Total Synthesis of Clavosolide A
via Tandem Allylic Oxidation/Oxa-Conjugate Addition Reaction

Joseph B. Baker^a, Hyoungsu Kim^{*,b}, Jiyong Hong^{*,a}

^aDepartment of Chemistry, Duke University, Durham, North Carolina 27708, United States

^bCollege of Pharmacy, Ajou University, Suwon 443-749, South Korea

* Corresponding author.

Tel.: +1 919 660 1545; fax: +1 919 660 1605.

E-mail address: jiyong.hong@duke.edu (J. Hong).

Tel.: +82 31 219 3448; fax: +82 31 219 3435.

E-mail address: hkimajou@ajou.ac.kr (H. Kim).

Abstract: The tandem allylic oxidation/oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect in conjunction with the NHC-mediated oxidative esterification was explored for the facile synthesis of clavosolide A.

Keywords: clavosolide, total synthesis, natural product, tandem reaction, oxa-conjugate addition, *gem*-disubstituent effect, tetrahydropyran

(–)-Clavosolide A (**1**, Figure 1) is a dimeric glycosidic macrolide isolated from the marine sponge *Myriastra clavosa* collected in the Philippines by Faulkner and co-workers.¹ Based on extensive spectroscopic studies and molecular modeling, they reported the proposed structure of clavosolide A (**2**, Figure 1) which includes a C₂-symmetric 20-membered macrolide, two 2,3-*trans*-2,6-*cis*-tetrahydropyrans, two permethylated D-xyloses, and two *trans*-cyclopropanes. Unique structural features of **1** have attracted considerable interest from the synthetic community.² Willis and co-workers reported the first total synthesis of the proposed structure (**2**) of the natural product, which led to the revision of the configuration of the *trans*-

cyclopropanes.^{2a} Later, the total synthesis of **1** by Lee and co-workers confirmed the structural revision.^{2b}

Figure 1. Proposed and revised structures of clavosolide A (**1**).

In broad connection with our interest in efficient syntheses of tetrahydropyran-containing natural products,³ herein, we report a facile synthesis of **1**, enlisting the tandem allylic oxidation/oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect in conjunction with the NHC-mediated oxidative esterification to stereoselectively construct the 2,3-*trans*-2,6-*cis*-tetrahydropyrans embedded in **1**.

Scheme 1. Retrosynthetic plan for clavosolide A (**1**).

Scheme 1 summarizes our approach for the stereoselective synthesis of clavosolide A (**1**) from the readily available 1,3-dithiane **6** and chiral epoxide **7**. The primary goal of our synthetic plan was to explore the tandem allylic oxidation/oxa-conjugate addition reaction for the stereoselective construction of the 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4**. To that end, we envisioned that a dimerization of monomer **3** appended with the xylose moiety could complete the synthesis of **1**. Monomer **3** could be prepared by glycosylation of **4** with a permethyl xylose followed by installation of the *trans*-cyclopropane moiety on 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4**. The sequence of tandem allylic oxidation/oxa-conjugate addition reaction³ and NHC-mediated oxidative esterification^{3a,b,6} was anticipated to stereoselectively

provide the key intermediate 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4**.

Scheme 2. Preparation of epoxide **7**.

The synthesis of clavosolide (**1**) started with the preparation of chiral epoxide **7** for dithiane coupling reaction. Preparation of **7** from the known allylic alcohol **8**⁴ was accomplished following the procedures reported by Smith and co-workers (Scheme 2).⁵ Briefly, formation of acyclic *tert*-butyl carbonate **9** (99%) followed by iodocyclization of **9** afforded the corresponding cyclic carbonate **10** (93%, dr = 5:1). Methanolysis of **10** and the concomitant epoxide formation of the resulting 1,2-iodohydrin gave epoxide **11** (95%), which was then protected to afford TIPS ether **7** (94%).

Scheme 3. Preparation of 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4**.

The coupling of the known 1,3-dithiane **6**^{3c,f} and chiral epoxide **7** provided diol **5** for the key tandem allylic oxidation/oxa-conjugate addition reaction (Scheme 3). The one-pot allylic oxidation/oxa-conjugate addition/oxidation of **5** (MnO₂, CH₂Cl₂, 25 °C, 5 h, then dimethyltriazolium iodide, DBU, MnO₂, MeOH, MS 4 Å, 25 °C, 12 h)^{3a,b} smoothly proceeded to afford the desired 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4** (84%) as a single diastereomer.⁷ The excellent stereoselectivity observed in the oxa-conjugate addition reaction can be rationalized by involving a highly rigid chair-like transition state conformation (**A**) induced by the 1,3-dithiane and the equatorially oriented methyl group. It is noteworthy that the sequence of 1,3-dithiane coupling and tandem reaction was highly stereoselective, operationally simple, and robust.

Scheme 4. Completion of total synthesis of clavosolide A (**1**).

With the key intermediate 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4** in hand, we directed our attention to the final stage of the synthesis. Iodine-mediated dithiane-deprotection of **4** (88%) followed by NaBH₄-reduction of the resulting ketone afforded secondary alcohol **12** in 90% yield (Scheme 4). Glycosylation of **12** with phenyl thioglycoside **13**^{2a} in the presence of MeOTf gave the desired β -anomeric monomer **14** (65%, dr = 3.8:1).⁸ The Simmons–Smith cyclopropanation of **14** provided cyclopropane **3** (71%) as a single diastereomer. Finally, TIPS-deprotection (65%), ester hydrolysis, and dimerization utilizing Shiina's procedure⁹ (72% for two steps) completed the synthesis of clavosolide A (**1**). The synthetic clavosolide A (**1**) was identical in all respects to the natural product.

In conclusion, the total synthesis of clavosolide A (**1**) has been accomplished with overall 3.6% yield in 13 steps for the longest sequence from the known allylic alcohol **8**. Highlights of the synthesis include the one-pot allylic oxidation/oxa-conjugate addition/oxidation reaction to stereoselectively construct 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4** from the readily available 1,3-dithiane **6** and chiral epoxide **7**. This synthetic approach would be broadly applicable to the synthesis of other clavosolides and their analogues for future biological studies.

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References

- (1) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386.
- (2) (a) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097. (b) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, *8*, 661. (c) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett.* **2006**, *47*, 2099. (d) Smith, A. B.,

III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (e) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319. (f) Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett.* **2006**, *47*, 7435. (g) Chakraborty, T. K.; Reddy, V. R.; Gajula, P. K. *Tetrahedron* **2008**, *64*, 5162. (h) Carrick, J. D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 769. (i) Son, J. B.; Kim, S. N.; Kim, N. Y.; Hwang, M.-H.; Lee, W.; Lee, D. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 653. (j) Peh, G. R.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 5614.

(3) (a) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577. (b) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880. (c) Lee, K.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 2722. (d) Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 3742. (e) Byeon, S. R.; Park, H.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 5816. (f) Lee, K.; Kim, H.; Hong, J. *Eur. J. Org. Chem.* **2012**, 1025 (g) Lee, K.; Kim, H.; Hong, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5735.

(4) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469.

(5) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703

(6) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331.

(7) Compound **4**: To a solution of diol **5** (117 mg, 0.24 mmol) in CH₂Cl₂ (4 mL, 0.06 M) at 25 °C was added MnO₂ (89 mg, 1.02 mmol). The resulting solution was stirred at 25 °C for 1 h. Additional equivalents of MnO₂ (89 mg, 1.02 mmol) were added every hour for 4 h. The reaction mixture was then treated with a mixture of dimethyltriazolium iodide (5 mg, 0.022 mmol, 9 mol%), DBU (410 µL, 1 M solution in CH₂Cl₂), MnO₂ (89 mg, 1.02 mmol), MeOH (400 µL), and MS 4Å (585 mg, 500 wt%). The resulting mixture was stirred for 12 h. The crude mixture was then filtered through a small plug of celite and concentrated *in vacuo*. The crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to provide 2,3-*trans*-2,6-*cis*-tetrahydropyran methyl ester **4** (104 mg, 0.20 mmol) in 84% as a clear oil; ¹H NMR (500

MHz, CDCl₃) δ 5.56 (dddd, $J = 15.5, 8.5, 8.5, 8.5$ Hz, 1 H), 5.39 (ddd, $J = 15.0, 8.5, 1.5$ Hz, 1 H), 4.31 (ddd, $J = 8.5, 8.5, 4.0$ Hz, 1 H), 3.89 (ddd, $J = 9.5, 9.5, 3.0$ Hz, 1 H), 3.81 (dddd, $J = 9.5, 9.5, 3.5, 1.5$ Hz, 1 H), 3.68 (s, 3 H), 3.12 (ddd, $J = 15.0, 12.5, 3.0$ Hz, 1 H), 2.89 (ddd, $J = 15.0, 12.5, 3.0$ Hz, 1 H), 2.59–2.68 (m, 3 H), 2.54 (dd, $J = 14.5, 3.0$ Hz, 1 H), 2.31 (dd, $J = 14.5, 9.5$ Hz, 1 H), 2.07–2.10 (m, 1 H), 1.78–1.86 (m, 2 H), 1.73 (dd, $J = 13.5, 10.5$ Hz, 1 H), 1.70 (dd, $J = 6.0, 1.5$ Hz, 3 H), 1.64 (dd, $J = 10.0, 7.0$ Hz, 1 H), 1.50 (ddd, $J = 13.0, 9.0, 3.5$ Hz, 1 H), 1.14 (d, $J = 7.0$ Hz, 3 H), 1.04 (s, 21 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.0, 134.2, 125.9, 73.9, 71.0, 70.6, 54.9, 51.7, 45.7, 44.3, 43.8, 39.7, 25.88, 25.83, 25.2, 18.24, 18.21, 17.8, 12.5.

(8) (a) Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301. (b) Watanabe, H.; Nakada, M. *J. Am. Chem. Soc.* **2008**, *130*, 1150.

(9) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822. (b) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312.

Graphical Abstract