ORGANIC
LETTERS

2007
Vol. 9, No. 13
2585−2588

Total Synthesis of Amphidinolide Y by Formation of Trisubstituted (*E*)-Double Bond via Ring-Closing Metathesis of Densely Functionalized Alkenes[§]

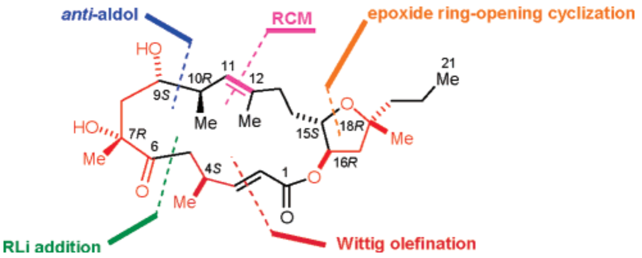
Jian Jin,[†] Yile Chen,[†] Yannian Li,[†] Jinlong Wu,[†] and Wei-Min Dai*,[†,‡]

Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, China, and Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

chdai@ust.hk; chdai@zju.edu.cn

Received May 10, 2007

ABSTRACT



Amphidinolide Y, a 17-membered cytotoxic macrolide isolated from marine dinoflagellates, has been synthesized via ring-closing metathesis to assemble the congested trisubstituted (*E*)-double bond. The seco precursor was prepared from readily available chiral synthons with the tetrahydrofuran ring formed via 5-endo epoxide ring-opening cyclization. It was found that the C6-keto seco substrate showed higher reactivity toward Grubbs' second generation catalyst while Schrock's Mo catalyst was completely inactive for formation of the macrocycle.

Metathesis reactions of alkenes and alkynes[1] have emerged as the enabling tools for carbon−carbon bond formation. In particular ring-closing metathesis (RCM) has been applied in total syntheses of complex natural products[1e] for assembling macrocycles as an alternative to the classic Pd-catalyzed cross-coupling reactions[2] and macrolactonization.[3] Amphidinolide Y **1** belongs to a family of biologically significant secondary metabolites (Figure 1).[4,5] It was isolated from cultures of symbiotic marine dinoflagellates *Amphidinium* sp. and exhibits cytotoxicity against L1210 and KB cell lines with IC_{50} values of 0.8 and 8.0 μg/mL, respectively. Macrolide **1** features a 17-membered ring lactone possessing trisubstituted and conjugate (*E*)-double bonds and a trans fused tetrahydrofuran ring. It exists as an equilibrium mixture of 6-keto and 6(9)-hemiacetal forms (**1a**/**1b** = 5:1−9:1) in $CDCl_3$[4,6] and can be oxidized with $Pb(OAc)_4$ to give

---

[§] Dedicate to Prof. Yoshimitsu Nagao on the occasion of his 65th birthday.

[†] Zhejiang University.

[‡] HKUST.

(1) For reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (f) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101. (g) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. Also see: *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley−VCH: Weinheim, Germany, 2003; Vols. 1, 2, 3.

(2) For a recent review, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

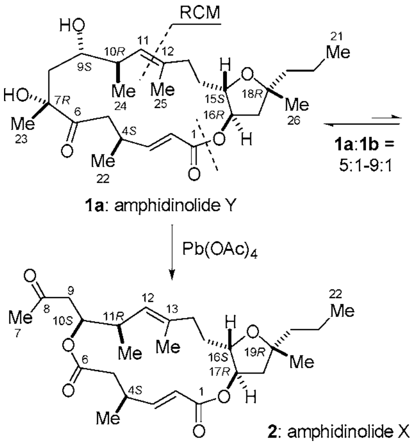
(3) For a recent review, see: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911−939.

(4) For isolation of amphidinolide Y, see: Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 9109−9112.

(5) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77−93.

(6) For the first total synthesis of amphidinolide Y, see: Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194−9204.

10.1021/ol0710360 CCC: $37.00



1a: amphidinolide Y

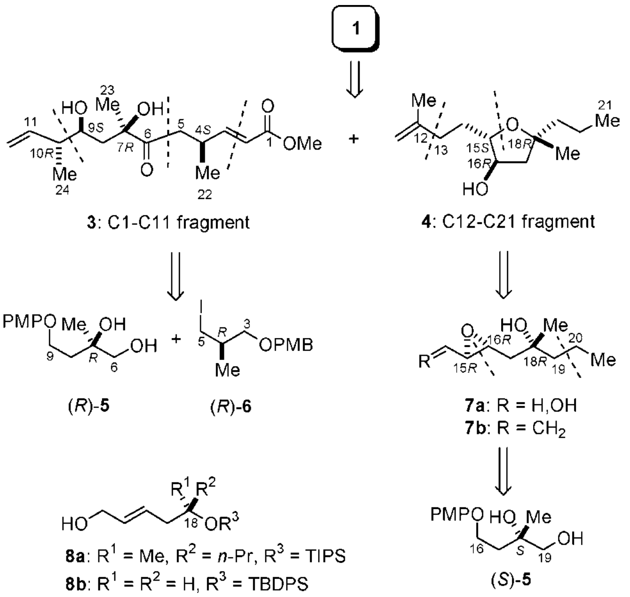
1b

2: amphidinolide X

Figure 1. Structures of amphidinolides X and Y and strategic bond disconnection of amphidinolide Y.

amphidinolide X **2**.[7,8] We envisaged a RCM strategy for constructing the congested α-branched trisubstituted (*E*)-double bond of **1** (Figure 1). We were specifically interested in addressing the influence of C7, C9, and C10 functionalities on RCM reactions in view of the fact that prior studies failed in assembling macrocyclic trisubstituted (*E*)-alkenes via RCM.[9] Moreover, it is of interest to establish a total synthesis of **1** not requiring protection of the C6-keto group and to execute the 17-membered ring formation without relying on the conformation-restricted acetal derivative of **1b**.[6]

According to the bond disconnections in Figure 1, the fragments **3** and **4** are obtained (Figure 2). The triol mono-PMP ether (*R*)-**5**,[10] readily prepared in >96% ee, was used as the C6−C9 subunit and was joined with the lithium species derived from iodide (*R*)-**6**.[11] It was then followed by performing an anti-selective aldol reaction[12] and the Wittig olefination. Thus, the C1−C11 fragment **3** was retrosynthetically disconnected into the chiral synthons (*R*)-**5** and (*R*)-**6**. The *B*-alkyl Suzuki cross-coupling[13] was used for cleaving the C12−C13 bond in **4,** and it is followed by a 5-*endo* epoxide ring-opening cyclization of **7** to form the tetrahydrofuran unit (Figure 2).[14] We prepared **8a** in >96% ee from (*S*)-**5** by forming the C19−C20 bond via Wittig olefination and hydrogenation.[14a] It was proved that **8a** gave higher enantioselectivity in Sharpless asymmetric allylic epoxidation than **8b**.[6,8] The acid-catalyzed 5-*endo* cyclization of epoxy alcohol **7a** failed[14a] but the activated vinyl epoxide **7b** underwent cyclization to give the desired product **9** (Scheme 1).[15,16] Moreover, the vinyl group in **9** could be used to facilitate the *B*-alkyl Suzuki cross-coupling reaction. Thus, **9** was protected as the TES ether **10** followed by



3: C1-C11 fragment

4: C12-C21 fragment

(*R*)-**5**

(*R*)-**6**

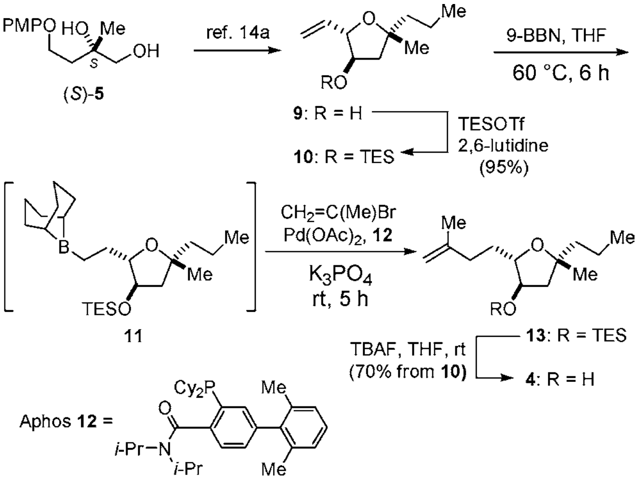
7a: R = H,OH
7b: R = CH$_2$

8a: R^1 = Me, R^2 = *n*-Pr, R^3 = TIPS
8b: R^1 = R^2 = H, R^3 = TBDPS

(*S*)-**5**

Figure 2. Retrosynthetic analysis of amphidinolide Y.

Scheme 1. Synthesis of C12−C21 Fragment **4**



(*S*)-**5**

9: R = H

10: R = TES

11

13: R = TES

4: R = H

---

(7) For isolation of amphidinolide X, see: Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339−5345.

(8) For the first total synthesis of amphidinolide X, see: Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970−15971.

(9) (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169−171. (b) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162−8169. (c) Mulzer, J.; Pichlmair, S.; Green, M. P.; Marques, M. M. B.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11980−11985. (d) Wilson, M. S.; Woo, J. C. S.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4237−4245. (e) Helmboldt, H.; Köhler, D.; Hiersemann, M. *Org. Lett.* **2006**, *8*, 1573−1576. (f) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292−5299. For formation of trisubstituted (*Z*)-alkenes using Schrock's Mo catalyst, see: (g) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302−10316 and references cited therein. (h) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597−1598. For use of RCM in total synthesis of amphidinolides E, T1, T3, T4, and T5, see: (i) Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512−15520 and references cited therein. (j) Va, P.; Roush, W. R. *Org. Lett.* **2007**, *9*, 307−310 and references cited therein.

(10) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805−10816.

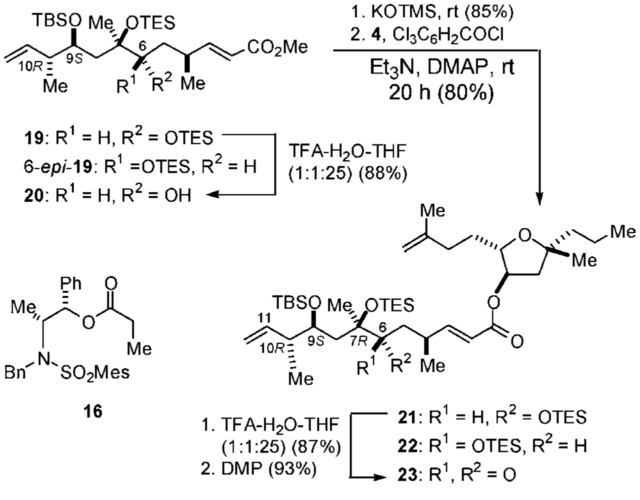
(11) (a) Heckrodt, T. J.; Mulzer, J. *Synthesis* **2002**, 1857−186. (b) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404−5406.

(12) For anti-selective aldehyde crotylation, see: (a) Brown, H. C.; Bhat, K. *J. Am. Chem. Soc.* **1986**, *108*, 293−294. (b) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294−296. (c) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375−4377.

hydroboration (1.5 equiv 9-BBN) to give **11**. The latter, without isolation, was coupled with 2-bromo-1-propene at room temperature in the presence of 3 equiv of K_3PO_4, 5 mol % $Pd(OAc)_2$, and 6 mol % of the Aphos **12**[17,18] to furnish **13**. After removal of the TES group in **13**, the C12−C21 fragment **4** was obtained in 70% overall yield from **10**.

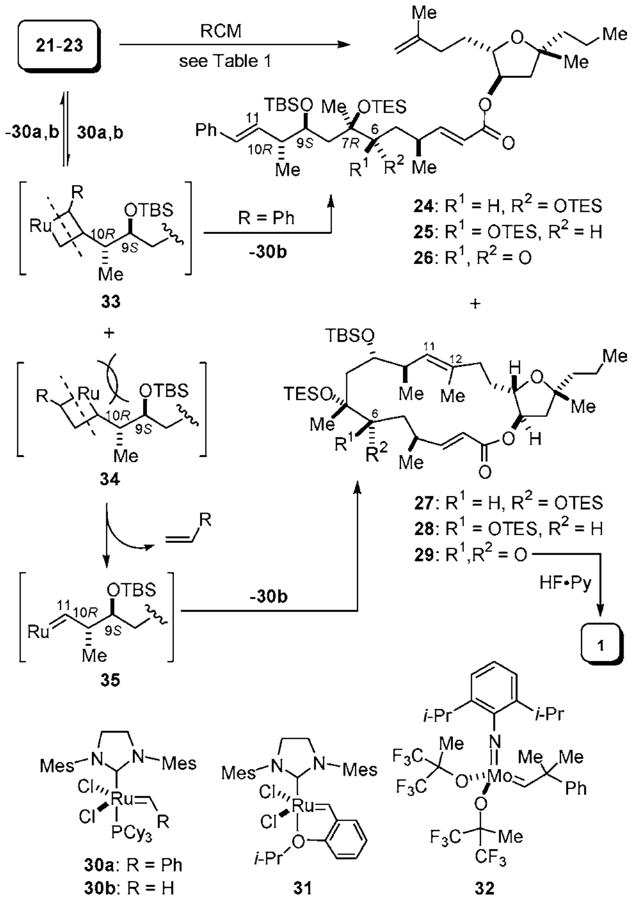
Synthesis of the seco intermediates **21**−**23** is shown in Scheme 2. The diastereomers **19** and 6-*epi*-**19** were prepared, in a parallel fashion, by a sequence of 17 step reactions from (*R*)-**5** in a combined overall yield of 16.7% (see Supporting Information for detail). The C9−C10 *anti*-aldol was installed by the reaction of chiral ester **16**[19] followed by Dibal-H reduction to remove the chiral auxiliary.[20] The C6 stereochemistry of **19** and 6-*epi*-**19** was determined by the Mosher esters[21] of **20**. Cleavage of the methyl ester in **19** by KOTMS[22] gave the carboxylic acid which was then condensed with **4** under the Yamaguchi conditions[23] to furnish the (6*S*)-ester **21**. The minor (6*R*)-epimer **22** was prepared from 6-*epi*-**19** in almost the same overall yield. The C6-ketone **23** could be synthesized from either **21** or **22**. For example, selective desilylation of **21** followed by DMP oxidation[24] formed **23** in 77% overall yield.

Scheme 2. Synthesis of Seco Intermediates **21**−**23**



Scheme 3 and Table 1 summarize the RCM reactions of **21**−**23**. It has been known that α-branched trisubstituted (*E*)-alkene embedded in a macrocycle poses a challenge for RCM.[9a−e] Moreover, structural variations including stereomers and protecting groups[25] may render RCM fruitless or may end up with the undesired (*Z*)-alkenes.[9f] Hoveyda et al. prepared a 14-membered trisubstituted (*Z*)-alkene using 20 mol % Schrock's catalyst **32**.[9g] In contrast, May and Grieco obtained a 1:1 mixture of 16-membered trisubstituted (*E*)-

Scheme 3. RCM Reactions of **21**−**23** and Total Synthesis of **1**



---

[13] For a recent review, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.

[14] (a) Chen, Y.; Jin, J.; Wu, J.; Dai, W.-M. *Synlett* **2006**, 1177−1180. For other syntheses, see: (b) Rodríguez-Escrich, C.; Olivella, A.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 989−992. (c) Doan, H. D.; Gallon, J.; Piou, A.; Vatèle, J.-M. *Synlett.* **2007**, 983−985.

[15] (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335−5340.

[16] (a) Narayan, R. S.; Sivakumar, M.; Bouhle, E.; Borhan, B. *Org. Lett.* **2001**, *3*, 2489−2492. (b) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416−1429.

[17] (a) Dai, W.-M.; Li, Y.; Zhang, Y.; Lai, K. W.; Wu, J. *Tetrahedron Lett.* **2004**, *45*, 1999−2001. (b) Dai, W.-M.; Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 1377−1381.

[18] The reaction of **11** with 2-bromo-1-propene could be accomplished by using 15 mol % $PdCl_2$ and 16 mol % dppf as the catalyst system (rt, 12 h) in 71% overall yield for the conversion of **10** to **4**.

[19] (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586−2587. (b) Inoue, T.; Liu, J.-F.; Buske, D.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250−5256. For application in total synthesis, see: (c) Amarasinghe, K. K. D.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 9366−9367. (d) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215−4234. (e) Fürstner, A.; Ruiz-Caro, J.; Prinz, H.; Waldmann, H. *J. Org. Chem.* **2004**, *69*, 459−467.

[20] Reduction using $LiAlH_4$ as reported in ref 19 caused cleavage and migration of TES ether, which could be avoided by using Dibal-H.

[21] (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

[22] Laganis, E. D.; Chenard, B. L. *Tetrahderon Lett.* **1984**, *25*, 5831−5834.

[23] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

[24] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (c) Boeckman, R. K., Jr.; Shao, P.; Mulins, J. J. *Org. Synth.* **2000**, *77*, 141−146.

[25] Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913−7919.

Table 1. Results of RCM Reactions of **21**−**23** in CH_2Cl_2

entry	substrates and conditions[a]	yield (%)[b]
1	**21**, 25 mol % **30a**, reflux, 20 h	NR[c] (**21**, >95)
2	**21**, 25 mol % **30a**, reflux, 5 d	ND[d] (**21**, 67)
3	**21**, 50 mol % **30a**, reflux, 5 d	ND[d] (**21**, 40)
4	**21**, 100 mol % **30a**, reflux, 30 h	**24**, 50; **27**, 40
5	**22**, 50 mol % **30a**, reflux, 5 d	*e*
6	**23**, 50 mol % **30a**, reflux, 3 d	**26**, 40; **29**, 40
7	**23**, 20 mol % **32**, reflux, 22 h	NR[c] (**23**, >95)
8	**23**, 20 mol % **32**, 60 °C, 22 h[f]	NR[c] (**23**, >95)

[a] The catalyst **30a** was added in portions. See text for details. [b] Estimated values based on ^{1}H NMR spectra of the reaction mixtures. For entries 4 and 6, the yields are for the isolated materials. [c] No reaction. [d] Not determined. Formation of **24** and **27** was confirmed along with the recovered **21**. [e] **22** was recovered together with unidentified byproduct(s). [f] PhH was used as the solvent.

and (*Z*)-alkenes with **32**.[9h] According to Ulman and Grubbs,[26] the bulkier monosubstituted alkenes were significantly resistant to metathesis, while geminally substituted terminal alkenes and *trans*-*β*-methylstyrene did not undergo metathesis at 35 °C with the first generation Ru catalyst. We assumed that a Ru initiator such as **30a** should first form two ruthenacyclobutanes **33** and **34** with the 2,3-configuration in **33** being favored for sterically hindered monosubstituted alkenes.[26] It is expected that the dense functionalities of C9-TBSO,[25] C7-TESO, and C6-TESO (for **21** and **22**) or C6-keto (for **23**), might deteriorate the productive RCM pathways by formation of the styrene-derived byproducts **24**−**26** via **33** when ruthenium(II) benzylidene **30a** is employed.

We found that **21** did not undergo reactions in PhMe or with the initiator **31**. Thus, the RCM reactions of **21**−**23** were carried out in CH_2Cl_2 with the initiator **30a**. It was found that **30a** must be added *in portions* and in total amounts higher than 25 mol % to see metathesis reactions occurring (Table 1, entries 1−3). When four portions of 25 mol % each of **30a** were injected into the reaction mixture of **21** at the reaction time of 0, 2, 4, and 6 h followed by refluxing for a total of 30 h, the desired RCM product **27** was isolated as an inseparable mixture with the byproduct **24** in 90% combined yield (entry 4 and Figure S1 in Supporting Information). In contrast, the (6*R*)-epimer **22** failed to produce the desired product **28** (entry 5 and Figure S2 in Supporting Information). To our delight, the C6-ketone **23** demonstrated higher reactivity after treatment with 5 portions of 10 mol % **30a**, each added at 12 h intervals with refluxing for a total of 3 days. The desired RCM product **29** (40%) and the byproduct **26** (40%) were isolated as an inseparable mixture (entry 6 and Figure S3 in Supporting Information). In contrast to the Ru catalyst **30a**, the keto substrate **23** remained unchanged when treating with 20 mol % Schrock's Mo catalyst **32** in CH_2Cl_2 (refluxing for 22 h, Table 1, entry 7) and in PhH (24 h at 60 °C, Table 1, entry 8).[9g,27] Finally, after global desilylation with HF•Py, **29** was converted into amphidinolide Y **1** in 87% yield as a 5:1 mixture (Scheme 3). Our synthetic **1** is identical with all reported spectral data.[4,6] The specific optical rotation of our sample **1** is $[\alpha]^{17}_{D}$ −32.7 (*c* 1.00, $CHCl_3$), which is in excellent agreement with the values of $[\alpha]^{17}_{D}$ −33 (*c* 1.00, $CHCl_3$)[4] and $[\alpha]^{17}_{D}$ −28.0 (*c* 1.00, $CHCl_3$).[6,28]

In summary, we have successfully accomplished the second total synthesis of amphidinolide Y **1** based on RCM of densely functionalized substrates for assembling the (*E*)-trisubstituted alkene. This strategy tolerates the α-oxygenated keto group which proves advantageous for facilitating the RCM reaction. The efficiency of the RCM reaction suffers from a collective steric effect of the multiple functionalities appended on the carbon chain where the reacting alkenes are hosted; our total synthesis is the first demonstration of RCM in constructing the unique 17-membered ring system of amphidinolide Y, which possesses both (*E*)-trisubstituted and (*E*)-conjugate double bonds. New catalysts and strategies are still needed for the RCM substrates of great structural complexity and diversity.

Acknowledgment. This work is supported in part by the research grants from The National Natural Science Foundation of China (Grant No. 20432020) and Zhejiang University, China. We thank Ms. Li-Ping Li, College of Pharmaceutical Sciences, Zhejiang University, for assistance in using JASCO P-1030 polarimeter. W.-M. Dai is the recipient of the Cheung Kong Scholars Award of The Ministry of Education of China.

Supporting Information Available: Experimental procedures, compound characterization, and Figures S1−S3. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710360

---

(26) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484−2489.

(27) Additional RCM reactions were investigated as given in Supporting Information.

(28) The results of amphidinolide Y total synthesis were presented at 3rd Yoshimasa Hirata Memorial Lecture, Nagoya, Japan, Feb. 6, 2007.