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Desmethyl Macrolides: Synthesis and Evaluation of 4,8,10-Tridesmethyl Cethromycin

Bharat Wagh,[†] Tapas Paul,[†] Charles DeBrosse,[†] Dorota Klepacki,[‡] Meagan C. Small,[§] Alexander D. MacKerell, Jr.,[§] and Rodrigo B. Andrade*,[†]

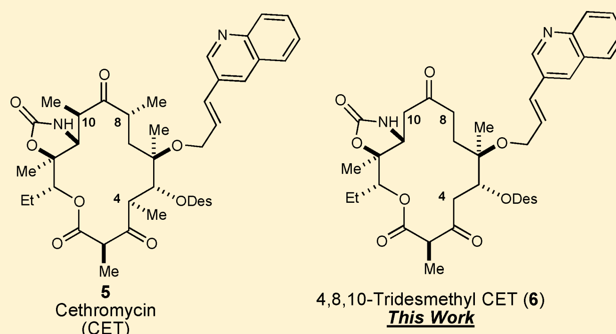
[†]Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, United States

[‡]Center for Pharmaceutical Biotechnology, University of Illinois, Chicago, Illinois 60607, United States

[§]Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland 21201, United States

Supporting Information

ABSTRACT: Antibiotic-resistant bacteria are emerging at an alarming rate in both hospital and community settings. Motivated by this issue, we have prepared desmethyl (i.e., replacing methyl groups with hydrogens) analogues of third-generation macrolide drugs telithromycin (TEL, **2**) and cethromycin (CET, **6**), both of which are semisynthetic derivatives of flagship macrolide antibiotic erythromycin (**1**). Herein, we report the total synthesis, molecular modeling, and biological evaluation of 4,8,10-tridesmethyl cethromycin (**7**). In MIC assays, CET analogue **7** was found to be equipotent with TEL (**2**) against a wild-type *E. coli* strain, more potent than previously disclosed desmethyl TEL congeners **3**, **4**, and **5**, but 4-fold less potent than TEL (**2**) against a mutant *E. coli* A2058G strain.



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

Bacterial resistance is an inevitable consequence of the use and abuse of antibiotic drugs, all of which have abbreviated life spans due to resistance elements passed vertically to bacterial progeny and horizontally to neighbors.[1] To exacerbate the problem, many pharmaceutical companies have terminated their antimicrobial research programs due to economic pressures; therefore, new sources of antibiotics are critical.[2] Recently, we initiated a structure-based drug design program that features a desmethylation strategy (i.e., replacing methyl groups with hydrogens) of third-generation macrolide antibiotic telithromycin (TEL, **2**),[3] which is derived from erythromycin (**1**), by total synthesis (Figure 1).

We have reported the total synthesis, molecular modeling, and biological evaluation of 4,8,10-tridesmethyl TEL (**3**),[4,5] 4,10-didesmethyl TEL (**4**),[6] and 4,8-didesmethyl TEL (**5**)[7] against both wild-type and macrolide-resistant bacteria; moreover, we found those compounds to be active against various bacterial strains (*vide infra*). Herein, we report related studies toward the ketolide antibiotic cethromycin (CET, **6**),[8] specifically its 4,8,10-tridesmethyl congener **7**.

Macrolides exert their antibiotic action by reversibly binding the bacterial ribosome in the exit tunnel of the 50S ribosomal subunit, thus blocking peptide synthesis.[9] Resistance to macrolides fall under three mechanistic classes: (1) drug modification by enzymatic action; (2) acquisition of an efflux pump; and finally, (3) ribosomal modification resulting from either ribonucleotide *N*-methylation (e.g., A2058) or single-point mutation (e.g., A2058G).[1]

Our desmethylation strategy, which addresses the third and most clinically pressing mechanism, is grounded in the elegant structural studies of both Steitz and Yonath who cocrystallized various macrolides with 50S ribosomal subunits of archaeon *Haloarcula marismortui* (Hm)[10] and eubacterium *Deinococcus radiodurans* (Dr), respectively.[11] The structure of CET (**6**) bound to Dr was obtained at a 3.5 Å resolution by Yonath and co-workers.[12] Consequences of the A2058G mutation are proposed to include (1) loss of hydrogen bonding to the C2′ hydroxyl of desosamine and (2) a steric clash between the exocyclic C2 amino group of guanine 2058 and the C4 methyl group on the macrolide drug (Figure 2), which was recently verified in computational studies of TEL (**2**) in the *E. coli* wild-type and A2058G mutant ribosomes.[13] Accordingly, we proposed that substituting a hydrogen for the C4 methyl group (i.e., desmethylation) would mitigate 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

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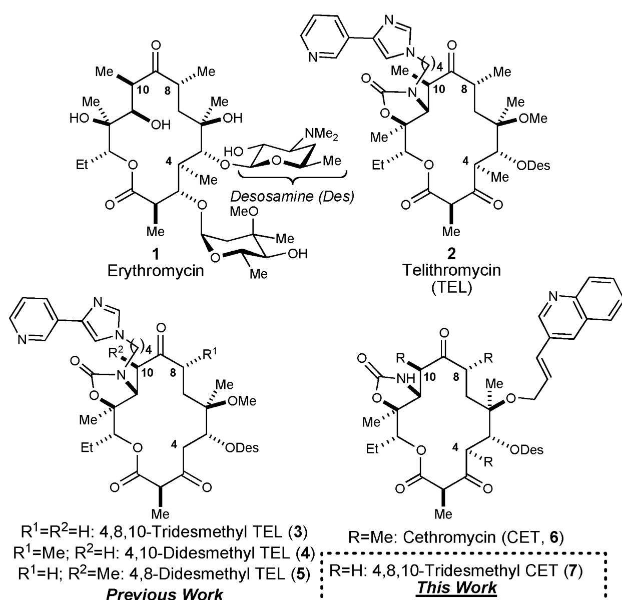


Figure 1. Structures of macrolide antibiotic drugs **1**, **2**, and **6** and desmethyl analogues **3**–**5** and **7**.

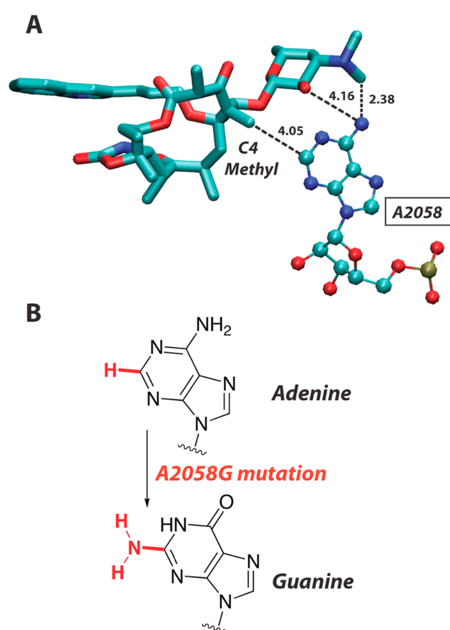


Figure 2. (A) Cethromycin and A2058 interactions in *D. radiodurans* with select distances in angstroms (Yonath et al., PDB = 1NWX). Image produced with VMD.[14] (B) Steric consequences of A2058G mutation.

dimethylamino group of desosamine and neighboring G2505 phosphate residue (not shown).[1]

Before launching synthetic efforts toward 4,8,10-tridesmethyl CET (**7**), we turned to molecular modeling to help predict the consequences of desmethylation on conformation. A priori, replacing methyl groups with hydrogen on the macrolactone framework is expected to result in (1) conformational flexibility caused by the removal of *syn*-pentane interactions along the C1–C5 or C7–C11 bonds as a result of 4, 8, or 10 desmethylation (Figure 1) and (2) the loss of van der Waals contributions (ΔG_{vdW}) from the respective methyl groups toward overall binding. To address the former, we employed the conformationally sampled pharmacophore (CSP) methodology,[15] which takes into account the inherent dynamic nature of molecules sampling a wide range of conformations using molecular dynamics simulations (Figure 3).

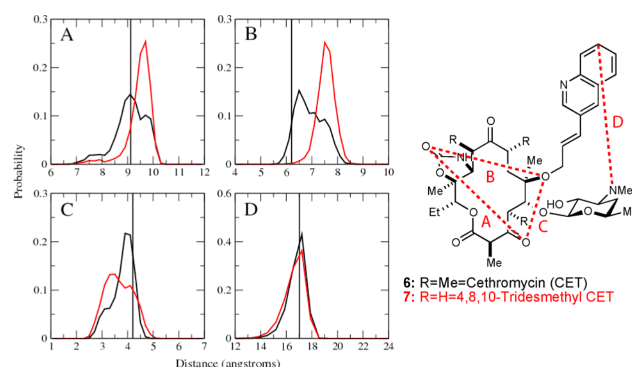


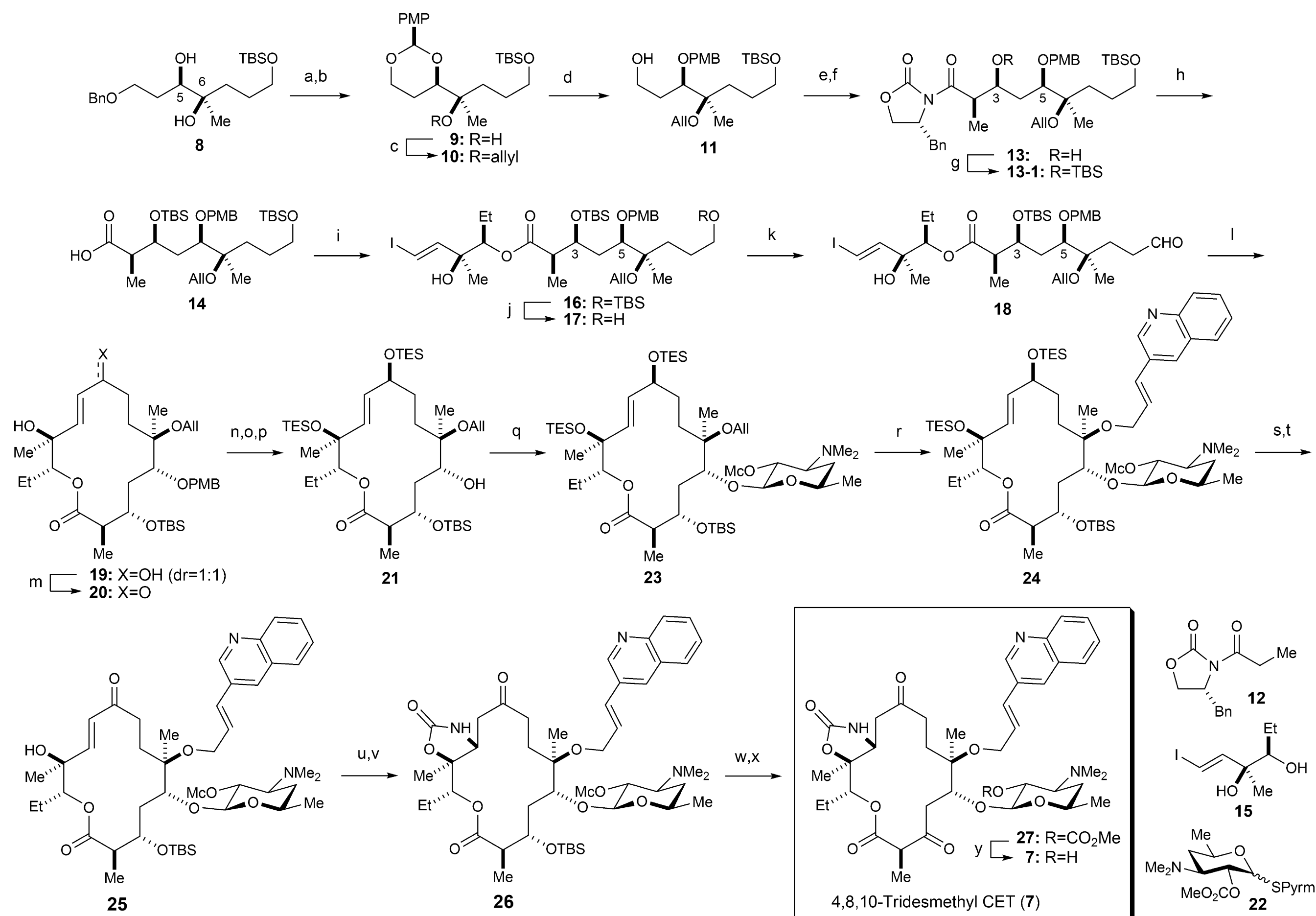
Figure 3. CSP probability distributions for cethromycin (**6**, black) and 4,8,10-tridesmethyl cethromycin (**7**, red). The vertical line corresponds to the crystallographic distances from PDB 1NWX. Atom pairs represented in A through D are shown in the inset figure.

Probability distributions of select distances from the CSP calculations are shown in Figure 3. While the distributions for tridesmethyl analogue **7** (red lines) differ from those of CET (**6**, black lines), in analogue **7**, sample conformations overlap with **6**, suggesting that **7** will bind the ribosome. To test this prediction and expand our desmethylation approach to include the cethromycin scaffold, we embarked on a total synthesis of **7** wherein synthetic material would be tested against a variety of wild-type and resistance bacteria using minimum inhibitory concentration (MIC) assays.

Experience obtained from the total syntheses of 4,8,10-tridesmethyl TEL (**3**)[4] proved extremely useful in the preparation of CET counterpart **7**. The total synthesis outlined in Scheme 1 began with diol **8**, which was used in the synthesis of **3**. To modify intermediate **8** for our purposes, we needed to differentiate vicinal C5 and C6 alcohols. Moreover, it was crucial to install an *O*-allyl group at the C6 position to later employ Abbott's Heck coupling tactic with 3-bromoquinoline.[16] To orthogonally protect the C5 hydroxyl, we chose the robust and versatile *para*-methoxybenzyl (PMB) ether. To this end, we removed the benzyl ether in **8** by hydrogenolysis and subjected the 1,3-diol intermediate to *para*-methoxybenzylidene dimethyl acetal and catalytic pyridinium *para*-toluenesulfonate (PPTS) to afford *para*-methoxyphenyl (PMP) acetal **9** in 70% over two steps. The free C6 hydroxyl was then allylated with KH and allyl bromide in the presence of catalytic iodide to give **10** in 82% yield.

The first major task toward preparing **7** was to install the complete C1–C13 framework, which we planned to accomplish with a regioselective, intermolecular Yamaguchi esterification reaction[17] between C1–C9 acid **14** and C10–C13 diol **15**, the latter of which we employed in the total synthesis of **3**.[5] To access **14**, we employed the venerable Evans aldol reaction[18] to establish the requisite stereochemistry at C2 and C3. This tactic was successfully employed in the preparation of all desmethyl analogues **3**–**5**.[4,6,7] To this end, DIBAL-mediated regioselective ring-opening of PMP-acetal **10** furnished primary alcohol **11** in 60% yield.[19] Swern oxidation of **11** gave an intermediary aldehyde, which was subjected to standard Evans aldol reaction conditions with propionimide **12** to secure **13** in

Scheme 1. Total Synthesis of 4,8,10-Tridesmethyl Cethromycin (7)[a]



[a]Reagents and conditions: (a) 10% Pd/C, H_2, ethanol; (b) *para*-methoxybenzyldehyde dimethyl acetal, PPTS, CH_2Cl_2, 70% over two steps; (c) KH, allyl bromide, TBAI, THF, 82%; (d) DIBAL-H in hexanes, PhMe, 0 °C, 60%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (f) **12**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C, dr > 20:1, 78% over two steps; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2; (h) LiOH, H_2O_2 THF/H_2O (4/1); (i) $Cl_3PhCOCl$, Et_3N, THF followed by **15**, DMAP, PhMe, 64% over three steps; (j) CSA, MeOH, 92%; (k) DMP, $NaHCO_3$, CH_2Cl_2, 85%; (l) $CrCl_2$, $NiCl_2$ (100:1), DMSO, 51%; (m) DMP, $NaHCO_3$, CH_2Cl_2, 85%; (n) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, $CHCl_3$, −78 °C, dr = 2.5:1; (o) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (p) DDQ, CH_2Cl_2, H_2O, 52% of C9-β over three steps; (q) AgOTf, DTBMP, 4 Å molecular sieves, **22**, PhMe/CH_2Cl_2, 0 °C to rt, 24 h, 65%; (r) $Pd(OAc)_2$, $NaHCO_3$, 3-bromoquinoline, *n*-Bu_4Cl, DMF, 80 °C, 60%; (s) TBAF, THF, 0 °C, 15 min; (t) DMP, CH_2Cl_2, 76% over two steps; (u) NaH, CDI, DMF/THF (10/1), −20 to 0 °C; (v) NH_4OH, CH_3CN/H_2O (9/1), 45% over two steps; (w) 1 M in TASF in DMF, 10 equiv of H_2O, DMF, rt; (x) NCS, Me_2S, Et_3N, CH_2Cl_2, 42% over two steps; (y) MeOH, rt, 70%.

78% over two steps (dr > 20:1). Protection of the C3 hydroxyl as its TBS ether and subsequent removal of the Evans auxiliary with LiOOH afforded acid **14**, which was used without further purification. In the event, regioselective Yamaguchi esterification of **14** and **15**[5] afforded ester **16** in 64% overall yield.

The second major task was to prepare the 14-membered macroketolactone, which was accomplished via an intramolecular Nozaki−Hiyama−Kishi coupling.[20−22] To this end, the primary TBS ether of **16** was selectively removed under acidic conditions in 92% yield. Oxidation of alcohol **17** with the Dess−Martin periodinane (DMP) buffered with solid $NaHCO_3$ proceeded smoothly to furnish macrocyclization precursor **18** in 85% yield. In the event, the addition of excess $CrCl_2$ and catalytic $NiCl_2$ to a solution of **18** in degassed DMSO (0.0025M) with stirring at rt for 20 h delivered 51% of **19** as a 1:1 mixture of diastereomeric allylic alcohols at C9. Subsequent oxidation of **19** with DMP gave macroketolactone **20** in 85% yield.

The third major task was the installation of the desosamine moiety at the C5 position. Again, we drew upon experience from the synthesis of **3**. Specifically, the C9-ketone was first subjected to Luche reduction conditions,[23] resulting in a 2.5:1 (β/α) mixture of inseparable diastereomers, followed by bis-silylation at C9 and C12 with TESOTf and 2,6-lutidine. Removal of C5-PMB ether with DDQ furnished glycosylation substrate **21**, which was isolated as a single diastereomer (C9-β) in 52% yield over three steps.[24] Acceptor **21** was then subjected to glycosylation with known thiopyrimidine (SPyrm) desosamine donor **22**[25,26] under the agency of AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to give **23** in 65% yield as a single diastereomer.

The fourth major task was the installation of cethromycin's 3-quinolinyl side-chain. To this end, we subjected **23** to the Jeffrey modification of the Heck reaction with 3-bromoquinoline to give **24** in 60% yield.[8] Fluoride-mediated cleavage of silyl ethers protecting groups at C9 and C12, followed by DMP oxidation thereof, afforded desosamine-bearing macroketolactone **25** (76% over two steps).

Endgame for **7** was realized in three stages. First, we installed the C11/C12 oxazolidinone using methods originally devel-

Table 1. MIC Values in μg/mL for 2−5 and 7[29]

				previous work			this work	
entry	strain	bacteria	wt/mutant	MIC 4,8,10-trides (3)[a]	MIC 4,10-dides (4)[b]	MIC 4,8-dides (5)[b]	MIC TEL (2)[a,b]	MIC 4,8,10-trides CET (7)[b]
1	SQ171/2058G	*E. coli*	A2058G	>512	>512	>512	>512	>256
2	DK/pKK3535	*E. coli*	wt	32	8	4	0.5	2
3	DK/2058G	*E. coli*	A2058G	64	16	32	1	1
4	UCN14	*S. aureus*	A2058U	32	>256	>256	>256	>256
5	ATCC33591	*S. aureus*	*ermA*	>128	>128	>64	>128	>64

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

oped by Baker and co-workers at Abbott.[27] Specifically, treatment of **25** with NaH and carbonyldiimidazole (CDI) followed by the addition of ammonium hydroxide effected a one-pot tandem carbamoylation/intramolecular aza-Michael sequence to stereoselectively access oxazolidinone **26** in 45% overall yield. Second, we set the oxidation state at C3 by sequential removal of the C3-OTBS ether with tris-(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F)[28] and Corey−Kim oxidation of the intermediary C3 carbinol, which proceeded in 68% over two steps. Third, methanolysis of **27** smoothly removed the carbonate protecting group on the C2′-hydroxyl of desosamine to deliver our target, 4,8,10-tridesmethyl CET (**7**), in 70% yield.

With **7** in hand, we proceeded to the biological evaluation of its antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* using minimum inhibitory concentration (MIC) assays with TEL (**2**) as comparator (Table 1). The data revealed that, while all ketolides were inactive against *E. coli* A2058G (entry 1) and *S. aureus* ermA mutant strains (entry 5), they all inhibited both *E. coli* wild-type (entry 2) and A2058G mutant strains (entry 3).

In the TEL series, we previously observed inhibitory activity was directly proportional to the number of methyl groups. In other words, tridesmethyl analogue **3** was less potent than either didesmethyl congener **4** or **5**, which were in turn less potent than **2**. Significantly, desmethyl CET analogue **7** exhibited similar potency to that of TEL (**2**) and thus was more active than all desmethyl TEL analogues **3**−**5** against both wild-type *E. coli* (entry 2) and A2058G mutant strains (entry 3). However, clinically relevant *S. aureus* UCN14 strain bearing an A2058U mutation was found to be susceptible to tridesmethyl TEL (**3**) but not **7** (entry 4).[30]

We rationalize the decreased potency of desmethyl TEL analogues **3**−**5** in terms of additional conformational flexibility vis-à-vis TEL (**2**), which is explained by the loss of *syn*-pentane interactions and corroborated by CSP analysis (Figure 3). We further posit the loss of van der Waals contacts at C4, C8, and C10 is operative. In the case of tridesmethyl CET congener (**7**), which was found to be equipotent with **2** in wild-type and muatnt *E. coli* (entries 2 and 3), it has been established that CET (**6**) is more potent than TEL (**2**) such that the removal of three methyl groups equalizes potency.[8]

In conclusion, we have prepared 4,8,10-tridesmethyl cethromycin (**7**), a desmethyl analogue of ketolide antibiotic cethromycin (**6**), by means of total synthesis. A total of 9 mg of **7** was prepared in 21 operations (41 steps overall, 30 steps in the longest linear sequence). Moreover, analogue **7** was more active than all desmethyl TEL analogues **3**−**5** and equipotent with telithromycin (**2**) against *E. coli* wild-type and mutant strains, further validating our desmethylation approach to addressing antibiotic resistance derived from ribosomal modification.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*(R.B.A.) E-mail: randrade@temple.edu.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CET, cethromycin; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; NHK, Nozaki−Hiyama−Kishi; MIC, minimum inhibitory concentration; CSA, camphorsulfonic acid; CSP, conformationally sampled pharmacophore; DMSO, dimethyl sulfoxide; PMP, *para*-methoxyphenyl; PMB, *para*-methoxybenzyl; DMAP, *N,N*-dimethylamino pyridine; DMP, Dess−Martin periodinane; DMF, *N,N*-dimethylformamide; Tf, trifluoromethanesulfonyl; TEL, telithromycin; TBAF, tetrabutylammonium fluoride; HREX MD, Hamiltonian replica exchange dynamics molecular dynamics; TEL, telithromycin; NCS, *N*-chlorosuccinimide; CDI, carbonyldiimidazole; Hm, *Haloarcula marismortui*; THF, tetrahydrofuran; TAS-F, tris(dimethylamino)sulfonium difluorotrimethylsilicate; Pyrm, pyrimidine; PPTS, pyridinium *para*-toluenesulfon-ate; DIBAL, diisobutyl aluminum hydride; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzo-quinone

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