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Development of a Concise and Diversity-Oriented Approach for the Synthesis of Plecomacrolides via the Diene–Ene RCM

Kui Lu, Mengwei Huang, Zheng Xiang, Yongxiang Liu, Jiahua Chen,* and Zhen Yang*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, and Laboratory of Chemical Genetics, Shenzhen Graduate School of Peking University, Beijing 100871, China
zyang@pku.edu.cn

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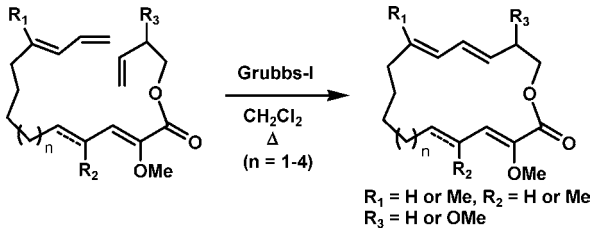
ABSTRACT



A concise synthesis of the core structures of plecomacrolide with ring sizes varying from 16 to 19 atoms was achieved for the first time by the diene–ene ring-closing olefin metathesis reaction. This approach should allow access to the structurally diverse analogues of plecomacrolide.

Plecomacrolides, such as bafilomycins,[1] hygrolidins,[2] and concanamycins,[3] are a set of cyclic macrolides with ring sizes varying between 16 and 18 atoms and different stereochemical orientations at the cores.[4] These molecules showed biological activities, including antitumor,[5] antiviral,[6] and immunosuppressant[7] properties. Bafilomycin A_1 is also a inhibitor for vacuolar H^+-ATPases,[8] the release of β-amyloid,[9] and mitogen-induced DNA synthesis.[10]

Because of their unique structural features, together with their biological activities, plecomacrolides have attracted ever-increasing attention for their efficient syntheses,[11] and several inventive total syntheses have been reported.[12]

Biologically, bafilomycins and concanamycins are not selective for any particular type of V-ATPases, toxicity was observed in the animal testing.[13] Thus, searching for an efficient access to quick construction of structurally diverse analogues is necessary for further studying their selectivity.

(1) Werner, G.; Hagenmaier, H.; Albertm K.; Kohlshorn, H.; Drautz, H. *Tetrahedtron Lett*. **1983**, *24*, 5193.
(2) Seto, H.; Akao, H.; Furihara, K.; Otake, N. *Tetrahedron Lett*. **1982**, *23*, 2667.
(3) Kinashi, H.; Someno, K.; Sakaguchi, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett*. **1981**, *22*, 3857.
(4) (a) Kinashi, H.; Sakaguchi, K.; Higashijima, T.; Miyazawa, T. *J. Antibiot*. **1982**, *35*, 1618. (b) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zähner, H. *J. Antibiot*. **1984**, *37*, 110. (c) Seto, H.; Tajima, I.; Akao, H.; Furihara, K.; Otake, N. *J. Antibiot*. **1984**, *37*, 610. (d) Kinashi, H.; Someno, K.; Sakaguchi, K. *J. Antibiot*. **1984**, *37*, 1333. (e) Deeg, M.; Hagenmaier, H.; Kretschmer, A. *J. Antibiot*. **1987**, *40*, 320. (f) Woo, J.-T.; Shinohara, C.; Sakai, K.; Hasumi, K.; Endo, A. *J. Antibiot*. **1992**, *45*, 1108. (g) Ishii, T.; Hida, T.; Iinuma, S.; Muroi, M.; Nozaki, Y. *J. Antibiot*. **1995**, *48*, 12.
(5) Wilton, J. H.; Hokanson, G. C.; French, J. C. *J. Antibiot*. **1985**, *38*, 1449.
(6) Ochiai, H.; Sakai, S.; Hirabayashi, T.; Shimizu, Y.; Terasawa, K. *Antiviral Res*. **1995**, *27*, 425.
(7) Kataoka, T.; Magae, J.; Kasamo, K.; Yamanishi, H.; Endo, A.; Yamasaki, M.; Nagae, K. *J. Antibiot*. **1992**, *45*, 1618.
(8) Bowman, E. M.; Siebers, A.; Altendorf, K. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7972.
(9) (a) Knops, J.; Suomensaari, S.; Lee, M.; McConlogue, L.; Seubert, P.; Sinha, S. *J. Biol. Chem*. **1995**, *270*, 2419. (b) Haas, C.; Capell, A.; Citron, M.; Teplow, D. B.; Selkoe, J. *J. Biol. Chem*. **1995**, *270*, 6186.
(10) Saurin, A. J.; Hamlett, J.; Clague, M. J.; Pennington, R. *Biochem. J*. **1996**, *313*, 65.
(11) For recent reviews regarding the synthesis see: (a) Toshima, K. *Curr. Org. Chem.* **2004**, *8*, 185. (b) Dai, W.-M.; Guan, Y.; Jin. J. *Curr. Med. Chem*. **2005**, *12*, 1947.

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However, in most of the previous publications, the macrolides of plecomacrolides were constructed by Yamaguchi's method, which limits the flexibility to make structurally diverse plecomacrolide analogues.[11,14]

Recently, because ruthenium carbene complexes not only exhibit high synthetic efficiency and activity, but also tolerate a range of functional groups,[15] application of those complexes for assembly of complex macrolides has opened up new avenues for large-ring construction.[16]

In view of the existing conjugated double bonds in plecomacrolides, we envisioned that the top conjugated double bonds could be installed by diene−ene ring-closing metathesis (RCM)[17] with simultaneous formation of the macrocycles. Interestingly, no such report appeared in the literature, which encouraged us to initiate our study. In this paper, we present our progress toward the synthesis of a structural macrolide via RCM. Our goal has always been the development of a versatile approach for diversity-oriented syntheses of the plecomacrolide analogues.

Our generic approach to the syntheses of plecomacrolides is shown in Figure 2. Retrosynthetically, macrolide **A** was expected to be formed via intramolecular RCM reaction from **B**, which could be made from **C** and **D** by dehydration.

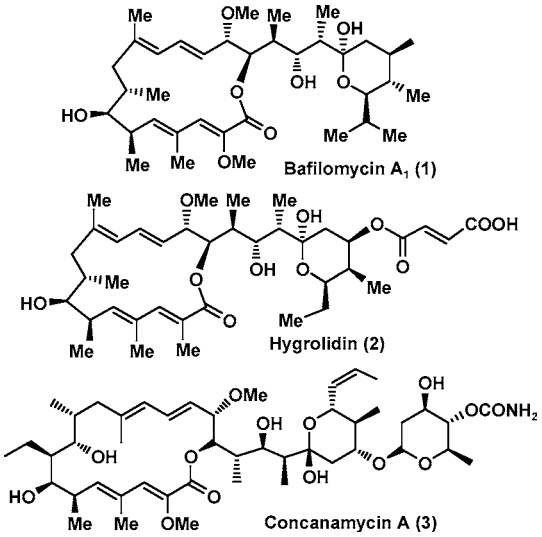


Figure 1. Naturally occurring plecomacrolides.

Intermediate **C** would be derived from **E** by two sequential double bond formations via Wittig and HWE reactions. This illustrated strategy demonstrated the potential to synthesize structurally diverse plecomacrolides by systematically cleaving three major regions (highlighted as purple, green, and blue in **A**).

Our study began with testing the feasibility of constructing 16-membered marcolide **10** via RCM (Scheme 1) from substrate **9** as illustrated in Scheme 1.

To this end, we designed an approach for synthesis of **9**. Accordingly, ester **4** was reduced to its alcohol by DIBAL-H, which was then oxidized to aldehyde **5** by Dess−Martin Periodinane (DMP). This aldehyde was reacted with carbomethoxyethylidene triphenylphosphorane followed by desilyilation and oxidation (DMP) to give aldehyde **6**.

To make substrate **9**, aldehyde **6** was coupled with the ylide derived from phosphonium salt Ph_3PCH_3Br (KHMDS,

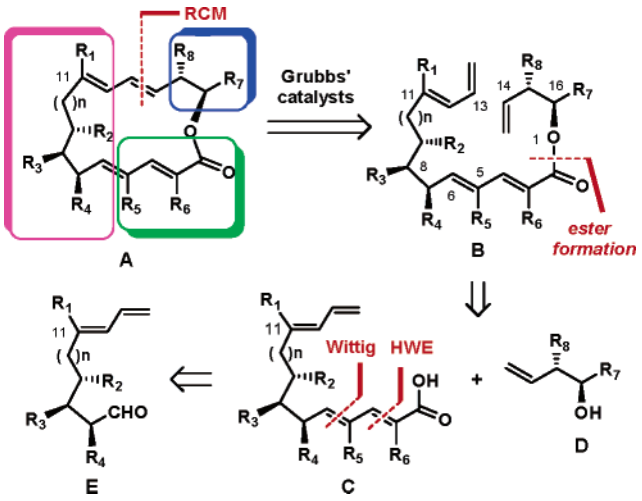


Figure 2. Retrosynthetic analysis.

(12) (a) Evans, D.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871. (b) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1997**, *62*, 3271. (c) Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1308. (d) Toshima, K.; Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **2001**, *66*, 1708. (e) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981. (f) Hanessian, J. A.; Ma. J.; Wang, W. *J. Am. Chem. Soc.* **2002**, *123*, 10200. (g) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **2002**, *67*, 733. (h) Makino, K.; Nakajima, N.; Hashimoto, S.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 9077.

(13) (a) Keeling D. J.; Herslöf, M.; Mattsson, J. P.; Ryberg, B. *Acta Physiol. Scand.* **1998**, *163*, 195. (b) Gaglisrdi, S.; Rees, M.; Farina, C. *Curr. Med. Chem.* **1999**, *6*, 1197. (c) Yoshimoto, Y.; Jyojima, T.; Arita, T.; Ueda, M.; Imoto, M.; Matsumura, S.; Toshima, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3525.

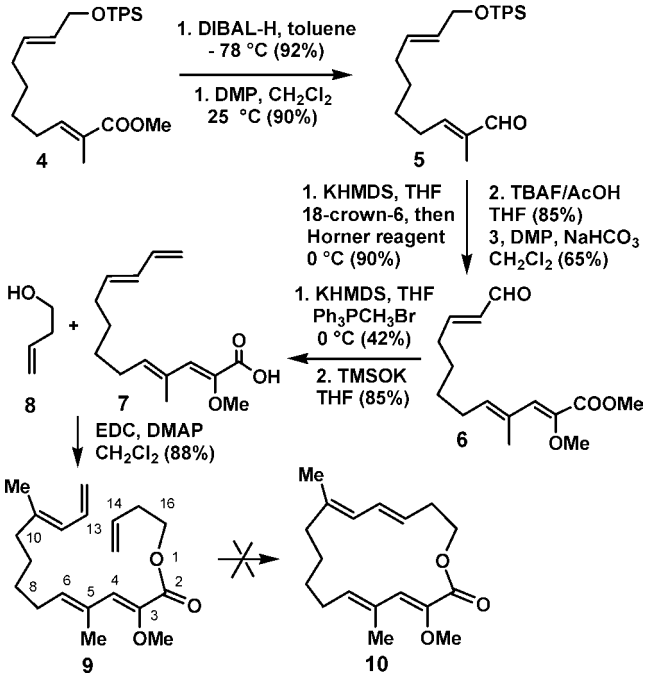
(14) (a) Werner, G.; Hagenmaier, H.; Albert, K.; Kohlshorn, H. *Tetrahedron Lett.* **1983**, *24*, 5193. (b) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5565. (c) Deeg, M.; Hagenmaier, H.; Kretschmer, A. *J. Antibiot.* **1987**, *40*, 320. (d) Gagliardi, S.; Gatti, P. A.; Belfiore, P.; Zocchetti, A.; Clarke, G. D.; Farania, C. *J. Med. Chem.* **1998**, *41*, 1883.

(15) For recent reviews of olefin metathesis see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (f) (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(16) (a) Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew Chem., Int. Ed.* **1999**, *38*, 2443. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664. (c) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (d) Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315.

(17) (a) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664. (c) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255. (d) Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825. (e) Yamamoto, K.; Biswas, K.; Caul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297. (f) Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett.* **2005**, *7*, 525.

Scheme 1. Attempted Formation of Macrolide **10** by RCM



THF), and the formed product was converted to its acid **7** by treatment with TMSOK. Thus, after coupling it with homoallylic alcohol **8**, the expected product **9** was obtained in 88% yield.

Unfortunately, when **9** was subjected to the treatment of both Grubbs' first- and second-generation catalysts under a variety of reaction conditions, no desired product **10** was obtained, and in most cases the starting material was decomposed.

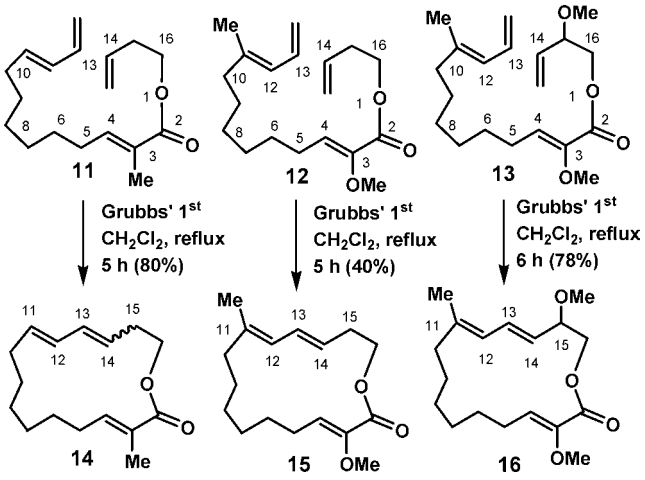
We attributed the difficulty in forming the macrocycle **10** to a problem in attaining the desired proximity of the reactive termini (head-to-tail) due to the existing conjugated double bond at $\Delta^{3,4}$ and $\Delta^{5,6}$. Thus, removal of the double bond at $\Delta^{5,6}$ should improve the flexibility of substrate, which might induce the cyclization.

Accordingly we made compound **11** without a double bond at $\Delta^{5,6}$, and its annulation was tested with Grubbs' first-generation catalyst (10 mol %) under the conditions listed in Scheme 2. We were very pleased to find that the expected product **14** was obtained in 80% yield as a mixture of *Z* and *E* isomers at $\Delta^{13,14}$ (Scheme 2).

Although we tried to identify the ratio of the *Z* and *E* isomers by ^{1}H NMR analysis, the complexity of the splitting pattern derived from the protons in the range of C11−C12 prevented this assignment. To overcome this difficulty, we believed that by addition of a methyl group at C11 or a methoxyl group at C15, the splitting patterns could be simplified. To this end, we proposed two additional models **12** and **13**, and the details for their preparation are provided in the Supporting Information.

The annulation of **12** and **13** was carried out with Grubbs' first-generation catalyst, and products **15** and **16** were obtained in 40% and 78% yields, respectively. To our delight,

Scheme 2. Formation of Macrolides via RCM Reaction



the coupling constants for the newly formed double bond at $\Delta^{13,14}$ are 15.0 and 15.3 Hz for compounds **15** and **16**, respectively, indicating the *E*-double bond was formed.[12b] For product **16** the *E*/*Z* ratio for the newly formed double bond at $\Delta^{13,14}$ is about 10/1.

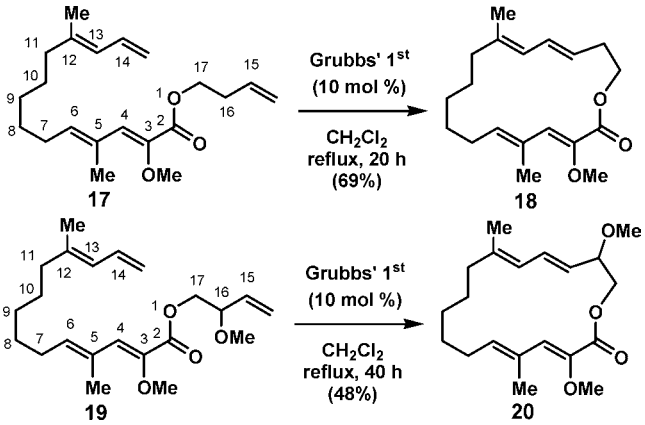
Although we succeeded in making the 16-membered macolides, one limitation of the above results was the absence of a conjugated double bond at the bottom of plecomacrolides. We therefore turned our attention to studying the syntheses of 17-, 18-, and 19-membered macrolides with essentially conjugated double bonds at both the bottom and the top.

We envisaged that cyclization tendency for the larger ring systems could be improved by addition one or more methylene units to **9**, in consideration of the ease of attainment of proximity for reactive termini (head-to-tail).

With this regard, we first tested 17-membered macrolide formation, and **17** and **19** (Scheme 3) were selected as models, and their syntheses are provided in the Supporting Information.

As expected, after treatment of **17** and **19** with Grubbs' catalyst, the products **18** and **20** were obtained in 69% and

Scheme 3. Syntheses of Macrolides **18** and **20**



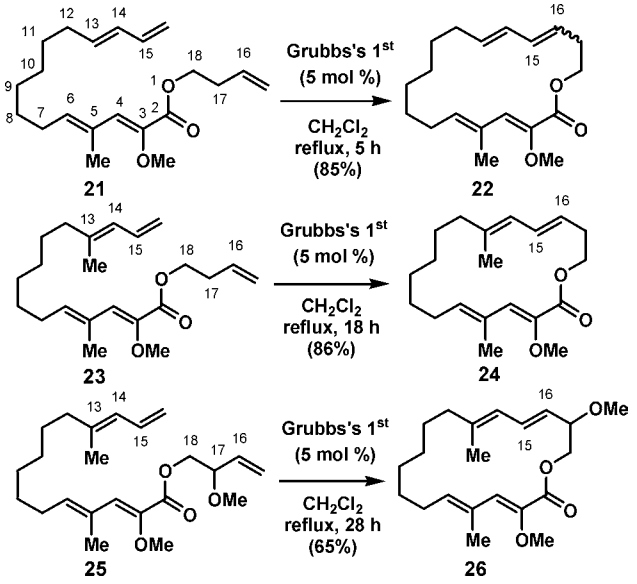
48% yields, respectively. However, their annulations needed 40 h to complete.

It is of particular note that compounds **18** and **20** were formed as an exclusive *E*-isomer. This result, together with the observation for formation of compound **15** (Scheme 2) from **12**, illustrated that the presence of the methyl group at C11 (**12**) and C12 (**17**) or the methoxyl group at C16 (**19**) probably either promotes a favorable conformation for the formation of *E*-isomer during the RCM reaction or increases the final thermodynamic stability of the *E*-isomer versus the *Z*-isomer.

At this stage, it seemed to be that both the atom lengths of the substrates and the substituents on the backbone have a profound influence on the outcomes of the RCM reaction speed and double bond geometry.

To evaluate this notion, substrates **21**, **23**, and **25** were made and their cyclizations were evaluated with Grubbs' first-generation of catalyst for making their corresponding 18-membered macrolides. As expected, the annulation proceeded smoothly, yielding the products **22**, **24**, and **26** in 85%, 86%, and 65% yields, respectively (Scheme 4).

Scheme 4. Syntheses of 18-Membered Macrolides via RCM

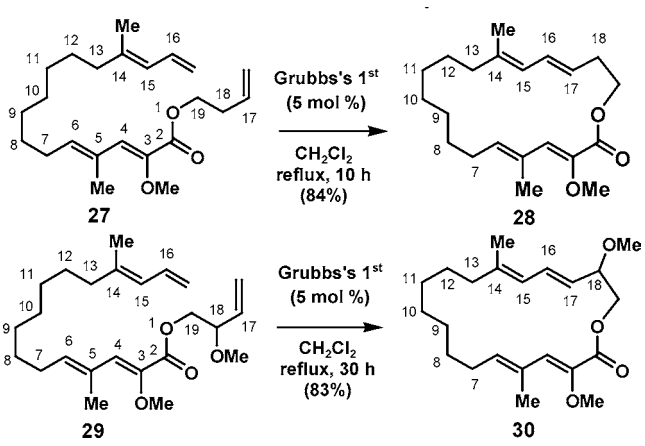


Interestingly, the cyclization time for effecting annulation extended as the substitutents on the backbone increased (cf. 5 h for **21**, 18 h for **23**, and 28 h for **25**). As for the geometrical outcomes, for product **22**, we can observe the *E*/*Z* isomers in the NMR spectrum for the newly formed double bond at $\Delta^{15,16}$, while for products **23** and **25**, the exclusive *E*-isomers were isolated from the reaction mixtures, indicating the critical influence of methyl and methoxyl groups at C13 and C17 on substrate reaction speed and geometrical product outcomes.

Encouraged by the above results, we would like to extend the scope of this method for making 19-membered macrolides **28** and **30** from substrates **27** and **29** by the diene−ene RCM.

To this end, substrates **27** and **29** were made accordingly, and their annulation was tested by Grubbs' first-generation catalyst, and the results are listed in Scheme 5. As expected,

Scheme 5. Syntheses of 19-Membered Macrolides via RCM



products **28** and **30** were obtained in 84% and 83% yields, respectively. On the geometrical aspect, the cyclyzation tendency for the formation of 19-membered macrolides is less effective than the formation of 17- and 18-membered macrolides, as evidence by the fact that the *E*/*Z* ratio at $\Delta^{16,17}$ for product **28** is about 6/1, while the exclusive *E*-isomers for **18** and **24** were isolated from the reaction mixture.

In summary, we have shown for the first time that diene−ene RCM is a suitable method for the formation of the framework of plecomacrolides. This strategy was used for the generation of a set of cyclic macrolides with ring sizes varying from 16 to 19 atoms. It was found that conformation and flexibility of substrates have a profound influence on the geometrical outcomes of macrolides.[18] Notably, we have achieved geometrical control of the macrolides by addition of substituents on the substrate backbones. Further studies aimed at synthesizing some plecomacrolides are currently underway in our laboratory and the results will be reported in due course.

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Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The control of substrate conformation in determining the success of RCM reactions, see: (a) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Furstner, A.; Langeman, K. *J. Org. Chem.* **1996**, *61*, 8746. (d) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (e) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291. (f) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (g) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 6299. (h) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (i) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919. (j) Commeureuc, A. G. J.; Murphy, J. A.; Dewis, M. L. *Org. Lett.* **2003**, *5*, 2785.