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Desmethyl Macrolides: Synthesis and Evaluation of 4,8-Didesmethyl Telithromycin

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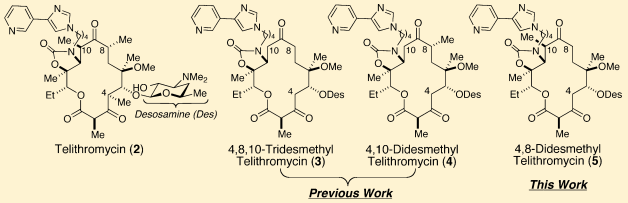
Supporting Information

ABSTRACT: There is an urgent need for novel sources of antibiotics to address the incessant and inevitable onset of bacterial resistance. To this end, we have initiated a structure-based drug design program that features a desmethylation strategy (i.e., replacing methyl groups with hydrogens). Herein, we report the total synthesis, molecular modeling, and biological evaluation of 4,8-didesmethyl telithromycin (**5**), a novel desmethyl analogue of the third-generation ketolide antibiotic telithromycin (**2**), which is an FDA-approved semisynthetic derivative of erythromycin (**1**). We found **5** to be eight times more active than previously prepared 4,8,10-tridesmethyl congener (**3**) and two times more active than 4,10-didesmethyl regioisomer (**4**) in MIC assays. While less potent than telithromycin (**2**) and paralleling the observations made in the previous study of 4,10-didesmethyl analogue (**4**), the inclusion of a single methyl group improves biological activity, thus supporting its role in antibiotic activity.



KEYWORDS: *total synthesis, ketolide antibiotics, antibiotic resistance, telithromycin, molecular modeling, desmethyl analogues*

Bacteria have evolved various resistance mechanisms to undermine antibiotic efficacy.[1] The therapeutic window between the introduction of a novel antibiotic and the onset of resistance to that drug can be frustratingly short, which complicates matters from a drug discovery point of view. Moreover, there has been a marked decline in active antimicrobial research programs in the pharmaceutical sector, resulting in a serious public health problem.[2] To address this, we initiated a structure-based drug design program wherein desmethyl analogues (i.e., $CH_3 \rightarrow H$) of the third-generation macrolide antibiotic telithromycin (TEL, **2**)[3] are prepared by total synthesis (Figure 1). To date, we have reported the total synthesis, molecular modeling, and biological evaluation of 4,8,10-tridesmethyl TEL (**3**)[4,5] and 4,10-didesmethyl TEL (**4**)[6] against both wild-type and macrolide-resistant bacteria, which were found to be active (vide infra). Herein, we extend our approach to 4,8-didesmethyl congener (4,8-didesmethyl TEL, **5**), our third desmethyl analogue of **2**.

All macrolide antibiotics target the 50S subunit of the bacterial ribosome by reversibly binding in the peptidyl transferase center, thus blocking protein synthesis.[7] Compound **2** is a third-generation semisynthetic drug used clinically since 2004 and is derived from the flagship macrolide antibiotic erythromycin (**1**).[3] All macrolide antibiotics based on the erythromycin scaffold are semisynthetic (i.e., prepared from erythromycin). Our approach is unique in that total synthesis is leveraged to access each analogue, which allows synthetic

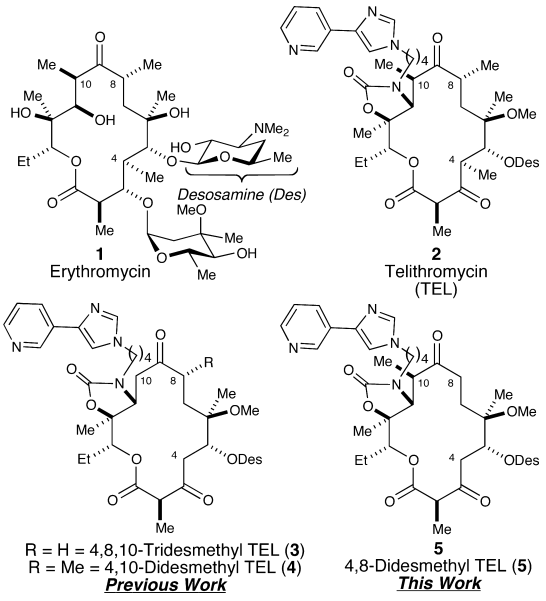


Figure 1. Structures of **1**, **2**, and de novo analogues **3**–**5**.

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flexibility to prepare macrolides with deep-seated changes for both drug discovery and chemical biology (i.e., molecular probes of fundamental processes).[8−10]

Mechanisms of antibiotic resistance are divided into three categories: (1) drug modification, (2) drug efflux, and (3) ribosomal (i.e., target) modification arising from either ribonucleotide N-methylation of residues critical for binding (e.g., A2058) by *erm* enzymes or single point mutations (e.g., A2058G).[1,11] Our desmethylation strategy was inspired by Steitz's elegant structural studies of macrolide drugs (e.g., **1** and **2**) cocrystallized with 50S ribosomal subunits of the archaeon *Haloarcula marismortui* (Hm).[12]

Unlike eubacteria that possess adenine at 2058, all archaea possess a guanine (*Escherichia coli* numbering) and do not efficiently bind macrolides **1** and **2**. However, a point mutation of guanine to adenine at position 2058 of 23S rRNA (i.e., G2058A) rendered mutants susceptible to the antibiotics, allowing the structure of **2** bound to the HmA2058 mutant at 2.6 Å resolution to be obtained (Figure 2A). Thus, Steitz

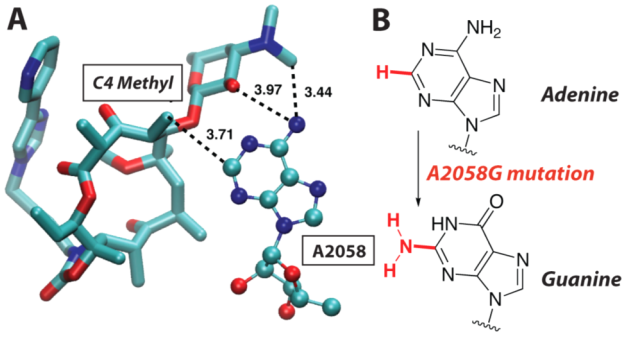


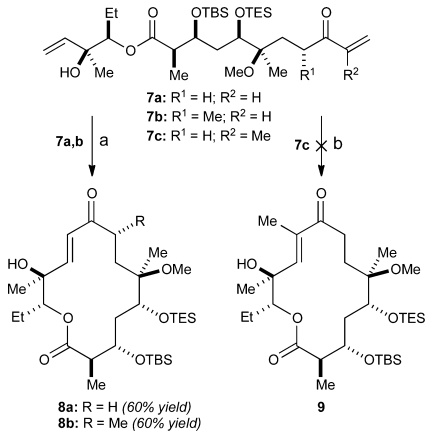
Figure 2. (A) TEL and A2058 interactions in *H. marismortui* with select distances in Angstroms (Steitz et al.; PDB ID 1YIJ). (B) Steric consequences of A2058G mutation. Image produced with VMD.[13]

showed that A2058G mutations in bacteria confer resistance by (1) loss of hydrogen bonding to the C-2′ hydroxyl of desosamine and (2) a steric clash of the exocyclic C-2 amino group of guanine 2058 with C-4 methyl of the macrolide drug (Figure 2B). We in turn hypothesized that replacing the C-4 methyl group with hydrogen (i.e., desmethylation) should relieve the steric clash component as other residues within the ribosome (e.g., 2059) can also form hydrogen bonds with desosamine's hydroxyl in addition to electrostatic interactions between the protonated dimethylamino group of desosamine and the neighboring phosphate residues.[1,11] Our rationale behind removing methyls at C-8 and C-10 was to (1) simplify chemical synthesis and (2) understand their roles in antibiotic function.

To test our desmethylation hypothesis and study the effects of specific methyl residues on the macrolactone ring, we embarked on a total synthesis of **5**. With **5** in hand, biological evaluation against a host of wild-type and resistant bacterial strains would follow (i.e., minimum inhibitory concentrations or MICs).[14] Molecular modeling would assist in the interpretation of the results.

Our experience with the total syntheses of 4,8,10-tridesmethyl analogue **3** and 4,10-didesmethyl analogue **4** informed the synthesis of target 4,8-didesmethyl analogue **5**.[4−6] Specifically, we found that the ring-closing metathesis (RCM) strategy was ideal for preparing 14-membered macroketolactones **8a** and **8b** in 60% isolated yields with Grubbs' second-generation catalyst (Scheme 1).[15] Application of this powerful method toward the synthesis of **9**, however, was ineffective in

Scheme 1. RCM Approaches to Macroketolactones 8 and 9[a]

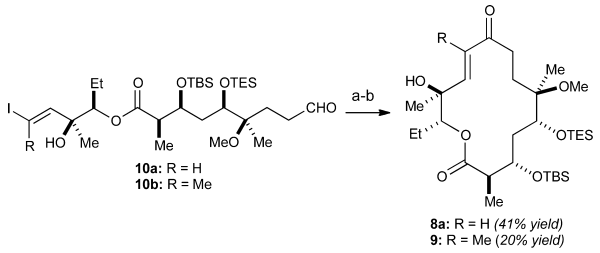


[a]Reagents and conditions: (a) G-II (20 mol %), CH_2Cl_2, 45 °C. (b) G-I, G-II, or HG-II (20 mol %), CH_2Cl_2, 45 °C.

our hands despite the choice of catalyst (e.g., Grubbs' first-generation catalyst and Hoveyda−Grubbs second-generation catalyst).[16] In fact, we were unable to isolate any product and attribute this exclusively to the steric congestion about trisubstituted enone, which is absent in congeners **8a** and **8b**.

At this stage, we revisited an alternate macrocyclization strategy also successfully employed in the synthesis of **8a**, namely, the intramolecular Nozaki−Hiyama−Kishi (NHK) reaction (Scheme 2).[17,18] This was realized by preparing vinyl

Scheme 2. Intramolecular NHK Routes to 8a and 9[a]



[a]Reagents and conditions: (a) $CrCl_2$, cat. $NiCl_2$, DMSO. (b) Dess−Martin periodinane (DMP), pyridine, CH_2Cl_2, 82%.

iodide **10a** bearing a pendant ω-aldehyde moiety. Treatment of **10a** with stoichiometric $CrCl_2$ and catalytic $NiCl_2$ in degassed dimethyl sulfoxide (DMSO) at ambient temperature for 12 h furnished a 1:1 mixture of diastereomeric allylic alcohols. Dess−Martin oxidation of the alcohols furnished macroketolactone **8a** in 41% overall yield.[5] To access **9** bearing a methyl group at C10, we prepared substrate **10b** and subjected it to the same conditions. Unfortunately, we obtained a maximum of 20% yield after oxidation.

As the synthesis of target **5** from **9** required installation of (1) the C5 desosamine sugar and (2) the biaryl side chain, we concluded that this approach was not viable. It was critical that we improve the overall synthetic efficiency by maximizing convergence. To this end, we recruited Martin's brilliant abiotic strategy toward the erythromycins wherein macrocyclization was performed on a substrate bearing carbohydrate residues D-desosamine and L-cladinose.[19] This order of events is in direct

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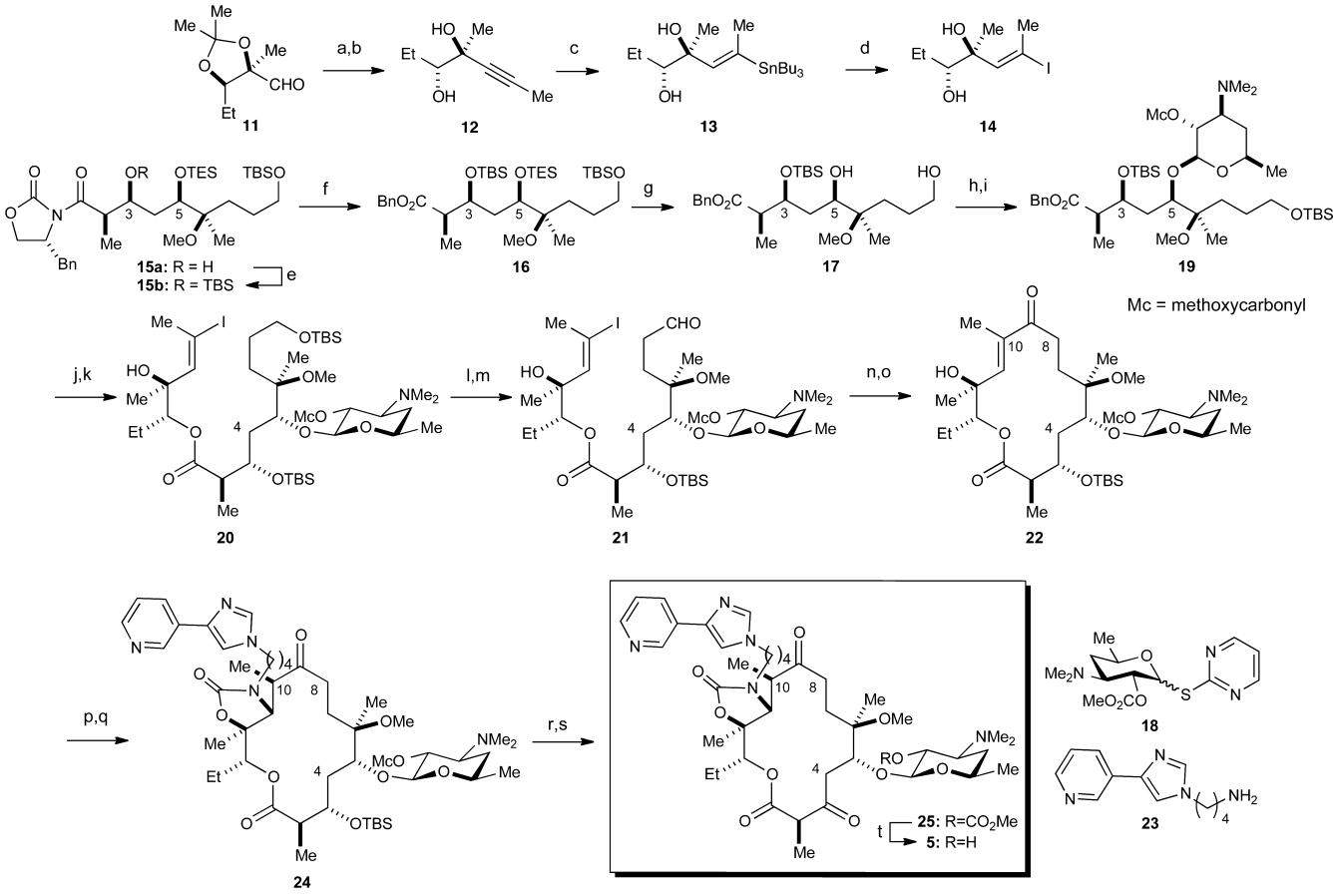
Scheme 3. Synthesis of 5[a]



[a]Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 67%. (b) *n*-BuLi, MeI, THF then 1 N HCl, MeOH, 64% over two steps. (c) $Pd_2(dba)_3$, Bu_3SnH, THF, 48%. (d) I_2, CH_2Cl_2, 82%. (e) TBSOTf, 2,6-lutidne, CH_2Cl_2, 0 °C. (f) *n*-BuLi, BnOH, THF, −78 °C to rt, 7 h, 63% over two steps. (g) CSA, MeOH, 0 °C, 1 h, 85%. (h) TBSCl, imidazole, DMF. (i) AgOTf, **18**, 4 Å MS, toluene/CH_2Cl_2, 72% over two steps. (j) 10% Pd/C, H_2, EtOH/EtOAc (1:1). (k) $C_6H_2Cl_3COCl$, NEt_3, THF, 3 h, **14**, DMAP, PhMe, 16 h, 72% over two steps. (l) HF·Pyr, THF/Pyr. (m) DMP, CH_2Cl_2, 73% over two steps. (n) $CrCl_2$/$NiCl_2$ (100/1), DMSO. (o) DMP, CH_2Cl_2, 18% over two steps. (p) NaH, CDI, DMF/THF(10/1), −15 to 0 °C, 30 min. (q) **23**, CH_3CN, H_2O, 72 h, 45% over two steps, dr = 6:1 at C-10. (r) TAS-F, H_2O, DMF, 16 h. (s) NCS, Me_2S, Et_3N, CH_2Cl_2, −20 to 0 °C, 55%. (t) MeOH, rt, 65%.

contrast to the biosynthetic sequenece wherein modular polyketide synthases first assemble the 14-membered ring by macrolactonization and then install the requisite sugars and perform site- and stereospecific C−H oxidations.[20]

The synthesis began with the preparation of requisite vinyl iodide **14** from known aldehyde **11** (Scheme 3).[21] Corey−Fuchs alkynylation, subsequent trapping with methyl iodide, and removal of the acetonide afforded **12** in 43% yield over three steps. Palladium-catalyzed hydrostannylation gave **13** in 48% yield, which was smoothly converted to vinyl iodide **14** by treatment with I_2 in 82% yield.[22] The C1−C9 aldol fragment **15a**, which was employed in the synthesis of tridesmethyl congener **3**,[4,5] was protected as its *tert*-butyldimethylsilyl (TBS) ether **15b** with TBSOTf and 2,6-lutidine. Removal of the Evans auxiliary was accomplished with lithium benzyloxide, furnishing ester **16** in 63% over two steps.[23]

The site- and stereoselective installation of the D-desosamine residue required protecting group manipulation. To this end, both the secondary C5-OTES and the primary C9-OTBS ethers were removed with camphorsulfonic acid (CSA) in 85% yield. Chemoselective reprotection of the primary C9 hydroxyl was effected with TBSCl and imidazole. Glycosylation of the C5 hydroxyl with Woodward's desosamine donor **18**[24,25] under the agency of AgOTf furnished **19** in 72% over two steps.

Macrocyclization of the 14-membered ring via the intramolecular NHK reaction commenced with hydrogenation of the benzyl ester in **19** to afford an intermediary acid.[17,18] Chemoselective coupling of this acid with diol **14** proceeded smoothly at the secondary alcohol, affording ester **20** in 72% yield over two steps. Removal of the primary C9-OTBS group with HF·pyridine (Pyr) in tetrahydrofuran (THF)/Pyr and oxidation to the aldehyde with Dess−Martin periodinane (DMP) furnished NHK substrate **21** (73% over two steps). Treatment of **21** with $CrCl_2$ and $NiCl_2$ (100:1) in degassed DMSO at rt and DMP-mediated oxidation of the diastereomeric mixture of C9 alcohols gave macroketolactone **22** in 18% yield over two steps.

The endgame for the synthesis of **5** required (1) installation of the biaryl side chain pioneered by Baker and co-workers at Abbott and (2) oxidation of the C3-hydroxyl to the ketone.[26] To this end, **22** was treated with NaH and carbonyldiimidazole (CDI) in a mixture of *N*,*N*-dimethylformamide (DMF)/THF (10:1) to form an intermediary imidazolyl carbamate. The addition of known biaryl butylamine **23**[27] triggered a one-pot amidation/intramolecular aza-Michael reaction that furnished

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oxazolidinone **24** in 45% overall yield as an inseparable 6:1 mixture of diastereomers at C-10 with the major isomer being the desired C10-(*R*) isomer. Two lines of evidence support our assignment. First, in the C10-(*R*) series, Baker observed a characteristic singlet for H-11, which results from its coplanar disposition to vicinal H-10. In the C10-(*S*) series, H-11 appears as a doublet (J = 1 Hz).[26] Second, our direct comparison with the ^{1}H NMR spectra of **5** and **2** is consistent with Baker's data, wherein the H-11 signal of **2** appears as a singlet.[3]

Removal of the C3-OTBS ether was accomplished with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F) in DMF/H_2O (10:1) at rt for 16 h.[28] Corey–Kim oxidation furnished the C3 ketone **25** in 55% yield over two steps, which was separated from the minor C10-(*S*) diastereomer at this step.[29] Stirring **25** in MeOH overnight at rt delivered **5** in 65% yield.

With desired analogue **5** in hand, we turned our attention to biological evaluation of antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus*.[14] Compound **2**, in addition to **3** and **4**, were used as comparators (Table 1).[4−6]

Table 1. MIC Values in μg/mL for 3−5 and 2

				Previous work			*This work*	
Entry	Strain	Bacteria	wt/mutant	MIC 4,8,10-trides (3)[a]	MIC TEL (2)[a]	MIC 4,10-dides (4)[b]	MIC 4,8-dides (5)[b]	MIC TEL (2)[b]
1	SQ171/2058G	*E. coli*	A2058G	>512	>512	>512	>512	>512
2	DK/pKK3535	*E. coli*	wt	32	0.5	8	4	0.5
3	DK/2058G	*E. coli*	A2058G	64	1	16	32	1
4	UCN14	*S. aureus*	A2058T	32	>256	>256	>256	>128
5	ATCC33591	*S. aureus*	*ermA*	>128	>128	>128	>64	>128

[a]Previous experiment carried out in EtOH. [b]Current experiment carried out in DMSO.

The data reveal that none of the macrolides **2**−**5** inhibited *E. coli* A2058G (entry 1) or *S. aureus ermA* mutants (entry 5). By contrast, all macrolides inhibited both *E. coli* wild-type (entry 2) and *E. coli* A2058G mutant strains (entry 3). The inhibitory activity was directly proportional to the number of methyl groups; in other words, tridesmethyl analogue **3** was less potent than either didesmethyl congener, which was less potent than **2**. This trend was recognized in the evaluation of **4**.[6] Curiously, the new 4,8-didesmethyl analogue **5** was 8-fold more potent than 4,8,10-tridesmethyl analogue **3** and 8-fold less potent than **2** against wild-type *E. coli*. Additionally, **5** was 2-fold more potent than regioisomeric 4,10-didesmethyl analogue **4** (entry 2). However, when compared to the *E. coli* A2058G mutant strain (entry 3), the potency of both didesmethyl analogues was inverted. Specifically, **4** was 16-fold less potent than **2** yet 2-fold more potent than 4,8-didesmethyl congener **5**. Finally, it is interesting to note that the only macrolide capable of inhibiting the *S. aureus* A2058T mutant (entry 4) was the simplest tridesmethyl analogue **3**. Altogether, these data reveal that replacing methyl groups on the macrolide ring with hydrogens modulates inhibitory activity and that this activity is strain dependent. X-ray crystallographic data of **2** bound to the ribosomes of *H. marismortuii*,[12] *D. radiodurans*,[30] and *E. coli*[31] reveal that while the macrolactone ring binds with an identical conformation to all ribosomes,[11] the biaryl side chain binds in three unique conformations depending on the species! This fact has broad implications for antimicrobial drug discovery, mandating more chemical space be explored to customize antibiotic chemotherapy for each targeted pathogen.

To facilitate interpretation of the MICs, we employed the conformationally sampled pharmacophore (CSP) approach using Hamiltonian Replica Exchange Molecular Dynamics (HREX MD), from which conformational properties of **2**−**5** were obtained.[32] Probability distributions of distances between select functional groups on **2** (black), **3** (blue), **4** (purple), and **5** (red) are shown in Figure 3A−D. The distributions for both

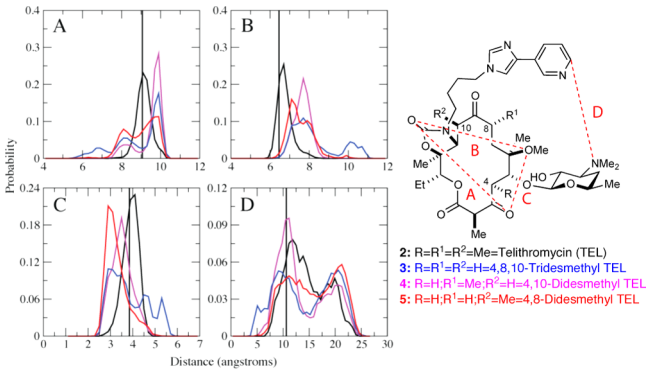

Figure 3. CSP probability distributions for **2** (black), **3** (blue), **4** (purple), and **5** (red). The vertical line corresponds to the crystallographic distances from PDB ID 1YIJ. Atom pairs represented in A−D are shown in the inset figure.

didesmethyl analogues overlap well with that of TEL, which is consistent with both analogues binding to the ribosome and exhibiting antimicrobial activity. Reduced MIC values for analogues **3**−**5** vis-à-vis **2** are presumably due to increased conformational flexibility. This is indicated by their broader distributions as compared to TEL in the CSP analysis (Figure 3A−C). The presence of an additional methyl in didesmethyl **5** versus tridesmethyl **3** reduces conformational flexibility, indicating that **5** is sampling more of the bioactive conformation, thereby contributing to the improved MIC values. Altogether, these results indicate a model where removal of the methyl groups leads to increased conformational flexibility and therefore lower biological activity. Other factors such as solubility (i.e., membrane permeability) and desolvation effects, which are not addressed with CSP, could also explain the decreased activity of the desmethyl congeners as compared to **2**.

In conclusion, **5** was prepared via total synthesis using an intramolecular NHK approach in 36 steps (26 steps in the longest linear sequence) from commercially available starting materials.[33] The efficiency of Martin's abiotic erythromycin synthetic strategy (i.e., cyclizing the 14-membered macrolactone ring with a pendant glycone) is evident when comparing the step count of the 4,10-didesmethyl congener **4**, which was prepared by a stepwise RCM/glycosylation approach in 44 steps overall (32 steps in the longest linear sequence).[19] The biological evaluation of **5** in MIC assays revealed inhibition in the growth of two bacterial strains, including an A2058G mutant. Significantly, the addition of an extra methyl group at C-10 resulted in an 8-fold increase in activity as compared to tridesmethyl analogue, providing evidence for the critical role of the methyl groups about the macrolactone scaffold in determining antibiotic activity. We are actively pursuing the synthesis and evaluation of other desmethyl TEL analogues, the results of which will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

General experimental protocols, computational methods, full structural assignment of **22**, and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

dba, dibenzylideneacetone; TBS, *tert*-butyldimethylsilyl; RCM, ring-closing metathesis; NHK, Nozaki–Hiyama–Kishi; MIC, minimum inhibitory concentration; CSA, camphorsulfonic acid; CSP, conformationally sampled pharmacophore; DMSO, dimethyl sulfoxide; DMAP, *N*,*N*-dimethylamino pyridine; DMP, Dess–Martin periodinane; DMF, *N*,*N*-dimethylformamide; Tf, trifluoromethanesulfonyl; TEL, telithromycin; HREX MD, Hamiltonian Replica Exchange Dynamics; NCS, *N*-chlorosuccinimide; CDI, carbonyldiimidazole; Hm, *Haloarcula marismortui*; THF, tetrahydrofuran; TASF, tris(dimethylamino)sulfonium difluorotrimethylsilicate; Pyr, pyridine

■ REFERENCES

(1) Wright, G. D. Molecular mechanisms of antibiotic resistance. *Chem. Commun.* **2011**, *47*, 4055–4061.

(2) Doern, G. V.; Heilmann, K. P.; Huynh, H. K.; Rhomberg, P. R.; Coffman, S. L.; Brueggemann, A. B. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. *Antimicrob. Agents Chemother.* **2001**, *45*, 1721–1729.

(3) Bryskier, A.; Denis, A. Ketolides: Novel antibacterial agents designed to overcome resistance to erythromycin A within gram-positive cocci. In *Macrolide Antibiotics*; Schonfeld, W., Kirst, H. A., Eds.; Verlag: Basel, 2002; pp 97–140.

(4) Velvadapu, V.; Paul, T.; Wagh, B.; Klepacki, D.; Guvench, O.; MacKerell, A., Jr.; Andrade, R. B. Desmethyl macrolides: Synthesis and evaluation of 4,8,10-tridesmethyl telithromycin. *ACS Med. Chem. Lett.* **2010**, *2*, 68–72.

(5) Velvadapu, V.; Paul, T.; Wagh, B.; Glassford, I.; DeBrosse, C.; Andrade, R. B. Total synthesis of (−)-4,8,10-tridesmethyl telithromycin. *J. Org. Chem.* **2011**, *76*, 7516–7527.

(6) Velvadapu, V.; Glassford, I.; Lee, M.; Paul, T.; DeBrosse, C.; Klepacki, D.; Small, M.; C.; MacKerell, A. D., Jr.; Andrade, R. B. Desmethyl macrolides: synthesis and evaluation of 4,10-didesmethyl telithromycin. *ACS Med. Chem. Lett.* **2012**, *3*, 211–215.

(7) Spahn, C. M.; Prescott, C. D. Throwing a spanner in the works: antibiotics and the translation apparatus. *J. Mol. Med.* **1996**, *74*, 423–439.

(8) For other examples, see Ghosh, P.; Zhang, Y.; Emge, T. J.; Williams, L. J. Modeling a Macrocyclic bis[spirodiepoxide] strategy to erythronolide A. *Org. Lett.* **2009**, *11*, 4402–4405.

(9) Liu, K.; Kim, H.; Ghosh, P.; Akhmedov, N. G.; Williams, L. J. Direct entry to erythronolides via a cyclic bis[allene]. *J. Am. Chem. Soc.* **2011**, *133*, 14968–14971.

(10) For a contrasting and elegant approach to macrolide analogues wherein the carbohydrate moiety has been modified while maintaining the aglycone intact, see Borisova, S. A.; Guppi, S. R.; Kim, H. J.; Wu, B.; Penn, J. H.; Liu, H.-W.; O'Doherty, G. A. A *de novo* approach to the synthesis of glycosylated methymycin analogues with structural and stereochemical diversity. *Org. Lett.* **2010**, *12*, 5150.

(11) Mankin, A. S. Macrolide myths. *Curr. Opin. Microbiol.* **2008**, *11*, 414–421 and references therein.

(12) Tu, D.; Blaha, G.; Moore, P. B.; Steitz, T. A. Structures of MLS_BK antibiotics bound to mutated large ribosomal subunits provide a structural explanation for resistance. *Cell* **2005**, *121*, 257–270.

(13) Humphrey, W.; Dalke, A.; Schulten, K. VMD: Visual Molecular Dynamics. *J. Mol. Graph.* **1996**, *14*, 33–38.

(14) Amsterdam, D. Susceptibility testing of antimicrobials in liquid media. In *Antibiotics in Laboratory Medicine*, 4th ed.; Lorain, V., Ed.; Williams & Wilkins: Baltimore, 1996; pp 52–111.

(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and activity of a new generation of ruthenium-based olefin metathesis catalysts coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligands. *Org. Lett.* **1999**, *1*, 953–956.

(16) See the Supporting Information for the synthesis of **7c**.

(17) For a review, see Furstner, A. Carbon-carbon bond formations involving organochromium (III) reagents. *Chem. Rev.* **1999**, *99*, 991–1045.

(18) For a similar approach using this tactic: Venkatraman, L.; Salomon, C. E.; Sherman, D. E.; Fecik, R. A. *J. Org. Chem.* **2006**, *71*, 9853.

(19) Breton, P.; Hergenrother, P. J.; Hida, T.; Hodgson, A.; Kraynack, E.; Kym, P.; Lee, W.-C.; Loft, M.; Judd, A.; Yamashita, M.; Martin, S. F. Total synthesis of erythromycin B. *Tetrahedron* **2007**, *63*, 5709.

(20) Katz, L. Manipulation of modular polyketide synthases. *Chem. Rev.* **1997**, *97*, 2557–2575.

(21) Yadav, J. S.; Pratap, T. V.; Rajender, V. Stereoselective formal total synthesis of (+)-methynolide. *J. Org. Chem.* **2007**, *72*, 5882–5885.

(22) Zhang, H. X.; Guibe, F.; Balavoine, G. Palladium- and molybdenum-catalyzed hydrostannation of alkynes. A novel access to regio- and stereodefined vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857–1867.

(23) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective aldol condensations. 2. *Erythro*-selective chiral aldol condensations via boron enolates. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2109.

(24) Woodward, R. B.; et al. Asymmetric total synthesis of erythromycin. 3. Total synthesis of erythromycin. *J. Am. Chem. Soc.* **1981**, *103*, 3215–3217.

(25) Velvadapu, V.; Andrade, R. B. Concise syntheses of D-desosamine, 2-thiopyrimidinyl desosamine donors and methyl desosaminide analogues from D-glucose. *Carbohydr. Res.* **2008**, *343*, 145–150.

(26) Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. Modification of macrolide antibiotics. Synthesis of 11-deoxy-11-(carboxyamino)-6-*O*-methylerythromycin A-11,12-(cyclic esters) via an intramolecular Michael reaction of *O*-carbamates with an α,β-unsaturated ketone. *J. Org. Chem.* **1988**, *53*, 2340–2345.

(27) Grant, E. B., III. Preparation of macrolide 9-alkyl- and 9-alkylidenyl-6-*O*-alkyl-11,12-carbamate ketolide clarithromycin derivatives as anti-bacterial agents. WO 2006047167 A2, May 4, 2006.

(28) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. Tris(dimethylamino)sulfonium difluorotrimethylsilicate, a mild reagent for the removal of silicon protecting groups. *J. Org. Chem.* **1998**, *63*, 6436–6437.

(29) Corey, E. J.; Kim, C. U. New and highly effective method for the oxidation of primary and secondary alcohols to carbonyl compounds. *J. Am. Chem. Soc.* **1972**, *94*, 7586−7587.
(30) Schlunzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A. Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. *Nature* **2001**, *413*, 814−821.
(31) Dunkle, J. A.; Xiong, L.; Mankin, A. S.; Cate, J. H. D. Structures of the Escherichia coli ribosome with antibiotics bound near the peptidyl transferase center explain spectra of drug action. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 17152−17157.
(32) Bernard, D.; Coop, A.; MacKerell, A. D., Jr. 2D Conformationally sampled pharmacophore: a ligand-based pharmacophore to differentiate delta opioid agonists from antagonists. *J. Am. Chem. Soc.* **2003**, *125*, 3103−3107.
(33) All compounds were fully characterized; please see the Supporting Information for details.