JOC*Article*

Synthesis of Erythromycin Derivatives via the Olefin Cross-Metathesis Reaction

Margaret C. Hsu,* Adam J. Junia,† Anthony R. Haight, and Weijiang Zhang‡

Process Chemistry Research and Development, Global Pharmaceutical R&D, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064

margaret.hsu@abbott.com

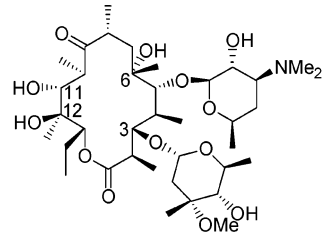
Received February 13, 2004

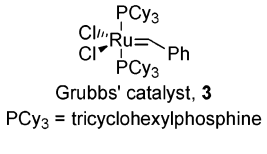
Olefin cross metathesis (CM) was applied to the synthesis of 6-*O*-substituted erythromycin derivatives. The reactions were catalyzed by transition metal alkylidene complexes, particularly bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (Grubbs' first-generation catalyst). This approach allowed for the elaboration of the 6-*O*-allyl group of highly functionalized macrolides at various stages of the synthetic sequence, affording 6-*O*-3-aryl-propenyl products with excellent *E*-selectivity. Little or no self-dimerization of the reacting components was found in the crude mixtures. Preliminary kinetic data accounts for the observed cross-selectivity based on substrate reactivity and steric factors.

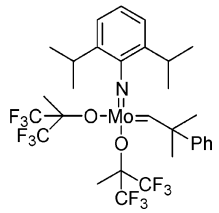
Introduction

ABT-773 (**1**) is a semi-synthetic ketolide anti-infective candidate previously selected for clinical development at Abbott Laboratories.[1] Beginning with erythromycin A (**2**), a sequence of chemical reactions are applied to effect the following overall transformations: (a) elaboration at the 6-hydroxyl group, (b) 11,12-cyclic carbamate formation from the corresponding diol, and (c) cladinose hydrolysis and oxidation at the 3-position.[2] Of these three transformations, the construction of the 6-*O*-3-(3′-quinolyl)-propenyl side chain poses the greatest opportunity for exploring various synthetic approaches. Herein, we report the application of olefin cross metathesis (CM) to erythromycin derivatives.

The application of olefin metathesis in organic syntheses has gained popularity in recent years[3] due, in large part, to the commercial availability of well-defined catalysts such as the Grubbs' (**3**)[4] and the Schrock's (**4**)[5] catalysts. A cursory overview of the chemical literature reveals that C−C double bond formation via olefin







† Current address: Department of Chemistry, 907 Washington Street, Northwestern University, Evanston, IL 60202.

‡ Current address: Theravance Inc., 901 Gateway Blvd., South San Francisco, CA 94080.

(1) (a) Or, Y. S.; Ma, Z.; Clark, R. F.; Chu, D. T.; Plattner, J. J.; Griesgraber, G. U.S. Patent 5,866,549, 1999. (b) Or, Y. S.; Ma, Z.; Clark, R. F.; Chu, D. T.; Plattner, J. J.; Griesgraber, G. U.S. Patent 6,028,-181, 2000. (c) Or, Y. S.; Ma, Z.; Clark, R. F.; Chu, D. T.; Plattner, J. J.; Griesgraber, G. U.S. Patent 6,075,133, 2000.

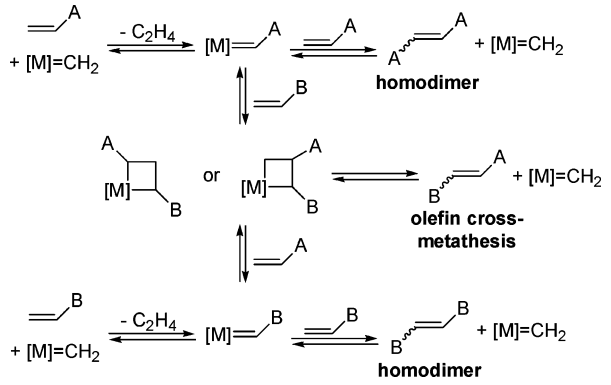
(2) Stoner, E. J.; Peterson, M. J.; Ku, Y.; Cink, R. D.; Cooper, A. J.; Deshpande, M. N.; Grieme, T.; Haight, A. R.; Hill, D. R.; Hsu, M. C.; King, S. A.; Leanna, M. R.; Lee, E. C.; McLaughlin, M. A.; Morton, H. E.; Napier, J. J.; Plata, D. J.; Raje, P. S.; Rasmussen, M.; Riley, D.; Tien, J. J.; Wittenberger, S. J. U.S. Patent 6,437,106 B1, 2002.

(3) For recent reviews on olefin metathesis, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (c) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519−529. (e) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−90. (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (g) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (h) Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1−16. (i) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29−40. (j) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056.

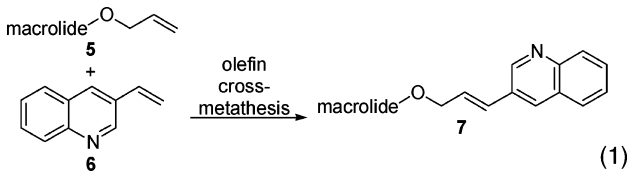
(4) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

10.1021/jo049737n CCC: $27.50 © 2004 American Chemical Society
Published on Web 05/01/2004

SCHEME 1



metathesis has been utilized extensively for intramolecular ring-closing (RCM) and for ring-opening reactions (including ring-opening metathesis polymerization), but few examples of olefin CM reactions are known.[6] Undoubtedly, the intermolecular reactions are complicated by competition between the desired CM and the undesired self metathesis to produce homodimers (Scheme 1). Nonetheless, these literature precedents suggest a potential for expanding the scope of olefin CM to complex substrates, especially applicable as a late-stage tool in designing a total synthesis. Inspired by the availability of 6-*O*-allyl erythromycin derivatives,[2] our strategy was to perform an intermolecular CM reaction between 6-*O*-allyl protected erythronolides (**5**) and vinylquinoline (**6**) to generate the alkene product **7** with the *E*-configuration (eq 1).

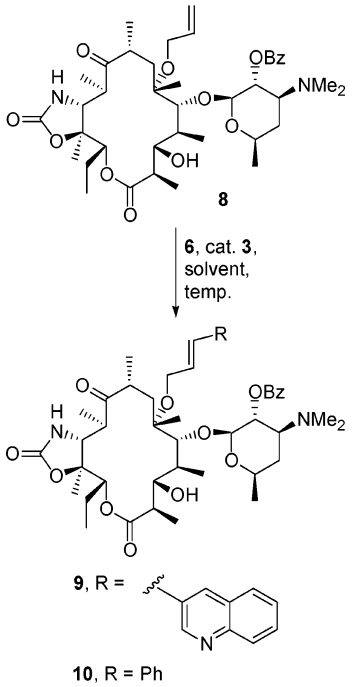


Results and Discussion

Table 1 summarizes the results of olefin CM reactions between **8** and **6** in methylene chloride with **3** as the catalyst. A general method was adopted to generate data for comparison based on the reaction of 1.0 equiv of **8** and 2.0 equiv of **6** in the presence of 10 mol % **3** for 20 h. It was speculated that an excess of one of the olefin components would drive the conversion forward to yield **9** (see Scheme 2). Compound **6** was chosen to be the excess reagent because it is more readily available than the highly derivatized macrolide, and any unreacted portion or its homodimer would not hinder product isolation.

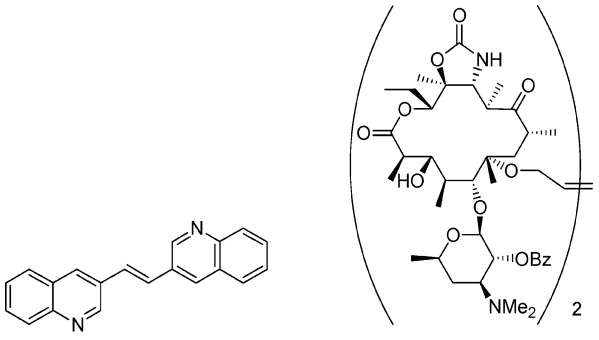
At ambient temperature, the conversion was unacceptably low under the typical reaction conditions (entry 1). Longer reaction times at reflux temperature significantly improved the yield, reaching 71% after 7 days (entries 2−5). Not surprisingly, the reaction progress was also

SCHEME 2



dependent on the catalyst loading when 5, 10, and 25 mol % catalysts were compared (entries 2, 6, and 7). At the highest loading of 25 mol % **3**, 75% product yield was obtained after refluxing for 65 h (entry 8).

The ratio of the two CM substrates was examined next. The typical conditions employ an extra equivalent of **6** relative to **8**. However, it was observed that the yield after 20 h was only slightly lower when the same molar amounts of **8** and **6** were employed, but with the tradeoff of increased amounts of impurities (entries 7 and 9). When 3.0 equiv of **8** and 1.0 equiv of **6** were subjected to the reaction conditions with 10 mol % catalyst, an impressively high yield of 64% was obtained after 20 h, and 79% yield after 65 h (entries 10 and 11). On the other hand, when the reaction was overwhelmed with 5.0 equiv of **6**, the opposite trend was observed in which a low yield of 23% was obtained after 20 h (entry 12). The kinetics of these three reactions were plotted in Figure 1. The graph indicates that, although it is theoretically possible for these three reactions to reach comparable yields, the kinetics of product appearance has a significant dependence on the stoichiometry of the two olefinic components.



In general, the olefin CM reaction between **8** and **6** produced very little undesired byproducts. Analyzed by

(5) (a) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287−2289. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DeMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886.

(6) For recent reviews on olefin cross metathesis, see: (a) Vol. 2, Chapter 2.8 of ref 3a. (b) Conner, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

TABLE 1. Olefin CM between 8 and 6 in the Presence of 3

entry	macrolide **8** (equiv)	3-vinyl-quinoline **6** (equiv)	catalyst **3** (mol %)	temp (°C)	reaction time (h)	product **9** (%)[a]	impurities (% PA)[b] **10**	**11**	**12**
1	1	2	10	ambient	20	5	2.1	ND	ND
2	1	2	10	40	20	35	2.8	ND	ND
3	1	2	10	40	65	59	1.5	1.1	ND
4	1	2	10	40	91	65	1.1	1.4	1.3
5	1	2	10	40	168	71	1.1	1.8	ND
6	1	2	5	40	20	27	ND	ND	ND
7	1	2	25	40	20	49	6.5	0.8	1.1
8	1	2	25	40	65	75	5.4	2.0	1.5
9	1	1	25	40	20	45	10.8	0.6	2.6
10	3	1	10	40	20	64	1.0	ND	13.7
11	3	1	10	40	65	79	ND	ND	25.0
12	1	5	10	40	20	23	1.4	0.6	ND

[a] Yield based on the limiting substrate, by HPLC potency relative to a standard solution of **9**. [b] Impurities with >0.5% peak area (PA) based on HPLC integration; not adjusted for UV response factor at 235 nm. ND = <0.5% PA.

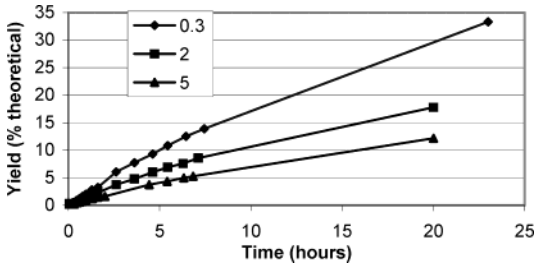


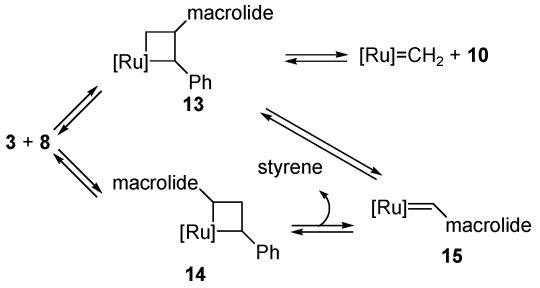
FIGURE 1. Kinetics of product formation is dependent on the stoichiometry of reactants. The plot label indicates the stoichiometry of **6** relative to **8** in the reaction mixtures (e.g., 5 means 5 equiv of **6** and 1 equiv of **8**).

HPLC, the peak integration consistently furnished >95:5 ratio in favor of the desired *E*-configuration in the newly formed disubstituted olefin,[7,8] and >90% of the macrolide was typically accountable as either starting material **8** or product **9**. The anticipated vinylquinoline homodimer **11** and macrolide homodimer **12** were observed in small quantities when an excess of **6** was present, indicating a slow depletion of **8** to nonproductive pathways. When **8** was present in equal amounts or greater, dimer **12** grew significantly (entries 9−11). These results suggest that macrolide dimerization occurs at a much slower rate than productive CM and is therefore suppressed when **6** is present in excess. The slow dimerization of **6** is consistent with the literature report that stilbene formation via dimerization of styrene is a slow process in the presence of the Schrock's catalyst (**4**).[5b]

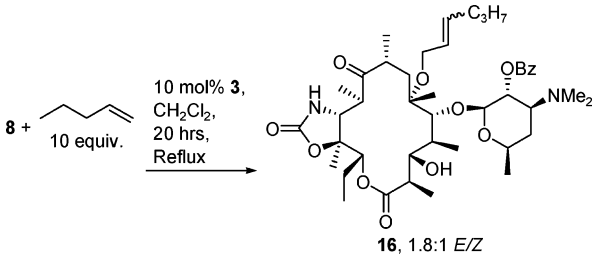
Along with the desired product, a cinnamyl impurity **10** was also generated in these CM reactions. Based on the mechanism, **10** can result from **13**, which can be derived either directly from **3** and **8** or via **15** and the free styrene released from the catalyst (Scheme 3).

The stability of the desired product **9** was challenged to determine if the reactions were susceptible to secondary metathesis reactions. In the presence of 1.0 equiv of styrene under reaction conditions, **9** was recovered without any detectable conversion to **10**. In this case, some styrene dimerized to give stilbene (~20% peak area (PA) by HPLC). These data allowed us to conclude that the product formation was an irreversible process.

SCHEME 3



SCHEME 4



The small amounts of homodimers **11** and **12** found in these CM reactions led us to investigate their individual reactivity under the reaction conditions. After refluxing in methylene chloride for 20 h in the presence of Grubbs' catalyst **3**, macrolide **8** was converted to a complex mixture consisting of recovered **8** (39.6% PA), cinnamyl ether **10** (11.9% PA), and homodimer **12** (43.6% PA). Styrene was also identified by HPLC (1.0% PA), indicating that **3** was initiated as proposed in Scheme 3. When 10 equiv of 1-pentene was included at the beginning of the reaction (Scheme 4), a large amount of the coupled product **16** (87.1% PA, 1.8:1 *E*/*Z* selectivity) was detected.[7,8] Being an unhindered alkene, 1-pentene dimerizes quickly to form 4-octene.[10] It can be rationalized that due to substrate sterics, **8** is not as reactive as unhindered terminal alkenes in intermolecular metathesis reactions.

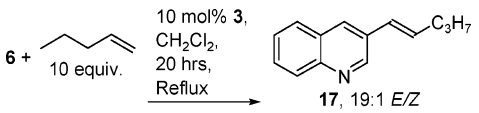
(7) The *E*/*Z* selectivity does not change over the course of the reaction.

(8) The rationale behind olefin selectivity is not completely understood. Literature precedence suggests chelation[9a,b] and electronics[9c] both modulate the olefin geometry.

(9) (a) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209−2212. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451−1454. (c) Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998−10999.

(10) 4-Octene was identified by GC, but its yield and *E*/*Z* selectivity were not determined.

SCHEME 5



When **6** was refluxed with 10 mol % **3** in methylene chloride (in the absence of **8**), most of the starting olefin was recovered after 20 h. A very small amount of homodimer **11** was detected by HPLC (<2.0% PA). With 10 equivalents of 1-pentene added (Scheme 5), the CM product (**17**, 94.6% PA, 19:1 *E*/*Z* selectivity) was formed along with 4-octene.[7,8,10] These data suggest that the quinoline-carbene species formed is electronically unfavorable to continue the catalytic cycle in the absence of a suitable coupling partner such as **8** or 1-pentene. In fact, the authentic sample of **11**, required for characterization purposes, was generated from reacting **6** with 9 mol % of Grubbs' second-generation catalyst[11] in refluxing methylene chloride for 4 days. In conclusion, these experiments showed that the differences in reactivity between **8** and **6** provide the key opportunity to pursue the CM pathway as the preferred one, where self-dimerization pathways are suppressed by high steric demands of **8** and the poor relative reactivity of **6**.[12]

Two other solvents commonly used with the Grubbs' catalyst were tested in the reaction between **8** and **6**. Toluene was investigated briefly and was found to be ineffective in dissolving **6**, resulting in very low conversion to **9**. On the other hand, 1,2-dichloroethane consistently provided results more inferior than did methylene chloride. This discrepancy led us to perform a kinetics study (Figure 2). When 1.0 equiv of **8** and 2.0 equiv of **6** were stirred with 10 mol % **3**, 1,2-dichloroethane initially created a more reactive system than methylene chloride; however, the catalyst activity stalled within 6 h. In methylene chloride, the catalyst remained active for over 20 h, shown by the continual increase in product over time (Table 1, entries 2−5).[13]

Other attempts to optimize the reaction were qualitatively examined. In their mechanistic and reactivity studies, Dias et. al have reported significant reaction rate enhancement by addition of CuCl to reaction mixtures.[14] With our substrates, a faster turnover was indeed observed initially, but the stability of the catalyst was poor, resulting in lower overall conversions to **9** with the added CuCl. It was speculated that the basicity of nitrogen atoms in **8** or **6** might interfere with the catalyst activity. Whereas the intramolecular RCM of amino diene-hydrochloride salts was successful,[15] the HCl salt of **8** reacted poorly to give only 8% conversion to the desired product. Contrary to literature examples of enhanced catalyst turnovers under an ethylene atmosphere,[16] no desired product was found with **8** and **6** under similar conditions.

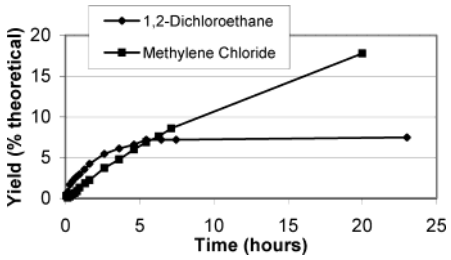
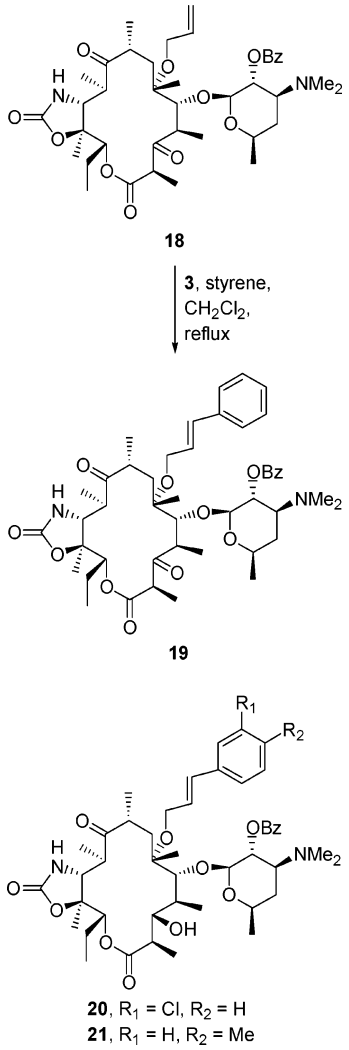


FIGURE 2. Kinetic study in 1,2-dichloroethane vs methylene chloride.

SCHEME 6



Several other catalytic systems were investigated. Other ruthenium-based catalysts (alkylidene,[17] homobimetallic,[18] allenylidene,[19] and Nolan's[20]) tend to give

(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(12) In the course of preparing this manuscript, reference 3a and the following article were published: Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

(13) Reactions in chloroform resulted in unsatisfactory results with several new impurities.

(14) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887−3897.

(15) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.

(16) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(17) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041.

(18) Dias, E. L.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2758−2767.

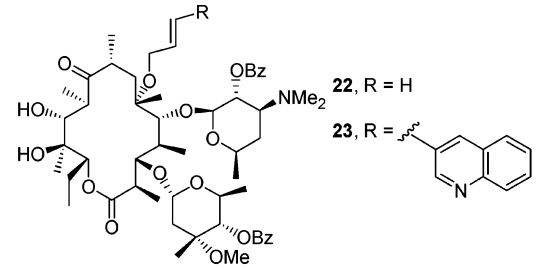
(19) (a) Furstner, A.; Ackermann, L. *Chem. Commun.* **1999**, 95−96. (b) Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2249−2250. (c) Furstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1998**, 1315−1316.

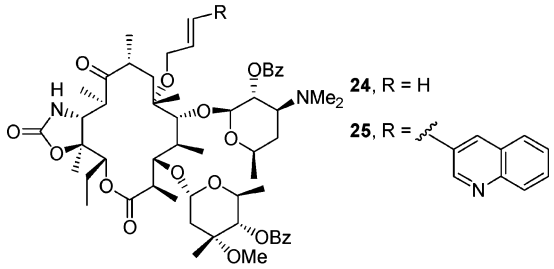
(20) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678.

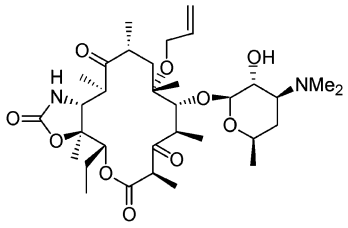
lower conversions than **3**. Grubbs' second-generation catalyst[11] was also inferior to **3** as a facilitator of the olefin CM reaction. Instead, its higher reactivity promoted homodimerization of the substrates. Nugent's tungsten catalyst[21] and Schrock's molybdenum catalyst[5] decomposed in the presence of our substrates, and no metathesis product was detected in either case.

The scope of the olefin CM involving a 6-*O*-allyl-protected macrolide was further demonstrated by treatment of **8** and **3** (catalytic) with 2.0 equiv of styrene in refluxing CH_2Cl_2 (Scheme 2) to generate **10**. The desired *E*-configuration of the newly formed olefin was identified by the large ^3J coupling between the two olefinic protons (15.8 Hz)[7,22] Under similar conditions, **18** also reacted with styrene to give **19** (see Scheme 6).[22] 3-Chlorostyrene and 4-methylstyrene also coupled with **8** (3.0 equiv) in the presence of 10 mol % **3** to yield products **20** and **21** after 20 h in 58 and 78% yield, respectively.[22,23]

Three other macrolide substrates were tested in olefin CM reactions with **6**. Utilizing the optimal conditions developed for **9**, although not practical, excess macrolide **22** (3.0 equiv) underwent olefin CM reaction with **6** (1.0 equiv) in refluxing methylene chloride (20 h) to give **23** in 86% yield based on the amount of the limiting reagent charged.[22,23] Under the same conditions, **24** furnished 64% yield of **25**.[22,23] Finally, **26** also reacted with **6** to yield ABT-773 (**1**, 39% yield) as the ultimate step in the synthesis of **1**.[22,23]







26

Conclusions

Olefin CM has been demonstrated for the construction of the 6-*O*-propenylquinoline side chain of ABT-773 (**1**) and intermediates. In most cases, reactions of **8** with **6** resulted in product **9** with >95:5 *E*-selectivity in modest to good yields. These CM reactions were generally clean with small amounts of homodimer. However, these reactions were complicated by the formation of the cinnamyl impurity **10**.

The data suggest that the large size of the macrolide substrates hindered formation of homodimer **12** under the reaction conditions. In the case of vinylquinoline **6**, the electronic nature of this substrate precluded dimerization to occur. These two advantages combined to favor the CM pathway. As of this report, we have not identified a catalyst more effective than **3** for the elaboration of 6-*O*-allyl erythronolides.

(21) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992−8998.
(22) Greater than 95:5 *E*/*Z* selectivity.
(23) Unoptimized yields.

Experimental Section

General Procedure for Olefin CM. To a 10-mL round-bottom flask was charged **8** (0.1 mmol), **6** (0.2 mmol), and CH_2Cl_2 (5.0 mL) followed by **3** (10 mol %). The solution was heated to reflux under either nitrogen or argon atmosphere. At the conclusion of the reaction, the mixture was diluted and assayed for product against an authentic sample of product.

Acknowledgment. We thank Dr. Casey Chun Zhou of the Structural Chemistry Department for her assistance with NMR studies of product mixtures, and Dr. Steve A. King of the Process Chemistry Research and Development Department for his helpful discussion.

Supporting Information Available: Includes the general methods section, plus synthesis and characterization data for compounds **6**, **10**−**11**, **16**−**17**, and **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049737N