ORGANIC LETTERS

2000
Vol. 2, No. 19
2951−2954

Synthesis of 2-Fluoro-6-*O*-propargyl-11,12-carbamate Ketolides. A Novel Class of Antibiotics

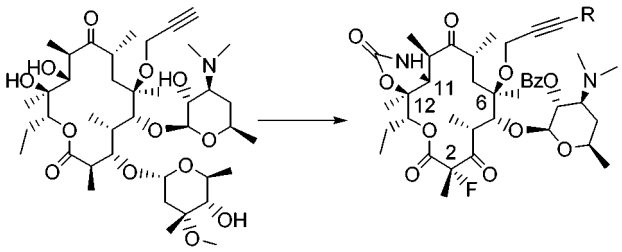
Ly T. Phan,* Richard F. Clark, Michael Rupp, Yat Sun Or, Daniel T. W. Chu, and Zhenkun Ma

Infectious Diseases Research, Abbott Laboratories, 200 Abbott Park Road, Abbott Park, Illinois 60064-3537

ly.phan@abbott.com

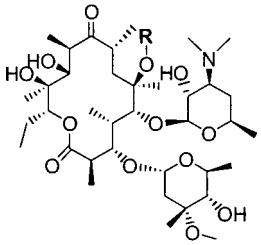
Received June 19, 2000

ABSTRACT



A novel class of 2-fluoro-6-*O*-propargyl-11,12-carbamate ketolide derivatives of erythromycin has been synthesized for antibacterial SAR studies. Replacement of the C2-hydrogen by a fluorine atom allows the synthesis of 6-*O*-propargylic ketones and electron-deficient 6-*O*-propargylic aromatic derivatives by preventing intramolecular C2-enolate Michael cyclization.

Macrolide antibiotics are a safe and effective drug class for the treatment of respiratory tract infections.[1] Erythromycin A (**1**, Figure 1), a 14-membered ring macrolide, has been widely prescribed for more than 40 years. A major drawback to erythromycin is its instability in the acidic medium of the stomach, resulting in GI irritation[2] and poor bioavailability. To minimize the acid instability, which is associated with intramolecular ketalization of the hydroxyl groups at C6 and C12 with the ketone at C9, selective methylation of the 6-hydroxyl has been performed.[3] The resulting 6-*O*-methyl compound, clarithromycin (**2**), has become a leading second generation macrolide antibiotic. However, due to the recent emergence of antibiotic resistance,[4] macrolides with activity against resistant bacteria are needed.



Erythromycin A R = H (**1**)
Clarithromycin R = CH_3 (**2**)

Figure 1.

Subsequent modifications of clarithromycin have led to compounds with enhanced activity against resistant pathogens. In particular, the incorporation of 11,12-carbamate and 3-keto (known as ketolide) structural features has shown promise.[5] Recent reports have further demonstrated that potent antibacterial activity against resistant strains can be achieved by introducing aromatic groups into the macrolide.[6]

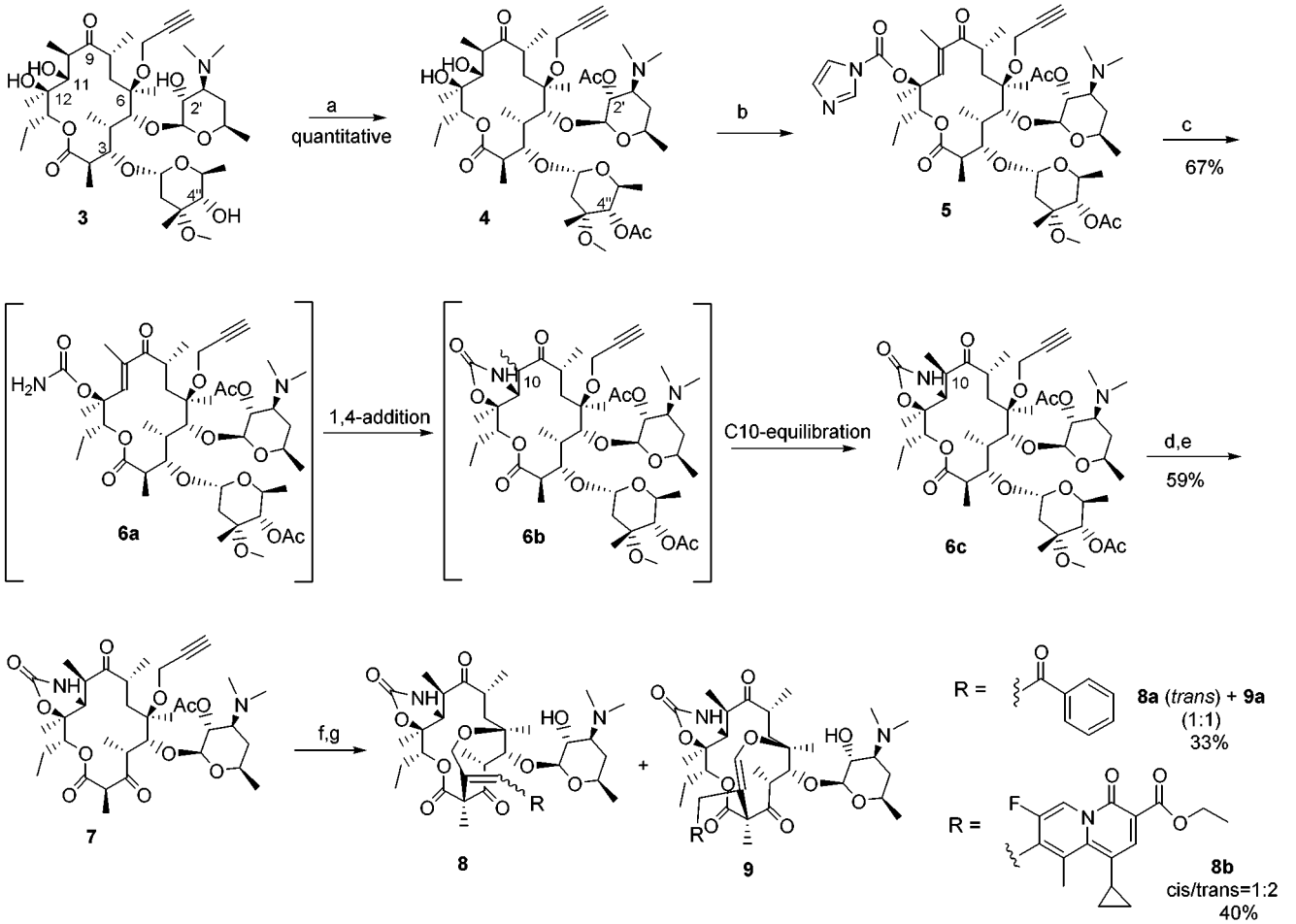
(1) For recent reviews, see: (a) Chu, D. T. W. *Med. Res. Rev.* **1999**, *19*(6), 497−520. (b) Bryskier, A. *Expert Opin. Invest. Drugs* **1999**, *8*(8), 1171−1194. (c) Bryskier, A. *Expert Opin. Invest. Drugs* **1997**, *6*, 1697−1709. (d) Chu, D. T. W. *Expert Opin. Invest. Drugs* **1995**, *4*(2), 65−94.

(2) (a) Kurath, P.; Jones, P.; Egan, R.; Perun, T. *Experientia* **1971**, *27*, 362. (b) Krowicki, K.; Zamojski, A. *J. Antibiot.* **1974**, *26*, 569−574.

(3) Morimoto, S.; Takahashi, Y.; Wantanabe, Y.; Omura, S. *J. Antibiot.* **1984**, *37*, 187−189.

10.1021/ol006226o CCC: $19.00
Published on Web 08/25/2000

Scheme 1



(a) Ac_2O (2.4 equiv), Et_3N, DMAP, CH_2Cl_2, rt, 24h. (b) NaH, CDI, THF/DMF (1:1), rt, 24h. (c) NH_3(aq), CH_3CN, rt, 24h.
(d) 2N HCl/EtOH, rt, 24h. (e) (i) NCS, Me_2S, CH_2Cl_2,-10°C, 2h; (ii) Et_3N.
(f) 8-chloropyridone or benzoyl chloride, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_3CN, 80°C, 24h. (g) MeOH, rt, 24h.

We have been investigating novel erythromycin A derivatives that contain these key structural features as a strategy for overcoming macrolide resistance. Selective alkylation of the 6-hydroxyl in **1** with an allyl or propargyl group has recently been achieved in our laboratories,[7] thus providing versatile intermediates for further derivatizations.

In this Letter, we report the first synthesis of 2-F-6-*O*-propargyl-11,12-carbamate ketolide derivatives which are potent antibacterial agents. Our initial approach was to utilize the 6-O-propargyl side chain in **7** (Scheme 1) as a point of attachment for a variety of aryl functionalities. Compound **7** was readily prepared in five steps from 6-*O*-propargyl erythromycin A (**3**).[7] The synthesis began with selective protection of the 2′,4″-hydroxyls of **3** as the bis-acetate **4**,[8] which was converted to 12-*O*-acyl imidazolide **5** by reacting **4** with NaH and excess 1,1′-carbonyl diimidazole. Treatment of crude **5** with liquid ammonia in acetonitrile gave carbamate **6a**. Upon prolonged exposure to ammonia, **6a** underwent an intramolecular Michael addition to give **6b** which subsequently equilibrated to **6c** exclusively.[9] Hydrolysis of the cladinose sugar with 2 N HCl in ethanol followed by Corey−Kim oxidation[10] of the resulting 3-hydroxy analogue provided ketolide **7**. Attempted arylation of the propargyl side chain of **7** with 8-chloropyridone[11] or acylation with benzoyl chloride using Sonogashira conditions[12] produced unexpected results. Cyclization products **8a** and **8b** were formed as a consequence of an intramolecular C2 enolate

(4) (a) Bax, R. P.; Anderson, R.; Crew, J.; Fletcher, P.; Johnson, T.; Kaplan, E.; Knaus, B.; Kristinsson, K.; Malek, M.; Strandberg, L. *Nat. Med. (N.Y.)* **1998**, *4*, 545−546. (b) Baquero, F. *J. Antimicrob. Chemother*. **1997**, *39*, Suppl. A, 1−6.

(5) Agouridas, C.; Denis, A.; Auger, J. 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.

(6) (a) Denis, A.; Agouridas, C.; Auger, J.-F.; 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.; Pejac, J. M.; Perron, S.*Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075−3080. (b) 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.

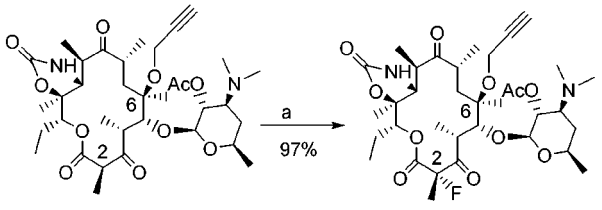
(7) (a) Clark, R. F.; Ma, Z.; Wang, S.; Griesgraber, G.; Tufano, M.; Yong, H.; Li, L.; Zhang, X.; Nilius, A.; Chu, W. T. W.; Or, Y. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 815−819.

(8) 2′-*O*-Benzoate was also prepared and carried through the synthetic sequence with similar result.

Michael addition. A 1:2 mixture of *cis*/*trans* isomers was obtained for **8b**. For **8a**, only *trans*-α,*β*-unsaturated ketone was isolated along with its *β*,*γ*-unsaturated ketone **9a** in a 1:1 mixture. A propensity for these undesired reactions limited our ability to explore electron-deficient aromatic systems.

To avoid intramolecular cyclization, a C2 blocking strategy was pursued. By replacing the C2 hydrogen with a fluorine atom, undesirable enolization of the *β*-ketoester was prevented. Conversion of propargyl ketolide **7** to the corresponding 2-F derivative **10** by sequential treatment with NaH followed by *N*-fluorobenzene sulfonimide[13] provided **10** as a single diastereomer (Scheme 2).[14] The stereochemistry of

Scheme 2



(a) (i) NaH (2 equiv), DMF, 0°C, 1 h., (ii) $(PhSO_2)_2NF$ (1.1 equiv), -5°C, 3 h.

the fluorine was determined from an X-ray crystal structure of coupling product **11f** (Figure 2). Furthermore, the X-ray

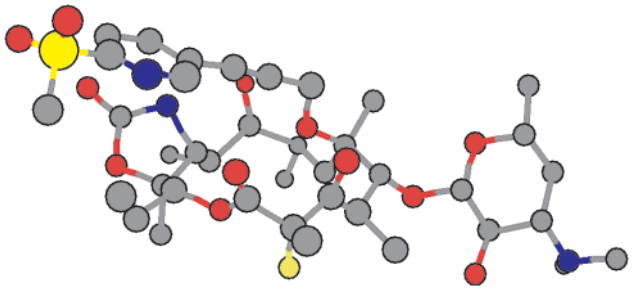
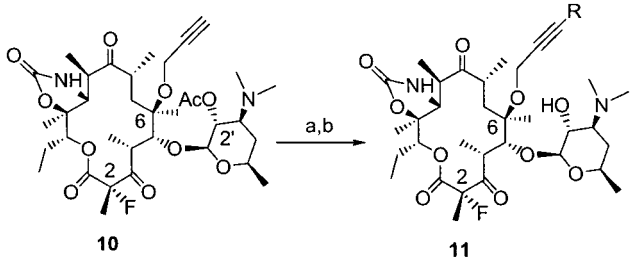


Figure 2. X-ray crystal structure of **11f**.

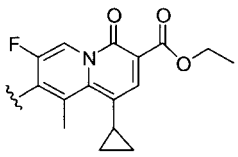
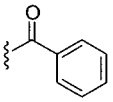
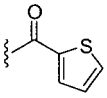
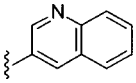
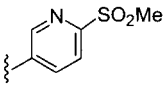
structure of **11f** revealed the conformation of the 6-*O*-propargylic side chain to be in the proximity of the C2-carbon of the *β*-ketoester.

Sonogashira coupling of various aryl[15] or acyl halides with **10** followed by deacylation of the 2′-protecting group provided modest to good yields of the desired products (Table

Table 1. Sonogashira Coupling of 2-F-6-*O*-propargyl Ketolide



(a) R-X, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_3CN, 80°C.
(b) MeOH, rt

entry	X	R		yield (%)
1	Cl		**11a**	14
2	Cl		**11b**	37
3	Cl		**11c**	45
4[15]	Br		**11d**	74
5[15]	Br		**11e**	80
6[17]	Br		**11f**	50

1). The deacylation was readily accomplished by stirring in methanol at room temperature, presumably due to neighboring group participation of the desosamine nitrogen.[16] Pre-

(9) C10-epimers also observed in other macrolide systems: (a) Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340−2345. (b) Griesgraber, G.; Or, Y. S.; Chu, D. T. W.; Nilius, A. M.; Johnson, P. M.; Flamm, R. K.; Henry, R. F.; Plattner, J. J. *J. Antibiot.* **1996**, *49*, 465−477.

(10) Corey, E. J.; Kim, C. U.; Misco, P. F. *Org. Synth.* **1978**, *58*, 122−126.

(11) For the synthesis of 8-chloropyridone, see: (a) Li, Q.; Chu, D. T. W.; Claiborne, A.; Cooper, C.; Lee, C. M.; Raye, K.; Berst, K.; Pamela, D.; et. al. *J. Med. Chem.* **1996**, *39*, 3070−3080. (b) Klein, L. L.; DeGoey, D. A.; Thomas, S. A.; Yeung, C. M.; Leone, C. L.; Grampovnik, D.; Lartey, P. A. *Bioorg. Med. Chem. Lett.* **1997**, 1167.

(12) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahetron Lett.* **1975**, *50*, 4467−4470.

(13) Excess fluorinating agent resulted in N-demethylation of the desosamine nitrogen.

(14) Related fluorination chemistry at the C2 position of ketolides has been reported: (a) Phan, L. T.; Or, Y. S.; Chen, Y.; Chu, D. T. W.; Ewing, P.; Nilius, M. B.; Raney, P.; Hensey-Rudloff, D.; Henry, R. F.; Mitten, M.; Plattner, J. J. Presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, Sept 24−27,

liminary evaluations have revealed promising biological profiles for these compounds. Thus, the scope of our ability to explore diverse acetylenic aromatic side chains at the C6-position has been expanded.

In summary, an efficient synthesis of 2-F-6-*O*-propargyl-11,12-carbamate ketolide (**10)** was developed which provided a versatile intermediate for the incorporation of a variety of aryl or acyl groups which were otherwise inaccessible. The biological data for this important new class of macrolides will be reported in due course.

Acknowledgment. The authors thank the Abbott Process Research Department for providing research intermediates, the Structural Chemistry Department for structural characterization, and Rodger Henry for the X-ray crystal structure determination.

Supporting Information Available: X-ray crystallographic analysis of compound **11f**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006226O

1998; Abstr. No. F-127. (b) Denis, A.; Agouridas, C.; Bonnefoy, A.; Bretin, F.; Fromentin, C.; Bonnet, A. Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, Sept 26−29, 1999; Abstr. No. F-2152.

(15) The C2-H analogues of **11d** and **11e** have also been prepared by coupling with **7** without intramolecular cyclization problems. Only products that were prone to Michael addition were susceptible toward intramolecular cyclization.

(16) With the 2′-*O*-benzoate protecting group, the deprotection occurred in MeOH at room temperature with a longer reaction time, 1−3 days, or at reflux in 3−4 h.

(17) The starting material has a 2′-*O*-benzoate protecting group in place of the 2′-*O*-acetate.