ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Total Synthesis of (+)-Clavilactone A and (−)-Clavilactone B by Ring-Opening/Ring-Closing Metathesis

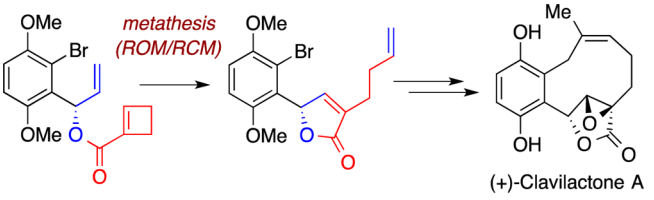
Ken-ichi Takao,* Ryuki Nanamiya, Yuuki Fukushima, Ayumi Namba, Keisuke Yoshida, and Kin-ichi Tadano

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

takao@applc.keio.ac.jp

Received September 26, 2013

ABSTRACT



The enantioselective total synthesis of natural enantiomers of clavilactones A and B has been achieved. A key feature of the synthesis is the use of a ring-opening/ring-closing metathesis, which allows the one-pot transformation of a strained cyclobutenecarboxylate into a γ-butenolide.

Clavilactones A **1**, B **2**, and C were originally isolated from cultures of the fungus *Clitocybe clavipes* as antifungal and antibacterial compounds by Arnone and co-workers in 1994 (Figure 1).[1] Their structures and relative configurations were determined by NMR studies and single-crystal X-ray diffraction analysis of the dimethyl ether derivative of **1**. The clavilactones contain a conformationally rigid 10-membered carbocycle connected to a hydroquinone or benzoquinone and an α,β-epoxy-γ-lactone. Later, clavilactones D **3** and E were also isolated from the same fungus by using different culture conditions.[2] Clavilactones A **1**, B **2**, and D **3** show potent inhibitory activity against epidermal growth factor receptor tyrosine kinases.[3] These findings indicate that the clavilactones represent a novel class of tyrosine kinase inhibitor. Because they show promise as lead compounds for antitumor agents, the clavilactones have attracted attention from synthetic chemists.[4,5] In 2006, Barrett and co-workers reported an elegant total synthesis of (+)-clavilactone B (the antipode of **2**), thereby establishing the absolute configuration of natural clavilactone.[6] Here we describe the first total synthesis of the natural enantiomers of clavilactones A **1** and B **2** by a conceptually novel method that relies on ring-opening/ring-closing metathesis (ROM/RCM).

Olefin metathesis is a powerful synthetic tool in modern organic chemistry.[7] Recently, new methods have been developed by combining several metathesis steps into a domino process. For example, ring-rearrangement metathesis is a highly efficient method for forming carbocycles and heterocycles.[8] A representative ring-rearrangement metathesis reaction is ROM/RCM, which involves intramolecular

(1) Arnone, A.; Cardillo, R.; Meille, S. V.; Nasini, G.; Tolazzi, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2165–2168.
(2) Merlini, L.; Nasini, G.; Scaglioni, L.; Cassinelli, G.; Lanzi, C. *Phytochemistry* **2000**, *53*, 1039–1041.
(3) Cassinelli, G.; Lanzi, C.; Pensa, T.; Gambetta, R. A.; Nasini, G.; Cuccuru, G.; Cassinis, M.; Pratesi, G.; Polizzi, D.; Tortoreto, M.; Zunino, F. *Biochem. Pharmacol.* **2000**, *59*, 1539–1547.
(4) Yasui, H.; Yamamoto, S.; Takao, K.; Tadano, K. *Heterocycles* **2006**, *70*, 135–141.
(5) Yoshimitsu, T.; Nojima, S.; Hashimoto, M.; Tsukamoto, K.; Tanaka, T. *Synthesis* **2009**, 2963–2969.
(6) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042–14043.
(7) For recent reviews on the synthetic application of metathesis, see: (a) Grubbs, R. H.; Wenzel, A. G.; Chatterjee, A. K. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M., Crabtree, R. H., Eds.; Elsevier: Amsterdam, 2007; Vol. 11, pp 179−205. (b) Mulzer, J.; Ohler, E.; Gaich, T. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M., Crabtree, R. H., Eds.; Elsevier: Amsterdam, 2007; Vol. 11, pp 207−269. (c) Mori, M.; Kitamura, T. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M., Crabtree, R. H., Eds.; Elsevier: Amsterdam, 2007; Vol. 11, pp 271−310. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (e) Takao, K.; Tadano, K. *Heterocycles* **2010**, *81*, 1603–1629.
(8) For a review on ring-rearrangement metathesis, see: Holub, N.; Blechert, S. *Chem.—Asian J.* **2007**, *2*, 1064–1082.

10.1021/ol4027842

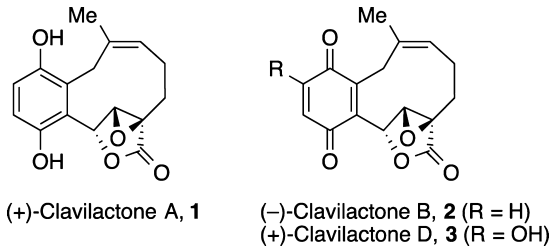
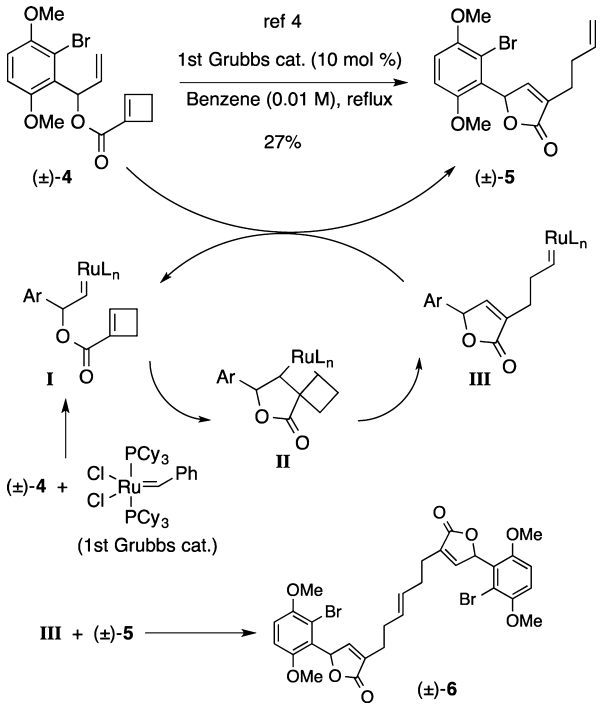


Figure 1. Structures of clavilactones A **1**, B **2**, and D **3**.

Scheme 1. ROM/RCM of Cyclobutenecarboxylate (±)-**4**

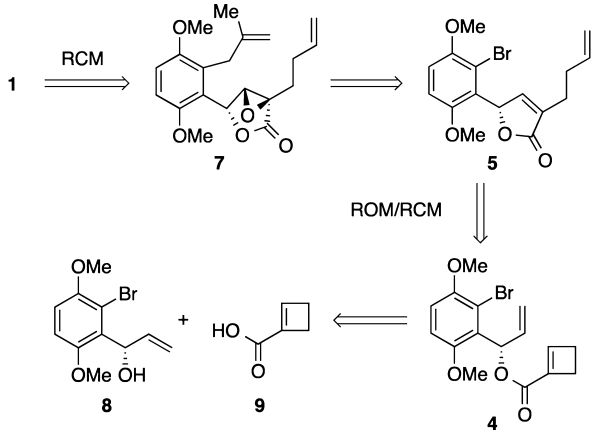


metathesis reactions of alkenyl-substituted carbocyclic alkenes. These one-pot reactions allow the rapid transformation of strained carbocyclic alkenes into new carbocycles or heterocycles, resulting in a rearranged ring system in the product. Previously, we reported the ROM/RCM of cyclobutenecarboxylate derivatives as a novel method for concise access to γ-butenolides (Scheme 1).[4,9] The exoalkene in substrate (±)-**4** is thought to react first with the Grubbs catalyst to form ruthenium carbene complex **I**, which is converted to complex **III** via metallacyclobutane **II**. In this transformation, the cyclobutene ring is opened and the new γ-butenolide ring is formed concomitantly. Another molecule of substrate (±)-**4** reacts with complex **III** to produce γ-butenolide (±)-**5** and complex **I**, which undergoes the second catalytic cycle. However, product (±)-**5** was obtained in low yield under these conditions, because complex **III** also reacts with the terminal alkene in (±)-**5** which produces a significant amount of the dimerized product ((±)-**6**). We have now greatly improved the reaction conditions for the synthesis of **5** and applied this method to the total synthesis of the clavilactones.

Our retrosynthetic analysis of (+)-clavilactone A **1** is shown in Scheme 2. We envisioned the formation of the 10-membered carbocycle by RCM of diene **7**. The preparation of **7** would be achieved by epoxidation and a cross-coupling reaction from γ-butenolide **5**. We intended to construct the γ-butenolide by ROM/RCM of cyclobutenecarboxylate **4**. Substrate **4** for ROM/RCM would be obtained by condensation of allylic alcohol **8** and cyclobutenecarboxylic acid (**9**). Acid **9** is a known compound that can be easily prepared from commercially available cyclobutanecarboxylic acid according to a literature procedure.[10]

At the outset, we investigated the asymmetric synthesis of allylic alcohol **8**, using the enantioselective alkynylation (Scheme 3). The substrate for alkynylation, aldehyde **11**,

Scheme 2. Retrosynthetic Analysis of (+)-Clavilactone A **1**



was prepared from 2-bromo-3,6-dihydroxybenzaldehyde (**10**)[11] by dimethyl etherification.[12] Several enantioselective alkynylations of 2,6-disubstituted benzaldehydes have been reported,[13] and the reaction of **11** with trimethylsilylacetylene under You's conditions (BINOL/Et_2Zn/*N*-methylimidazole/$Ti(OiPr)_4$)[14] resulted in a good yield and enantioselectivity

(9) As another example of metathesis of cyclobutenecarboxylate, the synthesis of copolymers of cyclobutenecarboxylates and cyclohexenes by alternating ROM polymerization has been reported: Song, A.; Parker, K. A.; Sampson, N. S. *J. Am. Chem. Soc.* **2009**, *131*, 3444–3445.

(10) (a) Campbell, A.; Rydon, H. N. *J. Chem. Soc.* **1953**, 3002–3008. (b) Dauben, W. G.; Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 3545–3549.

(11) Compound **10** was prepared from commercially available 2,5-dihydroxybenzaldehyde by regioselective bromination: Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649–1652.

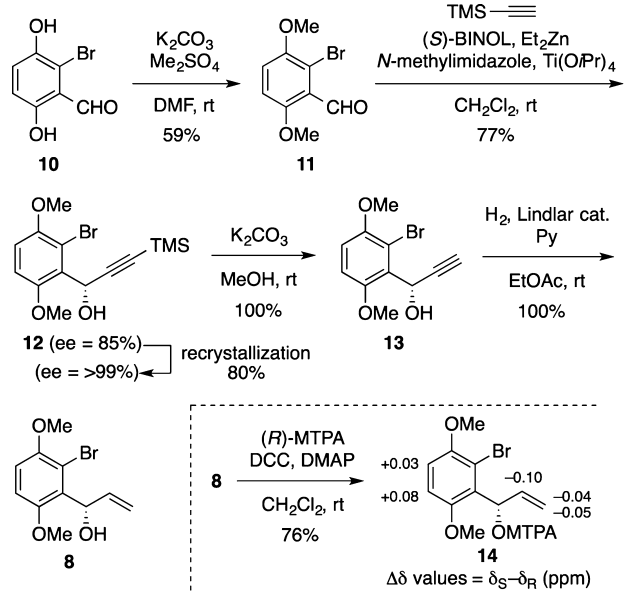
(12) For another synthesis of compound **11** from 2,5-dimethoxybenzaldehyde in three steps, see: Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484–10485.

(13) (a) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427–7430. (b) Qin, Y.-C.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335–9348. (c) Trost, B. M.; Weiss, A. H.; Jacobi von Wangelin, A. *J. Am. Chem. Soc.* **2006**, *128*, 8–9.

(14) Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 5457–5460.

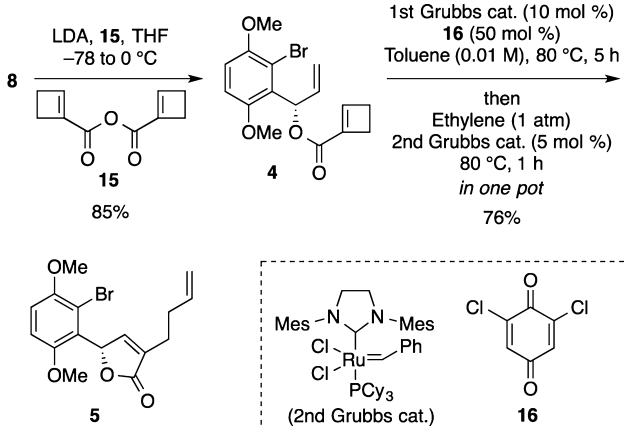
(77%, ee = 85%).[15] After recrystallization, almost enantiomerically pure alkynylated product **12** was obtained (ee = >99%). Removal of the trimethylsilyl group from **12** and subsequent Lindlar hydrogenation of the resulting alkyne **13** provided allylic alcohol **8**. The absolute configuration of **8** was determined from the $\Delta\delta$ values of the α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester **14** derived from **8** in their ^{1}H NMR spectra.[16]

Scheme 3. Synthesis of Allylic Alcohol **8**



Treatment of alcohol **8** with LDA and acid anhydride **15**, prepared from acid **9** with triphosgene,[17] gave cyclobutenecarboxylate **4** (Scheme 4). Preliminary studies of the ROM/RCM of **4** indicated that a large amount of dimerized side product **6** was formed as shown in Scheme 1. To suppress the dimerization, ROM/RCM of **4** was performed at a much lower concentration (0.001 M) using the first-generation Grubbs catalyst.[18] However, the yield of γ-butenolide **5** was only 28% and dimer **6** was still obtained in significant yield. The second-generation Grubbs catalyst or Hoveyda–Grubbs catalyst also gave unsatisfactory results. However, the one-pot ROM/RCM of **4** in toluene (0.01 M) using the first-generation Grubbs catalyst (10 mol %), followed by treatment of the resulting mixture with ethylene (1 atm) and the second-generation Grubbs catalyst (5 mol %), produced the desired product **5** in good yield (76%). The treatment with ethylene led to ethenolysis of dimer **6** to product **5**. Furthermore, the slow addition of the first-generation Grubbs catalyst improved the conversion rate, and the addition of benzoquinone **16**[19] prevented isomerization of the terminal alkene in **5**.

Scheme 4. Synthesis of γ-Butenolide **5**



Having established the method for constructing the γ-butenolide, we turned our attention to forming the epoxide. However, despite extensive efforts, the corresponding α,β-epoxy-γ-lactone could not be obtained from γ-butenolide **5**.[20] To circumvent this problem, γ-butenolide **5** was temporarily reduced with excess DIBALH to diol **17**, which was somewhat unstable, and immediately protected as silylene acetal **18** (Scheme 5).[21] The epoxidation of **18** with *m*-CPBA proceeded chemo- and stereoselectively, giving epoxide **19** as the major product.

With epoxide **19** in hand, we next focused on constructing the 10-membered carbocycle. Stille coupling of **19** and allylstannane **20**[22] using CuCl as a promoter provided diene **21**.[23] RCM of diene **21** using the second-generation Grubbs catalyst (20 mol %) initially produced the dimer, which was slowly converted into cyclized product **22**.[24] In this reaction, it was necessary to prolong the reaction time

(15) The ee of **12** was determined by chiral HPLC analysis.

(16) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Kusumi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 462–470.

(17) Kocz, R.; Roestamadji, J.; Mobashery, S. *J. Org. Chem.* **1994**, *59*, 2913–2914.

(18) Lesma, G.; Crippa, S.; Danieli, B.; Passarella, D.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron* **2004**, *60*, 6437–6442.

(19) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

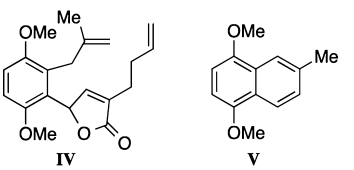
(20) There have been few successful examples of epoxidation of γ-aryl-γ-butenolides: Jakubowski, A. A.; Guziec, F. S., Jr.; Sugiura, M.; Tam, C. C.; Tishler, M.; Omura, S. *J. Org. Chem.* **1982**, *47*, 1221–1228. See also ref 5.

(21) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871–4874.

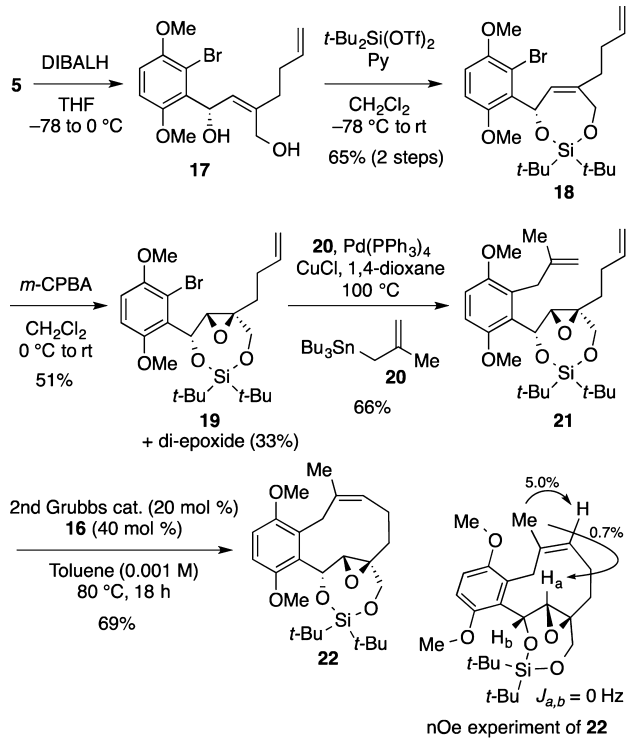
(22) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Org. Synth.* **1993**, *71*, 118–122.

(23) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.

(24) In our preliminary studies, attempted cyclization by the RCM of compound **IV** was unsuccessful, and only a dimerized product and/or naphthalene derivative **V** were obtained (see ref 4). We conclude that the epoxy ring is essential for the formation of the 10-membered carbocycle of clavilactone. Another explanation of our results was suggested by a referee. It could be that the silylene acetal in **21** is responsible for inducing a favorable conformation for RCM.



Scheme 5. Synthesis of 10-Membered Carbocycle **22**



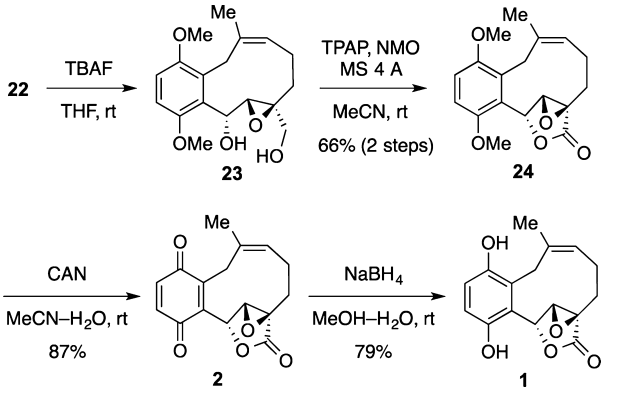
by slow addition of the catalyst. Heating a mixture of **21** and the catalyst (20 mol %) gave only the dimer. ^{1}H NMR analysis, including NOE experiments, of **22** indicated that the stereochemistry and conformation were similar to the natural product **1**.[25]

The final stage of the synthesis required reconstructing the γ-lactone. Removal of the silylene acetal from **22** provided diol **23**, which was oxidized with tetra-*n*-propylammonium perruthenate (TPAP) and NMO to γ-lactone **24** (Scheme 6).[26] The product, compound **24**, was identical to the dimethyl ether derived from natural clavilactone A **1**.[1,6]

(25) When the olefinic methyl group was irradiated, signal enhancements were observed for the olefinic proton (5.0%) and H_a (0.7%) but not for H_b. In addition, no vicinal coupling between H_a and H_b ($J_{a,b}$ = 0 Hz) was observed. The absolute configuration of **22** was definitely confirmed by transformation to compound **24**, whose absolute configuration had been unambiguously determined.[1,6]

(26) Bloch, R.; Brillet, C. *Synlett* **1991**, 829–830.

Scheme 6. Completion of the Total Synthesis of Clavilactones A **1** and B **2**



Treatment of **24** with CAN provided (−)-clavilactone B **2**.[6] The reduction of the quinone with $NaBH_4$ finally afforded (+)-clavilactone A **1**.[1] The properties of products **1** and **2** were identical in all respects to those reported for natural clavilactones A and B.[1]

In summary, we have achieved the first total synthesis of the natural enantiomers of clavilactones A **1** and B **2** (**1**; in 15 steps with 1.6% yield). The key features of the synthesis are two successful olefin metathesis reactions. First, an ROM/RCM sequence allowed the one-pot transformation of cyclobutenecarboxylate **4** into γ-butenolide **5**. Second, the formation of a 10-membered carbocycle was achieved by RCM of silylene acetal derivative **21**. Furthermore, the three contiguous stereocenters were derived from a single benzylic alcohol, which was generated asymmetrically through a Ti/BINOL alkynylation. Extension of this ROM/RCM strategy to the synthesis of other γ-lactone natural products is underway.

Acknowledgment. This work was supported by JSPS KAKENHI Grant Number 23550060 and Keio Gijuku Academic Development Funds.

Supporting Information Available. Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.