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# Short and Efficient Synthesis of a Vinyl-Substituted Tricyclic Erythromycin Derivative

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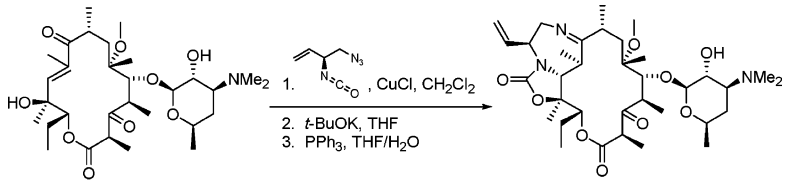
## ABSTRACT




**Tricyclic erythromycin A derivatives are known potent antibacterial agents, but the potential of substituted tricyclic erythromycin A derivatives remains largely unexplored. To study this lead, the tricyclic ring system was synthesized by an efficient three-step synthesis starting from the allylic alcohol utilizing a novel azidoisocyanate. These tricyclic analogues can be used as scaffolds to probe secondary ribosomal binding sites.**

Macrolides have been a mainstay for the treatment of respiratory tract infections for more than 40 years.[1] Macrolide effectiveness is a result of their ability to selectively bind to the bacterial ribosome and inhibit protein synthesis.[2] In the last 10 years, macrolide effectiveness has been diminished due to resistance.[3] Resistance arises from two main mechanisms. The first is ribosome methylation by erm methyltransferases, and the second mechanism is efflux. It is generally accepted that resistance mechanisms can be overcome by increasing the ribosome binding affinity. This hypothesis was addressed by the introduction of ketolides. These modified erythromycin analogues possess 3-keto and 11,12-carbamate functionalities with an aryl group strategically placed to maximize the ribosomal secondary interactions. The two most prominent ketolides, ABT-773[4] and telithromycin,[5] were shown to effectively address the issue of resistance (Figure 1). Another ketolide displaying a favorable profile against resistance is TE-802.[6] TE-802 is characterized by having a ketolide framework with an additional iminoethane bridge spanning the carbamate nitrogen and the C-9 position. TE-802 addresses efflux resistance, but it does not effectively overcome erm resistance. In both ABT-773 and telithromycin, the aryl group tethered to the ketolide core is responsible for overcoming erm resistance. It was theorized that compounds could be developed that would adopt a similar conformation and overcome both erm and efflux resistance. We report herein a short, efficient synthesis of vinyl-substituted, bridged tricyclic ketolides that may serve as useful building blocks for the synthesis of novel ketolides to combat macrolide resistance.

(1) For recent reviews, see: (a) Zhanel, G. G.; Dueck, M.; Hoban, D. J.; Vercaigne, L. M.; Embil, J. M.; Gin, A. S.; Karlowsky, J. A. *Drugs* **2001**, *61*, 443−498. (b) Ma, Z.; Nemoto, P. *Curr. Med. Chem.: Anti-Infect. Agents* **2002**, *1*, 15−34.

(2) Vester, B.; Douthwaite, A. *Antimicrob. Agents Chemother.* **2001**, *45*, 1−12.

(3) Doern, G. V.; Heilmann, K. P.; Huynh, H. K.; Rhomberg, P. R.; Coffman, S. L.; Brueggemann, A. B. *Antimicrob. Agents Chemother.* **2001**, *45*, 1721−1729.

(4) Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Muelbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137−4156.

(5) Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. D.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075−3080.

(6) (a) Asaka, T.; Kashimura, M.; Misawa, Y.; Morimoto, S.; Hatayama, K. U.S. Patent 5631355, 1994. (b) Kashimura, M.; Asaka, T.; Misawa, Y.; Matsumoto, K.; Morimoto, S. *J. Antibiot.* **2001**, *54*, 664−678.

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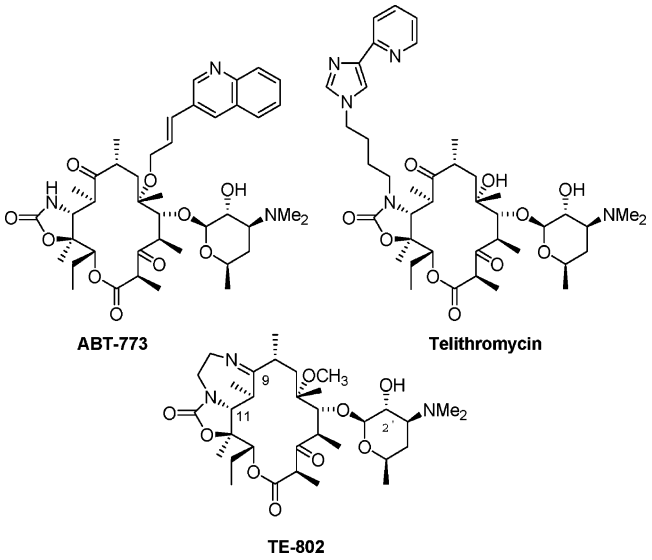
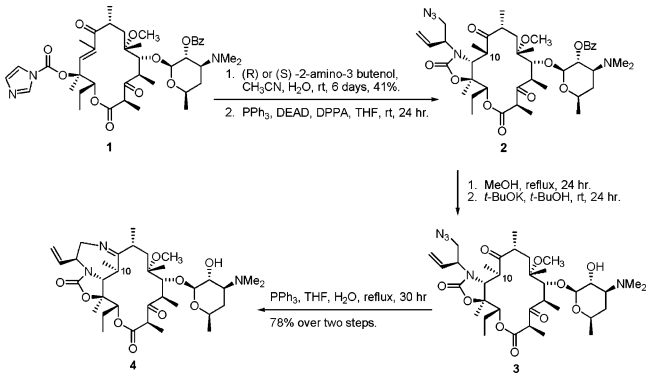



**Figure 1.** Structures of ABT-773, telithromycin, and TE-802.

Historically, the tricyclic erythromycin analogues have been synthesized according to Scheme 1.[7] As illustrated, the

**Scheme 1.** Original Synthesis of Tricyclic Erythromycin Derivatives

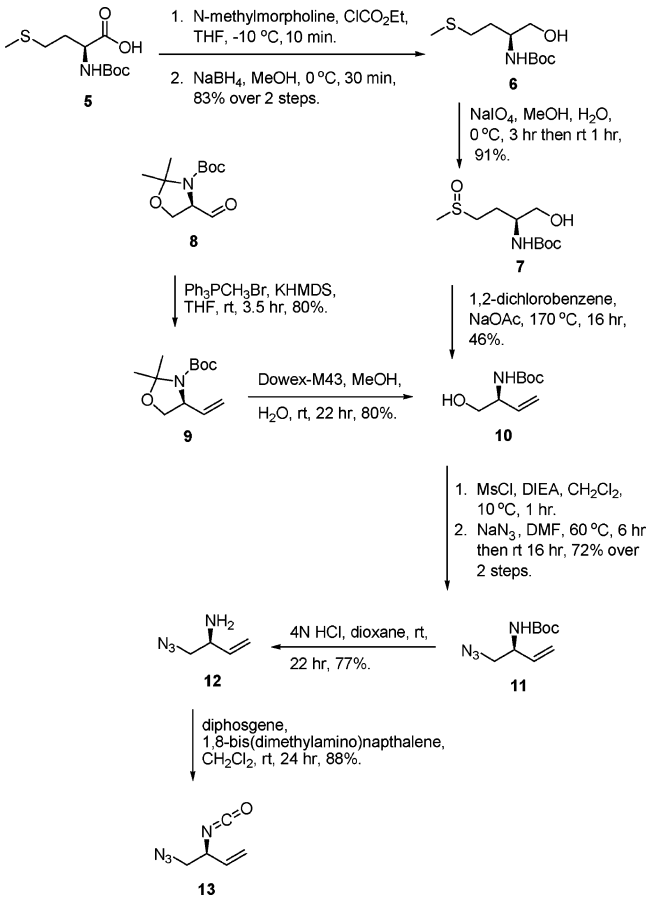



acylimidazolide **1**[8] was treated with either (*R*)- or (*S*)-2-amino-3-butenol depending on the desired isomer in a $CH_3CN/H_2O$ mixture at ambient temperature for 6 days. The resulting cyclic carbamate was accompanied by the formation of substantial amounts of allylic alcohol byproduct **14** and was extremely difficult to purify. The hydroxyl group was next converted to the azide **2** by treatment with diethylazodicarboxylate (DEAD) and diphenylphosphoryl azide (DPPA) in the presence of $PPh_3$. By refluxing in MeOH, the benzoate-protecting group was then removed from the 2′-position. During the cyclization to form compound **2**, epimerization of the C-10 methyl occurs. It was thus necessary to reepimerize C-10 back to the natural isomer. This was accomplished by treating the material with *t*-BuOK in *t*-BuOH at room temperature to give **3**. Finally, the tricyclic ring system could be formed by reduction of the azide with $PPh_3$ to afford the tricyclic derivative **4** in a 78% yield over two steps (Scheme 1).

Aside from the low yields and long reaction times, the major drawback to the original synthesis was the formation of the byproduct **14**. This proved to be difficult to remove from the reaction medium and was a major obstacle in producing sufficient quantities of **4** needed for further investigations. It was therefore necessary to develop a new synthesis and advantageously utilize the unwanted byproduct **14** from the original synthesis as starting material in the new procedure.

It was envisioned that if an appropriately substituted isocyanate such as **13** was condensed with allylic alcohol **14** and further manipulated, then ultimately the target tricycle **4** would be reached. To the best of our knowledge, there has only been one other reported synthesis of an azidoisocyanate.[9] Our synthesis proceeded through two routes that arrive at the common intermediate **10** (Scheme 2). The first route involved reduction of the commercially available *N*-Boc-methionine **5** to the alcohol **6** via the mixed anhydride in 83% according to the procedure of Kokotos, et al.[10] Treatment of the amino alcohol with sodium periodate

**Scheme 2.** Synthesis of the Azidoisocyanate **13**



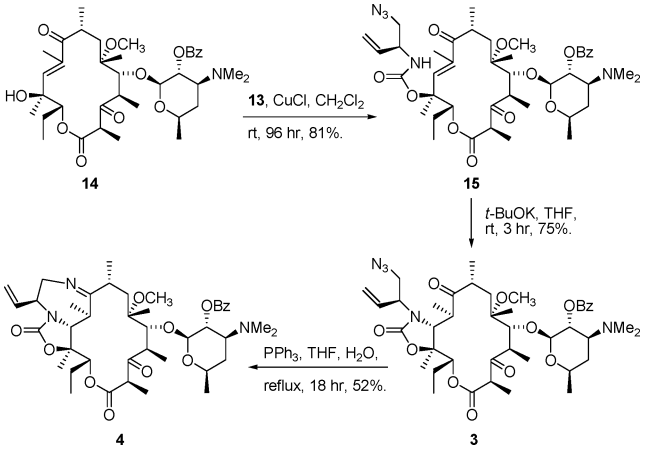

(7) Both the (*R*)- and the (*S*)-isomers were synthesized. For clarity and brevity, only the synthesis of the (*S*)-isomer is shown.

(8) Or, Y. S.; Phan, L. T.; Chu, D. T.; Spina, K. P.; Hallas, R.; Elliott, R. L. WO 9717356, 1997.

afforded the sulfoxide **7** in a 91% yield.[11] Finally, thermal elimination of the sulfoxide at 170 °C gave the common intermediate **10** in a 46% yield.[11] The second route utilized the well-known Garner's aldehyde, **8**. The aldehyde functionality was converted to the olefin **9** via the Wittig reaction utilizing methyltriphenylphosphonium bromide.[12] The isopropylidine was then selectively removed with Dowex-M43 to produce the common intermediate **10** in an 80% yield.[13] Compound **10** was then converted to the azide **11** in a one-pot, two-step procedure by first mesylating the primary alcohol with mesyl chloride and Hunig's base at −10 °C. Displacement with sodium azide in DMF at 60 °C produced **11** in a 72% yield over two steps. Removal of the Boc protecting group to afford **12** was accomplished in a 77% yield with 4 N HCl in dioxane. The azidoisocyanate **13** was then obtained in good yield by treatment of **12** with diphosgene and Proton Sponge.[14]

With the azidoisocyanate **13** in hand, we were then able to construct the erythromycin tricycle **4** (Scheme 3). When

**Scheme 3.** Improved Synthesis of the Tricyclic Erythromycin Analogues




the readily available allylic alcohol **14**[15] was reacted with **13** and DMAP in toluene at 90 °C, the reaction progressed to 90% completion within 2 weeks. Although the reaction was slow, the product was cleanly obtained. It was found, however, that the reaction could be significantly accelerated in the absence of heat by treatment with 1 equiv of CuCl.[16] Thus, when the azidoisocyanate **13** was condensed with the allylic alcohol **14** in the presence of CuCl in $CH_2Cl_2$ at room temperature, the condensation product **15** was obtained in a very clean reaction in an 81% yield within 72 h. Unfortunately the product did not spontaneously cyclize to carbamate **3** as it did in the original route. It was necessary to treat **15** with *t*-BuOK in THF to give **3**. This not only provided the carbamate but also provided the C-10 methyl group as the natural and desired isomer. To complete the synthesis, the azide **3** was reduced to the amine and cyclized with $PPh_3$ in a refluxing THF/$H_2O$ mixture, producing the protected tricycle **4** in a 52% yield.[17]

It is reasonable to think that the vinyl group might occupy the same general spatial vicinity as the quinolyl group in ABT-773 being positioned above the C-13 carbon (Figure 2).[18] Compound **4** would thus provide an interesting scaffold, which could be further elaborated to help probe secondary ribosomal interactions.

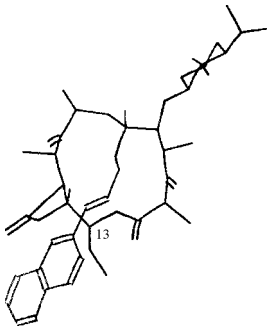



**Figure 2.** Minimized solution conformation of ABT-773.

In conclusion, we have developed a short, efficient, and high-yielding synthesis of a vinyl tricyclic erythromycin building block that utilizes a novel azidoisocyanate. This methodology eliminates the purification and epimerization problems associated with the original synthesis with greatly reduced reaction times. Compound **4** provides a structural motif that will allow for further exploration of secondary interactions of macrolides within the bacterial ribosome. To address increasing antibacterial resistance, this research presents a significant opportunity in the development of new macrolide antibiotics.

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**Supporting Information Available:** Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Mallams, A. K.; Davies, D. H. U.S. Patent 4180565, 1979.
(10) (a) Kokotos, G. S. *Synthesis* **1990**, 299−301. (b) Kokotos, G.; Markidis, T. *J. Org. Chem.* **2001**, *66*, 1919−1923.
(11) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071−1074.
(12) Avenoza. A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Assymetry* **1999**, *10*, 4653−4661.
(13) Beaulieu, P. L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196−4204.
(14) Sigurdsson, S. Th.; Seeger, B.; Kutzke, K.; Eckstein, F. *J. Org. Chem.* **1996**, *61*, 3883−3884.
(15) Arouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080−4100.
(16) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131−132.
(17) Unexpectedly, the cyclization of the (*R*)-isomer did not occur spontaneously upon reduction of the azide. It was, however, cyclized by treatment with acetic acid in EtOH at 80 °C to give the cyclized product in a 20% yield.
(18) See ref 4 and: 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*, 1045−1049.