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Synthesis of an Antibacterial Compound Containing a 1,4-Substituted 1*H*-1,2,3-Triazole: A Scaleable Alternative to the "Click" Reaction

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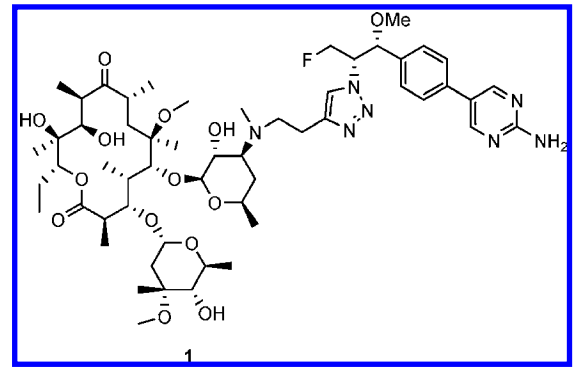
Abstract:

The copper-catalyzed "click" reaction of an azide with an alkyne has become a popular method to build up 1,4-substituted 1*H*-1,2,3-triazoles in medicinal chemistry and this approach was used on a laboratory scale during the preparation of novel macrolide 1. However, the manufacture of the key azide component, as well as its subsequent use in the presence of a copper catalyst on a large scale, was associated with potential safety concerns. Therefore, a sequence was developed in which construction of the 1,4-substituted 1*H*-1,2,3-triazole in 1 was accomplished *via* cyclocondensation of an α,α-dichloro tosyl hydrazone with an amine.



1

Introduction

Antimicrobial resistance in the community and hospital settings has been a growing public health concern due to the continuing emergence of multidrug-resistant bacterial strains.[1] A wide range of pathogens has been seen in hospital and community settings, including those associated with nosocomial Gram-positive infections, community respiratory-tract infections, and uncomplicated skin and soft tissue infections. Macrolides are a class of very effective antibiotics in those settings and they have traditionally shown excellent safety profiles.[2] Unfortunately, resistance is an emerging problem in this class of antibiotics. In order to combat this, structural enhancement of naturally occurring macrolides has proven to be an effective strategy.[3]

We recently required an efficient scaleable synthesis of a novel macrolide **1**, which displays promising antibacterial activity. As a key structural element, **1** contains a 1*H*-1,2,3-triazole fragment connected *via* a two-carbon linker to the desosamine nitrogen of clarithromycin.

The discovery route utilized the copper-catalyzed Huisgen cycloaddition reaction, popularized by Sharpless[4] and Meldal,[5] as the key transformation to build up the triazole ring in the synthesis of **1** (Scheme 1). This high-yielding and mild reaction was well suited for the rapid exploration of a range of novel substituted macrolides through the attachment of different side chains to an *N*-alkynylated macrolide core such as **5**.[6] However, there exists the potential for formation of highly explosive copper azide[7] during the course of the catalyzed cycloaddition reaction.[8] Additionally the required azide **3** was synthesized from **2** by a diazo transfer reaction using a large excess of triflic azide, a highly energetic and hazardous chemical.[9] In order to avoid these concerns we elected to investigate formation of the triazole by alternative means.[10] Attempting to perform the triazole formation without any copper catalyst gave a slow reaction, yielding a 2:1 ratio of the desired 1,4-regioisomer to its 1,5-regioisomer.[11]

In searching for safer alternative methods to scale-up the preparation of **1** reliably, we became interested in synthesizing the triazole by a method developed by Sakai more than 20 years

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(1) (a) Cosgrove, S. E.; Carmeli, Y. *Clin. Infect. Dis.* **2003**, *36*, 1433. (b) Seybold, U.; Kourbatova, E. V.; Johnson, J. G.; Halvosa, S. J.; Wang, Y. F.; King, M. D.; Ray, S. M.; Blumberg, H. M. *Clin. Infect. Dis.* **2006**, *42*, 647. (c) Tenover, F. C.; McDougal, L. K.; Goering, R. V.; Killgore, G.; Projan, S. J.; Patel, J. B.; Dunman, P. M. *J. Clin. Microbiol.* **2006**, *44*, 108.

(2) Omura, S. *Macrolide Antibiotics. Chemistry, Biology, and Practice*, 2nd ed.; Academic Press Inc.: New York, 2002.

(3) Kanyo, Z.; Bhattacharjee, A.; Chen, S.; Chen, Y.; Dalton, J.; Devito, J.; Farmer, J.; Franceschi, F.; Goldberg, J.; Hanselmann, R.; Ippolito, J.; Johnson, G.; Lawrence, L.; Lou, R.; McConnell, T.; Orbin, A.; Oyelere, A.; Park, M.; Salvino, J.; Sherer, E.; Sutcliffe, J.; Tang, Y.; Wang, D.; Wu, Y.; Duffy, E. Enhanced Macrolides: Overcoming Resistance by Improving Target Affinity, from 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 12-15, 2009, abstract F1-2050.

(4) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(5) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(6) Bhattacharjee, A.; Du, Y.; Duffy, E. M.; Job, G. E.; Lou, R.; Luo, Z.; O'Dowd, H.; Tang, Y.; Wu, Y. PCT Int. Appl.WO 2008106224, 2008, CAN: 149,332567.

(7) Patnaik P. *A Comprehensive Guide to the Hazardous Properties of Chemicals*, 3rd ed.; John Wiley: Chichester, 2007; p 620.

(8) For example CuN_3 could be formed by trace decomposition of **4**.

(9) (a) Cavender, C. J.; Shiner, V. J., Jr. *J. Org. Chem.* **1972**, *37*, 3567. (b) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C. H. *J. Am. Chem. Soc.* **2002**, *124*, 10773.

(10) Applying alternative technologies such as microreactor technology to the hazardous click reaction is a viable alternative which was excluded due to time constrains. For a special issue about microreactor technology see: Special Feature Section: Organic Synthesis by Microprocess Technology, Hessel, V., Besser, R., Guest Editors *Org. Process Res. Dev.* **2009**, *13*, 940−1031.

(11) A 1:1 mixture of **4** and **5** was refluxed in toluene for 5 days.

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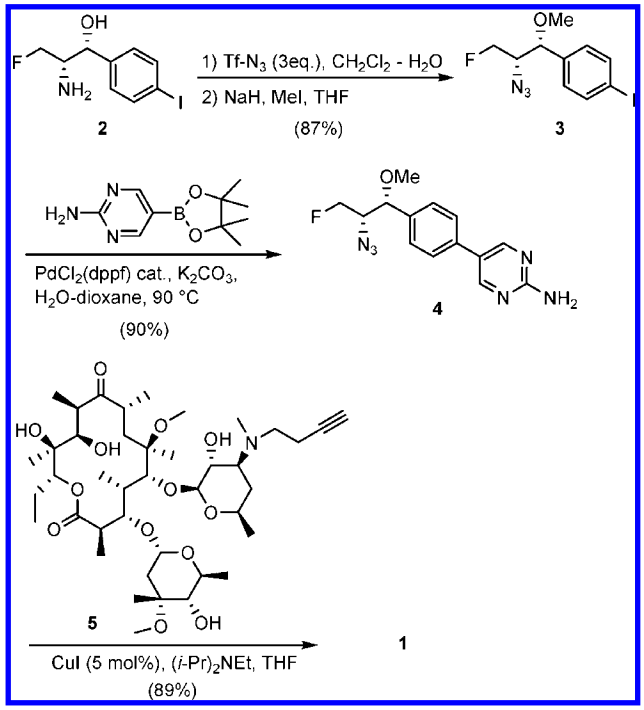
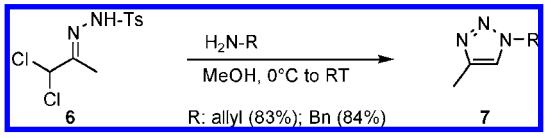
Scheme 1. **Discovery Synthesis of 1**



Scheme 2. **Sakai's Tosyl Hydrazone Cyclization**



ago.[12] In this approach, an amine is condensed with α,α-dichloro tosyl hydrazone to form a 1,4-substituted triazole under mild reaction conditions (Scheme 2).

However, this methodology has been used infrequently[13] and then only with unbranched amines and simple α,α-dichloro tosyl hydrazones. The advantage of avoiding the copper-catalyzed click reaction and using a tosyl hydrazone and an amine instead of an energetic azide to form the triazole ring in **1** was very compelling, and we decided to investigate the feasibility of this approach further.

Results and Discussion

We envisioned synthesizing the required triazole **9** through a cyclocondensation of α,α-dichloro tosyl hydrazone **10** with amine **11**. The active pharmaceutical ingredient (API) **1** could then be obtained through a late-stage alkylation of the side-chain **9** with *N*-desmethylclarithromycin **8** (Scheme 3).

Synthesis of 2-Aminopyrimidine 11. The synthesis of **11** commenced with the selective methylation of amino alcohol **2**[14] (Scheme 4). In the discovery route, there were no concerns with the selectivity in the *O*-methylation step because the amino group was masked as an azide. In the absence of protection of the amino group we were concerned with concomitant *N*-methylation of amino alcohol **2**. However, an initial attempt at methylating the amino alcohol **2** using KHMDS (1.2 equiv) in THF and methyl iodide gave less than 10% of *N*-methylated impurities.[15] The reaction proceeded cleanly up to ~90% conversion with only small amounts of *N*-methylation. Afterwards, the remaining starting material was slowly converted almost entirely to the *N*-methylated impurities. This observation implied the importance of an excess of base. Thus, increasing the amount of KHMDS to 1.35 equiv suppressed the *N*-methylation below 1%, and **12** was reproducibly synthesized in 98% yield. On initial scale up (2.35 kg of **2**) the reaction stalled after 95% conversion. Fortunately this tendency towards incomplete conversion was eliminated in subsequent batches of similar sizes by increasing the amount of methyl iodide to 1.36 equiv and KHMDS to 1.49 equiv and optionally adding 10% more of these reagents when the reaction stalled.

The Suzuki reaction to generate **11** was carried out without protection of the amine group in **12** and low catalyst loading using K_3PO_4 as base. In initial runs, K_2CO_3 was used as the base. However, during a laboratory scale-up run a new impurity **13** was detected at up to 3% based on HPLC area %. This impurity was most likely formed by carbamic acid formation of the liberated CO_2 with **11**/**12**, followed by ring closure. Switching the base to K_3PO_4 eliminated this impurity entirely, and two batches (2 × 2.46 kg of **12**) were converted quantitatively to **11**.

Synthesis of Triazole 17. The β-keto ester **15** was synthesized from dichloroacetyl chloride **14** by adapting a method developed by workers at Parke-Davis[16] (Scheme 5). This gave **15** reproducibly in 81% yield on a 1 kg scale of **14**.

Next β-keto ester **15** was converted to tosyl hydrazone **10** by treatment with tosyl hydrazine. Propionic acid is the commonly used solvent for this transformation.[17] However, we wanted to avoid this solvent due to the desire to telescope **10** into the triazole formation, which is performed under basic conditions. Several reaction solvents were investigated (Table 1), but in all of them various amounts of the byproduct **16** were formed. Fortunately, in MeCN this impurity precipitated out and was easily purged by a simple filtration after the reaction was complete, yielding **10** in 80% yield.

In initial laboratory scale reactions for the triazole formation, the supernatant containing **10** was telescoped into a solution of

(12) (a) Sakai, K.; Tsunemoto, D.; Kobori, T.; Kondo, K.; Hida, N. Eur. Pat. Appl. EP 103840, 1984. CAN: 101, 72730. (b) Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179.

(13) (a) Harada, K.; Oda, M.; Matsushita, A.; Shirai, M. *Heterocycles* **1998**, *48*, 695. (b) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499.

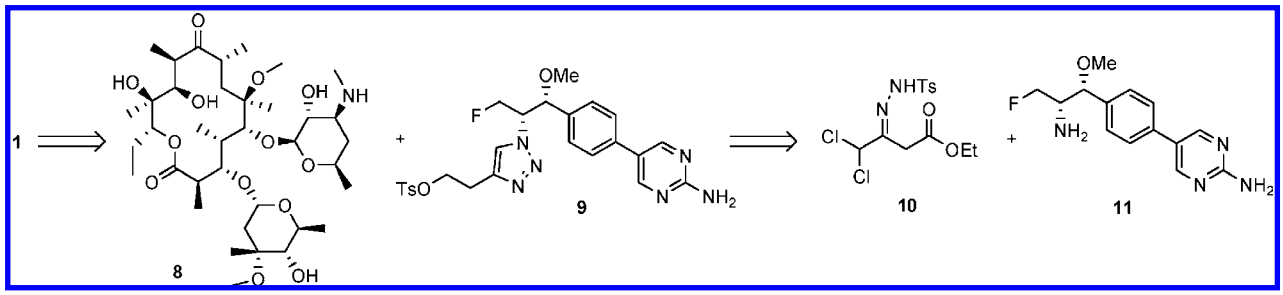
(14) Compound **2** was synthesized by a vendor according to the following references: (a) Bhattacharjee, A.; Du, Y.; Duffy, E. M.; Job, G. E.; Lou, R.; Luo, Z.; O'Dowd, H.; Tang, Y.; Wu, Y. PCT Int. Appl. WO 2008106224, 2008; CAN: 149, 332567. (b) Schumacher, D. P.; Clark, J. E.; Murphy, B. L. Eur. Pat. Appl. EP 359516, 1990, CAN: 113, 115291. (c) Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 16394.

(15) For related methylations see: (a) Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892. (b) Pyne, S. G. *J. Org. Chem.* **1986**, *51*, 81. (c) Glennon, R. A.; Bondarev, M. L.; Khorana, N.; Young, R.; May, J. A.; Hellberg, M. R.; McLaughlin, M. A.; Sharif, N. A. *J. Med. Chem.* **2004**, *47*, 6034.

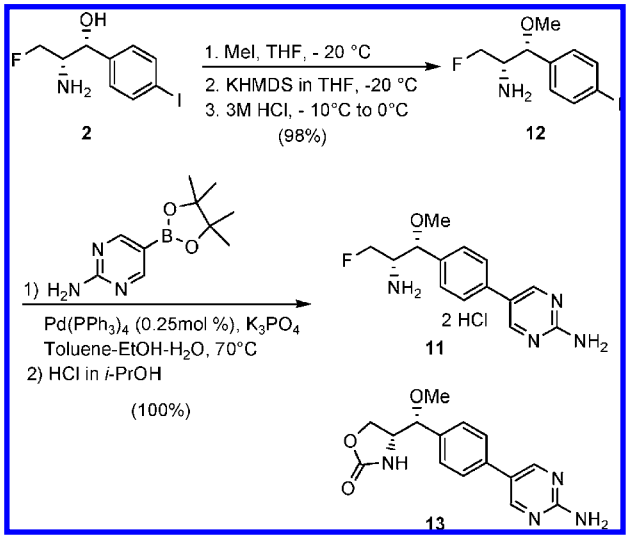
(16) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.

(17) Bott, K. *Chem. Ber.* **1975**, *108*, 402.

Scheme 3. **Retrosynthesis of 1**



Scheme 4. **Synthesis of 11**



Scheme 5. **Synthesis of 17**

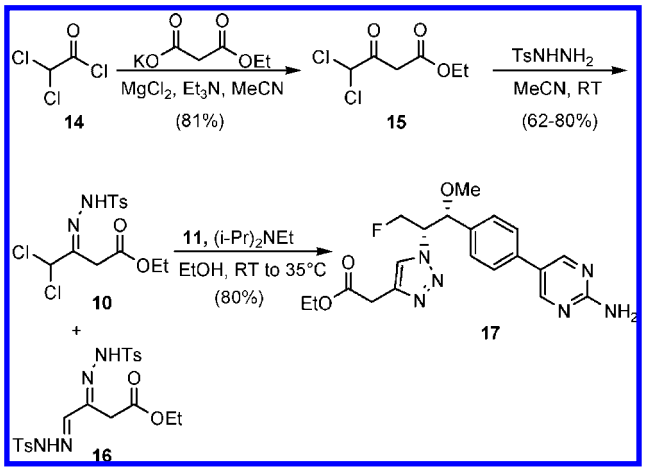


Table 1. **Solvent effect on the ratio of 10 vs 16**

	ratio **10**:**16**		
solvent	crude	filtrate	yield (%)[b]
propionic acid	9:1	N/A[a]	N/A
EtOAc	5:1	6:1	90
toluene	6:1	>99:1	56
MeCN	5:1	>99:1	80
MeOH	1:1	3:1	59

[a] No precipitation was observed. [b] Solution yields of filtrate determined by HPLC.

11 in EtOH at 10−25 °C. An excess of 0.6 equiv of **10** is required for this transformation to go to completion. The excess of **10** is converted to a soluble polymeric residue during the reaction which is visible as a tarry residue in **17** after aqueous workup. Recrystallization of crude **17** gave pure material, albeit in low yield. Fortunately, the tarry residue can rather be easily purged by incorporating an acid−base extraction during the workup of **17**, affording material in 80% yield and of ∼93% purity by HPLC.

While scaling up this sequence, the impurity profile of **10** and **17** became progressively worse on a 3.9 kg scale of **15**. Preliminary safety assessment of **10** by DSC showed a decomposition at 116−145 °C with a decomposition energy of 135 J/g. Thus, **10** was deemed to be relatively safe to be handled as a solid.[18] Instead of telescoping the MeCN solution of **10**, it was decided to isolate **10** by precipitation from the partially concentrated crude solution at −15 °C. This approach efficiently purged most impurities and **10** was obtained in a somewhat diminished yield of 62%. The damp crystals were redissolved in MeCN and used for the triazole formation, yielding 3.1 kg of **17** in 80% yield.

Sakai proposed a general mechanism for the triazole formation (Scheme 6, **19**−**21**).[19] In this, α,α-dichlorotosylhydrazone **18** is deprotonated to vinyldiazine **19**. Subsequent amine addition and toluenesulfinic acid elimination forms **20**, which cyclizes after deprotonation to the triazole **21**. During optimization of this reaction, we observed two transient compounds by HPLC. Analysis of those intermediates by LC−MS gave molecular weights consistent with those of **22** and **23**. This result suggests a slightly different mechanistic picture in which the amine adds to the vinyldiazine **19**, but the tosyl group is retained until later in the reaction sequence (Scheme 6, **22**−**21**).

Reduction of Ester 17. Several reducing reagents were screened for the reduction of ester **17** to alcohol **24** (Table 2). However, all resulted in various amounts of the over-reduced dihydroaminopyrimidine **25** (Scheme 7). Preliminary attempts at oxidizing the over-reduced impurity back to **24** were successful, but unfortunately the isolated alcohol **24** contained new unidentified impurities which were difficult to purge.[20] Of the reducing reagents investigated, the combination of $CaCl_2$−$NaBH_4$[21] or $MgCl_2$−$NaBH_4$[22] gave the lowest amount of over-reduction.

(18) Rowe, S. M. *Org. Process Res. Dev* **2002**, *6*, 877.
(19) Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179.
(20) Chloramine-T, NCS, and H_2O_2 were successfully used for the oxidation of **25**.
(21) (a) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702. (b) Clark, J. E.; Fischer, P. A.; Schumacher, D. P. *Synthesis* **1991**, 891.
(22) (a) Brown, H. C.; Mead, E. J.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209. For an example with KBH_4−$MgCl_2$ see: (b) Qiu, Y.-C.; Zhang, F.-L.; Zhang, C.-N. *Tetrahedron Lett.* **2007**, *48*, 7595.

Scheme 6. **Proposed mechanism of triazole formation**

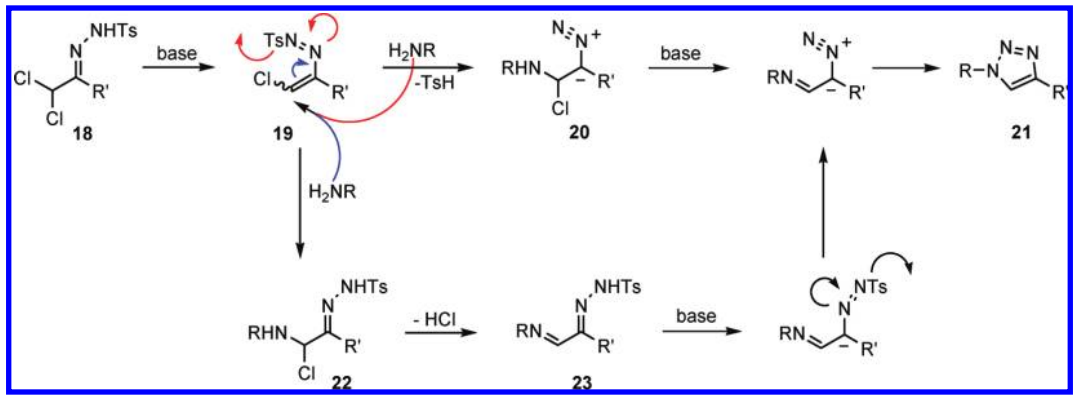
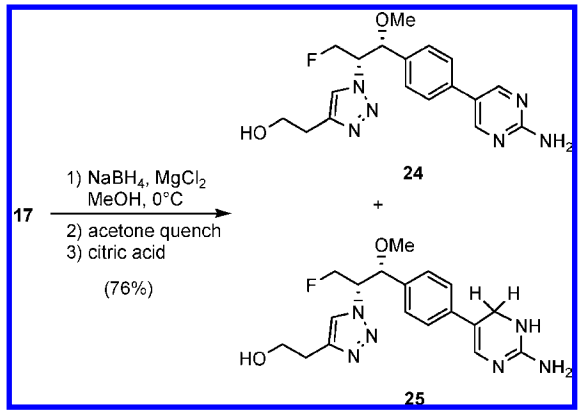


Table 2. **Effect of reducing reagents**

reagent	solvent	ratio **24**:**25**
$LiBH_4$	THF/MeOH, 1:1	7:3
KBH_4	THF	7:3
DIBAL	CH_2Cl_2	>1:99
$NaBH_4-CaCl_2$	MeOH	9:1
$NaBH_4-MgCl_2$	MeOH	9:1
$NaBH_4-CeCl_3$	MeOH	6:4

Scheme 7. **Reduction of 17**



The combination of $MgCl_2$ and $NaBH_4$ was chosen for scale-up due to its faster and cleaner reaction profile. Further optimization revealed the importance of the workup. When the reaction is quenched directly with an aqueous citric acid solution, the impurity **25** rapidly increases, and up to an additional 20% of this impurity was seen. Thus, the aqueous acidic quench did not effectively destroy any excess of borohydride species but rather accelerated the over-reduction. To avoid this over-reduction during workup, an initial acetone quench was incorporated, which completely consumed any active borohydride species before the aqueous acidic workup. After further optimization, the reduction was cleanly accomplished with a maximum over-reduction of 5%. The mild citric acid wash removed small amounts of byproduct **25**, and alcohol **24** was isolated in 76% yield and >98% purity.

Synthesis of Tosylate 9. Activation of **24** was best accomplished using a tosyl group. Other leaving groups that were investigated[23] either gave no improvement or resulted in significant amounts of the vinyl elimination byproduct **26**. Tanabe's procedure[24] in which the tosyl chloride is activated with trimethyl amine[25] as the catalyst worked especially well, yielding **9** quantitatively on a 0.9 kg scale of **24** (Scheme 8).

***N*-Desmethylation of Clarithromycin 27.** The *N*-desmethylation of the commercially available clarithromycin **27** was accomplished by a modification of a procedure developed by Freiberg.[26] Iodine is added in portion to a solution of **27** and NaOAc in refluxing aqueous MeOH at pH 8. Of note is the importance of slowly distilling off some of the solvent to remove volatiles from the reaction mixture. If this is omitted, the reaction stalls at ~50% conversion. Several 2 kg batches of **27** were converted to **8** in this way with an average yield of 62%.

Alkylation of Macrolide 8. The alkylation of macrolide **8** with tosylate **9** was conducted in MeCN with K_2CO_3 as base. Self-polymerization of **9** was a justified concern and was observed to an extent of ~10%. As a result, unreacted macrolide **8** remained after the reaction was complete. Fortunately, a short-path silica gel plug followed by a recrystallization from MeCN removed the residual unalkylated macrolide **8**. When 1.2 kg of **9** was converted, the final product **1** was obtained in 61% yield and 98.2% purity by HPLC.

In conclusion, safety concerns prevented the use of the popular Sharpless and Meldal copper-catalyzed azide−alkyne cycloaddition to synthesize **1**. This limitation was successfully overcome by applying Sakai's α,α-dichloro tosyl hydrazone approach to synthesize 3 kg of **1**. The main challenge to further scale-up consists of eliminating several concentrations of product solutions to oils. We anticipate that simple solvent exchanges and telescoping the resulting solutions into the subsequent step will allow a straightforward entry into the plant.

Experimental Section

General. HPLC analysis was performed using a Waters Sunfire C18 column (150 mm × 4.6 mm, 3.5 μm silica). Mobile phase A: 0.3% H_3PO_4 in water. Mobile phase B: 0.3% H_3PO_4 in MeCN. Flow rate: 1 mL/min. Gradient: 0 min 5% B, 1 min 5% B, 10 min 100% B, 12 min 100% B, 17 min 5% B. UV detection: 220 nm. Retention times (min): **1** (8.35), **2** (7.36), **9** (9.44), **11** (2.12), **12** (7.72), **17** (8.33), **24** (7.34), **25** (7.13).

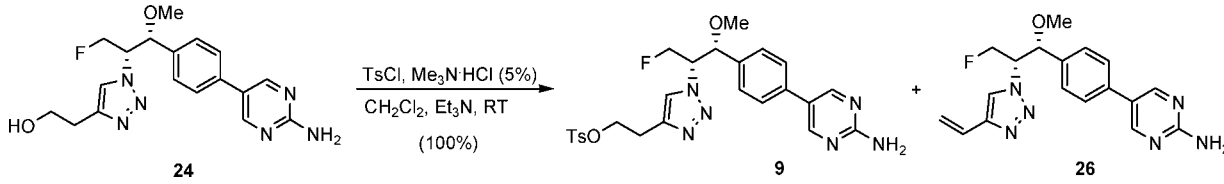
(23) Mesylate, brosylate, nosylate, and bromide were investigated.

(24) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.

(25) Only 20% conversion after 24 h was seen without trimethyl amine as catalyst.

(26) Freiberg, L. A. U.S. Patent 3,725,385, 1973; CAN: 77, 19965.

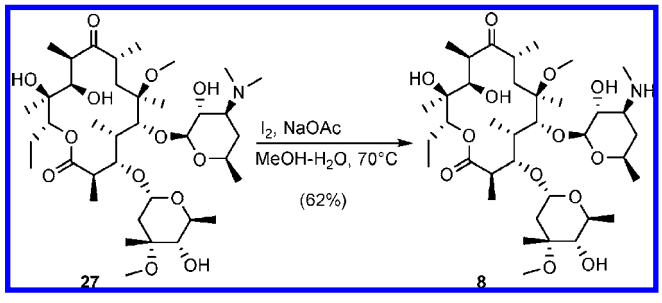
Scheme 8. **Synthesis of tosylate 9**



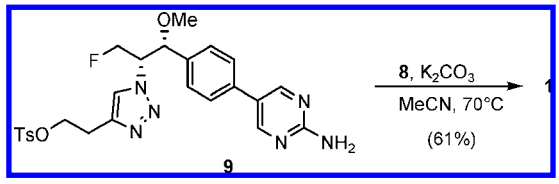
(1*S*,2*R*)-1-Fluoromethyl-2-(4-iodophenyl)-2-methoxy-ethylamine 12. To a solution of amino alcohol **2 (**2.35 kg, 8.0 mol) in THF (7.1 L) was added methyl iodide (1.5 kg, 10.9 mol) at −25 °C. KHMDS (20% in THF, 11.8 kg, 11.9 mol) was added over 1 h 40 min between −25 and −20 °C. The reaction was stirred for 1 h at −25 to −20 °C. HPLC indicated 98% conversion to **12**. An additional amount of methyl iodide (168 g, 1.2 mol) and KHMDS (20% in THF, 1.2 kg, 1.2 mol) was added, and the mixture was stirred for 1 h between −25 to −20 °C. The reaction was quenched with 3 M HCl (10.0 L) at below −10 °C. The reaction mixture was diluted with water (3.9 L) and heptane (5.6 L) at 0 °C, and the phases were separated. The organic solution was extracted with water (1.9 L), and the combined aqueous solutions were washed with heptane (3.5 L). The resulting acidic aqueous solution was adjusted to pH = 11 with 50% aqueous NaOH (2 kg) at below 10 °C and extracted with EtOAc (11.8 L). The organic extract was concentrated, and the residual oil was azeotropically dried with toluene (4.7 L) to give **12** (2.8 kg containing 0.36 kg toluene, 98%) as a light-yellow oil. An analytical sample was obtained by drying to constant weight. $[\alpha]^{25}_{D} = -58.9$ (*c* 2.39, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63 (s, 2H), 3.02 (dddd, J = 4.8, 4.8, 6.5 Hz, J_F = 21.2 Hz, 1H), 3.25 (s, 3H), 4.10 (d, J = 6.2 Hz, 1H), 4.16 (ddd, J = 5.1, 9.2 Hz, J_F = 47.1 Hz, 1H), 4.34 (ddd, J = 4.5, 9.1 Hz, J_F = 47.2, 1H), 7.07 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.3 (d, J_F = 18.8 Hz), 57.4, 83.7 (d, J_F = 5.5 Hz), 84.7 (d, J_F = 168.9 Hz), 93.8, 129.3, 137.9, 138.9; IR (thin film) 1588, 2934, 3317, 3386 cm^{-1}; ES-HRMS *m/z*: [M^+ − OMe + 1H] calcd for $C_9H_{11}FIN$ 277.9837, found 277.9835.

5-[4-((1*R*,2*S*)-(2-Amino-3-fluoro-1-methoxypropyl))phenyl]pyrimidin-2-ylamine Dihydrochloride 11. A mixture of K_3PO_4 (5.18 kg, 24.4 mol), 2-aminopyrimidine-5-boronic acid pinacol ester (1.8 kg, 8.12 mol), **12** (2.82 kg containing 0.37 kg of toluene, 7.96 mol), toluene (10.3 L), ethanol (3.5 L), and water (3.5 L) was stirred and degassed with nitrogen for 30 min before the addition of $Pd(PPh_3)_4$ (23 g, 20 mmol). Degassing was continued for another 30 min, and the reaction was refluxed for 3.5 h. The mixture was cooled to 35 °C, and water (5.7 L) was added followed by ethyl acetate (9.6 L). The lower aqueous layer was removed and extracted with ethyl acetate (4.9 L). The organic layers were combined, and the solvent was evaporated. The resulting oil was dissolved in ethyl acetate (12 L) and 2-propanol (7 L) and held below 20 °C while sparging with HCl gas (800 g, 27.9 mol). The resulting slurry was stirred for 30 min at 15 °C and filtered. The filter cake was washed with ethyl acetate (3 × 4.9 L) and dried at 40 °C/vacuum, yielding **11** (2.78 kg, 100%) as light-yellow crystals. Mp >235 °C (dec); $[\alpha]^{25}_{D} = -58.2$ (*c* 1.86, MeOH); ^{1}H NMR (d_6-DMSO, 300 MHz): δ 3.16 (s, 3H), 3.70 (m, 1H), 4.12 (ddd, J = 3.1, 10.9 Hz, J_F = 46.5 Hz, 1H), 4.44 (d, J = 9.7, 1H), 4.59 (ddd, J = 1.5, 10.9 Hz, J_F = 49.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 8.2 (broad s, 3H), 8.62 (d, J = 4.1 Hz, 3H), 8.93 (s, 2H); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 54.8 (d, J_F = 18.4 Hz), 56.3, 79.6 (d, J_F = 4.4 Hz), 80.6 (d, J_F = 169.5 Hz), 121.4, 126.2, 128.5, 133.6, 136.0, 155.0, 157.4; IR of free base (thin film): 1473, 1635, 2985, 3186, 3317 cm^{-1}; ES-HRMS *m/z*: [M^+ + 1H] calcd for $C_{14}H_{18}FN_4O$ 277.1459, found 277.1457.

Scheme 9. ***N*-Desmethylation of clarithromycin 27**



Scheme 10. **Alkylation of macrolide 8**



4,4-Dichloro-3-oxobutyric Acid Ethyl Ester, 15. To a suspension of potassium ethyl malonate (2.37 kg, 13.9 mol) in MeCN (20.7 L) was added triethylamine (2.9 L, 20.8 mol) at 0−5 °C followed by four portions of $MgCl_2$ (1.62 kg, 16.7 mmol) over 1 h at below 15 °C. The thick slurry was warmed to 20−25 °C and held for 2 h before cooling again to 0−5 °C. Dichloroacetyl chloride (1 kg, 10.4 mol) was added over 1 h at below 15 °C. The reaction mixture was warmed to 20−25 °C and held for 18 h. The resulting thick paste was thinned by the addition of ethyl acetate (5.9 L), and the slurry was cooled to 0−5 °C. The mixture was acidified with 1 M HCl (13.6 L) at 0−15 °C, and the aqueous layer was removed. Note: CO_2 will be released during the acidification. The organic layer was washed twice with 1 M HCl (7 L), and the solvent was evaporated, yielding **15** (1.64 kg containing 0.55 kg of ethyl acetate, 81%) as an oil. An analytical sample was obtained by drying to constant weight. ^{1}H NMR ($CDCl_3$, 300 MHz): Keto isomer δ 1.27 (t, J = 7.0 Hz, 3H), 3.83 (s, 2H), 4.21 (q, J = 7.0 Hz, 2H), 6.05 (s, 1H). Enol isomer δ 1.29 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 5.48 (s, 1H), 6.01 (s, 1H), 12.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): Keto isomer δ 13.95, 42.4, 61.9, 69.7, 165.9, 189.2. Enol isomer δ 14.05, 61.2, 66.8, 90.6, 168.5, 171.9; IR (thin film): 1733, 1753, 2941, 2986 cm^{-1}; ES-HRMS *m/z*: (M^+ + 1Na) calcd for $C_6H_8Cl_2O_3$ 220.9743, found 220.9739.

4,4-Dichloro-3-(4-methyl-phenyl-sulfonyl-hydrazono)butyric Acid Ethyl Ester, 10. To a solution of **15** (3.89 kg, 19.5 mol) in MeCN (11 L) was added tosyl hydrazide (3.93 kg, 21.1 mol) at 15−25 °C in five portions over 1 h. The thickening suspension was stirred at 20−25 °C for 18 h. Afterwards, the precipitate was removed by vacuum filtration, and the filter cake was rinsed with MeCN (2.2 L). The filtrate was concentrated by removing MeCN (6 L) on a rotary evaporator. The concentrated hydrazone solution was held at −15 °C for 48 h and filtered, yielding **10** as damp, beige crystals (4.44 kg, 62%). An analytical sample was obtained by drying to constant weight. Mp 99−101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.2 Hz, 3H), 2.44 (s, 3H), 3.62 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 6.19 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 9.64 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 21.8, 32.6, 63.0, 72.0, 128.2, 129.9, 135.3, 144.7, 146.7, 169.5; IR (thin film): 1716, 1739, 2982, 3231 cm^{-1}; Anal. Calcd for $C_{13}H_{16}N_2O_4SCl_2$: C, 42.72; H, 4.28; N, 7.87. Found: C, 42.52; H, 4.39; N, 7.63.

(1-{(1*S*,2*R*)-2-[4-(2-Aminopyrimidin-5-yl)-phenyl]-1-fluoromethyl-2-methoxy-ethyl}−1*H*-[1,2,3]triazol-4-yl)-acetic Acid Ethyl Ester, 17. To a suspension of **11** (3.2 kg, 9.16 mol) in ethanol (11.2 L) was added *N*,*N*-diisopropylethylamine (9.9 L, 56.8 mol) within 30 min at 0−15 °C. A solution of **10** (4.42 kg, 12.1 mol) in MeCN (4.8 kg) was added over 1.5 h at below 25 °C. The reaction was held at 20−25 °C for 1 h and then warmed to 35 °C and held for 8 h. The reaction mixture was split into three parts, and each was diluted with ethyl acetate (9.5 L). Each portion was cooled to 0−5 °C and extracted with 1 M HCl (3 × 7.8 L). The combined aqueous extracts were basified to pH 11 with 50% aqueous NaOH solution (2 kg) at 0−5 °C. The cold aqueous solution was extracted with ethyl acetate (2 × 9.5 L), and the combined organic extracts were evaporated. The oil from all three workup portions were combined, taken up in ethanol (16 L), and concentrated on a rotary evaporator, yielding **17** (5.88 kg containing 2.84 kg ethanol, 80%) as an oil. An analytical sample was obtained by crystallizing the dry residue from ethyl acetate. Mp 94−99 °C; $[\alpha]^{25}_D$ −151.1 (*c* 1.57, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (t, J = 6.9 Hz, 3H), 3.22 (s, 3H), 3.87 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 4.65 (ddd, J = 5.7, 9.9 Hz, J_F = 46.6 Hz, 1H), 4.71 (ddd, J = 4.4, 9.8 Hz, J_F = 46.3 Hz, 1H), 4.78 (d, J = 6.9 Hz, 1H), 5.00 (dddd, J = 4.4, 5.6, 6.9, J_F = 17.0 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.85 (s, 1H), 8.53 (s, 2H); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 14.0, 31.3, 56.5, 60.4, 64.9 (d, J_F = 18.3 Hz), 80.4 (d, J_F = 7.0 Hz), 82.4 (d, J_F = 171.2), 121.5, 123.6, 125.3, 127.8, 2 × 135.5, 139.7, 155.9, 163.0, 170.0; IR (thin film): 1635, 1734, 3191, 3323 cm^{-1}; ES-HRMS *m*/*z*: (M^+ + 1H) calcd for $C_{20}H_{24}FN_6O_3$ 415.1888, found 415.1886.

2-(1-{(1*S*,2*R*)-2-[4-(2-Aminopyrimidin-5-yl)-phenyl]-1-fluoromethyl-2-methoxy-ethyl}−1*H*-[1,2,3]triazol-4-yl)ethanol 24. To a solution of **17** (16.0 g, 38.6 mmol) in methanol (160 mL) was added $MgCl_2$ (4.78 g, 50.2 mmol) at 20 °C. After stirring for 30 min, granular $NaBH_4$ (2.33 g, 61.8 mmol) was added in three portions over 90 min (1.0 g, 26.4 mmol) at below 5 °C. The mixture was stirred further for 30 min and quenched by adding acetone (14.2 mL, 193 mmol). A 15% aqueous NaCl solution (160 mL) was added, and the mixture was stirred for 30 min followed by addition of 1 M citric acid (50 mL) and CH_2Cl_2 (150 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were concentrated, and the residue was dissolved in ethyl acetate (40 mL) and stirred for 3 h. Heptane (10 mL) was slowly added to the suspension and stirred for 30 min. The suspension was filtered and dried at 60 °C/vacuum, yielding **24** (10.98 g, 76%) as a tan solid. Mp 135−137 °C; $[\alpha]^{25}_D$ = −140.8 (*c* 1.28, MeOH); ^{1}H NMR (d_6-DMSO, 300 MHz): δ 2.79 (t, J = 6.9 Hz, 2H), 3.06 (s, 3H), 3.64 (dt, J = 5.3, 6.9 Hz, 2H), 4.59 (ddd, J = 3.5, 10.1 Hz, J_F = 45.8 Hz, 1H), 4.68 (ddd, J = 7.2, 10.1 Hz, J_F = 47.4 Hz, 1H), 4.73 (t, J = 5.3 Hz, 1H), 4.84 (d, J = 7.1 Hz, 1H), 5.17 (dddd, J = 3.6, 7.0, 7.3 Hz, J_F = 19.6 Hz, 1H), 6.81 (s, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.97 (s, 1H), 8.60 (s, 2H); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 29.2, 56.5, 60.4, 64.7 (d, J_F = 18.3 Hz), 80.5 (d, J_F = 6.9 Hz), 82.5 (d, J_F = 171.5 Hz), 121.5, 122.3, 125.3, 127.8, 135.4, 135.5, 144.2, 155.9, 162.9; IR (thin film): 2938, 3199, 3330 cm^{-1}; ES-HRMS *m*/*z*: [M^+ + 1H] calcd for $C_{18}H_{22}FN_6O_2$ 373.1783; found 373.1783.

***N*-Desmethylclarithromycin 8.** To a mixture of clarithromycin **27** (2.2 kg, 2.94 mol), water (3.08 L), NaOAc (3.2 kg, 39.5 mol), and methanol (30.8 L) was added iodine (792 g, 3.12 mol) at 50 °C. This was followed by heating the mixture to gentle reflux. During the course of the reaction volatiles were slowly distilled off, and a 50% NaOH solution (∼100 mL) was added every 15 min to adjust the pH to 8. Additional charges of iodine (106 g, 0.42 mol) were added after 1 and 1.5 h. Upon completion of the reaction, the reaction was cooled to room temperature, and the pH of the mixture was adjusted to pH 10 by addition of 50% aqueous NaOH solution (200 mL). Ethyl acetate (8.25 L) was added to the reaction mixture and the solvent was stripped to a volume of ∼12 L with an additional volume of ethyl acetate (8.25 L) being added during the solvent strip. To the biphasic mixture was added ethyl acetate (17.6 L) and 5% aqueous Na_2SO_3 solution (8.4 L). The mixture was heated to 32 °C until all solids dissolved, and the lower aqueous layer was removed. The organic layer was washed with water (3 × 1 L) and concentrated to ∼7 L. The precipitate was filtered, washed with ethyl acetate (1 L), and dried on the filter. Note: Compound **8** forms a stable 1:1 solvate with ethyl acetate. The solid was then suspended in MeCN (8.8 L), and the residual ethyl acetate was removed by azeotropic distillation (∼4.5 L solvent removed). The suspension was cooled to 0−5 °C, stirred for 1 h, and filtered. The cake was washed with MeCN (200 mL) and dried at 50 °C/vacuum, yielding **8** (1.34 kg, 62%) as white crystals. Mp 231−233 °C; $[\alpha]^{25}_D$ = −69.1 (*c* 0.73, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (t, J = 7.4 Hz, 3H), 1.05 (d, J = 7.5 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H), 1.12 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.21 (d, J = 7.5 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.26 (s, 3H), 1.30 (d, J = 6.2 Hz, 3H), 1.42 (s, 3H), 1.48 (dq, J = 11.2, 7.2 Hz, 1H), 1.58 (dd, J = 15.1, 4.9 Hz, 1H), 1.62−2.0 (m, 7H), 2.30 (d, J = 9.6 Hz, 1H), 2.35 (d, J = 15.4 Hz, 1H), 2.41 (s, 3H), 2.47 (ddd, J = 11.5, 4.3, 2.5 Hz, 1H), 2.60 (m, 1H), 2.67 (broad s, 1H), 2.87 (m, 1H), 3.00 (m, 2H), 3.04 (s, 3H), 3.13 (dd, J = 9.6, 7.5 Hz, 1H), 3.22 (broad s, 1H), 3.32 (s, 3H), 3.53 (ddq, J = 10.6, 4.3,

1.7 Hz, 1H), 3.67 (d, $J = 7.0$, 1H), 3.75 (d, $J = 4.5$ Hz, 1H), 3.77 (d, $J = 4.3$ Hz, 1H), 3.99 (s, 1H), 4.00 (dq, $J = 6.0$, 3.2 Hz, 1H), 4.42 (d, $J = 7.5$ Hz, 1H), 4.92 (d, $J = 4.5$ Hz, 1H), 5.06 (dd, $J = 11.1$, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.7, 10.8, 12.5, 16.1, 16.2, 18.2, 18.9, 19.9, 21.2, 21.4, 21.6, 33.4, 35.1, 37.5, 37.6, 39.2, 39.5, 45.2, 45.3, 49.6, 50.8, 60.5, 65.9, 68.6, 69.3, 72.9, 74.3, 75.2, 76.9, 77.4, 78.1, 78.5, 81.3, 96.3, 102.5, 175.8, 221.0; IR (thin film): 1684, 1723, 2977, 2500−3400, 3379, 3524, 3566 cm^{-1}; Anal. Calcd for $C_{37}H_{67}NO_{13}$: C, 60.55; H, 9.20; N, 1.91. Found: C, 60.60; H, 9.32; N, 1.75.

Toluene-4-sulfonic Acid 2-(1-{(1*S*,2*R*)-2-[4-(2-Aminopyrimidin-5-yl)-phenyl]-1-fluoromethyl-2-methoxy-ethyl}-1*H*-[1,2,3]triazol-4-yl)ethyl Ester 9. To a mixture of **24** (855 g, 2.3 mol) and Me_3NHCl (10.9 g, 0.11 mol) in CH_2Cl_2 (17.1 L) was added triethylamine (800 mL, 5.74 mol). Tosyl chloride (657 g, 3.45 mol) was added over 1 h at 0−5 °C, and the mixture was stirred for 6 h at 0−5 °C. Excess tosyl chloride was quenched with *N*,*N*-dimethylaminopropylamine (128 g, 1.38 mol) at 0−5 °C. The mixture was stirred for 30 min, and then 1 M citric acid solution (5.7 L) was added. The layers were separated, and the organic layer was washed with 1 M citric acid solution (2 × 5.7 L) diluted with a 26% aqueous NaCl solution (2 L), 7% aqueous $NaHCO_3$ (5.7 L) diluted with a 26% aqueous NaCl solution (2 L), and 26% aqueous NaCl solution (5.7 L). The solvent was evaporated, and the crude oil was solvent chased with MeCN (4.3 L) to *ca*. half volume to yield **9** as a solution in MeCN (2.33 kg containing 1.21 kg of **9**, 100%). An analytical sample was obtained by evaporating a sample to constant weight. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.39 (s, 3H), 3.02 (t, $J = 6.3$ Hz, 2H), 3.07 (s, 3H), 4.26 (t, $J = 6.3$ Hz, 2H), 4.59 (ddd, $J = 3.5$, 10.1 Hz, $J_F = 46.0$ Hz, 1H), 4.74 (ddd, $J = 7.2$, 10.2 Hz, $J_F = 47.7$ Hz, 1H), 4.84 (d, $J = 6.8$ Hz, 1H), 5.22 (dddd, $J = 3.5$, 6.9, 7.0 Hz, $J_F = 19.0$ Hz, 1H), 6.84 (s, 2H), 7.29 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.61 (d, $J = 8.23$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H), 8.02 (s, 1H), 8.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 26.0, 57.4, 65.8 (d, $J_F = 19.7$ Hz), 69.1, 81.1 (d, $J_F = 5.1$ Hz), 81.8 (d, $J_F = 174.9$ Hz), 122.6, 123.9, 126.5, 127.8, 127.9, 130.0, 132.8, 135.7, 136.1, 142.7, 145.0, 156.5, 162.6; IR (thin film): 2958, 3188, 3320, 3485 cm^{-1}; ES-HRMS *m*/*z*: [M$^+$ + 1H] calcd for $C_{25}H_{28}FN_6O_4S$ 527.1871; found 527.1871.

5-(4-{2-[4-(2-Amino-ethyl)-[1,2,3]triazol-1-yl]-3-fluoro-1-methoxypropyl}phenyl)pyrimidin-2-yl-*N*-desmethylclarithromycin, 1. A suspension of **9** (2.33 kg, 52 wt % in MeCN, 2.3 mol), powdered K_2CO_3 (475 g, 3.44 mol), and **8** (1.69 kg, 2.3 mol) in MeCN (12.1 L) was stirred at 70 °C for 56 h and then cooled to 50 °C, and water (1.2 L) was added. The mixture was concentrated to ∼3 L, and the resulting slurry was partitioned between ethyl acetate (12.1 L) and water (6 L). The organic layer was concentrated to yield an oil (4.22 kg), which was passed through a plug of silica gel (17 kg, 70−230 mesh), eluting with 2 wt % NH_3 in methanol/ethyl acetate (1:9). The initial 162 L were combined and stripped. MeCN (16 L) was added to the residual oil and heated to reflux. The clear solution was diluted with MeCN (6 L) and seeded at 50 °C. The mixture was slowly cooled to ambient temperature and stirred for 4 h. The suspension was filtered, washed with MeCN (2 × 2 L), and dried at 55 °C/vacuum, yielding **1** (1.54 kg, 61%) as beige crystals. Mp 231−233 °C; $[\alpha]^{25}_D = -96.7$ (*c* 0.56, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (t, $J = 7.4$ Hz, 3H), 1.08 (d, $J = 7.5$ Hz, 3H), 1.10−1.15 (m, 9H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.21 (d, $J = 5.9$ Hz, 3H), 1.25 (s, 3H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.40 (s, 3H), 1.45 (dq, $J = 11.2$, 7.1 Hz, 1H), 1.58 (dd, $J = 15.2$, 5.0 Hz, 1H), 1.62−1.75 (m, 2H), 1.78−1.96 (m, 3H), 2.32 (s, 3H), 2.32−2.40 (m, 2H), 2.55 (m, 2H), 2.71 (m, 1H), 2.80−3.08 (m, 7H), 3.04 (s, 3H), 3.21 (s, 3H), 3.21 (m, 2H), 3.32 (s, 3H), 3.45 (s, 1H), 3.48 (m, 1H), 3.66 (d, $J = 7.4$ Hz, 1H), 3.75 (d, $J = 6.7$ Hz, 1H), 3.77 (d, $J = 3.9$ Hz, 1H), 4.00 (s, 1H), 4.01 (m, 1H), 4.44 (d, $J = 7.2$ Hz, 1H), 4.57 (m, 1H), 4.73 (m, 1H), 4.77 (d, $J = 7.4$ Hz, 1H), 4.92 (d, $J = 4.2$ Hz, 1H), 4.97 (m, 1H), 5.05 (dd, $J = 10.9$, 2.0 Hz, 1H), 5.23 (s, 2H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.49 (d, $J = 8.2$ Hz, 2H), 7.56 (s, 1H), 8.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.2, 10.8, 12.5, 16.15, 16.2, 18.2, 18.9, 20.0, 21.2, 21.6, 21.7, 25.3, 30.1, 35.1, 36.8, 37.4, 39.4, 39.5, 45.3, 45.4, 49.7, 50.8, 53.4, 57.6, 65.7, 65.8 (d, $J_F = 13.4$ Hz), 65.9, 68.9, 69.3, 71.0, 72.9, 74.5, 78.2, 78.6, 78.7, 81.0, 81.3 (d, $J_F = 5.1$ Hz), 81.9 (d, $J_F = 174.8$ Hz), 96.4, 103.0, 121.8, 124.3, 126.7, 128.1, 136.1, 136.3, 145.8, 156.6, 162.6, 176.1, 221.0; IR (thin film): 1728, 2972, 3207, 3348 cm^{-1}; ES-HRMS *m*/*z*: [M$^+$ + 1H] calcd for $C_{55}H_{86}FN_7O_{14}$ 1088.6290; found 1088.6277.

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