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Synthesis of New Artemisinin-Derived Dimers by Self-Cross-Metathesis Reaction

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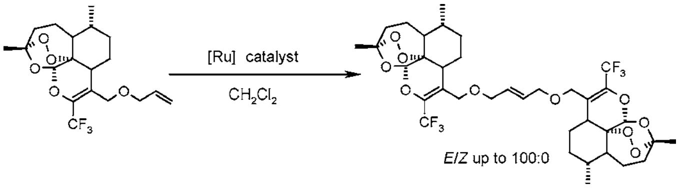
ABSTRACT



New artemisinin-derived dimers, fluorinated or not, have been prepared by a self-cross metathesis reaction in the presence of first- or second-generation ruthenium catalysts without degradation of the endoperoxide bridge and with a good *E*/*Z* selectivity (up to 100:0).

Artemisinin **1**, a sesquiterpene lactone isolated from a Chinese herb, *Artemisia Annua L.*, is an important antimalarial drug with high activity against the multidrug-resistant form of *Plasmodium falciparum*.[1] While the antimalarial mechanism of action of artemisinin is still under debate,[2] several studies have established that the opening in vivo of the endoperoxide moiety (pharmacophore) produced free radicals responsible for the death of malaria parasites.[3] Moreover, focusing on this reactive peroxide bridge, it has been shown that artemisinin and its derivatives are also toxic against tumor cells, the most potent being their corresponding dimers.[4] Consequently, the synthesis of symmetric artemisinin derivative dimers has received a great deal of attention. Most of them are dimers at C-10 and are derived from ethers of dihydroartemisinin[4,5] or from more metabolically robust nonacetal analogues (Figure 1).[6] Their preparation generally involves the addition of various kinds of linkers on the corresponding oxonium salt.[4−6] A few others are dimers at C-16 and are prepared from the naturally occurring artemisiten, via a Michael reaction (Figure 1).[7] We describe in

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[1] Klayman, D. L. *Science* **1985**, *228*, 1049.

[2] (a) Laurent, S. A. L.; Robert, A.; Meunier, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 2060. (b) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945. (c) Haynes, R. K.; Krishna, S. *Microbes Infect.* **2004**, *6*, 1339.

[3] (a) Cummings, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *3*, 253. (b) Eckstein-Ludwig, U.; Webb, R. J.; Van Goethem, I. D. A.; East, J. M.; Lee, A. G.; Kimura, M.; O'Neill, P. M.; Bray, P. G.; Ward, S. A.; Krishna, S. *Nature* **2003**, *424*, 957. (c) Haynes, R. K.; Ho, W. Y.; Chan, H. W.; Fugmann, B.; Stetter, J.; Croft, S. L.; Vivas, L.; Peters, W.; Robinson, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1382. (d) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397.

[4] (a) Woerdenbag, H. J.; Moskal, T. A.; Pras, N.; Malingré, T. M. *J. Nat. Prod.* **1993**, *56*, 849. (b) Beekman, A. C.; Woerdenbag, H. J.; Kampiga, H. H.; Konings, A. W. T. *Phytother. Res.* **1996**, *10*, 140. (c) Beekman, A. C.; Barentsen, A. R. W.; Woerdenbag, H. J.; Uden, W. V.; Pras, N. *J. Nat. Prod.* **1997**, *60*, 325. (d) Beekman, A. C.; Wierenga, P. K.; Woerdenbag, H. J.; Van Uden, W.; Pras, N.; Konings, A. W. T.; El-Feraly, F. S., Galal, A. M.; Vikström, H. V. *Planta Med.* **1998**, *64*, 615. (e) Lai, H. E.; Singh, N. P. PCT Int. Appl. WO 2003103588, 2003. (f) Jeyadevan, J. P.; Bray, P. G.; Chadwick, J.; Mercer, A. E.; Byrne, A.; Ward, S. A.; Park, B. K.; Williams D. P.; Cosstick, R.; Davies, J.; Higson, A. P.; Irving, E.; Posner, G. H.; O'Neill, P. M. *J. Med. Chem.* **2004**, *47*, 1290. (g) Posner, G. H.; McRiner, A. J.; Paik, I. H.; Sur, S.; Borstnik, K.; Xie, S.; Shapiro, T. A.; Alagbala, A.; Foster, B. *J. Med. Chem.* **2004**, *47*, 1299.

[5] Zheng, Q. H.; Darbie, L. G. PCT Int. Appl. WO 9701548, 1997.

[6] (a) Posner, G. H.; Ploypradith, P.; Parker, M. H.; O'Dowd, H.; Woo, S. H.; Northrop, J.; Krasavin, M.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 4275. (b) Posner, G. H.; Northrop, J.; Paik, I. H.; Borstnik, K.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, T. A. *Bioorg. Med. Chem.* **2002**, *10*, 227. (c) Jung, M.; Lee, S.; Ham, J.; Lee, K.; Kim, H.; Kim, S. K. *J. Med. Chem.* **2003**, *46*, 987. (d) Posner, G. H.; Park, I. H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060.

10.1021/ol052056+ CCC: $30.25

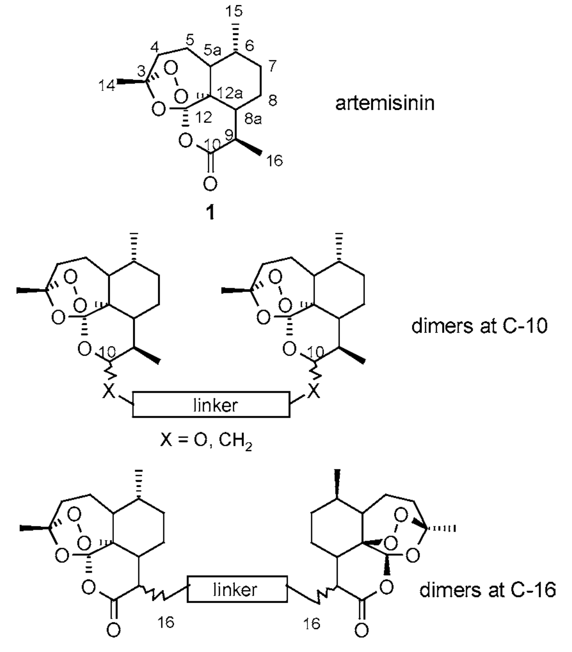


Figure 1. Artemisinin **1** and general structure of known artemisinin-derived homodimers.[4−6]

this paper our investigations on the olefin cross-metathesis reaction as a new approach to prepare structurally more diversified dimers of artemisinin derivatives.

During the past few years, the olefin metathesis reaction has emerged as a powerful reaction for the construction of complex molecules.[8] Most of the reported works are focused on the use of the ring-closing metathesis reaction (RCM) for the synthesis of cyclic and heterocyclic compounds.[8] For this reaction, ruthenium-based catalysts **2**[9] and **3**[10] are particularly efficient due to their stability, their reactivity, and above all, their functional group tolerance (Figure 2). The olefin cross-metathesis (CM) reaction, and the self-cross-metathesis reaction in particular, have received more recent attention.[8]

The difficulty to control the *E*/*Z* selectivity, along with the bulkiness of artemisinin derivatives, could a priori represent a drawback for the dimerization of this family of compounds by metathesis reaction. However, the most important question raised by this approach was the unknown tolerance of the peroxide function toward ruthenium catalysts. The endoperoxide bridge, which is essential for the biological

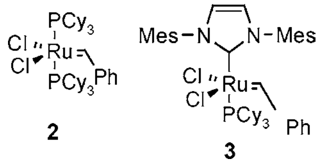
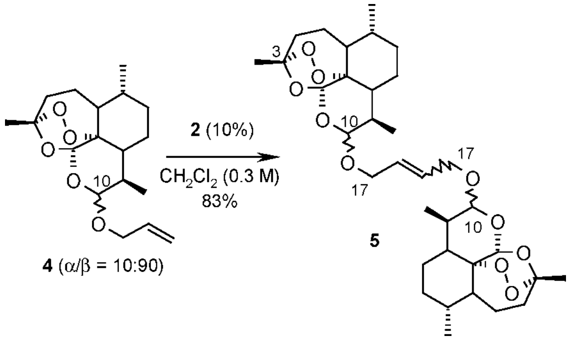


Figure 2. Ruthenium catalysts **2** and **3**.

activity of artemisinin derivatives, is known to be sensitive to the reductive action of various metals, not only iron salts or complexes involved in the biological mechanism of action, but also Mn, Pd, and Cu.[11] Noteworthy, with few other ones, such as Zn, the sensitivity of this endoperoxide depends on the reaction conditions.[6e,11a,d]

The olefin metathesis reaction was first studied with a readily available artemisinin derivative. For this purpose, the allylic ether **4**[12] of dihydroartemisinin appeared to be the most interesting choice. Treatment of **4** (α/β = 10:90) with Grubbs catalyst **2** (10%) in CH_2Cl_2 (0.3 M) at room temperature led, after 24 h of reaction, to the clean formation of homodimers **5** with 85% conversion (Scheme 1).[13] Noteworthy, a typical chemical shift of C-3 on the ^{13}C NMR spectra (δ_{C-3} = 104.0 ppm) clearly indicated that the peroxide bridge has not been reduced by Grubbs−ruthenium complex **2** under these reaction conditions.[14] After purification by chromatography, dimer **5** (β,β is the major diastereomer at C-10) was isolated in 83% yield as a mixture of *E* and *Z* stereoisomers (ratio >90:10). As expected, the ^{1}H and ^{13}C NMR spectra of this C_2-symmetric homodimeric product showed only half of the

Scheme 1. Self-Cross-Metathesis Reaction of C-10 Allylic Ether Artemisinin Derivative **4** with First-Generation Grubbs Catalyst **2**



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(7) Ekthawatchai, S.; Kamchonwongpaisan, S.; Kongsaeree, P.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. *J. Med. Chem.* **2001**, *44*, 4688. For a review, see: Jung M.; Lee, K.; Kim, H.; Park, M. *Cur. Med. Chem.*, **2004**, *11*, 1265.

(8) For recent reviews on the olefin metathesis reaction, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Connor, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (d) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *46*, 93. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (f) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (g) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239.

(9) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(10) Huang, J.; Stevens, E. D.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(11) (a) Liu, J. M.; Ni, M. Y.; Fan, Y. F.; Tu, Y. Y.; Wu, Z. H.; Wu, Y. L.; Zhou, W. S. *Acta Chim. Sinica* **1979**, *37*, 129. (b) Robert, A.; Meunier, B. *J. Am. Chem. Soc.* **1997**, *119*, 5968. (c) Wu, Y. K.; Liu, H. H.; *Helv. Chim. Acta* **2003**, *86*, 3074. (d) Drew, M. G. B.; Metcalfe, J.; Ismail, F. M. D. *THEOCHEM* **2004**, *711*, 95.

(12) Singh, C.; Tiwari, P. *Tetrahedron Lett.* **2002**, *43*, 7235.

(13) Heating the reaction at dichloromethane reflux did not improve the percentage of conversion, but led only to decomposition products.

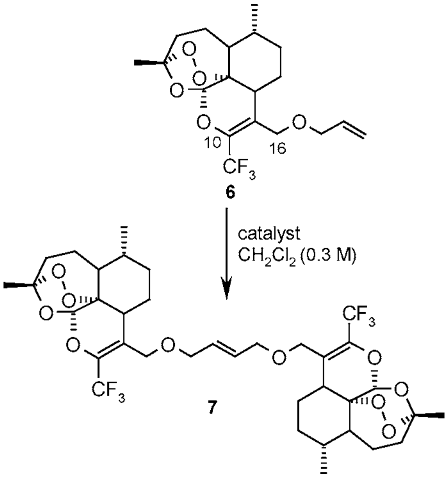
(14) When the endoperoxide bridge is reduced with Zn into the corresponding ether, δ_{C-3} typically shifts to 107−109 ppm; see refs 6b and 10a.

set of signals for all protons and carbon atoms. However, the ratio of the inseparable *E* and *Z* isomers was determined from analysis of the ^{13}C NMR spectra of the dimer **5**. Indeed, it is generally accepted that the carbon α to a double bond (C-17 in **5**) is more shielded in the *Z* isomer than in the *E* isomer due to the γ effect ([$\delta_E > \delta_Z$]).[15] The comparison of the chemical shift of C-17 in both *Z*/*E* isomers of dimer **5** allowed us to confirm the *E* configuration for the major isomer ($\delta_{C-17} = 67.6$ ppm) and the *Z* conformation for the minor one ($\delta_{C-17} = 62.5$ ppm).

After this successful application of the olefin cross-metathesis reaction to artemisinin derivatives, we were keen to extend this approach to other artemisinin-derived dimeric structures. With this goal in mind, we were particularly interested in the synthesis of novel C-16 dimers metabolically stabilized by a trifluoromethyl substituent at C-10.[16] The preparation of CF_3–artemisinin derivatives functionalized in C-16, which could be excellent precursors of these new dimers, have been recently reported.[16b]

Dimerization of the 10-CF_3-16-allylic ether **6**[16b] was examined first (Table 1). Treatment of **6** with a catalytic amount of the ruthenium catalyst **2** (5 or 10%), at room temperature, led to the homodimer **7** with 80% conversion (Table 1, entries 1 and 2). Furthermore, since C-10-fluorinated artemisinin derivatives are more stable than the nonfluorinated ones,[16] we also investigated the reaction at reflux of dichloromethane. Under these conditions, in the presence of only 5% of catalyst **2**, a complete conversion of the starting ether **6** was obtained, within 1.5 h instead of 6 h (Table 1, entry 3).[17] Dimer **7** was finally isolated in good yield (71%) as a 90:10 mixture of *E* and *Z* isomers (vide supra). The second-generation catalyst **3**, containing *N*-heterocyclic carbene ligand, is known to be far superior to **2** in terms of reactivity. This catalyst also generally affords higher *E*/*Z* selectivity and exhibits an excellent functional group tolerance.[8,10] Treatment of the allylic ether **6** with 10% of catalyst **3**, at room temperature, led to the homodimer **7** (90% of conversion). Despite a long reaction time (24 h), the reaction was completely selective in regard to the olefin geometry, and dimer **7** was obtained as a single *E* isomer (Table 1, entry 4).

Table 1. Self-Cross-Metathesis Reaction of Allylic Ether Artemisinin Derivative **6** with Catalysts **2** and **3**

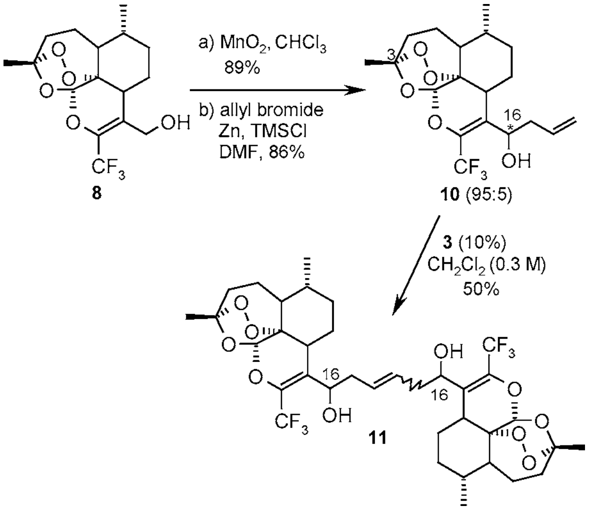


entry	catalyst (%)	*T* (°C)	time	conversion of **6** (%)	isolated yield of **7** (%) (ratio *E*/*Z*)
1	**2** (5)	rt	6[a]	80	(90:10)[b]
2	**2** (10)	rt	4[a]	80	(90:10)[b]
3	**2** (5)	reflux	1.5	100	71 (90:10)
4	**3** (10)	rt	24	90	69 (100:0)

[a] A longer reaction time did not improve the percentage of conversion. [b] **7** was not isolated.

We next undertook the synthesis of artemisinin derivative dimers containing a free alcohol function. The previously reported allylic alcohol **8**[16b] was oxidized with MnO_2 into the corresponding aldehyde **9** (isolated with 89% yield). This latter then reacted easily with allyl bromide in the presence of zinc under Barbier's conditions,[18] providing the alcohol **10**. It is worth noting that the peroxide bridge was not sensitive to Zn under these reaction conditions (vide supra).[14] Alcohol **10** was isolated in high yield (86%) as a 95:5 mixture of two diastereoisomers at C-16 (Scheme 2).[19] Despite the presence of a free alcohol function,[20] the reaction was attempted from **10** with catalyst **2**. Only starting material

Scheme 2. Preparation and Self-Cross-Metathesis Reaction of Allylic Alcohol Artemisinin Derivative **10**



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(15) Breitmaier, E. *Structure Elucidation by NMR in Organic Chemistry*; John Wiley and Sons: New York, 2002; pp 48–51.

(16) For the effect of fluoroalkyl substitution of artemisinin derivatives at C-10, see: (a) Abdouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Gantier, J. C.; Thanh Nga, T. T.; Truong Dinh, T *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2717. (b) Grellepois, F.; Chorki, F.; Ourévitch, M.; Charneau, S.; Grellier, P.; McIntosh, K. A.; Charman, W. N.; Pradines, B.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. P. *J. Med. Chem.* **2004**, *47*, 1423. (c) Magueur, G.; Crousse, B.; Charneau, S.; Grellier, P.; Bégué, J. P.; Bonnet-Delpon, D. *J. Med. Chem.* **2004**, *47*, 2694.

(17) When the reaction was performed at reflux, some decomposition products were detected.

was completely recovered under any conditions we tried (5 or 10% of catalyst, at rt or at reflux of dichloromethane). Thankfully, reaction of the alcohol **10** with a catalytic amount (10%) of the ruthenium-based imidazolinylidene complex **3** at room temperature led to the formation of the corresponding homodimer **11**, which was then isolated in 50% yield as a mixture of *E* and *Z* isomers (>90:10 ratio).

Preliminary growth inhibitory activities were evaluated in vitro at the National Cancer Institute (NCI) using a diverse panel of 60 human cancer cell lines.[21] Dimers **5** and **7** were efficient in cancer cell growth inhibition with a GI_{50}[22] less than 10 nM in many cases. In particular, TGI (total growth inhibition) data[21] show the selectivity and the potency of dimers **5** and **7** against a few cancer cell lines (e.g., leukemia HL-60, nonsmall cell lung cancer NCI-H226, colon cancer COLO 205, and KM-12, CNS cancer SF-295).

In summary, new artemisinin-derived dimers have been prepared by self-cross-metathesis reaction in the presence of ruthenium catalysts without alteration of the endoperoxide bridge and with a very good *E*/*Z* selectivity (up to 100:0). Noteworthy, this study opens a new access to various dimers linked at C-10 or at C-16, fluorinated or not, but also highlights a valuable approach for the functionalization of artemisinin derivatives. The selectivity and potent anticancer activities of dimers **5** and **7** make these compounds worthy of further investigations.

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Supporting Information Available: Experimental procedures, full characterization of all new compounds, and copies of NMR spectra of homodimers **5**, **7**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For a review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(19) The configuration at C-16 of major alcohol **10** has not been determined.

(20) Werner, H.; Grünwald, C.; Stüer, W.; Wolf, J. *Organometallics* **2003**, *22*, 1558.

(21) Boyd, M. R.; Paull, K. D. *Drug Dev. Res.* **1995**, *64*, 91.

(22) GI_{50} is the concentration of drug that inhibits percentage growth by 50%; TGI is the concentration of drug required to achieve total growth inhibition (i.e., cytostasis).