoun, *J. Am. Chem. Soc.* **2000**, *122*, 2742–2748; d) I. Efremov, L. A. Paquette, *J. Am. Chem. Soc.* **2000**, *122*, 9324–9325; e) D. Bourgeois, J. Mahuteau, A. Pancrazi, S. P. Nolan, J. Prunet, *Synthesis* **2000**, 869–882; f) M. E. Krafft, Y.-Y. Cheung, C. A. Juliano-Capucio, *Synthesis* **2000**, 1020–1026; g) D. Bourgeois, A. Pancrazi, L. Ricard, J. Prunet, *Angew. Chem. Int. Ed.* **2000**, *39*, 726–729; h) I. Hanna, L. Ricard, *Org. Lett.* **2000**, *2*, 2651–2654; i) M. E. Krafft, Y.-Y. Cheung, K. A. Abboud, *J. Org. Chem.* **2001**, *66*, 7443–7448; j) E. M. Codesido, R. Rodriguez, L. Castedo, J. R. Granja, *Org. Lett.* **2002**, *4*, 1651–1654; k) M. E. Krafft, Y.-Y. Cheung, S. A. Kerrigan, K. A. Abboud, *Tetrahedron Lett.* **2003**, *44*, 839–843; l) A. Srikrishna, D. H. Dethe, P. R. Kumar, *Tetrahedron Lett.* **2004**, *45*, 2939–2942; m) R. G. -Fandino, M. J. Aldegunde, E. M. Codesido, L. Castedo, J. R. Granja, *J. Org. Chem.* **2005**, *70*, 8281–8290; n) K. Michalak, M. Michalak, J. Wicha, *Tetrahedron Lett.* **2005**, *46*, 1149–1153; o) S. Schiltz, C. Ma, L. Ricard, J. Prunet, *J. Organomet. Chem.* **2006**, *691*, 5438–5443; p) A. Michaut, J. Rodriguez, *Angew. Chem.* **2006**, *118*, 5870–5881; *Angew. Chem. Int. Ed.* **2006**, *45*, 5740–5750; q) M. J. Aldegunde, L. Castedo, J. R. Granja, *Org. Lett.* **2008**, *10*, 3789–3792; r) L. Mitchell, J. A. Parkinson, J. M. Percy, K. Singh, *J. Org. Chem.* **2008**, *73*, 2389–2395; s) C. Ma, S. Schiltz, X. F. L. Goff, J. Prunet, *Chem. Eur. J.* **2008**, *14*, 7314–7323; t) R. Mizutani, T. Miki, K. Nakashima, M. Sono, M. Tori, *Heterocycles* **2009**, *78*, 2295–2314.
- [15] THF was used as a cosolvent to dissolve **4** in the solution.
- [16] M. Frigero, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
- [17] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
- [18] R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29.
- [19] I. C. Stewart, T. Ung, A. A. Pletnev, J. M. Berlin, R. H. Grubbs, Y. Schrodli, *Org. Lett.* **2007**, *9*, 1589–1592.