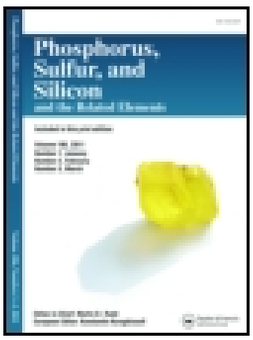


Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: 1042-6507 (Print) 1563-5325 (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Total synthesis involving sulfur chemistry

Tohru Fukuyama

To cite this article: Tohru Fukuyama (2019): Total synthesis involving sulfur chemistry, Phosphorus, Sulfur, and Silicon and the Related Elements, DOI: 10.1080/10426507.2019.1602619

To link to this article: https://doi.org/10.1080/10426507.2019.1602619

Published online: 09 Apr 2019.

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
https://doi.org/10.1080/10426507.2019.1602619

Total synthesis involving sulfur chemistry

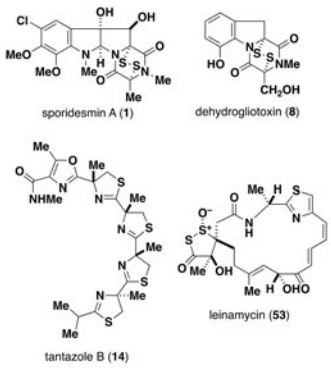
Tohru Fukuyama

University of Tokyo, Tokyo, Japan

ABSTRACT

Novel findings during the course of the total synthesis of sulfur-containing natural products are described. These natural products include sporidesmin A, dehydrogliotoxin, tantazole B, and leinamycin.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 27 March 2019
Accepted 29 March 2019

KEYWORDS
Natural products; total synthesis; epidithiodiketopiperazine; thiazoline; dithiolanone

I encountered with sulfur chemistry for the first time when Professor Yoshito Kishi, my Ph.D. mentor, asked me to help another graduate student synthesize sporidesmin A (**1**) at Harvard University (Figure 1).[1]

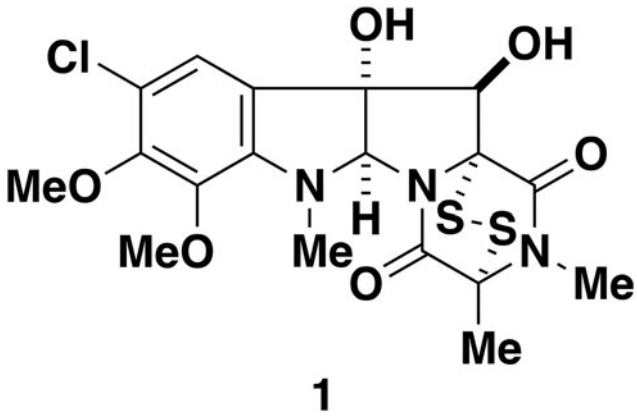
It was already known in our labs that the thioacetal **2** undergoes a regiospecific methylation to give **3**, which could then be converted to epidithiodiketopiperazine **4** under mild conditions (Scheme 1).[2] My task was to establish a more robust route to **3** for further exploration (Scheme 2). Initial reaction conditions were extremely harsh in that a mixture of methylidenethiol **5**, *p*-anisaldehyde, and TFA was heated at 100 °C in a steel bomb using hydrogen sulfide as a solvent. While checking the reaction mixture by TLC, I realized a subtle increase of the desired compound **6** where the reaction mixture and the starting material **5** were co-spotted. I suspected that trithiane **7**, a by-product of the reaction, might have played an important role. Indeed, when **5** was heated with **7** and $BF_3{\cdot}Et_2O$ in refluxing CH_2Cl_2, a diastereomeric mixture **6** was obtained in high yield. We next turned our attention to the total synthesis of dehydrogliotoxin (**8**) in which the regiospecific deprotonation of the bridgehead proton of the bicyclic thioacetal such as **2** was clearly demonstrated (Scheme 3). Upon treatment with *n*-BuLi at −78 °C, **9** underwent a facile cyclization to give **10**. On the other hand, **11** did not cyclize under the same conditions, but instead gave the alkylation product **12** after addition of $ClCH_2OMe$. Both **10** and **12** were successfully converted to dehydrogliotoxin (**8**) in several steps.[3]

Tantazole B (**13**) caught my eye at the Gordon Conference on Natural Products in 1989. The unique structure includes four consecutive thiazoline rings capped by an oxazole ring. The proposed structure was later revised as **14** by total synthesis in our labs (Figure 2). It was known that *N*-acylaziridines **15** can be transformed to thiazolines **17** via *N*-thioacylaziridines **16** (Scheme 4). When **18** was treated with Lawesson's reagent, however, the rearrangement proceeded in the undesired direction, giving exclusively the diastereomeric thiazoline **19**.

The attempted conversion of **20** to the desired thiazoline via thioamide **21** failed presumably due to the facile formation of thioacylaziridine **22**, yielding once again the undesired thiazoline **23** (Scheme 5).

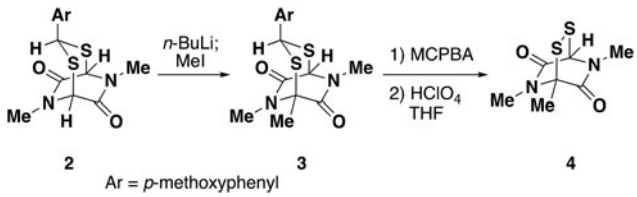
We next attempted an aza-Wittig reaction of **30** in the hope that the reactivity of thioester is comparable to that of ketones (Scheme 6). To our big surprise, upon treatment of azide **30** with Ph_3P, oxazoline **32** was obtained instead of the desired thiazoline. Apparently, a rapid acyl migration to the nitrogen atom followed by migration of the triphenylphosphonium species to the sulfur atom occurred to give

CONTACT Tohru Fukuyama tohru.fukuyama@post.harvard.edu



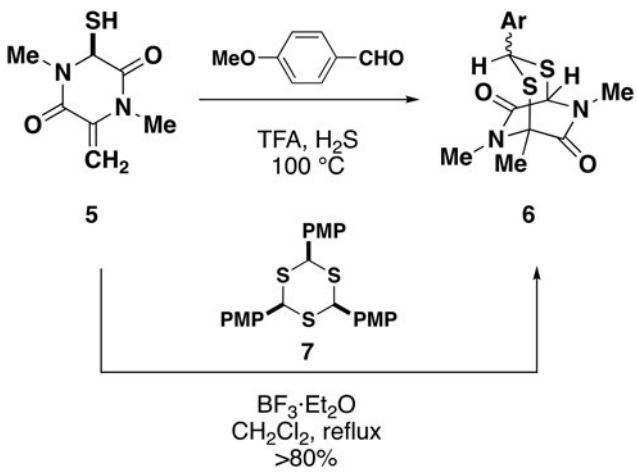
1

Figure 1. Structure of sporidesmin A.



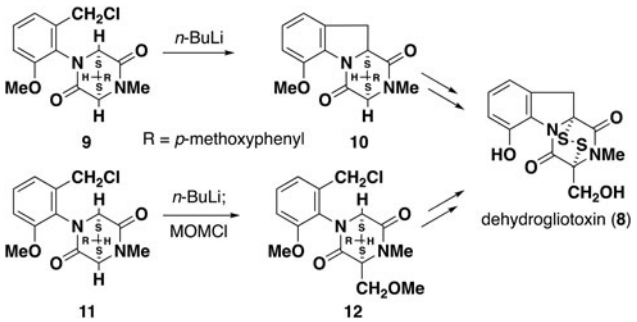
2 3 4

Scheme 1. Regiospecific alkylation.



5 6 7

Scheme 2. Construction of thioacetal **6**.

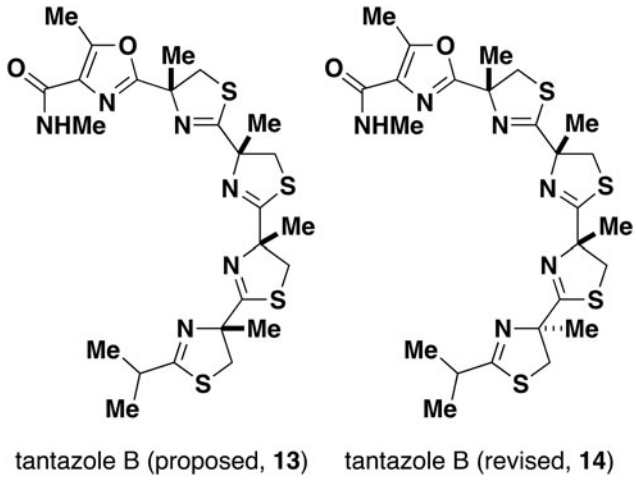


9 10 11 12

Scheme 3. Total synthesis of dehydrogliotoxin (**8**).

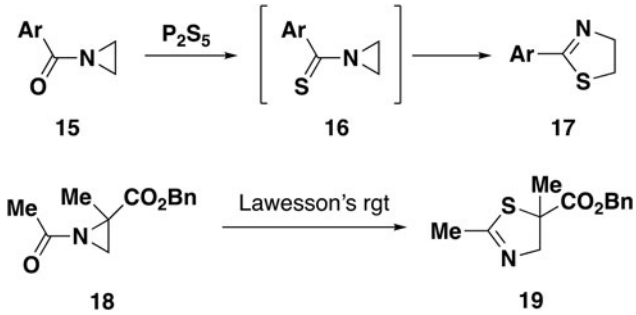
the intermediate **31**, which underwent the Mitsunobu-type reaction to give the oxazoline **32**.

It occurred to us that cyclization of **33** under acidic conditions would form **34** from which preferred protonation would take place on the oxygen atom instead of the sulfur atom,



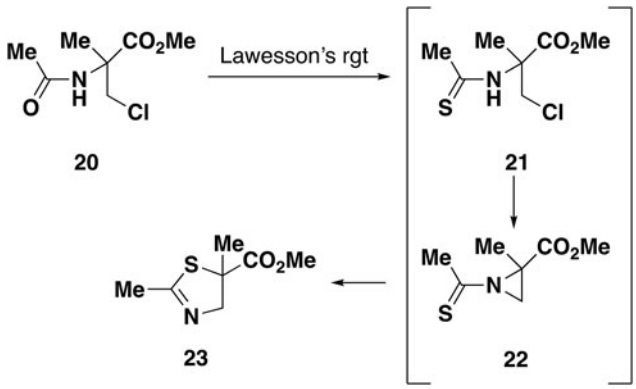
tantazole B (proposed, **13**) tantazole B (revised, **14**)

Figure 2. Proposed and revised structures of tantazole B.



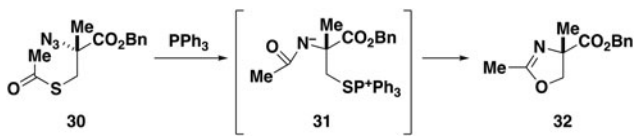
15 16 17 18 19

Scheme 4. Conversion of *N*-acylaziridines to thiazolines.



20 21 22 23

Scheme 5. Facile formation of *N*-thioacylaziridine.

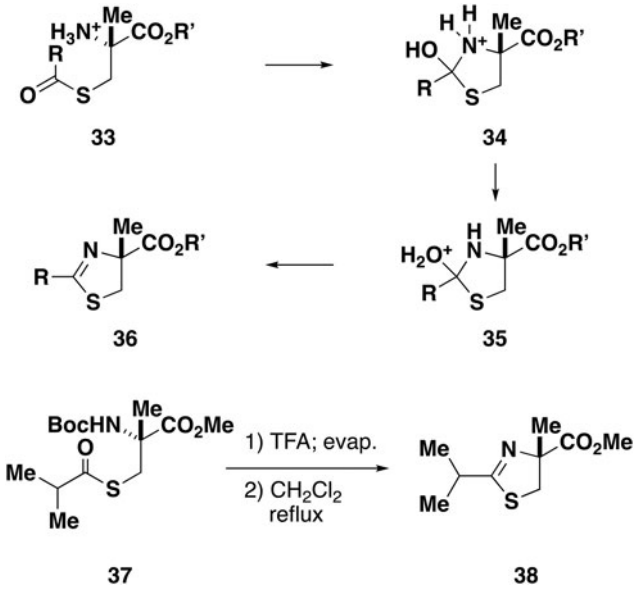


30 31 32

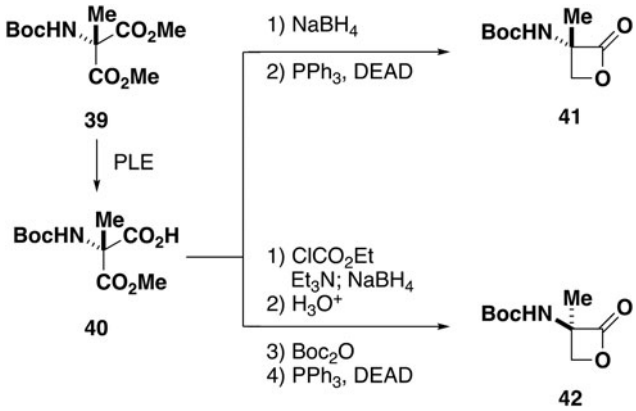
Scheme 6. Unsuccessful aza-Wittig reaction.

giving the intermediate **35**. The ensuing dehydration would lead to the formation of the desired thiazoline **36** (Scheme 7). Indeed, removal of the Boc group of **37** with TFA followed by evaporation and heating in refluxing CH_2Cl_2 furnished the desired **37** for the first time.

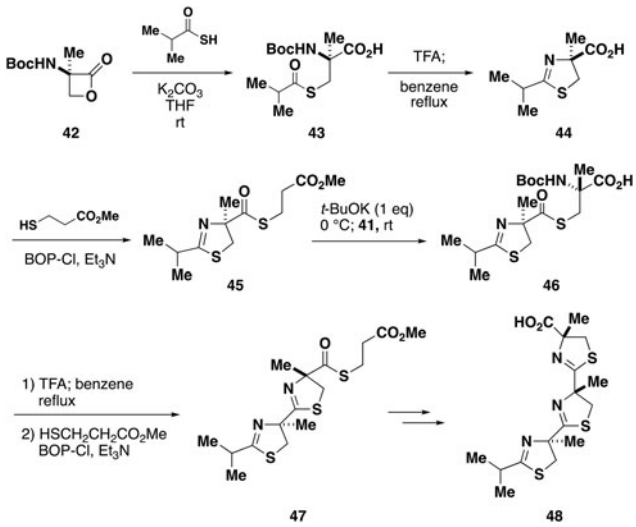
Having established a procedure for constructing the requisite thiazoline, we next focused on an efficient



Scheme 7. Successful formation of thiazoline.

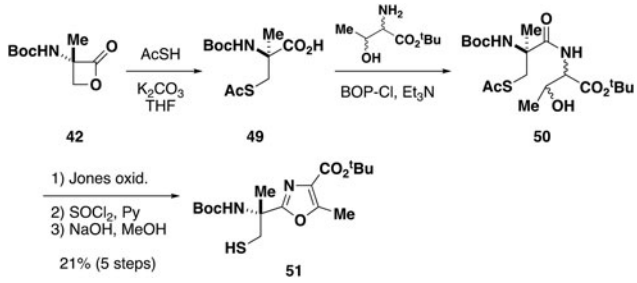


Scheme 8. Preparation of β-lactones.

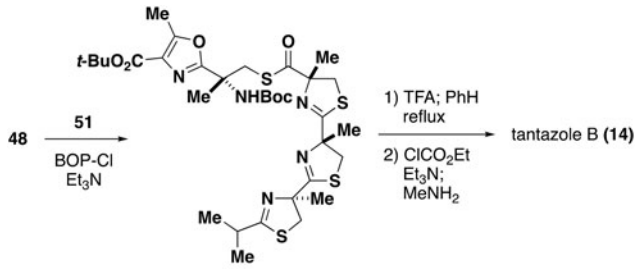


Scheme 9. Iterative preparation of consecutive thiazoline rings.

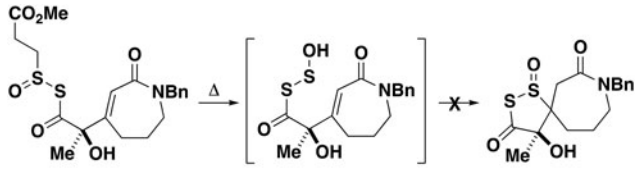
preparation of both enantiomers of *N*-Boc-2-methylcysteine. For reiterative construction of a "thiazoline chain," use of a β-lactone block such as **41** and **42** appeared quite attractive



Scheme 10. Preparation of the oxazole moiety.



Scheme 11. Completion of the total synthesis.



Scheme 12. Attempted construction of the dithiolanone structure.

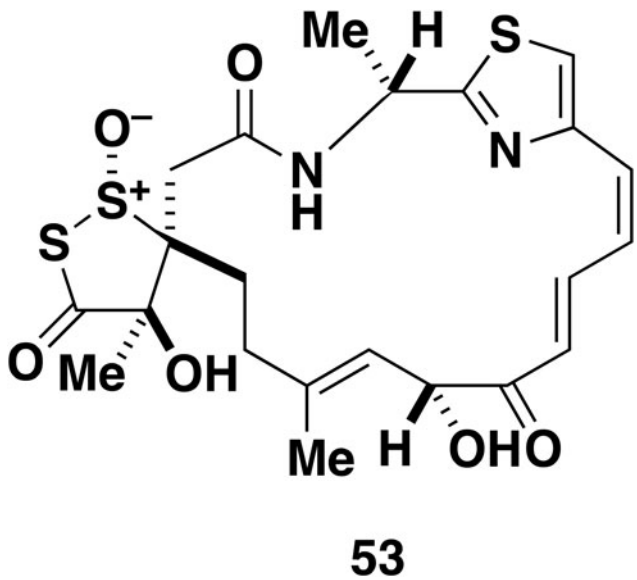
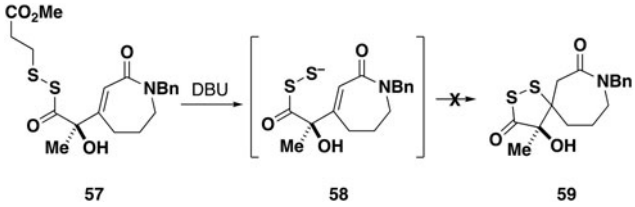


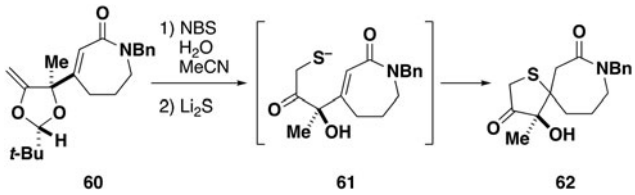
Figure 3. Structure of leinamycin.

(Scheme 8). As illustrated in Scheme 8, both **41** and **42** could be synthesized from the same intermediate **40** which in turn could be prepared from the readily available malonate derivative **39** by enzymatic (PLE) hydrolysis.

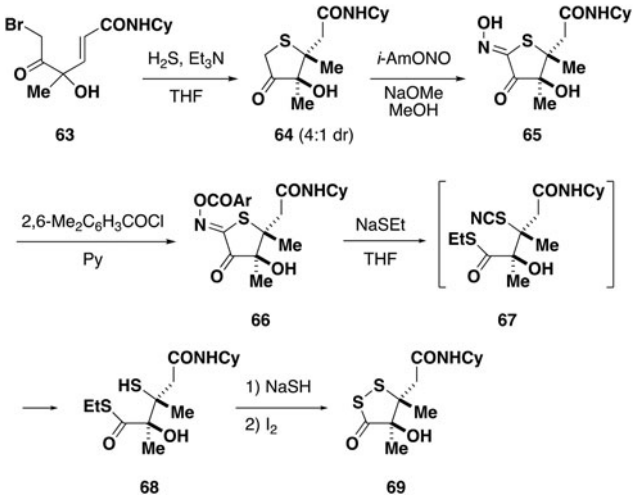
When (+)-β-lactone **42** was treated with commercially available thioisobutyric acid and K_2CO_3 in THF at room



Scheme 13. Attempted intramolecular Michael addition.



Scheme 14. Formation of a five-membered sulfide.



Scheme 15. Successful construction of the dithiolanone structure.

temperature, facile ring opening proceeded to give thioester **43** in 87% yield (Scheme 9). Deprotection of the Boc group with TFA, evaporation, and heating in refluxing benzene afforded the thiazoline **44**. Since thiocarboxylic acid is not a very easy functional group to handle, we opted to convert **44** to thioester **45** using methyl 3-mercapotopropionate and BOP-Cl. The requisite thiocarboxylate could be readily generated from **45** by treatment with *t*-BuOK at 0 °C, to which (–)-*β*-lactone **41** was added to give thioester **46**. Reiteration of the protocol twice led to carboxylic acid **48** via **47**. Since there was no high-yielding procedure available for oxazoles starting from carboxylic acids, oxazole **51** was separately prepared from **42** as shown in Scheme 10.

Condensation of acid **48** and thiol **51**with BOP-Cl gave amide **52** uneventfully which was converted to tantazole B (**14**) in two isolated steps (Scheme 11). As shown in Figure 2, Moore reported the structure of tantazole B as **13**, which, of course, was the one we synthesized first.[4] However, the optical rotation of the synthetic tantazole B was –320° whereas the reported value was –94°. Therefore, we systematically changed the stereochemistry of the methyl groups and found that **14** was identical to the natural product (Scheme 12).[5]

Leinamycin (**53**) is one of the most interesting compounds synthesized in our laboratories (Figure 3). Its unique spirocyclic structure consisting of 1,2-dithiolan-3-one 1-oxide is undoubtedly one of a kind among natural products.

In our model studies, a straightforward construction of the dithiolanone oxide was first attempted by thermolysis of **54**. Unfortunately, no desired product **56** was obtained. We next tried an intramolecular Michael addition of acyldithiolate **58** to form the dithiolanone **59** (Scheme 13). Apparently, elimination of elemental sulfur was much faster than the Michael addition, giving only the uncyclized thiocarboxylic acid. Since a variety of tether-assisted intramolecular Michael addition of sulfur nuclephiles failed, we were compelled to try the formation of a five-membered sulfide (Scheme 14). Gratifyingly, facile formation of a diastereomeric mixture of five-membered sulfide **62** was achieved by treatment of bromoketone, derived from **60**, with Li_2S at room temperature. The next task was to remove one carbon atom from **62** in preparation for construction of the dithiolanone ring. As illustrated in Scheme 15, we solved this problem by means of Beckmann fragmentation. Thus, bromoketone **63** was converted to a 4:1 diastereomeric mixture of cyclic sulfide **64** by treatment with H_2S and Et_3N. The major product proved to be our desired compound on the basis of NOE studies. Transformation of ketone **64** to oxime **65** proceeded uneventfully under conventional conditions. For the critical Beckmann fragmentation, the oxime **65** was activated by esterification with 2,6-dimethylbenzoyl chloride. Upon treatment of **66** with excess NaSEt, the fragmentation occurred smoothly to give the desired thioester **68** by way of thiocyanate **67**. Conversion of thioester **68** to thiocarboxylic acid with NaSH followed by oxidation with iodine afforded the dithiolanone **69**. This protocol was successfully applied to the total synthesis of leinamycin (**53**).[6]

Total synthesis of sulfur-containing natural products imposes a special challenge because of the highly reactive nature of sulfur. We look forward to seeing further development of novel sulfur chemistry in this area.

References

[1] Kishi, Y.; Nakatsuka, S.; Fukuyama, T.; Havel, M. Total Synthesis of Sporidesmin A. *J. Am. Chem. Soc.* **1973**, *95*, 6493–6495. DOI: 10.1021/ja00800a079.

[2] Kishi, Y.; Fukuyama, T.; Nakatsuka, S. New Method for the Synthesis of Epidithiodiketopiperazines. *J. Am. Chem. Soc.* **1973**, *95*, 6490–6491. DOI: 10.1021/ja00800a077.

[3] Kishi, Y.; Fukuyama, T.; Nakatsuka, S. Total Synthesis of Dehydrogliotoxin. *J. Am. Chem. Soc.* **1973**, *95*, 6492. DOI: 10.1021/ja00800a078.

[4] Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. Tantazoles, Unusual Cytotoxic Alkaloids from the Blue-Green Alga Scytonema Mirabile. *J. Am. Chem. Soc.* **1990**, *112*, 8195–8197. DOI: 10.1021/ja00178a070.

[5] Fukuyama, T.; Xu, L. Total Synthesis of (-)-Tantazole B. *J. Am. Chem. Soc.* **1993**, *115*, 8449–8450. DOI: 10.1021/ja00071a065.

[6] Kanda, Y.; Fukuyama, T. Total Synthesis of (+)-Leinamycin. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452. DOI: 10.1021/ja00071a066.