JOC Article

Allylation of Erythromycin Derivatives: Introduction of Allyl Substituents into Highly Hindered Alcohols

Eric J. Stoner,* Matthew J. Peterson,[1] Michael S. Allen, John A. DeMattei,[2] Anthony R. Haight, M. Robert Leanna, Subhash R. Patel, Daniel J. Plata, Ramiya H. Premchandran,[3] and Michael Rasmussen

Global Pharmaceutical Research and Development, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064-6290

eric.stoner@abbott.com

Received June 23, 2003

Functionalized erythromycin 9-oxime derivatives are 6-*O*-allylated under mild conditions using substituted allyl *tert*-butyl carbonates under palladium(0) catalysis. This allylation works well where traditional ether-forming protocols function poorly. Allyl *tert*-butyl carbonates provide higher yields in this reaction than lesser substituted carbonates such as ethyl or isopropyl. Aryl-substituted allyl carbonates or carbamates may be employed as well and, when used, produce *trans*-olefinic products.

Introduction

Nearly 50 years after its discovery, erythromycin A (**1**, Figure 1) remains one of the most widely used antibiotics in the world.[4] Additionally, antibiotics based on this macrolide skeleton continue to be powerful treatments against a wide variety of infections. Erythromycin A, however, has a poor pharmacokinetic profile with limitations that include instability in gastric acid, short elimination half-life, gastrointestinal irritation, and a limited spectrum of activity.[5] Moreover, the developing global resistance of bacteria to erythromycin A and other antibiotics is a pivotal factor in the continuing search for more effective medicines.[6]

One key feature of new macrolide antibiotics is modification of the macrolide ring to reduce degradation in gastric acid. The acid-induced formation of the 6,9-hemiketal initiates a cascade of reactions that results in compounds that lack the desired antibiotic properties, but which often possess undesirable motilin activity.[7] One solution to this problem is to "block" the 6-hydroxyl position with an alkyl substituent, thereby preventing formation of the 6,9-hemiketal and its degradative pathway.[8] In clarithromycin **2** (Biaxin), for example, the introduction of the 6-*O*-methyl substituent has been demonstrated to ameliorate gastrointestinal irritation and provide enhanced overall activity relative to erythromycin.[5]

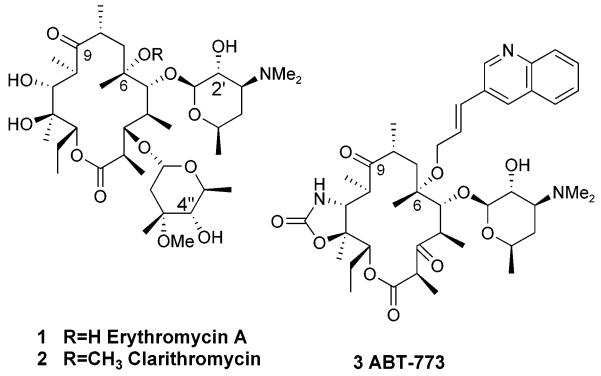


FIGURE 1. Macrolide antibiotics.

A third-generation macrolide structure, the ketolides, characterized by the removal of the cladinose sugar and subsequent oxidation to the 3-ketone, has recently emerged from our laboratories.[9] Abbott's ketolide clinical candidate, ABT-773 (**3**), is additionally 6-*O*-substituted with a *trans*-2-propenyl-3-(3-quinoline) (PQ) linkage.[10]

Results and Discussion

O-Alkylation at the 6-position in functionality-rich macrolides via Williamson ether formation protocols is

* To whom correspondence should be directed.

(1) Current address: Theravance, Inc. 901 Gateway Blvd, S. San Francisco, CA 94080.

(2) Array BioPharma, 3200 Walnut St., Boulder, CO 80301.

(3) Current address: MediChem, 12305 S. New Avenue, Lemont, IL 60439.

(4) Flynn, E. H.; Sigal, M. V., Jr.; Wiley, P. F.; Gerzon, K. *J. Am. Chem. Soc.* **1954**, *76*, 3121.

(5) (a) Charles, L.; Segretti, J. *Drugs* **1997**, *53* (3), 349. (b) Clark, R. F.; Ma, Z.; Wang, S.; Griesgraber, G.; Tufano, M.; Yong, H.; Li, L.; Zhang, X.; Nilius, A. M.; Chu, D. T. W.; Or, Y. S. *Biorg. Med. Chem. Lett.* **2000**, *10* (8), 815.

(6) (a) Ball, P.; Baquero, F.; Cars, O.; File, T.; Garau, J.; Klugman, K.; Low, D. E.; Rubinstein, E.; Wise, R. *J. Antimicrobial Chem.* **2002**, *49* (1), 31. (b) Blondeau, J. M.; DeCarolis, E.; Metzler, K. L.; Hansen, G. T. *Expert Opin. Investig. Drugs* **2002**, *11* (2), 189.

(7) (a) Klein, L. L.; Freiberg, L. A.; Kurath, P.; Henry, R. F. *J. Org. Chem.* **1993**, *58* (11), 3209. (b) Burnelle-Curty, C.; Faghih, R.; Pagano, T.; Henry, R. F.; Lartey, P. A. *J. Org. Chem.* **1996**, *61* (15), 5153.

(8) Another solution is the conversion of the ring to an azalactone via Beckmann rearrangement as in azithromycin: Yang, B. V.; Goldsmith, M.; Rizzi, J. P. *Tetrahedron Lett.* **1994**, *35* (19), 3025.

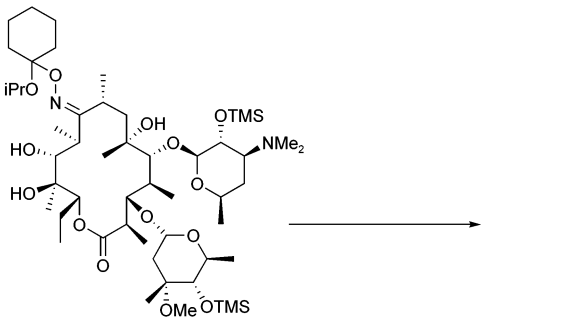
(9) For an excellent review of ketolide chemistry and activity see: Ma, Z.; Nemoto, P. A. *Curr. Med. Chem.—Anti-Infective Agents* **2002**, *1* (1), 15.

(10) (a) Or, Y. S.; Clark, R. F.; Wang, S.; Chu, D. T. W.; Nilius, A. M.; Flamm, R. K.; Mitten, M.; Ewing, P.; Alder, J.; Ma, Z. *J. Med. Chem.* **2000**, *43* (6), 1045. (b) Or, Y. S.; Ma, Z.; Clark, R. F.; Chu, D. T.; Plattner, J. J.; Griesgraber, G. U.S. Patent 5,866,549, 1999.

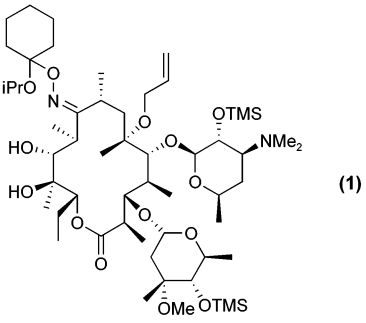
10.1021/jo034883z CCC: $25.00
Published on Web 10/16/2003

not a trivial matter and involves the careful balancing of many factors: base, alkylating agent, protecting groups, rate, and order of addition of reagents and temperature. Even after extensive optimization, formation of the desired 6-*O*-methyl isomer in **2** is accompanied by undesired overalkylated species.[11] Unfortunately, attempts to introduce groups larger than methyl at the 6-position via the same protocols have generally resulted in poor conversions and product purity.[11c] To develop an efficient synthesis of **3** requires the development of alternative methodologies.

In an early synthesis of **3**, the 6-*O*-PQ moiety was introduced in two steps: allylation under conditions similar to those employed for the methylation in **2**, followed by Heck coupling with bromoquinoline.[12,13] The initial allylation protocol required slow addition (3−5 h) of a DMSO/THF solution of $KOC(CH_3)_3$ to a *dilute* solution of protected erythromycin A oxime **4** and allyl bromide affording, under the best circumstances, only a 60−75% conversion to **5** with substantial production of overallylated species (eq 1, condition A).



4



5 **(1)**

Conditions:
A: allyl bromide, KO*t*-Bu, DMSO/THF (1:1), 0°C, Yield <45%
B: allyl *t*-butyl carbonate (**6**), $Pd(OAc)_2$, Ph_3P, THF, Yield 77% (unoptimized)

The isolated yields from this process were generally 40−50%, and all attempts to further improve this procedure have thus far failed.

The transition-metal-catalyzed allylation of nucleophiles has proven to be a versatile methodology in organic synthesis. A variety of nucleophiles have been shown to efficiently couple with palladium π-allyl complexes, and with advances in the regioselective and enantioselective reactions, the utility of the chemistry continues to be expanded.[14] The palladium-catalyzed allylation of alcohols, however, has been utilized to a much lesser extent, owing to the generally poor nucleophilicity of alcohols. Most examples of oxygen nucleophiles have been limited to phenols,[15] intramolecular allylations, and other substrate specific systems.[16]

While Sinou's group has reported moderate to excellent yields in the allylation of carbohydrate substrates using allyl ethyl carbonate, an excess (2−6 equiv) of the allylating agent was required.[17] It seemed likely that the spectator alkoxy group liberated from the carbonate competes with the desired nucleophile for the π-allyl palladium reagent. We reasoned that the increased steric requirements of the spectator *tert*-butoxy group could be utilized to competitively favor allylation of the desired alcohol.[18,19] Thus, exposure of **4** to 1.45 equiv of allyl *tert*-butyl carbonate **6** in the presence of $Pd(OAc)_2/Ph_3P$ in refluxing THF afforded the desired 6-*O*-allyl derivative **5** in **77**% isolated yield (eq 1, condition B).

The effects of the spectator group are quite pronounced (see Table 1). In attempts to convert protected oxime **4** to its 6-*O*-allyl derivative **5**, allyl methyl[20] and allyl ethyl carbonate proved equally inefficient and unselective, despite the use of large excesses of reagent. Allyl isopro-

(11) (a) Watanabe, Y.; Morimoto, S.; Adachi, T.; Kashimura, M.; Asaka, T. *J. Antibiotics* **1993**, *46* (4), 647. (b) Morimoto, S.; Adachi, T.; Matsunaga, T.; Kashimura, M.; Asaka, T.; Watanabe, Y.; Sota, K.; Sekiuchi, K. U.S. Patent 4,990,602, 1991. (c) Morimoto, S.; Misawa, Y.; Adachi, T.; Nagate, T.; Watanabe, Y.; Omura, S. *J. Antibiotics* **1990**, *43* (5), 286.

(12) For an improved synthesis of ABT-773 incorporating this chemistry, see: Plata, D. J.; Leanna, M. R.; Rasmussen, M.; McLaughlin, M. A.; Condon, S. L.; Kerdesky, F. A. J.; King, S. A.; Peterson, M. A.; Stoner, E. J.; Wittenberger, S. J., submitted.

(13) (a) Stoner, E. J.; Peterson, M. J.; Ku, Y.-Y.; Cink, R. D.; Cooper, A. J.; Deshpande, M. N.; Grieme, T.; Haight, A. R.; Hill, D. R.; Hsu, M. C.-P.; King, S. A.; Leanna, M. R.; Lee, E. C.; McLaughlin, M. A.; Morton, H. E.; Napier, J. J.; Plata, D. J.; Raje, P. R.; Rasmussen, M.; Riley, D.; Tien, J. J.-H. J.; Wittenberger, S. J. U.S. Patent 6,437,106, 2002. (b) Allen, M. S.; Premchandran, R. H.; Chang, S.-J.; Condon, S.; DeMattei, J. A.; King, S. A.; Kolackowski, L.; Manna, S.; Nichols, P. J.; Patel, H. H.; Patel, S. R.; Plata, D. J.; Stoner, E. J.; Tien, J. J.-H. J.; Wittenberger, S. J. U.S. Patent 6,579,986, 2002.

(14) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol 2. (b) Trost, B. M.; Van Vranken, D. L. *Chem Rev*. **1996**, *96* (1), 395. (c) Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5. (d) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley and Sons: New York, 1995. (e) Harrington, P. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W. Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 798−903

(15) (a) Larock, R. C.; Lee, N. H. *Tetrahedron Lett*. **1991**, *32* (44), 6315. (b) Muzart, J.; Genet, J.-P.; Denis, A. *J. Organomet. Chem*. **1987**, *326* (1), C23.

(16) (a) Burke, S. D.; Jiang, L. *Org. Lett*. **2001**, *3*, 1953. (b) Vares, L.; Rein, T. *Org. Lett*. **2000**, *2* (17), 2611. (c) Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron Asym*. **1999**, *10*, 1069. (d) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *J. Chem. Res. (S)* **1998**, 105. (e) Thorey, C.; Wilken, J.; Henin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett*. **1995**, *36*, 5527. (f) Massacret, M.; Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett*. **1994**, *35*, 6093. (g) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc*. **1998**, *120*, 12702. (h) Cuiper, A. D.; Kellogg, R. M. *Chem. Commun*. **1998**, 655

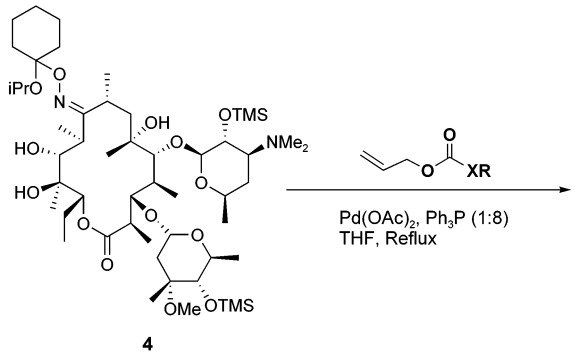
(17) (a) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett*. **1989**, *30* (35), 4669. (b) Lakhmiri, R.; Lhoste, P.; Sinou, D. *Synth. Commun*. **1990**, *20* (10), 1551. (c) Kumar, V.; Gopalakrishnan, V.; Ganesh, K. N. *Bull. Chem. Soc. Jpn*. **1992**, *65* (6), 1665. (d) Lakhmiri, R.; Lhoste, P.; Kryczka, B.; Sinou, D. *J. Carbohydr. Chem*. **1993**, *12* (2), 223. (e) Lakhmiri, R.; Lhoste, P.; Boullanger, P.; Sinou, D. *J. Chem. Res. (S)* **1990**, 342.

(18) An alternative approach is incorporation of the desired alcohol in the allyl carbonate: Oltvoort, J. J.; Kloosterman, M.; VanBoom, J. H. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 501.

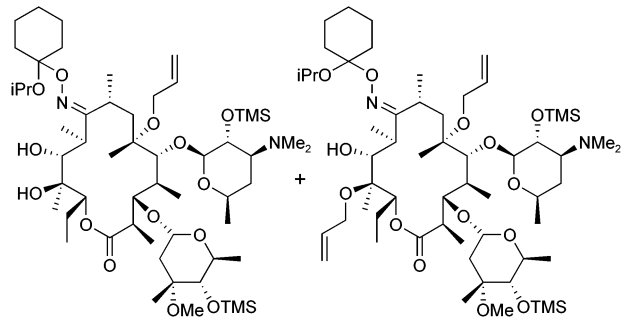
(19) Reviews of π-allyl palladium chemistry (a) Trost, B. M. *Acc. Chem. Res*. **1980**, *13* (11), 386. (b) Tsuji, J. *Tetrahedron* **1986**, *42* (16), 4361.

(20) Commercially available.

TABLE 1. Effects of Carbonate/Carbamate Substitution on Allylation



4



5 **7**

		% yield[a]		
XR	equiv	**5**	**4**	**7**
OCH_3	7.0	67	28	5
OC_2H_5	7.0	69	19	11
O-*i*-C_3H_7	1.8	80	13	7
N(*i*-C_3H_7)$_2$	1.8	41	59	0
	2.9	71	29	0
O-*t*-C_4H_9 (**6**)	1.5	96	0	4
	4.0	0	0	100

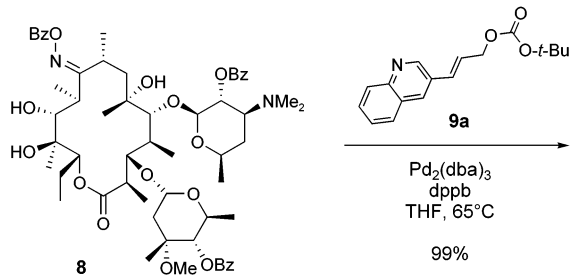
[a] Ratios obtained from HPLC (205 nm) and are uncorrected for response factors.

pyl carbonate,[21] which liberates more hindered isopropoxide as the spectator, produces higher conversions. Allyl *N*,*N*-diisopropyl carbamate[22] may be employed as well; however, high overall conversions do not seem attainable without the use of a considerable excess of reagent. Of the carbonates and carbamate examined, only allyl *tert*-butyl carbonate **6** produced a high degree of selective monoallylation. The use of a larger excess of **6** (4.0 equiv) affords exclusively 6,12-bis-*O*-allylated compound **7**.

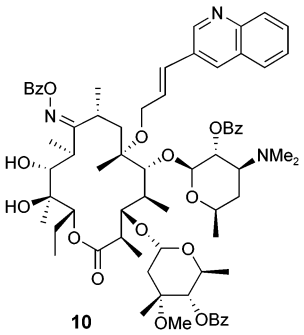
The regioselectivity of methylation in **2** for the 6-hydroxy position has been studied by computational methods and appears to be derived from altered acidities of the macrolide hydroxyls.[11a,23] As an extension of this work, we have explored this allylation chemistry with respect to more accessible aliphatic alcohols[24] and have noted that alcohol acidity plays a significant role in selectivity. All of the oximes examined in this work are of the *E*-configuration shown (the thermodynamically preferred isomer).[25] The procedure used for the isolation of the parent erythromycin 9-oxime, the starting material for all of our substrates, incorporates a crystallization protocol that virtually eliminates the other geometrical isomer, which is typically present in from 5 to 7%.[11]

We have observed this allylation strategy to be useful for erythromycin derivatives with a wide variety of protecting groups (see Tables 2 and 3). Labile trimethylsilyl ethers (as in **4** and **13**) remain intact during allylation, whereas other alkylation protocols resulted in their cleavage, contributing to significant purification difficulties. A variety of protecting groups may also be successfully employed on the 9-oxime as well. Both acyl moieties (as represented by benzoate **8**) and ketals (**4**) may be used with success. When the free oxime (**13**) is present, initial allylation with **6** occurs at the more nucleophilic oxime-hydroxyl, yielding 9-*O*-allyl derivative **14** (see Table 3, entry 10). Subsequent allylation of **14** with **6** occurs, as expected, at the 6-hydroxyl, affording 6,9-bis-*O*-allyl adduct **15** (see Table 3, entry 11).

A principle advantage of this methodology is the ability to use substituted allyl carbonates as well. For example, carbonate **9a** couples cleanly with **8**, affording the corresponding 6-*O*-PQ derivative **10**.



8



10 (2)

We have demonstrated that **8** reacts equally well with cis-primary carbonate **9b** or secondary carbonate **9c** (Table 3, entries 3−5). Ketal-protected oxime **4** acts similarly and is allylated in high yield with carbonates **9a**−**c**, affording **12** (Table 3, entries 7−9). In each case, the crude yield is nearly quantitative and only the trans-

(21) Brettle, R.; Khan, M. A. *J. Chem. Res.* **1989**, *1*, 240.

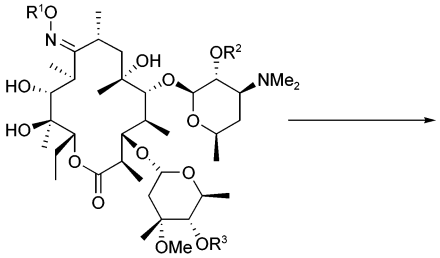
(22) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.

(23) Goto, H.; Kawashima, Y.; Kashimura, M.; Morimoto, S.; Osawa, E. *J. Chem. Soc., Perk. Trans 2* **1993**, 1647. The results obtained by these computational methods are consistent with observed experimental data in ref 11.

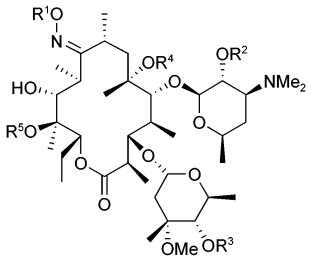
(24) (a) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. *J. Org. Chem.* **2003**, *68*, 8092−8096. (b) Another application of this chemistry has been published based on prior verbal communication: Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58* (10), 2027.

(25) Erythromycin A oxime (*E* and *Z* isomers): (a) Egan, R. S.; Freiberg, L. A.; Washburn, W. H. *J. Org. Chem.* **1974**, *39* (17), 2492, (b) Massey, E. H.; Kittchell, B.; Marti, L. D.; Gerzon, K.; Murphy, H. W. *Tetrahedron Lett.* **1970**, *11* (2), 157. (c) Hatton, I. K.; Tyler, J. W. *Tetrahedron Lett.* **1989**, *30* (5), 605.

TABLE 2. Starting Materials and Allylation Products



Starting Materials	R^1	R^2	R^3
4	$C_6H_{11}O$-*i*-Pr	TMS	TMS
8	Bz	Bz	Bz
13	H	TMS	TMS



Products	R^1	R^2	R^3	R^4	R^5
5	$C_6H_{11}O$-*i*-Pr	TMS	TMS	C_3H_5	H
7	$C_6H_{11}O$-*i*-Pr	TMS	TMS	C_3H_5	C_3H_5
10	Bz	Bz	Bz	PQ	H
11	Bz	Bz	Bz	C_3H_5	H
12	$C_6H_{11}O$-*i*-Pr	TMS	TMS	PQ	H
14	C_3H_5	TMS	TMS	H	H
15	C_3H_5	TMS	TMS	C_3H_5	H

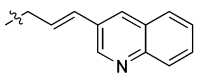
PQ = 

TABLE 3. Allylation of Erythromycin A Oxime Derivatives

entry	starting material	carbonate	product	% yield[a]
1	**4**	**6**	**5**	77
2	**4**	**6** (xs)	**7**	75
3	**8**	**9a**	**10**	99
4	**8**	**9b**	**10**	89
5	**8**	**9c**	**10**	95
6	**8**	**6**	**11**	91
7	**4**	**9a**	**12**	92[b]
8	**4**	**9b**	**12**	94
9	**4**	**9c**	**12**	97
10	**13**	**6**	**14**	94
11	**13**	**6** (xs)	**15**	82

[a] Isolated yield of material >95% pure. [b] Crude yield.

terminally substituted olefin (**10**, **12**) is detected.[26] With respect to the synthesis of ABT-773 (**3**), this new allylation protocol represents a significant development in that two problematic, low yielding steps from the original synthetic protocol (Williamson ether formation and Heck coupling) are replaced with a single high-yielding convergent transformation.[12]

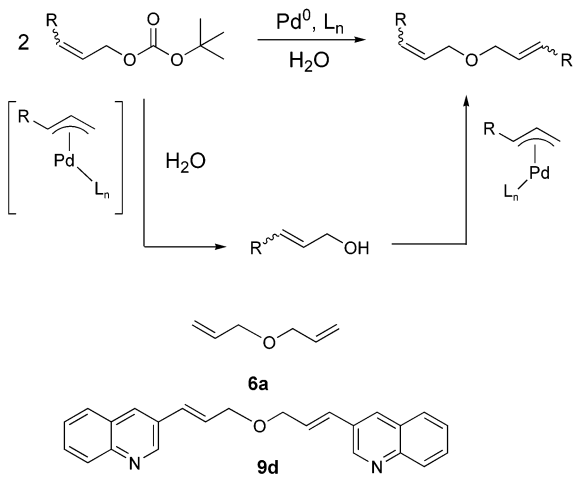


FIGURE 2. Formation of bis-allyl ethers.

In general, either THF or toluene may be employed as solvent for these allylations. Since the reaction must be run under strictly anhydrous conditions (water content < 2 mol %), toluene offers the advantage of more efficient removal of water by azeotropic distillation. This is accomplished by the in vacuo distillation of a portion of the toluene from the starting materials *prior* to the addition of the catalyst. A similar, albeit less efficient, process may be accomplished with THF.

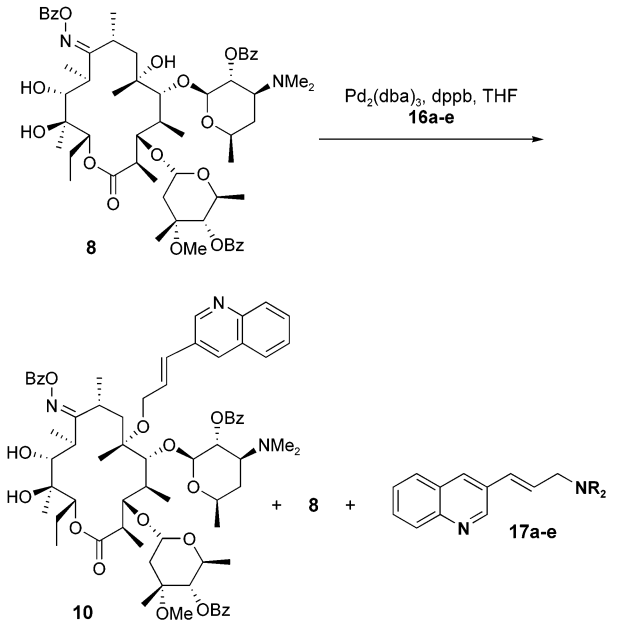
Water is detrimental to the reaction by competing as a nucleophile *twice*, affording dimeric allyl ethers, after the initial formation of an intermediate allyl alcohol (Figure 2). While bisallyl ether **6a** (from **6**) has not been observed (and is not of concern to us due to its volatile nature), dimeric ethers arising from **9a**−**c**, such as **9d**, have been detected and represent a minor purification issue. Ether **9d** is the principle carbonate-related impurity in "wet" allylations and can be independently prepared by the reaction of **9a** with water in the presence of a Pd(0) catalyst. The formation of bis-allyl ethers in this manner is an interesting testament to the low reactivity of our substrates as even trace amounts of water are removed by ether formation prior to the initiation of our desired macrolide allylation. Under strictly anhydrous conditions, however, only a slight molar excess of carbonate (∼1.05 equiv) is required to give complete consumption of starting material.

Although a variety of Pd(0) catalysts will work effectively in this allylation, we prefer to use the $Pd(OAc)_2$/Ph_3P system rather than $Pd_2(dba)_3$ or $Pd(Ph_3P)_4$ for economic and stability reasons.[27] In general, laboratory-scale allylations use 0.5−1 mol % palladium, while larger scale reactions can be accomplished with significantly less catalyst (0.05% or less). The preferred ligands are dppb or Ph_3P.[28] Reactions are typically performed at reflux temperature and are complete in 1−3 h with 1 mol % catalyst loading.

(26) Reviews of selectivities and basic aspects of π-allyl palladium chemistry: (a) Tsuji, J. *Pure Appl. Chem.* **1989**, *61* (10), 1673. (b) Trost, B. M. *Angew. Chem., Int. Ed. Eng.* **1989**, *28*, 1173.

(27) In situ formation of Pd(0) from $Pd(OAc)_2$: Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11* (9), 3009.

TABLE 4. Allylation of Oxime 8 with Carbamates 16a−e



		% yield[a]	
carbamate	equiv	product (**10**)	amine (**17a−e**)[b]
16a	2.6	36	35
16b	3.1	63	19
16c	2.4	20	0
16d	1.6	0	100
16e	2.4	<5	>90

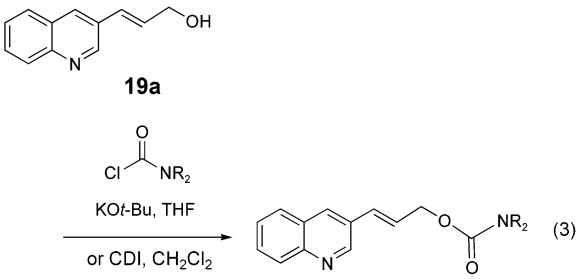
[a] Relative HPLC ratios unadjusted for response factors. Remaining material is predominantly starting material **8**. [b] Amines **17a−e** were characterized by mass spectroscopy only.

Polymer-supported Pd catalysts were not examined with respect to this chemistry, owing in part to the rapid development and scale-up of the key allylated intermediate. Although residual metal contamination can be a significant issue in pharmaceutical intermediates, the allylation in ABT-773 occurs early in the synthesis, and residual palladium is reduced significantly throughout the remaining synthetic procedures prior to final active pharmaceutical ingredient (API) isolation.

Although reactions of this type involving more nucleophilic partners (malonates, phenols, amines) have been performed at 25 °C or colder, in our hands allylations of these highly hindered macrolides have not been observed below 50 °C. We have demonstrated that the π-allyl species forms at room temperature by trapping experiments with *n*-Bu_3SnH.

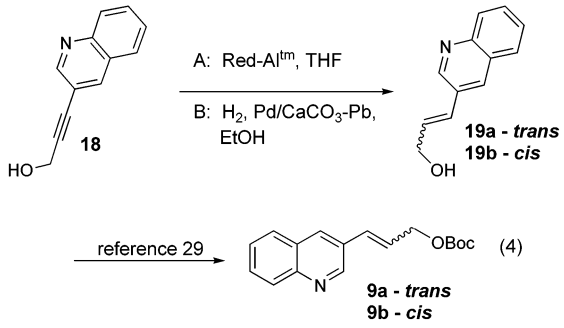
Our early sucesses with an allyl carbamate (Table 1) led us to reexamine this functionality with respect to the PQ side chain. To this end, substituted carbamates **16a−e** were prepared and their utility examined in the allylation of oxime **8** (see eq 3, Table 4). These reactions suffered from the generation of a competitive nucleophilic amine once the π-allyl Pd species was formed. Not surprisingly, the most hindered carbamates (**16a−c**) produced the highest conversions of starting material **8** to product **10**. Morpholine-derived carbamate **16d** and imidazolide **16e** proved to be unproductive in this allylation, affording as the principle product the corresponding allylamines **17d−e**. These results further emphasize the special nature of the *tert*-butyl carbonate for these allylations. As demonstrated, reactions of **8** with carbonates **6** or **9a−c** are very high yielding using small excesses of reagent.

The carbamates employed were prepared by reaction of *trans*-alcohol **19a** with commercially available carbamoyl chlorides (affording **16a−d**) or 1,1′-carbonyldiimidazole (CDI) (affording **16e**).



16a (R = c-C_6H_{13}), 95%
16b (R = C_6H_5), 80%
16c (R = i-Pr), 100%
16d (NR_2 = morpholine), 44%
16e (NR_2 = 1-imidazole), 96%

The *tert*-butyl carbonates (**6**, **9a−c**) used in these allylations are conveniently obtained by the reaction of the appropriate alcohols with di-*tert*-butyl dicarbonate under phase transfer conditions.[29] For example, allyl alcohol is converted into **6** in 68% yield. Carbonates **9a** or **9b** are prepared from alkenols **19a** and **19b**, which are derived from propargylquinoline alcohol **18**[30] via one of two reductive protocols (eq 4). *trans*-Alkenol **19a** was



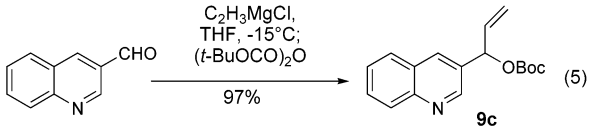
generated by chemical reduction of the alkyne using Red-Al. The cis-isomer **19b** was prepared by partial hydrogenation in the presence of a Lindlar-type catalyst (5% $Pd/CaCO_3-Pb$). A secondary sulfur-based catalyst poison, 3,6-dithia-1,8-octanediol, is employed to slow the hydrogenation and provide control over alkane formation. This hydrogenation also generated small amounts of **19a**, which was effectively removed by crystallization. Secondary carbonate **9c** was prepared by treatment of commercially available 3-quinolinecarboxaldehyde with vinyl

(28) Less reactive carbonates **9a−c** do not react well using Ph_3P as ligand: dppb is preferred.

(29) Houlihan, F.; Bouchard, F.; Frèchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153.

(30) (a) Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D. *J. Med. Chem.* **1996**, *39* (16), 3179. (b) Yamanaka, H.; Shiraiwa, M.; Edo, K.; Sakamoto, T. *Chem. Pharm. Bull.* **1979**, *27* (1), 270.

Grignard, followed by in situ quenching of the resulting alkoxide with di-*tert*-butyl dicarbonate (eq 5).



9c (5)

Experimental Section

Representative Allylation Procedure. 2′,4″-*O*-dibenzoyl-6-*O*-PQ-erythromycin A 9-*O*-Benzoyloxime (10) (Table 3, Entry 3). To a suitable reaction vessel was charged erythromycin A oxime tribenzoate **8** (41.1 g, 38.6 mmol, 1 equiv) and *trans*-carbonate **9a** (12.6 g, 44.2 mmol, 1.15 equiv) in 300 mL of toluene. The solvent was removed in vacuo and 300 mL of THF added (K.F. titration 0.01%). The catalyst $Pd_2(dba)_3$ (170 mg, 0.005 equiv) and dppb (160 mg, 0.01 equiv) were added, and the reaction mixture was degassed by evacuation and venting to nitrogen three times. The reaction was heated to reflux for 3 h, cooled to room temperature, and reduced to dryness in vacuo. The crude residue (49 g, 105% theory) was dissolved in 100 mL of CH_3CN at 60 °C, filtered, and reduced to dryness, affording 46.8 g of **10** (99%) as a pale yellow foam (>96% purity by HPLC).

Summary

We have demonstrated a new and highly effective method for the Pd-catalyzed *O*-allylation of the sterically hindered 6-hydroxyl of erythromycin derivatives with substituted allyl *tert*-butyl carbonates. This allylation protocol allows for the full elaboration of the 6-OH in ABT-773 in one synthetic step, with high yield and selectivity. This methodology offers significant advantages over traditional means for the functionalization of macrolides. Among these benefits are operational simplicity; substantial increases in yield, throughput, and product purity; milder reaction conditions; and reduction of hazardous waste. This methodology has been applied to the synthesis of production-scale batches of erythromycin A intermediates. The method should be applicable to a wide array of subtrates with inaccessible or hindered alcohol functionalities.[24a,24b]

Acknowledgment. The authors thank Drs. Momir Cirovic, Steven Hollis, and Ian Malcolm for their invaluable assistance with NMR interpretation and compound characterization.

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

JO034883Z