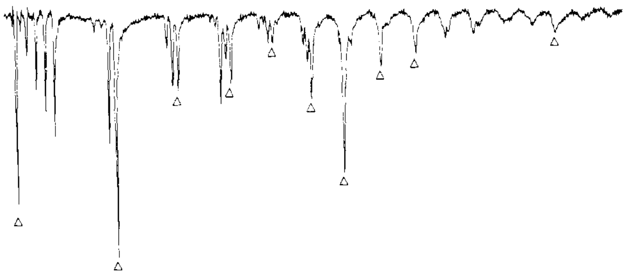

Figure 1. $Bi_xNa_y^+$ cluster distribution. Marked peaks correspond to (x,y) = (1,0), (2,3), (3,4), (4,5), (5,5), (6,5), (7,4), (8,5), (9,6), and (14,7). Ionization via 248 nm, 5.5 mJ/cm^2.

Table I. Anionic Zintl Ions of Bismuth

Zintl ion	ion observed
Bi_3^{3-}	$Bi_3Na_4^+$
Bi_4^{2-}	$Bi_4Na_3^+$
Bi_5^{3-}	$Bi_5Na_4^+$
Bi_7^{3-}	$Bi_7Na_4^+$

numbers of sodium atoms. Cationic clusters $Bi_xNa_{y+1}^+$, corresponding to Bi_x^{y-}, appear as magic numbers in the distribution for every reported anionic Zintl ion of bismuth,[1] with the exception of Bi_2^{4-}. Instead $Bi_2Na^{3+} \doteq Bi_2^{2-}$ is observed, suggesting the electronic octet rule determines the stability of this small cluster. $Bi_7Na_4^+$, which is isoelectronic with Bi_7^{3-}, is particularly prominent, and though the trivalent anion of antimony heptamer has been isolated,[2] the existence of the analogous bismuth species previously has not been unambiguously established. Additionally, clusters corresponding to Bi_4^{4-}, Bi_6^{4-}, Bi_8^{4-}, Bi_9^{5-}, and Bi_{14}^{6-} are exceptionally abundant, and it is expected some of these may exist in solution. In general, "magic numbers" correspond to the largest cluster within a group; the ion possessing an additional alkali atom is only weakly, if at all, observed.

Asymmetric tailing of the alkali-saturated peaks to longer arrival times is seen in the figure and is evidence that fragmentation of larger cluster ions represents a significant contribution to the observed intensities of these species. It is concluded that larger clusters sequentially evaporate excess alkali atoms until the stable Zintl ionic configuration is obtained. This is the most likely fragmentation channel is bismuth–bismuth bond energies[3] are typically twice that of sodium–sodium bonds.[4]

These mass spectra should thus be interpreted as indicative of cluster ion stabilities, and not the actual neutral cluster distribution. The absence of such "tailing" for clusters possessing fewer alkali atoms than the Zintl structure suggests these species contain negligible contributions from fragmentation of larger cluster ions and are apparently stable under these ionization conditions. Magic numbers observed in the bismuth/alkali clusters distribution correspond to reported Zintl ions possessing the same number of bismuth atoms. It is concluded that the alkali atoms cover the surface of the anionic bismuth Zintl ion, which determines the structures and stabilities of these ions and to which the alkali atoms merely donate electron density. Further chemical evidence supporting this assertion is based on studies of a number of reactions of these mixed clusters which show that the sodium can be reacted away and the remaining distribution is similar to that typically obtained for the pure bismuth system; details will be presented in future communications.

Due to the relatively small number of loosely held electrons versus the large number of nearest neighbors in metal clusters, analogies to the delocalized electron-deficient multicenter bonding characteristic of boron compounds have been proposed to account for "magic numbers" observed for a number of metallic systems.[5] For example, the observed stability of $Pb_2Sb_3^+$ may be interpreted as resulting from its $2n + 2$ valence electrons characteristic of "closo" boranes. Correspondence with the known Zintl ion Pb_5^{2-} has also been invoked to explain the prominence of this ion in the mass spectrum.[6] In contrast to bismuth/sodium clusters, where sodium ions surround the homoatomic bismuth Zintl ion core, the antimony atoms participate in the geometrical structure of the heteroatomic lead/antimony Zintl ions.

While cesium–lead and cesium–tin clusters have previously been reported[7] and found to exhibit maxima for stoichiometries corresponding to known Zintl ions of these divalent post-transition metals, these clusters are all accountable using Wades rules. Since bismuth and antimony are typically trivalent, anionic clusters of these elements very quickly exceed the maximum $2n + 8$ electrons accountable under Wades rules for "hypo" compounds. In particular, the previously mentioned Bi_7^{3-} possesses $2n + 10$ valence electrons, and Bi_{14}^{6-} has $2n + 20$! Hence, anionic Zintl ions of these species are particularly intriguing due to the inability of current theories to account for them and lack of other corresponding metallic compounds with which they may be compared.

Acknowledgment. Financial support by the U.S. Department of Energy, Grant No. DE-FGO2-88ER60648, is gratefully acknowledged.

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(1) Corbett, J. D. *Chem. Rev.* **1985**, *85*, 383. Lohn, L. L., Jr. *Inorg. Chem.* **1981**, *20*, 4229.

(2) Critchlow, S. C.; Corbett, J. D. *Inorg. Chem.* **1984**, *23*, 770.

(3) Rovner, L.; Drowart, A.; Drowart, J. *Trans. Faraday Soc.* **1967**, *63*, 2906.

(4) Bréchignac, C.; Cahuzac, Ph.; Roux, J.-Ph.; Pavolini, D.; Spiegelmann, F. *J. Chem. Phys.* **1987**, *87*, 5694.

(5) Wheeler, R. G.; LaiHing, H. K.; Wilson, W. L.; Duncan, M. A. *J. Chem. Phys.* **1988**, *88*, 2831.

(6) Schild, D.; Pflaum, R.; Sattler, K.; Recknagel, E. *J. Phys. Chem.* **1987**, *91*, 2649.

(7) Martin, T. P. *J. Chem. Phys.* **1985**, *83*, 78.

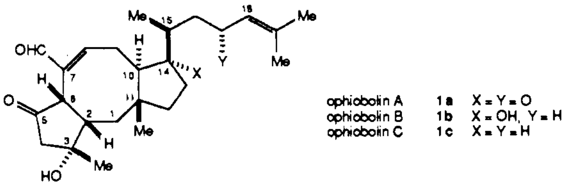
Total Synthesis of (+)-Ophiobolin C

Michael Rowley, Masamitsu Tsukamoto, and Yoshito Kishi*

Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, Massachusetts 02138

Received December 12, 1988

The ophiobolins (**1**) were characterized in the mid-1960s as the first naturally occurring sesterterpenes.[1] Since that time they have received much synthetic attention because of their complex molecular architecture and interesting biological activity.[2] Several approaches to these natural products have appeared in the literature,[3] focusing primarily on construction of the 5-8-5 ring system. To our knowledge, however, no total synthesis of ophiobolins has been reported thus far, probably due to the difficulties associated with the ring system, in particular the eight-membered ring, and also in the control of stereochemistry both on and outside the rings. We recently published an approach to this fused ring system[4] and now present a total synthesis of (+)-ophiobolin C (**1c**).



We started with the previously prepared alcohol **2**.[4] The exocyclic olefin was ozonolyzed, and, after the primary alcohol

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(1) Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitaka, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1965**, *87*, 4968–4970. Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211–2216.

(2) Ishibashi, K. *J. Agr. Chem. Soc. Jpn.* **1962**, *36*, 649–652.

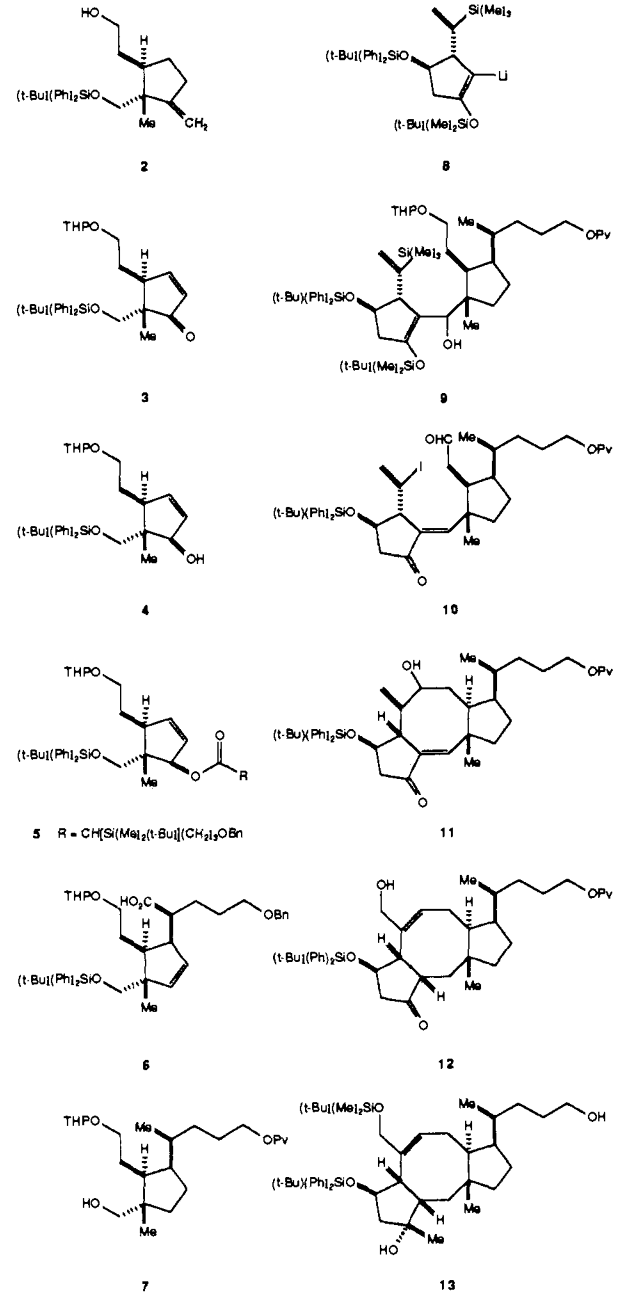
(3) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541–3557, and references therein. Rigby, J. H.; Senanayake, C. *J. Org. Chem.* **1987**, *52*, 4634–4635.

(4) Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909–4912.

was protected (DHP/PPTS[5]/CH_2Cl_2/room temperature), this cyclopentanone was oxidized to the α,β-unsaturated ketone **3** by the method of Saegusa[6] in 88% overall yield.[7] Reduction ($NaBH_4$/$CeCl_3$[8]/MeOH/-30 °C) of **3** yielded a 3:1 mixture of the allylic alcohols favoring the desired β-isomer **4**.[9] We originally planned to incorporate the entire C-ring side chain at this stage through a Claisen rearrangement. Unfortunately, however, we found that the C.18–C.19 trisubstituted olefin did not survive under the conditions used to convert a vinylsilane to a vinyl iodide (vide infra). Thus, we needed to execute the synthesis with a modified form of the C-ring side chain. The ester **5**, prepared from **4** and $ClOCCH[Si(Me)_2(t\text{-}Bu)](CH_2)_3OBn$[10] [$KN(TMS)_2$/THF/-78 °C], was subjected to tandem Brook[11] and Claisen rearrangements at 230 °C in xylene, to give the expected silyl esters.[12] Acid hydrolysis [1 M HCl-MeOH-Et_2O (1:1:1)/room temperature] of this product mixture yielded the corresponding acid in 72% overall yield with 6:1 stereoselectivity favoring the desired stereoisomer **6**. After esterification (CH_2N_2/Et_2O/0 °C), the acid **6** was reduced to the primary alcohol ($LiAlH_4$/Et_2O/0 °C), which was then mesylated (MsCl/Et_3N/CH_2Cl_2/0 °C) and reduced ($LiAlH_4$/Et_4O/room temperature). Hydrogenation [H_2 (1 atm)/PtO_2/EtOAc/room temperature] of this product, followed by hydrogenolysis [H_2 (1 atm)/$Pd(OH)_2$/EtOH/room temperature],[13] pivaloylation (PvCl/Py/room temperature), and desilylation (n-Bu_4NF/DMF/50 °C), furnished the primary alcohol **7**[14] in 57% overall yield from **6**. The relative stereochemistry of **6**, and hence **7**, was tentatively assigned on the basis of a mechanistic consideration including an analysis of steric interactions in the probable transition states. This stereochemical assignment was later proven correct by successful conversion of **7** into ophiobolin C.

Having completed the synthesis of the right hand portion of ophiobolin C, we now followed a route very similar to that established in our model studies. Swern oxidation[15] of the alcohol **7** and treatment with the vinyllithium reagent **8**[4] (2.5 equiv/Et_2O/-78 °C), followed by pivaloylation (PvCl/Et_3N/DMAP/CH_2Cl_2) to convert back the partially deacylated product, gave the vinylogous hemiacetal **9** in 85% yield based on **7**. The vinylogous hemiacetal **9** was hydrolyzed [48% aqueous HF-THF (1:100 v/v)/0 °C → room temperature] to the E-enone in 90% yield, iododesilylated [ICl (2 equiv)/CH_2Cl_2/-78 °C → 0 °C, then n-Bu_4NF made acidic with HF (>2 equiv)/THF/0 °C/1 min], deprotected [p-TsOH/CH_2Cl_2-MeOH (3:2)/room temperature], and subjected to Swern oxidation to give the vinyliodide aldehyde **10** in 52% yield over three steps. The key bond formation was accomplished by using an intramolecular Ni(II)/Cr(II)-mediated coupling reaction;[16] treatment of **10** with a large excess of chromium(II) chloride containing 0.5% w/w nickel(II) chloride in a mixture of dimethyl sulfoxide and dimethyl sulfide (1% v/v) for 2 h at room temperature gave the cyclized product **11** in 73% yield as a single diastereomer.[17]

Chart I



At this stage we needed to reduce the enone double bond and transpose the allylic alcohol. Both of the required functional group manipulations were performed by using three steps: epoxidation of the exocyclic double bond [t-BuOOH/$VO(acac)_2$/C_6H_6/room temperature],[18] formation of the thiocarbonate from the secondary alcohol [$4\text{-}MeC_6H_4OC(S)Cl$ (excess)/Py/DMAP/CH_2Cl_2/room temperature], and then reduction (n-Bu_3SnH/AIBN/C_6H_6/re-

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(5) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.

(6) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(7) All the new compounds reported in this paper gave satisfactory spectroscopic data including ^1H and ^{13}C NMR, IR, UV, and MS.

(8) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(9) Several attempts were made to improve the stereo- and regioselectivity of this reduction without significant success. Under the specified conditions, the desired alcohol **4** was isolated in 66% yield. In addition, a mixture of the undesired allylic alcohol and overreduced saturated alcohol was obtained in 28% yield. This mixture was recycled via PCC oxidation and $NaBH_4$-$CeCl_3$ reduction. The total yield of **4** after one recycle was 81%.

(10) This acid chloride was synthesized from the corresponding α-silyl aldehyde in two steps: (1) RuO_2/$NaIO_4$/CCl_4-MeCN-H_2O (3:3:4)/room temperature and (2) $(COCl)_2$/DMF-CH_2Cl_2/room temperature. The α-silyl aldehyde was prepared by adopting the literature procedure: Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251–6253.

(11) Brook, A. G.; MacRae, D. M.; Limburg, W. W. *J. Am. Chem. Soc.* **1967**, *89*, 5493–5495.

(12) We also studied the Claisen rearrangement via silylketene acetals: Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. However, trapping the enolate anion with (t-Bu)$(Me)_2SiCl$ or (t-Bu)$(Me)_2SiOTf$ gave a substantial amount of C-silylated product, presenting a technical difficulty in isolating the desired product and causing a low overall yield.

(13) An attempted one-step reduction of **6** over Pearlman's catalysis gave a complex mixture.

(14) $[\alpha]_D$ of the triol monopivaloate derived from **7**: -12.9° (c 0.1, $CHCl_3$).

(15) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(16) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050.

(17) In our model system (ref 4) was also obtained a single isomer, in which the hydroxyl group at the new chiral center was on the β face. Comparison of these samples would suggest that the same is true in this case; however, the stereochemistry has not been proved.

(18) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

J. Am. Chem. Soc. 1989, 111, 2737–2739

flux/3 min)[19,20] gave the primary alcohol **12** in 52% overall yield from **11**. The stereoselectivity of the enone reduction was approximately 4:1, favoring the desired diastereomer.

The primary alcohol was protected [t-Bu(Me)$_2$SiCl/imidazole/DMF/room temperature] not only to differentiate it from the alcohol produced in the next reaction but also to protect the β-silyloxyketone from elimination upon treatment with Grignard reagents.[21] The ketone was then treated with methylmagnesium bromide (Et$_2$O/0 °C → room temperature) to give a 13:1 mixture of tertiary alcohols favoring the desired **13** in 68% overall yield from **12**. At this stage, and in the earlier tin hydride reduction, the relative stereochemistry of the products was assigned by analogy to the model system[4] and was proven correct by successful conversion to ophiobolin C.

Swern oxidation, Wittig reaction [(Me)$_2$C=P(Ph)$_3$ (30 equiv)/THF/−78 °C → 0 °C], deprotection (n-Bu$_4$NF/THF/room temperature/2 h), and Swern oxidation furnished synthetic ophiobolin C (**1c**; mp 118–120 °C) in 46% overall yield from **13**. On comparison of spectroscopic (^{1}H and ^{13}C NMR, IR, UV, $[\alpha]_D$, MS) and chromatographic data, the synthetic substance was superimposed on an authentic sample.[22] In addition, no depression was observed on mixed melting point determination.

Acknowledgment. Financial support from the National Science Foundation (CHE 86-105050) is gratefully acknowledged.

Supplementary Material Available: ^{1}H NMR spectra of key intermediates and ^{1}H and ^{13}C NMR spectra of (+)-ophiobolin C (18 pages). Ordering information is given on any current masthead page.

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[19] Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363–2367.

[20] Leusink, A. J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, 2221–2225.

[21] Examination of a molecular model suggests that the primary hydroxy group of **12** is in close proximity to a proton at the C.4 position.

[22] We are grateful to Professor S. Nozoe, Tohoku University, for providing us with a very generous sample of natural ophiobolin C.

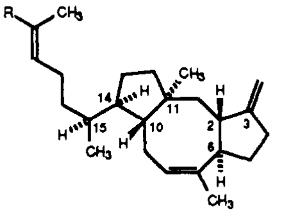
Synthetic Studies Directed toward Naturally Occurring Cyclooctanoids. 1. Total Synthesis of (±)-Ceroplastol I

Robert K. Boeckman, Jr.,* Argyrios Arvanitis, and
Matthew E. Voss

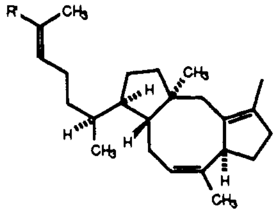
Department of Chemistry, University of Rochester
Rochester, New York 14627

Received January 19, 1989

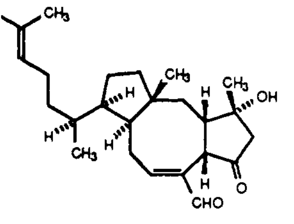
Our interest in the development of general protocols for the highly stereoselective construction of natural substances which contain functionalized eight-membered rings led us to consider the relatively small group of sesterterpenes exemplified by ceroplastol I (**1**),[1] the closely related structures ceroplastol II (**2**),[2] albolic acid (**3**),[3] and the ophiobolins, such as ophiobolin C (**4**).[4] A number of the ophiobolins show biological and potent phytological effects.[5-7] The challenges associated with the construction of these systems have stimulated a number of synthetic approaches;[8] however, only very recently has the first report of successful assembly of a naturally occurring member of the class appeared.[9,10]



1 R = CH$_2$OH
25 R = CH$_2$OCOPh[3,5-(NO$_2$)$_2$]



2 R' = CH$_2$OH
3 R' = CO$_2$H



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The central feature of our strategy is the construction of the eight-membered ring via fragmentation of an appropriately functionalized bicyclo[3.3.1]nonanone system as was described in our prior model studies.[11] The choice of this strategy was dictated by the need to minimize the potential for isomerization of the exocyclic olefin and transannular reactions involving the highly reactive trisubstituted eight-membered ring olefin. We felt establishment of the required relative stereochemistry about the eight-membered ring could be conveniently achieved utilizing the rigid template provided by the bicyclic precursors to the medium ring. Herein we describe the implementation of this strategy to a concise and overall highly stereoselective total synthesis of (±)-**1**.

Base-catalyzed Michael addition of the known racemic β-ketolactone **5**[12] to enone **6**[11] and acid-induced cyclization of the intermediate diketone afforded an inconsequential mixture (4.5:1) of crystalline epimeric tricyclic lactones **7** (mp 89–90 °C) in 60% yield (Scheme I).[13] The mixture of lactones **7** underwent decarboxylation upon base treatment, and the resulting hydroxy enones were directly transformed to the related methoxymethyl ethers **8** in 70% overall yield (twice distilled Kugelrohr, 110–130 °C at 0.5 mm).[14]

Introduction of the C$_{11}$ quaternary center in **1** with complete stereoselectivity was then achieved by alkylation of the α' enolate derived from **1** with (Z)-2-chloroacrylate **9**.[11,15] Alkaline hydrolysis and exposure of the resulting Z enone acrylate to TFAA provided the δ trienol lactone **10**, possessing the required stereodefined framework for introduction of the C$_{10}$ ring junction center in **1**, in 63% overall yield.[16] The C$_2$ and C$_{10}$ centers were

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[1] Rios, T.; Colunga, F. *Chem. Ind.* (*London*) **1965**, 1184.

[2] Itake, Y.; Watanabe, I.; Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1968**, *90*, 1092.

[3] Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1317. Rios, T.; Gomez, F. *Tetrahedron Lett.* **1969**, 2929.

[4] Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitaka, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1965**, *87*, 4968. Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211.

[5] Nozoe, S.; Itai, A.; Tsuda, K.; Okuda, S. *Tetrahedron Lett.* **1967**, 4113.

[6] Ishibashi, K. *J. Agr. Chem. Soc. Jpn.* **1962**, *36*, 649.

[7] For example, see: Leung, P. C.; Taylor, W. A.; Wang, J. H.; Tipton, C. L. *J. Biol. Chem.* **1984**, *259*, 2742.

[8] Rowley, M.; Kishi, Y. *Tetrahedron Lett.* **1988**, *29*, 4909. Kato, N.; Nakanishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109. Rigby, J. H.; Senanayake, C. *J. Org. Chem.* **1987**, *52*, 4634 and references therein.

[9] Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. Kato, N.; Takeshita, H.; Kataoka, H.; Ohbuchi, S.; Tanaka, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 165.

[10] See: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, the preceding paper in this issue, reporting the first synthesis of a natural ophiobolin (ophiobolin C).

[11] Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1977**, *41*, 3630.

[12] Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. Both enantiomers of **5** have been prepared in our laboratories by this protocol by using appropriate chiral auxiliaries: (3R,7R)-**5** ($\alpha^{25}{}_D$ −89.0° and (3S,7S)-**5** ($\alpha^{25}{}_D$ +89.7°). See: Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.

[13] All new substances exhibited spectroscopic data (IR, NMR (300 or 500 MHz), and MS) in accord with the assigned structure and provided acceptable combustion or high resolution analytical data.

[14] Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

[15] All compounds reported are racemic unless otherwise stated. The stereochemical frame of reference changes from Scheme I (six-membered ring) to Scheme II (eight-membered ring) which accounts for the apparent stereochemical changes in Scheme II.

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