HETEROCYCLES, Vol. 100, No. 9, 2020, pp. 1355 - 1370. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 25th March, 2020, Accepted, 22nd April, 2020, Published online, 27th April, 2020
DOI: 10.3987/REV-20-928

RECENT ADVANCES IN THE TOTAL SYNTHESIS OF CLAVILACTONES

Akihiro Ogura and Ken-ichi Takao*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan.
e-mail: takao@applc.keio.ac.jp

Abstract – Clavilactones are meroterpenoids containing a 10-membered carbocycle fused to an α,β-epoxy-γ-lactone and a hydroquinone or benzoquinone. This review describes the total synthesis of clavilactones achieved by four research groups, focusing on their innovative synthetic strategies.

CONTENTS

1. INTRODUCTION

Clavilactones A (**1**), B (**2**), and C (**3**) were isolated from cultures of the basidiomycetous fungus *Clitocybe clavipes*, whose fruiting body is the edible mushroom *Agaricus clavipes*, and were found to have antifungal and antibacterial activities by Arnone and co-workers in 1994 (Figure 1).[1] These compounds were determined to have meroterpenoid skeletons containing a 10-membered carbocycle fused to an α,β-epoxy-γ-lactone and a hydroquinone or benzoquinone. In 2000, Merlini and co-workers isolated the related compounds clavilactones D and E (**5**) from the same fungus, and the structure of clavilactone D was originally assigned as **4** by NMR studies.[2] Further biological studies identified the clavilactones as epidermal growth factor receptor tyrosine kinase inhibitors.[3] Because of their unique structures and important biological activities, clavilactones have attracted the attention of synthetic chemists, and several

innovative synthetic strategies have been reported. This review summarizes the total synthesis of clavilactones achieved by four research groups, namely, the Barrett, Takao, Li, and Yoshimitsu groups, focusing on their distinctive synthetic strategies. In addition, their studies on the structural revision of clavilactone D are described.

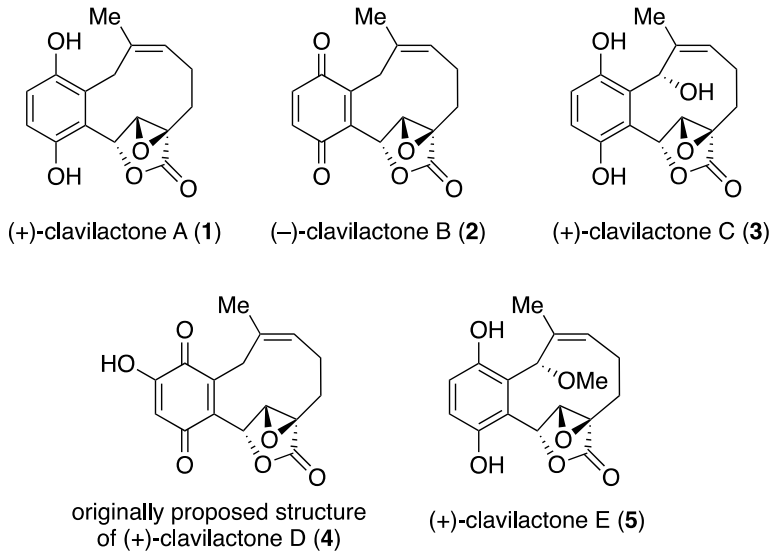
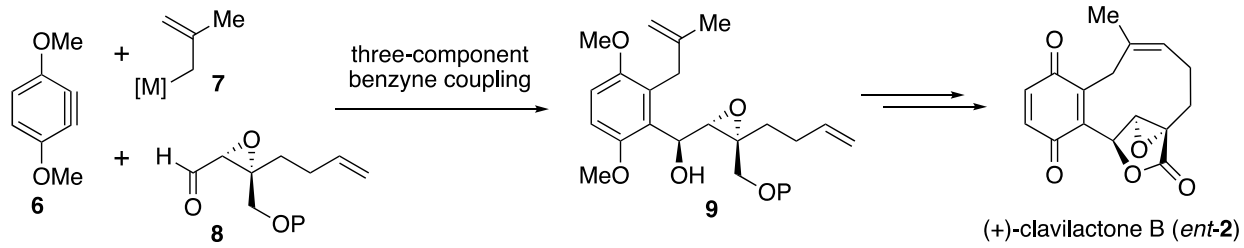


Figure 1. Structures of clavilactones A–E

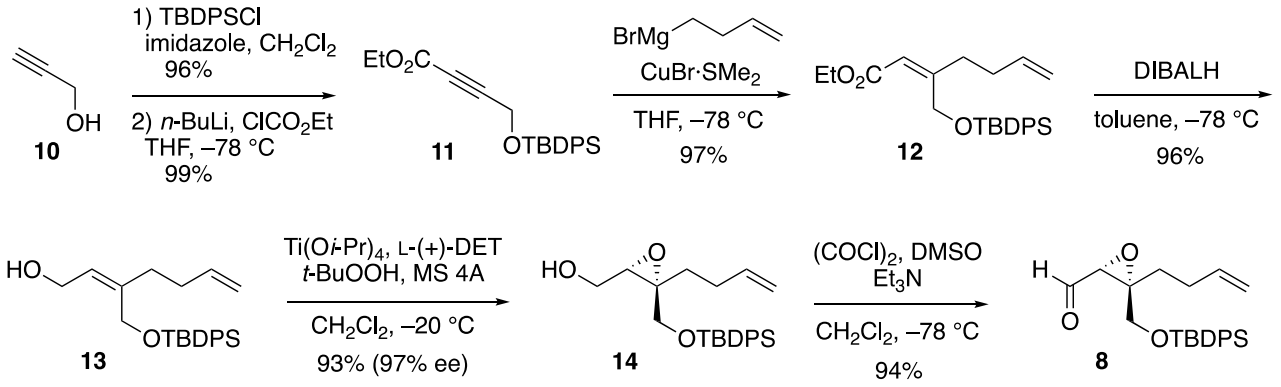
2. BARRETT'S TOTAL SYNTHESIS OF (+)-CLAVILACTONE B

In 2006, Barrett and co-workers used a three-component benzyne coupling reaction to achieve the first total synthesis of (+)-clavilactone B (*ent*-**2**) (Scheme 1).[4] This highly convergent process involved the reaction of benzyne **6** with organometallic reagent **7** and epoxy aldehyde **8** in a one-pot operation to afford the key intermediate **9**, which was successfully converted into *ent*-**2**.[5]



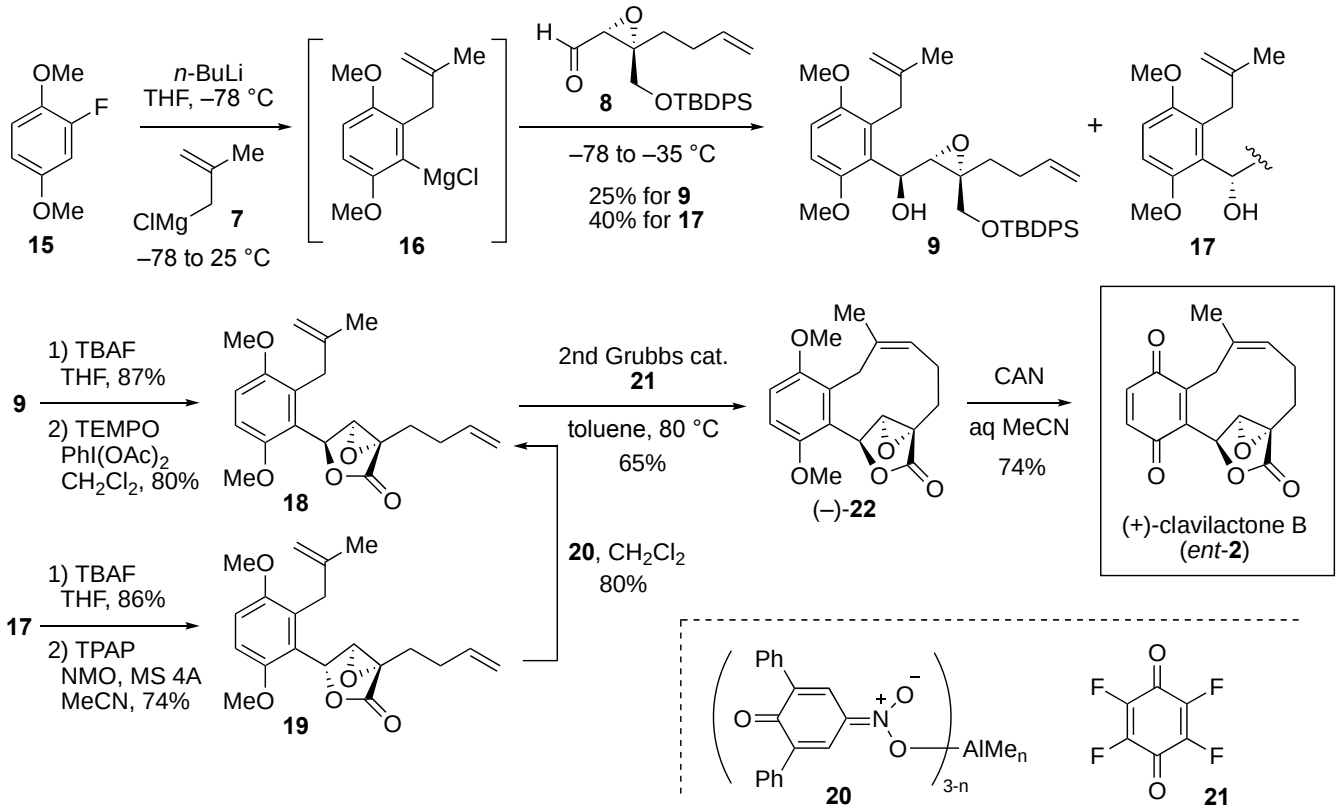
Scheme 1. Three-component benzyne coupling strategy

Barrett's approach started from the synthesis of epoxy aldehyde **8** as a substrate for the key reaction (Scheme 2). Silylation of propargylic alcohol (**10**) followed by *C*-acylation gave propargylic ester **11**. 1,4-Addition of a Grignard reagent to **11** afforded unsaturated ester **12** with high *Z*-selectivity. Reduction of ester **12**, followed by asymmetric Sharpless epoxidation of the resultant allylic alcohol **13**, gave enantio-enriched epoxide **14** (97% ee), which was oxidized to epoxy aldehyde **8**.



Scheme 2. Synthesis of epoxy aldehyde **8**

Fluorobenzene **15** was used as a benzyne precursor (Scheme 3). Treatment of **15** with *n*-BuLi gave the corresponding *o*-fluoroaryllithium, which was allowed to fragment to benzyne. The methallyl Grignard reagent **7** was added to the benzyne to produce the aryl Grignard reagent **16** in situ. Finally, a reaction with epoxy aldehyde **8** gave the two diastereomeric coupling products **9** and **17**. The major product **17** had the undesired stereochemistry of the benzylic hydroxy group. The correct diastereomer **9** was converted into γ-lactone **18** through removal of the silyl group and chemoselective oxidation of the resultant diol. The major product **17** was similarly converted into γ-lactone **19**, which was treated with the bulky aluminum complex **20** to afford **18** in good yield.

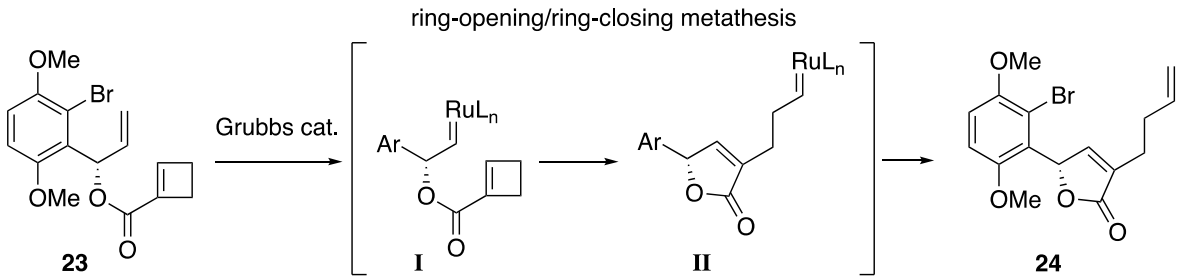


Scheme 3. Total synthesis of (+)-clavilactone B (*ent*-**2**) by Barrett's group

Although attempted isomerization of **19** using $TiCl_n(Oi\text{-}Pr)_{4-n}$ (n = 0–4) or BX_3 (X = Br, F) resulted in decomposition, the novel Lewis acid **20** catalyzed benzylic C–O bond scission. Ring-closing metathesis (RCM) of diene **18** was achieved by using the second-generation Grubbs catalyst and benzoquinone derivative **21** to form a 10-membered carbocycle with a *Z*-configured trisubstituted olefin. Use of benzoquinone derivative **21** prevented isomerization of the terminal olefin in **18**.[6] The resulting product (–)-**22** was treated with ceric ammonium nitrate (CAN) to provide (+)-clavilactone B (*ent*-**2**). This synthesis established the absolute configuration of natural clavilactones.

3. TAKAO'S TOTAL SYNTHESIS OF (+)-CLAVILACTONE A AND (–)-CLAVILACTONE B

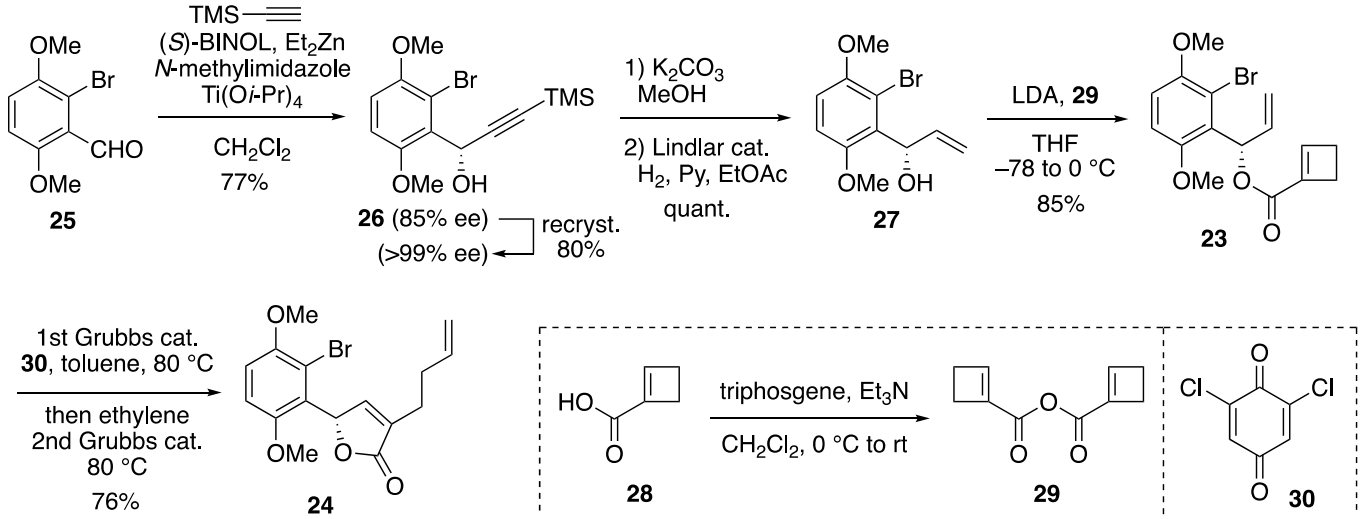
Around the same time as Barrett's total synthesis, the Takao group reported a novel ring-opening/ring-closing metathesis (ROM/RCM) of a cyclobutenecarboxylate to access a γ-butenolide (Scheme 4).[7,8] The *exo*-olefin in substrate **23** reacts with Grubbs catalyst to form ruthenium carbene complex **I**, which is converted to a new complex **II** via a metallacyclobutane intermediate. A second molecule of substrate **23** reacts with complex **II** to produce γ-butenolide **24**. In this transformation, the strained cyclobutene ring is opened and the γ-butenolide ring is newly formed. This approach culminated in the total synthesis of (+)-clavilactone A (**1**) and (–)-clavilactone B (**2**) in 2013.[9]



Scheme 4. Ring-opening/ring-closing metathesis strategy

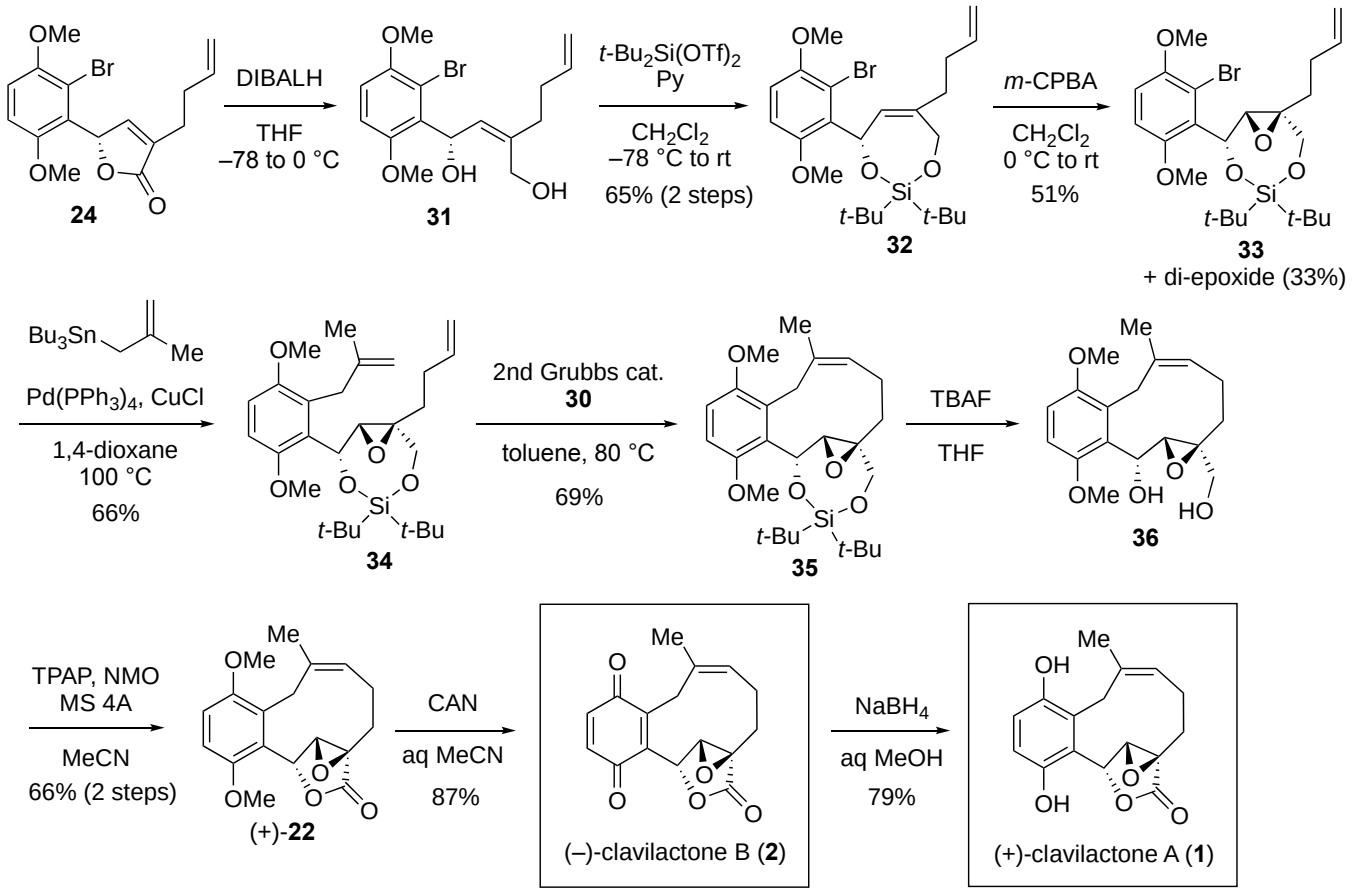
In Takao's synthesis, the initial objective was to prepare optically active allylic alcohol **27** (Scheme 5). To this end, they used You's enantioselective alkynylation.[10] Using You's conditions, the reaction of aldehyde **25** resulted in good yield with high enantioselectivity. Recrystallization provided almost enantiomerically pure alkynylated product **26**. Removal of the silyl group from **26**, followed by Lindlar hydrogenation of the resultant alkyne, gave allylic alcohol **27**. Although cyclobutenecarboxylic acid (**28**) was a known compound,[11] no effective method for synthesizing cyclobutenecarboxylate esters had been established. Acid anhydride **29** was prepared as the acylating reagent from **28** by treatment with triphosgene and Et_3N. Acylation of **27** was achieved by using lithium diisopropylamide (LDA) and **29** to provide cyclobutenecarboxylate **23**. The next stage was ROM/RCM of **23** to access γ-butenolide **24**. Preliminary studies indicated that the reaction gave a significant amount of the dimerized product of **24**,

diminishing the yield of **24**. Therefore, ROM/RCM of **23** was performed using the first-generation Grubbs catalyst and benzoquinone **30**,[6] then the resulting mixture of **24** and its dimerized product was treated with ethylene and the second-generation Grubbs catalyst in a one-pot operation. The dimerized product underwent ethenolysis to provide a high yield of **24**.



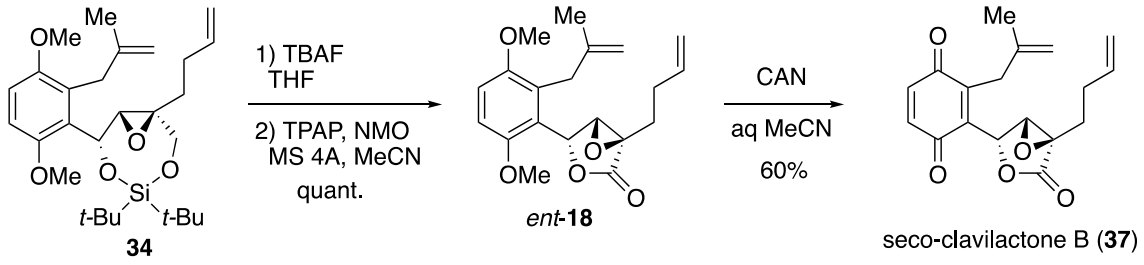
Scheme 5. Synthesis of γ-butenolide **24**

Epoxidation of γ-butenolide **24** was expected to afford an α,β-epoxy-γ-lactone but the corresponding product could not be obtained despite extensive efforts. Therefore, **24** was temporarily reduced to diol **31**, which was protected as silylene acetal **32** (Scheme 6). Treatment of **32** with *m*-chloroperoxybenzoic acid (*m*-CPBA) stereoselectively gave epoxide **33** as a major product. Stille reaction of **33** afforded diene **34**. RCM of **34** constructed the 10-membered carbocycle to provide the cyclized product **35**. Removal of the silylene acetal from **35** gave diol **36**, which was selectively oxidized to γ-lactone (+)-**22**. Oxidation of (+)-**22** with CAN provided (–)-clavilactone B (**2**). Finally, the quinone in **2** was reduced to afford (+)-clavilactone A (**1**). This work demonstrated the utility of the ROM/RCM strategy for the synthesis of γ-lactone natural products. Recently, a ring-opening/ring-closing/cross metathesis reaction of cyclobutenecarboxylates, an extension of the ROM/RCM strategy, was developed to achieve the total syntheses of (+)-aquatolide and related humulanolides by Takao's group.[12] The ROM/RCM strategy has been successfully used by other groups to synthesize γ-butanolide.[13]



Scheme 6. Total synthesis of (+)-clavilactone A (**1**) and (–)-clavilactone B (**2**) by Takao's group

To examine the novel bioactivity of clavilactones, several analogues were synthesized in collaborative research with Simizu's group. Of these analogues, seco-clavilactone B (**37**), prepared from epoxide **34**, was found to be a novel actin polymerization inhibitor (Scheme 7).[14]

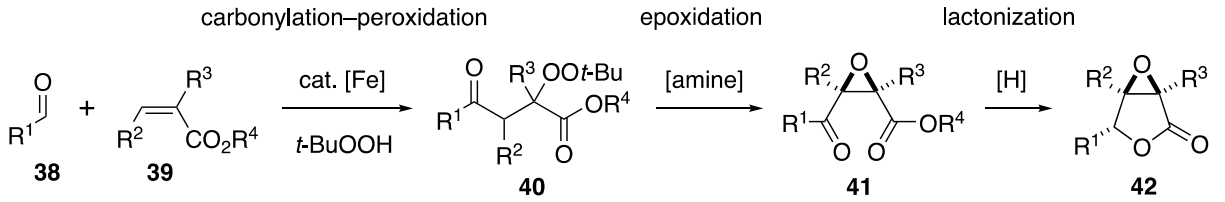


Scheme 7. Synthesis of seco-clavilactone B (**37**)

4. LI'S TOTAL SYNTHESIS OF (±)-CLAVILACTONE A AND (±)-CLAVILACTONE B

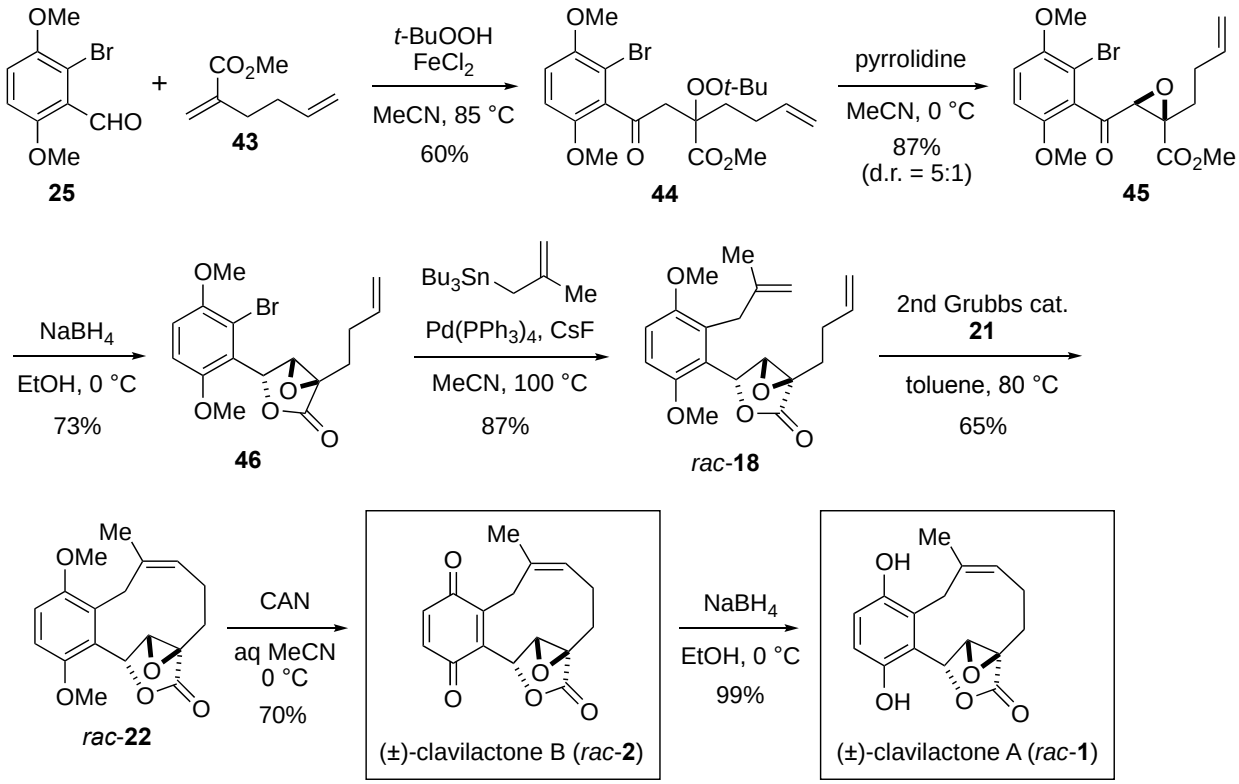
Li's group achieved the total synthesis of (±)-clavilactones A and B (*rac*-**1** and *rac*-**2**) using their unique method for γ-lactone formation.[15] As shown in Scheme 8, this method provides a general and concise way to synthesize α,β-epoxy-γ-lactones **42** through iron-catalyzed carbonylation–peroxidation of olefins **39** with aldehydes **38** and *t*-butyl hydroperoxide. This is followed by base-induced epoxidation of the

resultant α-alkoxycarbonyl-β-keto peroxides **40** and then lactonization by selective reduction of dicarbonyl epoxides **41**.[16]



Scheme 8. Strategy involving carbonylation–peroxidation, followed by epoxidation and lactonization

The synthesis began with $FeCl_2$-catalyzed carbonylation–peroxidation of α,β-unsaturated ester **43** with aryl aldehyde **25** and *t*-BuOOH. The reaction gave α-methoxycarbonyl-β-keto peroxide **44** in good yield. Treatment of **44** with pyrrolidine furnished epoxide **45** as a diastereomeric mixture in a 5:1 ratio. Reduction of **45** with $NaBH_4$ proceeded with high chemo- and stereoselectivity and α,β-epoxy-γ-lactone **46** was obtained as a single diastereomer.



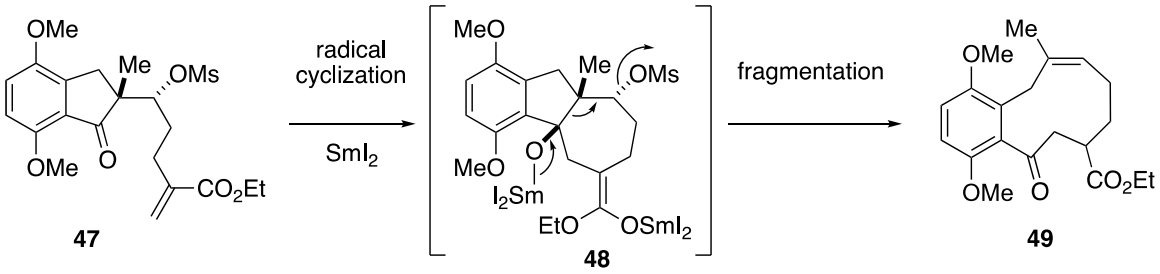
Scheme 9. Total synthesis of (±)-clavilactone A (*rac*-**1**) and (±)-clavilactone B (*rac*-**2**) by Li's group

A methallyl group was introduced onto **46** by Stille coupling to provide the racemate of Barrett's intermediate (*rac*-**18**). By a similar reaction sequence, *rac*-**18** was converted into (±)-clavilactone B

(*rac*-**2**). In addition, (±)-clavilactone A (*rac*-**1**) was also synthesized. The synthesis of the originally proposed structure of (±)-clavilactone D (*rac*-**4**) is described in Section 6.

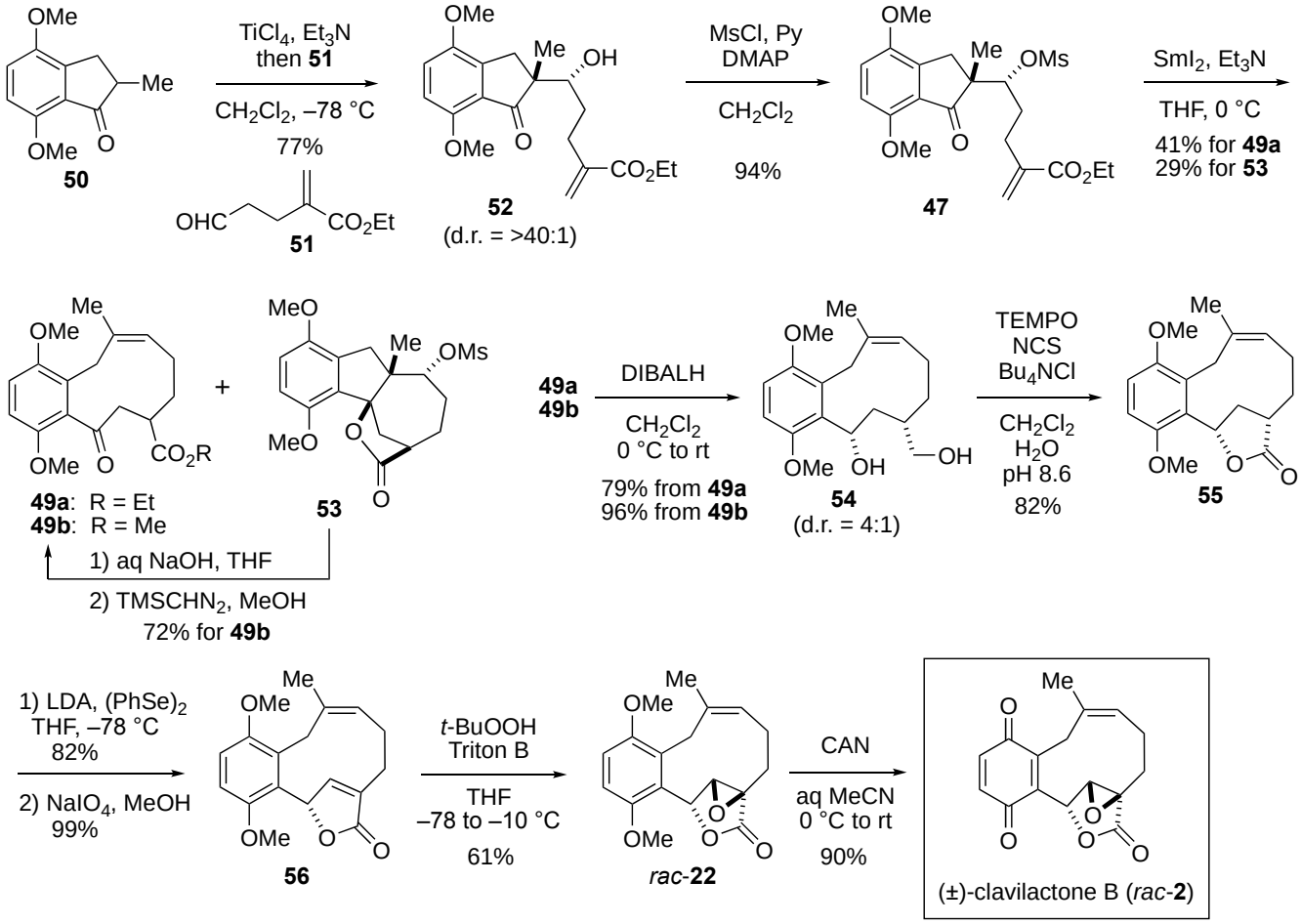
5. YOSHIMITSU'S TOTAL SYNTHESIS OF (±)-CLAVILACTONE B

Yoshimitsu's group established a new route to (±)-clavilactone B (*rac*-**2**) that featured the SmI_2-mediated radical cyclization–fragmentation of indanone derivative **47** (Scheme 10).[17] The ketyl radical generated from **47** attacks the α,β-unsaturated ester moiety to form a 7-membered ring, and the resultant intermediate **48** then undergoes Grob fragmentation to provide 10-membered carbocycle **49** with high *Z*-selectivity.[18]



Scheme 10. Radical cyclization–fragmentation strategy

Fragmentation requires an antiperiplanar relationship between the leaving group and the internal C–C bond to be cleaved. The stereoselective aldol reaction of indanone **50** with aldehyde **51** was investigated for constructing a suitable substrate (Scheme 11). When $TiCl_4$ and Et_3N were used, the reaction gave aldol **52** with excellent diastereoselectivity (d.r. = >40:1). Mesylation of **52** provided substrate **47** for the key reaction. Extensive attempts to optimize the conditions identified a combination of SmI_2 and Et_3N to be effective for the radical cyclization. The optimized reaction gave the desired product **49a**, along with tetracyclic lactone **53** formed from intermediate **48** by protonation and lactonization. Fortunately, subjecting byproduct **53** to hydrolytic fragmentation followed by esterification furnished methyl ester **49b**. The fragmentation products **49a** and **49b** contained a 10-membered carbocycle with a *Z*-trisubstituted olefin. Keto esters **49a** and **49b** were reduced to diol **54** in a diastereomeric ratio of *syn*/*anti* = 4:1. Chemoselective oxidation of diol **54** formed γ-lactone **55**. In this reaction, the minor *anti*-diastereomer of **54** was also transformed into γ-lactone **55** through epimerization of the aldehyde intermediate. Lactone **55** was converted into γ-butenolide **56** through selenylation followed by oxidative elimination. Treatment of γ-butenolide **56** with *t*-BuOOH and Triton B furnished epoxide *rac*-**22** stereoselectively. CAN oxidation of *rac*-**22** completed the total synthesis of (±)-clavilactone B (*rac*-**2**).

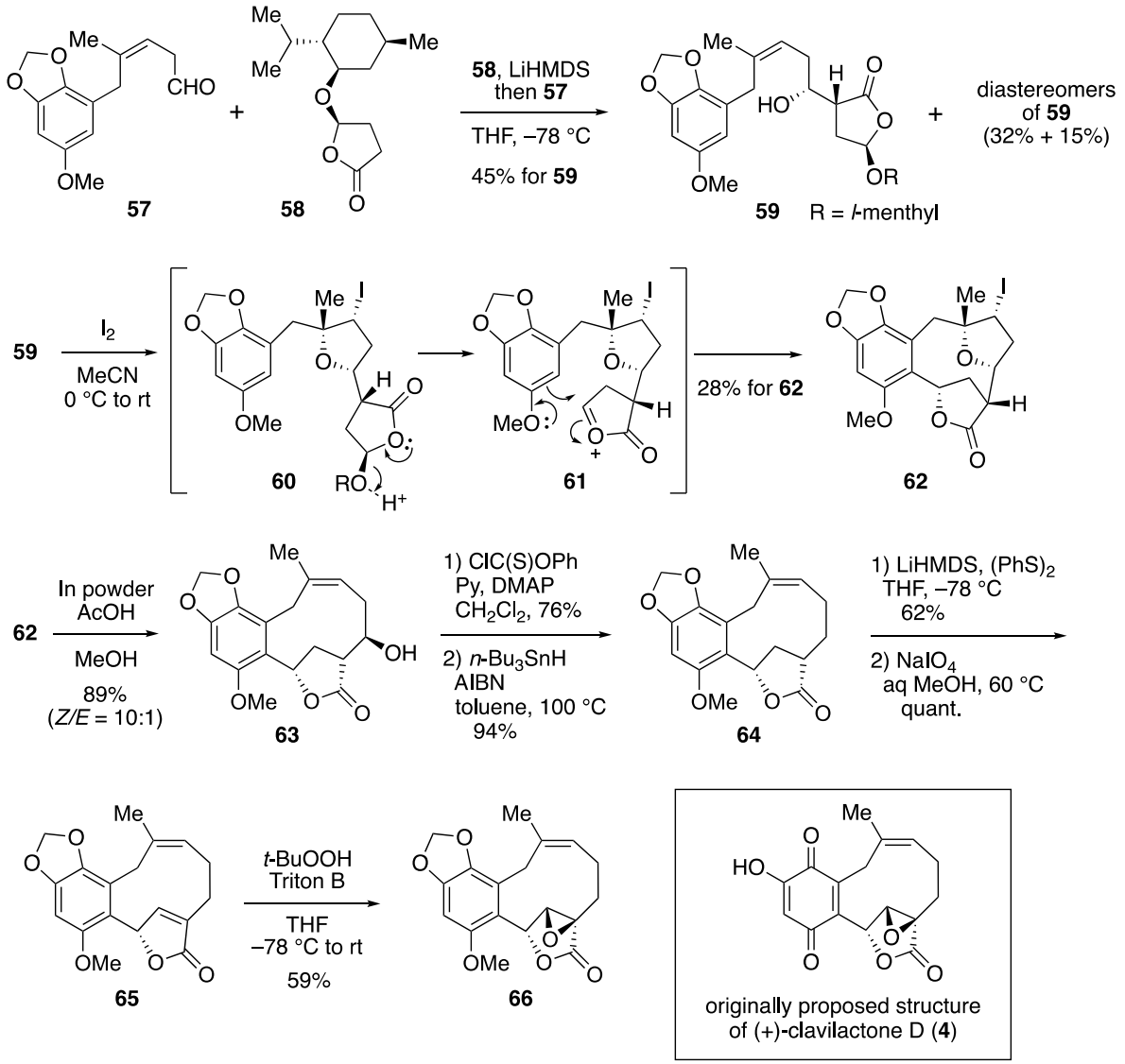


Scheme 11. Total synthesis of (±)-clavilactone B (*rac*-**2**) by Yoshimitsu's group

6. SYNTHESIS AND STRUCTURAL REVISION OF (+)-CLAVILACTONE D

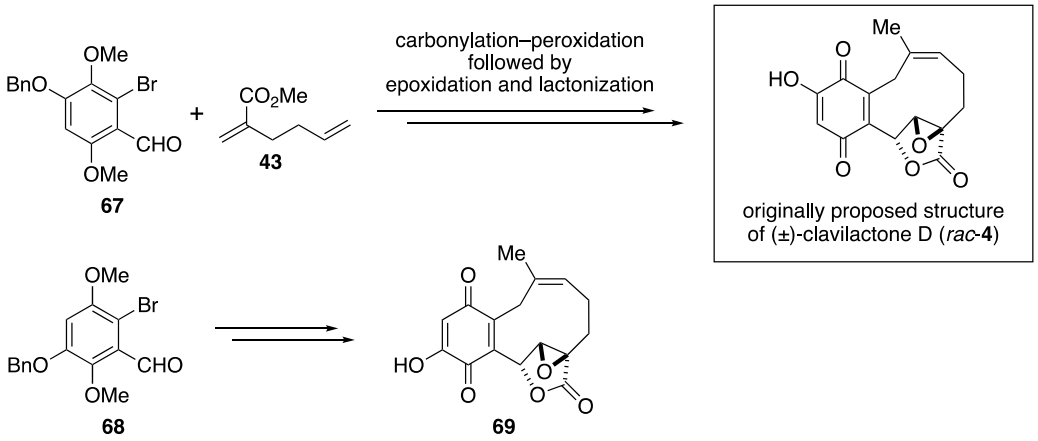
(+)-Clavilactone D exhibited the most potent inhibitory activity against protein tyrosine kinases (IC_{50} = 5.5 μM) among the clavilactones, suggesting its potential as a novel anti-cancer drug.[3] The structure was originally assigned as **4** substituted with a hydroxy group on the quinone ring of (–)-clavilactone B (**2**).[2] The first synthetic study of **4** was reported by Yoshimitsu's group in 2009 (Scheme 12).[19] Their synthesis involved sequential cyclization initiated by iodo etherification followed by Friedel–Crafts-type cyclization; this approach was named the 'lariat' cyclization strategy. The aldol reaction of aldehyde **57** with lactone **58** bearing the menthyl chiral auxiliary provided aldol adducts in a ratio of 3:2:1. Iodo etherification of major aldol adduct **59** led to tetrahydrofuran derivative **60** along with its diastereomers. Next, the menthyloxy group in **60** was eliminated via the protonation with the resultant hydrogen iodide to afford oxocarbenium intermediate **61**, which was captured by the aromatic ring to generate polycyclic product **62**. The diastereomers of **60** did not undergo Friedel–Crafts-type cyclization. Polycyclic compound **62** was subjected to reductive regeneration of the *Z*-olefin, furnishing clavilactone skeleton **63**. β-Elimination of the hydroxy group in **63** was unsuccessful and thus compound **63** was converted into **64** by radical deoxygenation. Thiophenylation of γ-lactone **64** followed by oxidation and elimination

provided γ-butenolide **65**. The epoxidation of **65** occurred chemo- and stereoselectively to provide compound **66**, which constituted the proposed skeleton of (+)-clavilactone D (**4**).



Scheme 12. Synthetic study of the originally proposed structure of (+)-clavilactone D (**4**) by Yoshimitsu's group

In 2014, the Li group synthesized the originally proposed structure of (±)-clavilactone D (*rac*-**4**) starting from aryl aldehyde **67** and α,β-unsaturated ester **43** using their established synthetic strategy (Scheme 13).[15] Surprisingly, the NMR data of synthesized *rac*-**4** did not match those of natural clavilactone D. The position of the hydroxy group was thought to be misassigned and thus regioisomer **69** was also synthesized from compound **68** via a similar route. However, the NMR spectra of **69** were still inconsistent with the original data. The Yoshimitsu group similarly reported an inconsistency in the proposed structure of **4**,[20] conclusively showing that the structure of natural clavilactone D needed revision.



Scheme 13. Synthesis of the originally proposed structure of (±)-clavilactone D (*rac*-**4**) and its regioisomer **69** by Li's group

Finally, the structure of clavilactone D was revised by the Takao group in 2017.[21] They compared the NMR data of natural clavilactone D with those of Li's synthetic samples *rac*-**4** and **69**. As shown in Figure 2, the signal peak of H-3 or H-2 in the spectra of *rac*-**4** and **69** appeared downfield to the corresponding peak of the natural product. A similar difference was observed in the ^{13}C NMR spectra. These findings indicated that clavilactone D has a stronger electron-donating group than a hydroxy group. In addition, the molecular weight of clavilactone D was in doubt. In the paper reporting the isolation of clavilactone D, the molecular ion was recorded as *m/z* 302 for M^+ by chemical ionization (CI).[2] Since the molecular ion in CI is usually observed as $[M+H]^+$, the correct molecular weight was estimated to be 301. Therefore, the Takao group proposed the revised structures **70** and **71**, containing an amino group on the quinone ring. To confirm the structural revision, total syntheses of **70** and **71** were conducted.

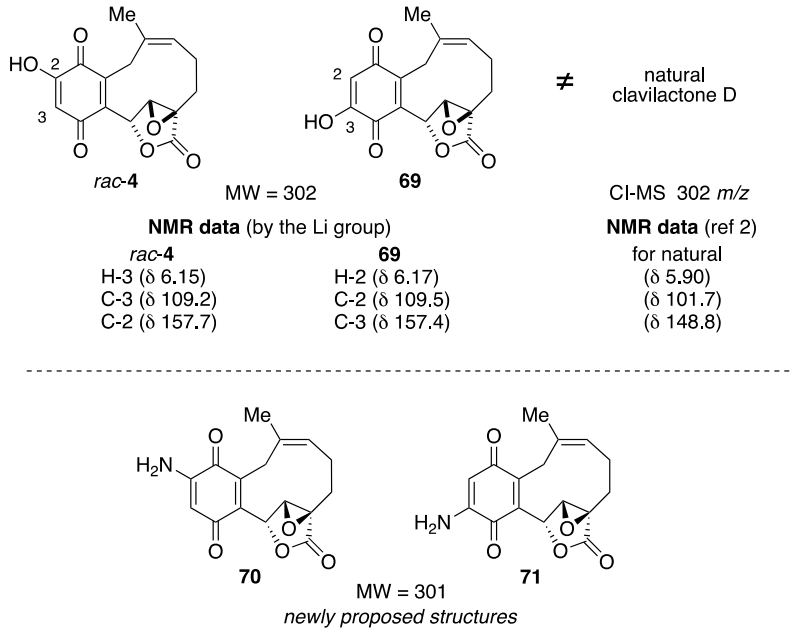
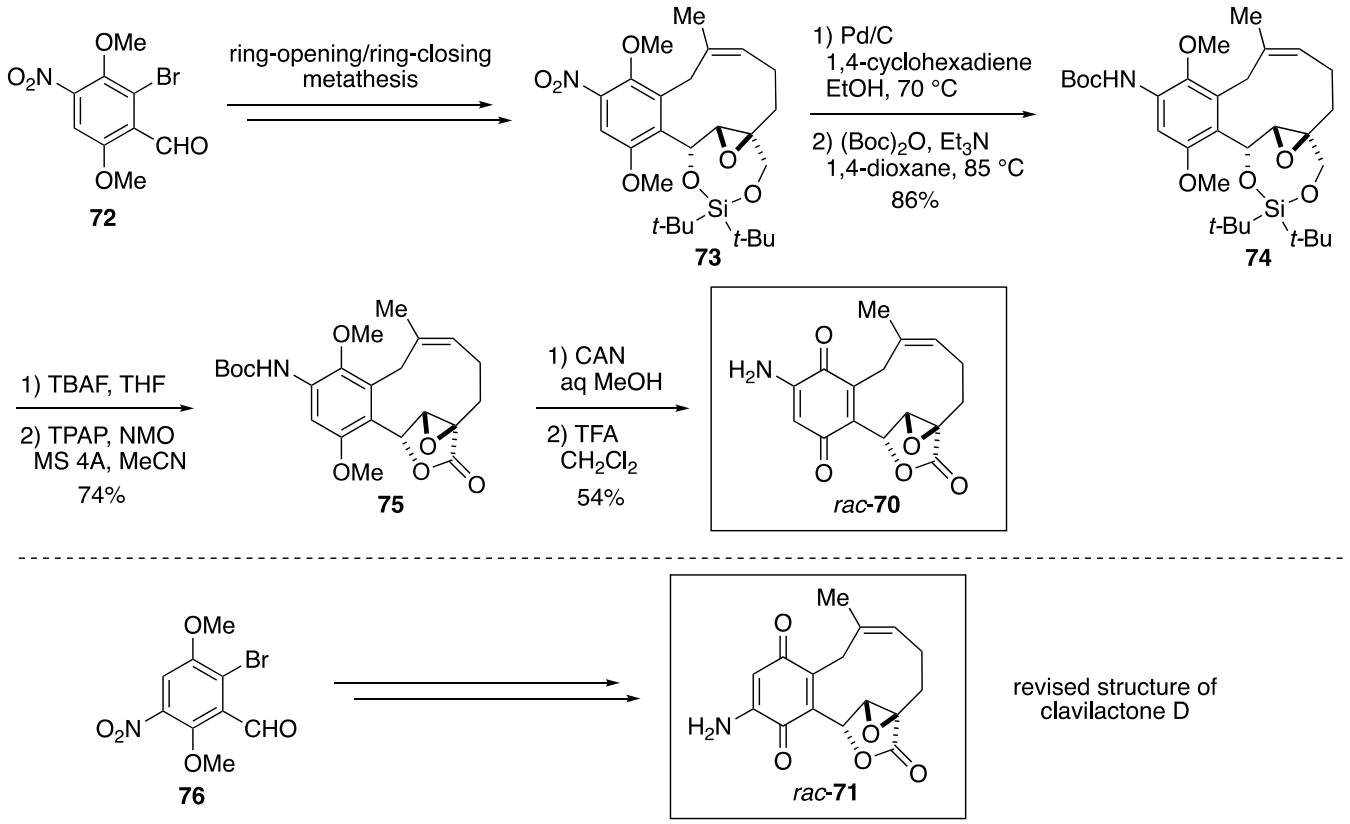


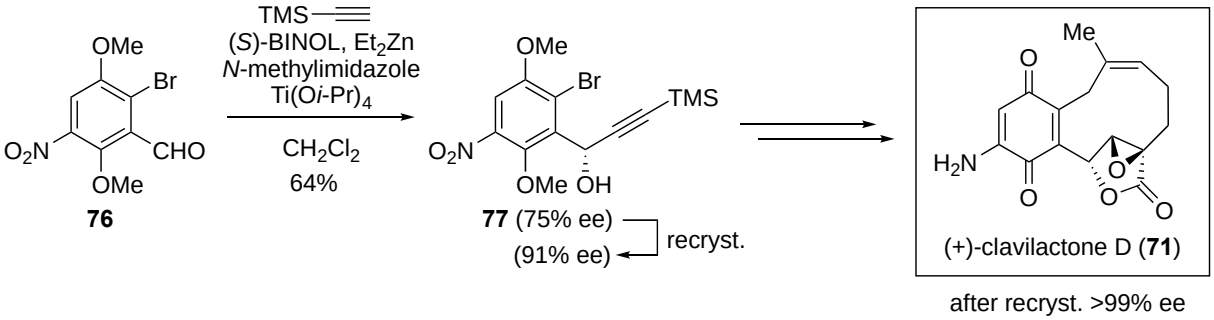
Figure 2. Original structure and proposed structural revisions of clavilactone D

Penta-substituted benzene **72** was used as the starting material for the synthesis of **70** (Scheme 14). A nitro group was used as a precursor of the amino group. Through ROM/RCM, compound **72** was converted into **73** as a racemic mixture. The nitro group in **73** was chemoselectively reduced under transfer hydrogenation conditions, and the resulting amine was protected as *t*-butyl carbamate **74**. Reconstruction of the γ-lactone provided **75**. Treating dimethyl ether **75** with CAN, followed by removal of the Boc group, provided the target molecule *rac*-**70**. However, the NMR data for *rac*-**70** disagreed with the published natural product data whereas the NMR data of regioisomer *rac*-**71**, synthesized similarly from **76**, matched those of the natural product. Consequently, the true structure of clavilactone D was revised to **71**, with an amino group at C-3 instead of a hydroxy group at C-2 in the originally proposed structure **4**. Shortly afterwards, the Li group reached the same conclusion by synthesizing *rac*-**71** using their strategy.[22]



Scheme 14. Synthesis and structural revision of clavilactone D by Takao's group

Furthermore, the Takao group accomplished the asymmetric synthesis of natural (+)-clavilactone D (**71**) using You's enantioselective alkynylation strategy (Scheme 15).[23] Alkynylated product **77** was obtained in moderate enantiomeric excess, but this was improved by recrystallization. (+)-Clavilactone D (**71**) was finally synthesized in an almost enantiomerically pure form and the absolute stereochemistry of **71** was confirmed.



Scheme 15. Total synthesis of (+)-clavilactone D (**71**) by Takao's group

Subsequently, several new clavilactones were isolated from *Clitocybe clavipes* and some showed antiproliferative activity against human cancer cell lines (Figure 3).[24] Notably, clavilactone F was assigned the structure of **70**, previously synthesized by Takao's group, meaning that the total synthesis of clavilactone F had already been completed.

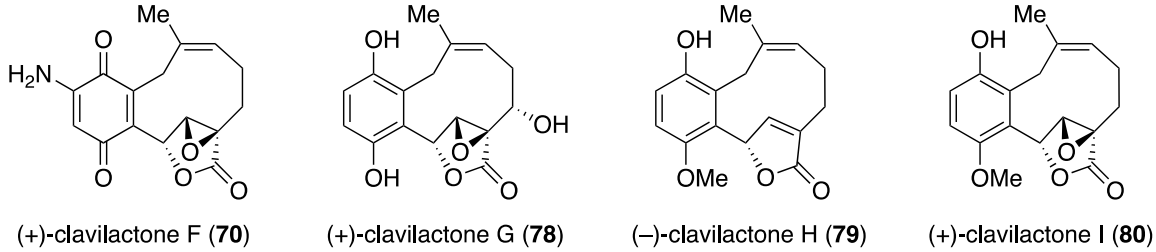


Figure 3. Structures of clavilactones F–I

7. CONCLUSION

Four research groups have achieved the total synthesis of clavilactones using distinctive synthetic strategies. The Barrett group succeeded in the first total synthesis of (+)-clavilactone B (*ent*-**2**) through a three-component benzyne coupling strategy, establishing the absolute configuration of natural clavilactones. The Takao group developed an ROM/RCM strategy using a cyclobutenecarboxylate to accomplish the total synthesis of (+)-clavilactone A (**1**) and (–)-clavilactone B (**2**). Subsequently, the Li group achieved the total synthesis of (±)-clavilactones A and B (*rac*-**1** and *rac*-**2**) using carbonylation–peroxidation followed by epoxidation and lactonization. The Yoshimitsu group established a new route featuring a SmI_2-mediated radical cyclization–fragmentation to access (±)-clavilactone B (*rac*-**2**). In addition, a synthetic study of the originally proposed structure of (+)-clavilactone D (**4**) was reported by Yoshimitsu's group. The total synthesis of *rac*-**4** was achieved by Li's group. Finally, synthesis and structural revision of (+)-clavilactone D (**71**) was achieved by Takao's group. Clavilactones are synthetically challenging and have fostered the development of a variety of valuable methodologies.

Despite the considerable recent advances described in this review, we anticipate new synthetic strategies for clavilactones using unprecedented methods in the near future.

ACKNOWLEDGEMENTS

We thank Professor Kin-ichi Tadano (Itsuu Laboratory) for helpful discussions and comments.

REFERENCES

1. A. Arnone, R. Cardillo, S. V. Meille, G. Nasini, and M. Tolazzi, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2165.
2. L. Merlini, G. Nasini, L. Scaglioni, G. Cassinelli, and C. Lanzi, *Phytochemistry*, 2000, **53**, 1039.
3. G. Cassinelli, C. Lanzi, T. Pensa, R. A. Gambetta, G. Nasini, G. Cuccuru, M. Cassinis, G. Pratesi, D. Polizzi, M. Tortoreto, and F. Zunino, *Biochem. Pharmacol.*, 2000, **59**, 1539.
4. I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, and A. G. M. Barrett, *J. Am. Chem. Soc.*, 2006, **128**, 14042.
5. For examples of related three-component benzyne coupling, see: P. D. Pansegrau, W. F. Rieker, and A. I. Meyers, *J. Am. Chem. Soc.*, 1988, **110**, 7178; H. Tomori, J. M. Fox, and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 5334; H. Yoshida, H. Fukushima, J. Ohshita, and A. Kunai, *Angew. Chem. Int. Ed.*, 2004, **43**, 3935.
6. S. H. Hong, D. P. Sanders, C. W. Lee, and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 17160.
7. H. Yasui, S. Yamamoto, K. Takao, and K. Tadano, *Heterocycles*, 2006, **70**, 135.
8. As another example of metathesis of cyclobutenecarboxylate, the synthesis of copolymers of cyclobutenecarboxylates and cyclohexenes by alternating ROM polymerization has been reported: A. Song, K. A. Parker, and N. S. Sampson, *J. Am. Chem. Soc.*, 2009, **131**, 3444; A. Song, J. C. Lee, K. A. Parker, and N. S. Sampson, *J. Am. Chem. Soc.*, 2010, **132**, 10513; A. Song, K. A. Parker, and N. S. Sampson, *Org. Lett.*, 2010, **12**, 3729. For examples of ROM/RCM using cyclobutenes, see: W. J. Zuercher, M. Hashimoto, and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, **118**, 6634; K. C. Nicolaou, J. A. Vega, and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2001, **40**, 4441; M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura, and Y. Sato, *J. Org. Chem.*, 2005, **70**, 1066.
9. K. Takao, R. Nanamiya, Y. Fukushima, A. Namba, K. Yoshida, and K. Tadano, *Org. Lett.*, 2013, **15**, 5582.
10. F. Yang, P. Xi, L. Yang, J. Lan, R. Xie, and J. You, *J. Org. Chem.*, 2007, **72**, 5457.
11. A. Campbell and H. N. Rydon, *J. Chem. Soc.*, 1953, 3002; W. G. Dauben and J. R. Wiseman, *J. Am. Chem. Soc.*, 1967, **89**, 3545.
12. K. Takao, H. Kai, A. Yamada, Y. Fukushima, D. Komatsu, A. Ogura, and K. Yoshida, *Angew. Chem. Int. Ed.*, 2019, **58**, 9851.

13. J. Xiang, Y. Ding, J. Li, X. Zhao, Y. Sun, D. Wang, L. Wang, and Y. Chen., *Angew. Chem. Int. Ed.*, 2019, **58**, 10587; J. Xiang, X. Zhao, J. Li, Y. Ding, C. Wang, L. Wang, and Y. Chen., *Org. Lett.*, 2019, **21**, 6485; M. B. Halle and R. A. Fernandes, *RSC Adv.*, 2014, **4**, 63342.
14. S. Miyazaki, Y. Sasazawa, T. Mogi, T. Suzuki, K. Yoshida, N. Dohmae, K. Takao, and S. Simizu, *FEBS Lett.*, 2016, **590**, 1163.
15. L. Lv, B. Shen, and Z. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 4164.
16. K. Liu, Y. Li, W. Liu, X. Zheng, Z. Zong, and Z. Li, *Chem. Asian J.*, 2013, **8**, 359; K. Liu, Y. Li, X. Zheng, W. Liu, and Z. Li, *Tetrahedron*, 2012, **68**, 10333; W. Liu, Y. Li, K. Liu, and Z. Li, *J. Am. Chem. Soc.*, 2011, **133**, 10756.
17. H. Suizu, D. Shigeoka, H. Aoyama, and T. Yoshimitsu, *Org. Lett.*, 2015, **17**, 126.
18. For example of related radical cyclization–fragmentation, see: G. A. Molander, Y. Le Huérou, and G. A. Brown, *J. Org. Chem.*, 2001, **66**, 4511.
19. T. Yoshimitsu, S. Nojima, M. Hashimoto, K. Tsukamoto, and T. Tanaka, *Synthesis*, 2009, 2963.
20. T. Yoshimitsu, S. Nojima, M. Hashimoto, and T. Tanaka, *Proceedings of the 35th Symposium on Progress in Organic Reactions and Syntheses*, Kanazawa, Japan, Nov 16–17, 2009.
21. K. Takao, R. Nemoto, K. Mori, A. Namba, K. Yoshida, and A. Ogura, *Chem. Eur. J.*, 2017, **23**, 3828.
22. L. Lv, B. B. Snider, and Z. Li, *J. Org. Chem.*, 2017, **82**, 5487.
23. K. Takao, K. Mori, K. Kasuga, R. Nanamiya, A. Namba, Y. Fukushima, R. Nemoto, T. Mogi, H. Yasui, A. Ogura, K. Yoshida, and K. Tadano, *J. Org. Chem.*, 2018, **83**, 7060.
24. Z. Sun, N. Zhu, M. Zhou, X. Huo, H. Wu, Y. Tian, J. Yang, G. Ma, Y.-L. Yang, and X. Xu, *Org. Chem. Front.*, 2019, **6**, 3759; Z. Sun, X. Xu, H. Liang, X. Xia, G. Ma, and L. Shi, *Molecules*, 2019, **24**, 4015.

Akihiro Ogura was born in Tokyo, Japan in 1985. He received his Ph.D. in 2013 from University of Tokyo under the guidance of Professor Tohru Fukuyama. He then moved to RIKEN to conduct postdoctoral research with Professor Katsunori Tanaka. In 2016 he joined the Takao Group at Keio University as a research associate. His research interests are directed toward the development of novel catalytic reactions and the total synthesis of structurally interesting natural products.

Ken-ichi Takao was born in Tokyo, Japan in 1967. He received his Ph.D. in 1995 from Keio University under the direction of Professor Kin-ichi Tadano. He worked at Sagami Chemical Research Center for one year, and then from 1996 to 1998, he was employed at Tokyo University of Science (Professor Susumu Kobayashi) as an instructor. In 1998 he moved to Keio University, where he is now a professor. In the meantime, he worked with Professor William R. Roush as a visiting researcher at Scripps Florida (2005–2006). His research interests are focused on the total synthesis of biologically and structurally interesting natural products and the development of stereoselective synthetic organic reactions.