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Improved Synthesis of Capuramycin and Its Analogues

Yong Wang, Shajila Siricilla, Bilal A. Aleiwi, and Michio Kurosu*[a]

Abstract: Capuramycin and its congeners are considered to be important lead molecules for the development of a new drug for multidrug-resistant (MDR) *Mycobacterium tuberculosis* infections. Extensive structure–activity relationship studies of capuramycin to improve the efficacy have been limited because of difficulties in selectively chemically modifying the desired position(s) of the natural product with biologically interesting functional groups. We have developed efficient syntheses of capuramycin and its analogues by using new protecting groups, derived from the chiral (chloro-4-methoxyphenyl)(chlorophenyl)methanols, for the uridine ureido nitrogen and primary alcohol. The chiral nonracemic (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol derivative is a useful reagent to resolve *rac*-3-amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, the (*S*)-configuration isomer of which plays a significant role in improving the mycobactericidal activity of capuramycin.

Keywords: capuramycin · drug design · *mycobacterium tuberculosis* · peptidoglycan biosynthesis · protecting groups · total synthesis

Introduction

The emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (Mtb) seriously threatens tuberculosis (TB) control and prevention efforts.[1] Moreover, HIV–AIDS patients are susceptible to TB infection[2] and there are significant problems associated with treatment of AIDS and Mtb co-infected patients. Rifampicin and isoniazid [a key component of the directly observed treatment, short-course (DOTS) therapy] induce the cytochrome P450 3A4 enzyme in the liver, which shows significant interaction with protease inhibitors for HIV infection.[3] In addition, rifampicin strongly interacts with non-nucleoside reverse transcriptase inhibitors. Thus, clinicians avoid starting highly active antiretroviral therapy (HAART), which consists of three or more highly potent reverse transcriptase inhibitors and protease inhibitors, until the TB infection has been cleared.[4] Thus, there is significant need and interest in developing new TB drugs. However, over the last 40 years, only bedaquiline (Sirturo), an ATP synthase inhibitor, has been approved for the treatment of MDR-Mtb infections as a monotherapeutic agent, in 2012.[5] The ultimate goal of the development of treatments for MDR-Mtb strains is to find novel antibacterial agents that 1) interfere with unexploited bacterial molecular targets, 2) can shorten a TB drug regimen (one- to three-month regimen), 3) can apply to combination TB chemotherapy, and 4) do not interfere with the ability of HAART to treat HIV patients who are co-infected with Mtb.

Since peptidoglycan (PG) is an essential bacterial cell-wall polymer, the machinery for PG biosynthesis provides a unique and selective target for antibiotic action. However, only a few enzymes in PG biosynthesis, such as the penicillin-binding proteins (PBPs), have been extensively studied.[6] Thus, the enzymes associated with the early PG biosynthesis enzymes [MurA, B, C, D, E, and F, MraY (phospho-MurNAcpentapeptide translocase or translocase I), and MurG] are considered to be a source of unexploited drug targets.[7] Our interest in unexploited molecular targets related to PG biosynthesis is MraY,[8] which catalyzes the transformation of UDP-*N*-acylmuramyl-L-alanyl-γ-D-glutamyl-*meso*-diaminopimelyl-D-alanyl-D-alanine (the Park nucleotide) into prenylpyrophosphoryl-*N*-acylmuramyl-L-Ala-γ-D-glu-*meso*-DAP-D-Ala-D-Ala (lipid I).[9] MraY is inhibited by nucleoside-based complex natural products, such as muraymycins,[10] liposidomycin,[11] caprazamycin,[12] pacidamycin,[13] capuramycin,[14] and other related natural products.[15] Capuramycin (**1**) and its analogues have exhibited significant mycobacterial growth inhibitory activities in vitro and in vivo (Figure 1) and very low toxicity in mice.[16] Moreover, capuramycin killed Mtb much faster than other first-line TB drugs (>90% of the bacilli were killed within 48 h), and thus could dramatically reduce the timeframe for effective antiTB chemotherapy. Therefore, capuramycin and its congeners are considered to be important lead molecules for the development of a new drug for MDR-Mtb infections.

Since the discovery of capuramycin as a specific spectrum antimycobacterial agent, extensive structure–activity relationship (SAR) studies of capuramycins have been limited because of difficulties in modifying the complex natural product at the desired position(s) with a wide range of func-

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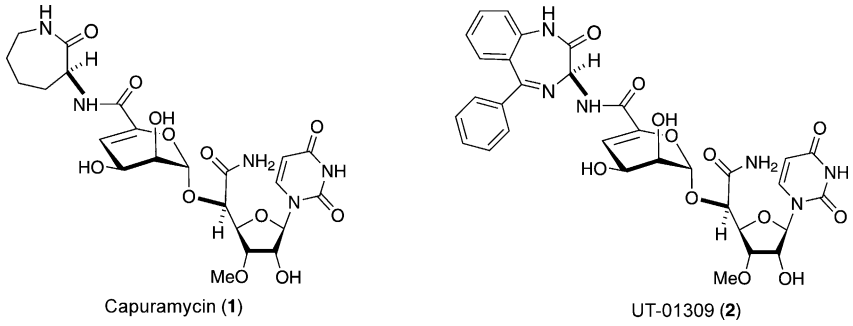


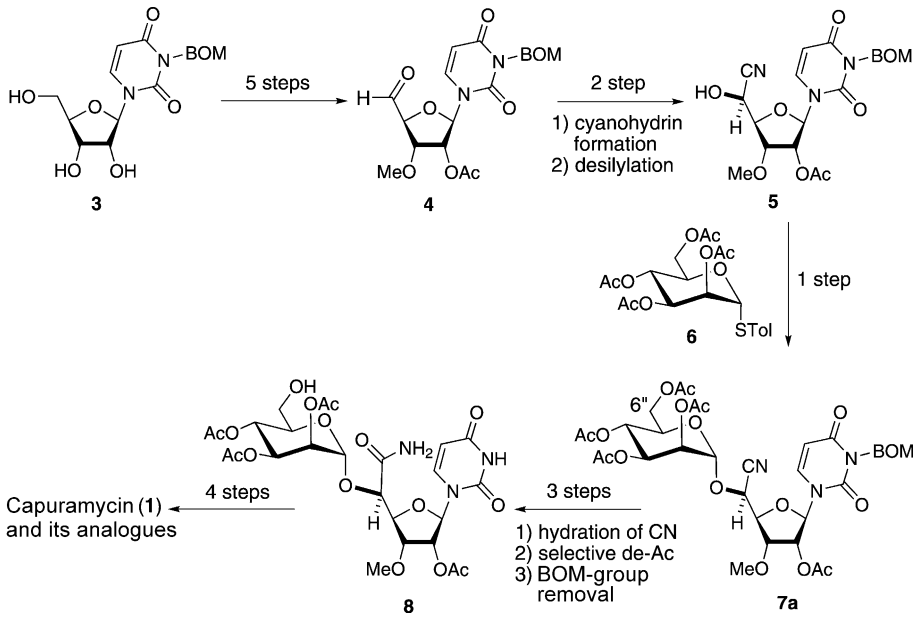
Figure 1. Structures of capuramycin (**1**) and UT-01309 (**2**).

tional groups. Accordingly, it is essential to establish a concise and convergent synthesis of capuramycin that is amenable to the synthesis of analogues for SAR studies. The first total synthesis of capuramycin was reported in 1994 by Knapp et al. Their synthesis requires 22 linear steps from diisopropylidene-D-glucofuranose, and relatively lengthy synthesis of the *manno*-pyranuronate glycosyl donor.[17] We have developed a concise synthesis of capuramycin in which the intact molecule can be synthesized in 15 steps from the known intermediate **3** (Scheme 1).[18] Although each step in our previously reported capuramycin synthesis is a high-yielding conversion when applied on a small to medium scale, several steps are not ideal for the synthesis of a large amount of capuramycin and its analogues for in vivo studies by using rodents.

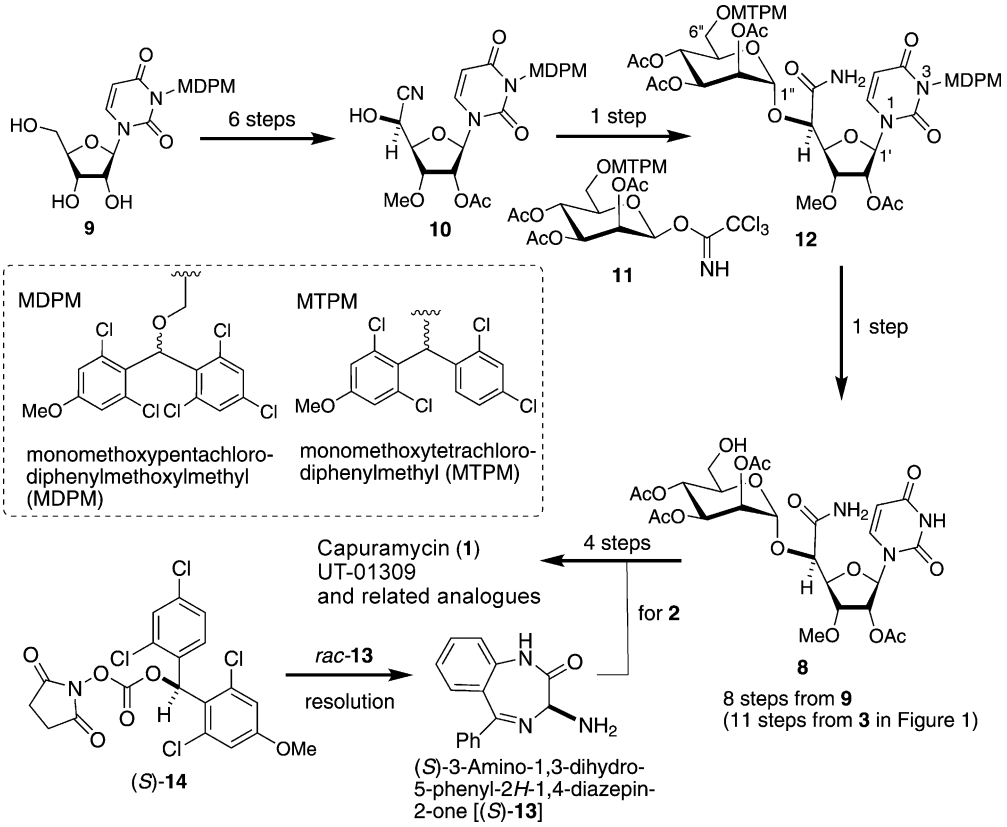
α-Mannosylation of **5** with the thioglycoside **6** requires diluted conditions (0.05 M) and long reaction times (12–16 h). Selective deacetylation at the 6″-position of **7a** has to be stopped at around 30–70% conversion to avoid the over-reactions and the recovered starting material is recycled to perform the same reaction multiple times. Hydrogenolytic cleavage of the benzyloxymethyl (BOM) group of the uridine ureido nitrogen under heterogeneous conditions often yields the over-reduced product in which the C5–C6 double bond of the uracil moiety is saturated.[19] Recently, we identified a new capuramycin analogue, UT-01309 (**2**), containing (*S*)-3-amino-1,4-benzodiazepine-2-one [(*S*)-**13**], which showed improved antimycobacterial activity (2.5 vs. 12.0 μg mL^{-1} for **1** against *M. tuberculosis*).[20] Significantly, UT-01309 (**2**) is active against drug-resistant *M. tuberculosis* and did not exhibit cytotoxicity against Vero monkey kidney cells and HepG2 human hepatoblastoma cells, even at 250 μg mL^{-1} concentrations (see below). Thus, we are very interested in in vivo evaluation of **2** in comparison with capuramycin (**1**) and related molecules. Herein, we report the improved synthesis of capuramycin (**1**) and its analogue UT-01309 (**2**) through use of 1) novel protecting groups for the uridine ureido nitrogen and primary alcohol, and 2) the chiral carbonate reagent for the resolution of *rac*-3-amino-1,4-benzodiazepine-2-one (**13**).

Results and Discussion

Our synthetic strategy to improve the syntheses of capuramycin (**1**) and capuramycin analogue UT-01309 (**2**) is illustrated in Scheme 2. We have developed new protecting groups, (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)-methyl [monomethoxytetrachlorodiphenylmethyl (MTPM)] and (2,6-dichloro-4-methoxyphenyl)(2,4,6-*O*-diphenylmethyl trichloroacetimidateophenyl)methoxymethyl [monomethoxydiphenylmethoxylmethyl (MDPM)] for primary alcohols and ureido nitrogen atoms, respectively.[21] These protecting groups showed significant relative stability under a wide variety of conditions utilized for the syntheses of natural and unnatural products. However, the MTPM and MDPM protecting groups can be conveniently removed by using 30% trifluoroacetic acid (TFA) in CH_2Cl_2. The use of these protecting groups for the uridine ureido nitrogen (3-position) and the primary alcohol (6″-position) will significantly improve the synthesis of capur-



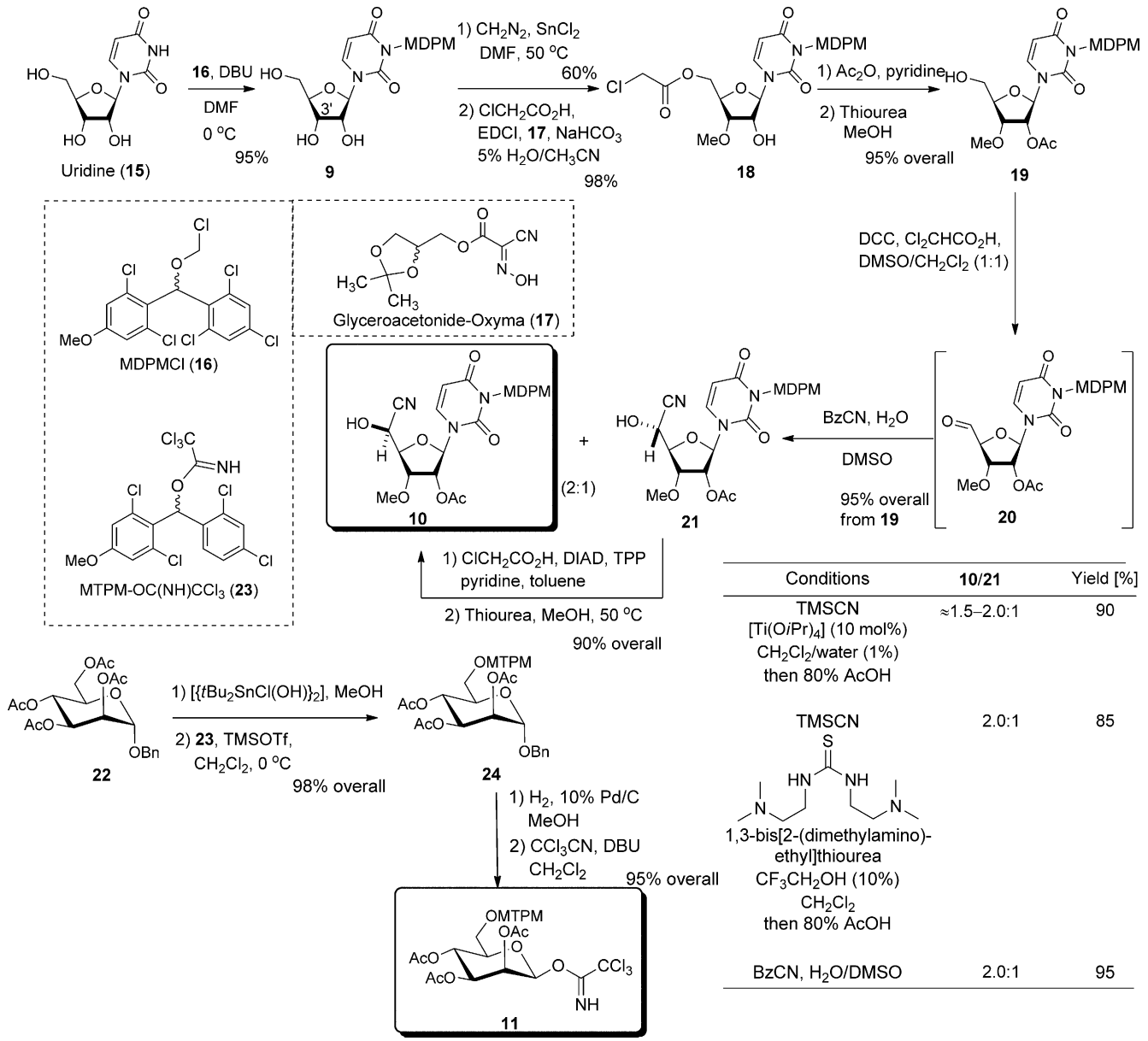
Scheme 1. Previously reported syntheses of capuramycin (**1**; Tol = tolyl).



Scheme 2. Improved synthetic strategy for capuramycin analogues.

amycin analogues (Scheme 2). (*S*)-3-Amino-1,4-benzodiazepin-2-one [(*S*)-**13**] is an important functional group to improve antimycobacterial activity of capuramycin analogues. For our SAR studies of capuramycin analogues, it is desirable to have a versatile resolution protocol for racemic amino acids that are not commercially available. We expected that the optically pure carbonate (*S*)-**14**, derived from unsymmetrical (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol, could resolve a diastereomeric mixture of the carbamates through convenient chromatography and be readily removed under mild conditions.[22]

Synthesis of (2*S*)-uridylhydroxyacetonitrile 10 and mannosyl donor imidate 11: MDPM and MTPM groups have significant advantages over other ordinal protecting groups for the syntheses of capuramycin analogues in that these new protecting groups 1) are stable in the presence of a wide variety of acids, 2) are not susceptible to hydrogenation under standard conditions, and 3) can be removed efficiently by solvolytic cleavage with 30% TFA at room temperature within 2 h without addition of a cation scavenger.[21] We synthesized over 10 g of MDPMCl (**16**) and MTPM-imidate (**22**) by following established procedures.[21] The uridine ureido nitrogen was protected with MDPMCl (**16**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the MDPM-protected uridine **9** in 95% yield (Scheme 3). Selective alkylation of **9** at the secondary alcohol (3′-position) was achieved by using $SnCl_2$-mediated methylation conditions to yield the desired monomethoxy derivative in 60% yield.[23] Selective chloroacetylation of the primary alcohol of the diol was performed with $ClCH_2CO_2H$, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), $NaHCO_3$, and glyceroacetonide–Oxyma (**17**) in 5% H_2O/CH_3CN to give rise to **18** in 98% yield.[24] The regiochemistry of **18** was unequivocally determined by extensive ^1H NMR decoupling studies and 2D NOESY experiments.[25] Although the ordinal esterification conditions [e.g., $ClCH_2CO_2H$, *N*,*N*-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 or $ClCH_2COCl$, pyridine in CH_2Cl_2) provided a mixture of **18** and the over-reaction products, we did not observe the formation of the secondary alcohol ester under the conditions applied to the synthesis of **18**. Acetylation of the secondary alcohol of **18**, followed by removal of the chloroacetyl group with thiourea in MeOH, afforded **19** in 95% overall yield.[26] The primary alcohol in **19** was oxidized under Pfitzner–Moffatt conditions (DCC, Cl_2CHCO_2H, $DMSO/CH_2Cl_2$) to provide the corresponding aldehyde **20**, which was utilized without purification.[27] We have extensively studied cyanohydrin formation reactions of the uridylaldehyde derivatives by using trimethylsilyl cyanide (TMSCN).[28] In all cases, Lewis acid promoted trimethylsilyl cyanation reactions of the uridylaldehydes furnished a mixture of the TMS-protected cyanohydrins, favoring the undesired (*R*)-configuration products (e.g., **21**), in low yields. Lewis base catalyzed trimethylsilyl cyanation reactions (e.g., Ph_3PO, *N*-methylmorpholine *N*-



Scheme 3. Syntheses of the glycosyl donor **10** and acceptor **11**.

oxide (NMO), 1,4-diazabicyclo[2.2.2]octane (DABCO), cinchona alkaloids) did not provide the products due to the fact that the uridylaldehydes were not stable in the presence of Lewis and Brønsted bases. In previous studies, we have observed that the Ti-mediated conditions gave the desired (*S*)-configuration cyanohydrin as the major product with satisfactory yield.[18] Similarly, TMSCN addition to **20** with [Ti(O*i*Pr)$_4$] (10 mol%) in CH_2Cl_2/H_2O (1%) provided a mixture of **10** and **21** in 90% yield with a **10**/**21** ratio of 1.5–2.0:1 after desilylation.[29] In our recent studies, we found that the trimethylsilyl cyanation reaction of **20** with 1,3-bis[2-(dimethylamino)ethyl]thiourea also gave a mixture of **10** and **21** with comparable selectivity and yield to the reaction with [Ti(O*i*Pr)$_4$] in CH_2Cl_2/H_2O (1%). Moreover, we observed that hydrocyanation of **20** with benzoyl cyanide (BzCN) in DMSO/H_2O afforded a 2:1 mixture of **10** and **21** in 95% yield from **19**.[30] Because water-catalyzed hydrocyanation with BzCN is operationally simple and results in high-yielding conversion, we decided to scale-up the conversion of **19** to **10** under these conditions and the undesired stereochemistry of **21** was inverted by a modified Mitsunobu reaction [diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP), $ClCH_2CO_2H$, pyridine (1:1:1:1)]. The chloroacetyl group in the ester was selectively removed with thiourea in MeOH. Thus, we could achieve the synthesis of the mannosyl acceptor **10** in 7 steps from uridine (**15**) with 34% overall yield without the inversion process (**21**→**10**) or in 9 steps with 45% overall yield including the Mitsunobu reaction, followed by deprotection.

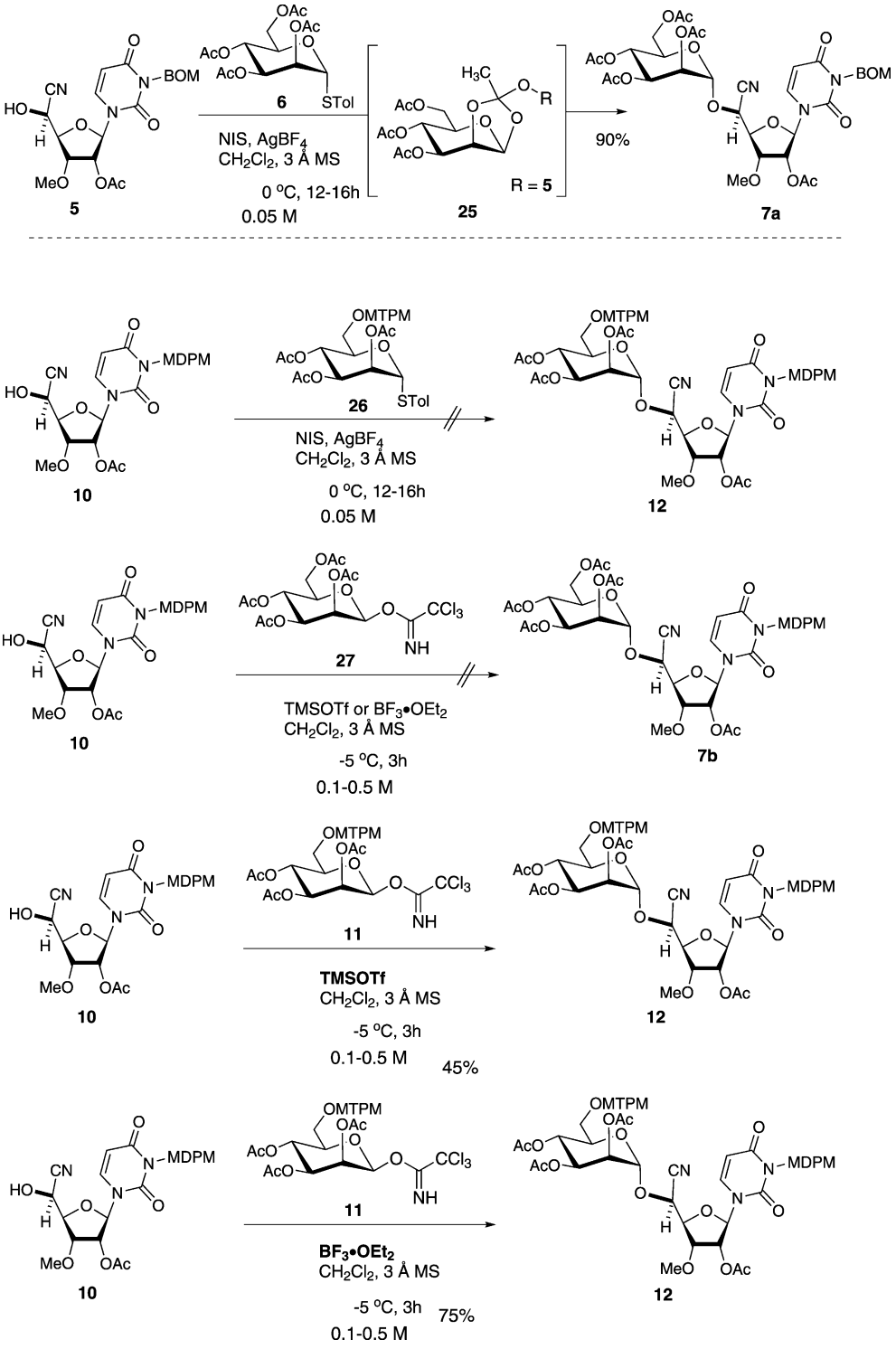
The mannosyl donor **11** was synthesized in 4 steps from α-benzyl glycoside **22** (Scheme 3). The primary acetate in **22** was selectively removed with $[\{t\mathrm{Bu_2SnCl(OH)}\}_2]$[31] and the generated alcohol was protected with MTPM-imidate **23** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), to afford **24** in 93% overall yield.[21] Hydrogenolytic cleavage of the anomeric benzyl ether, followed by the imidate-formation reaction, provided **11** in 95% overall yield.[32]

Mannosylation of cyanohydrin 10 with 11: In our previous capuramycin synthesis, we searched for an effective promoter to catalyze the mannosylation of **5** with thioglycoside **6** (Scheme 1). We found that α-selective mannosylation of **5** with **6** was achieved through the combination of *N*-iodosuccinimide (NIS) and $AgBF_4$ in CH_2Cl_2 (at 0.05 M concentrations; Scheme 4).[18,33] Interestingly, the NIS/$AgBF_4$-promoted mannosylation of **5** provided the orthoester **25** within 15 min, which underwent the rearrangement within 16 h to afford **7a** exclusively in 90% yield. Orthoester **25** could be distinguished from **7a** in the ^{1}H NMR spectrum of the crude reaction mixture; **25** showed a characteristic chemical shift of $\delta = 1.78$ ppm (CH_3).[34] All triflate ion associated glycosylation reactions with **6** [e.g., NIS/trifluoromethanesulfonic acid (TfOH) or *N*-bromosuccinimide (NBS)/TfOH] yielded a mixture of α- and β-mannosides.[35] Under the NIS/$AgBF_4$ promoted conditions, mannosylation of the MDPM-protected compound **10** with the thioglycoside **26** did not provide the desired product **12**. The acceptor **10** was stable under the NIS/$AgBF_4$ conditions, whereas thioglycoside **26** was completely consumed to form complex mixtures. Although mannosylation of **10** with α-mannopyranose 2,3,4,6-tetraacetate 1-(2,2,2-trichloroethanimidate) (**27**) did not provide the desired product **7b**, TMSOTf- and $BF_3{\cdot}OEt_2$-catalyzed mannosylation of **10** with the imidate **11** did provide the desired product **12** in 45 and 75% yield, respectively. It is worth noting that the mannosylation with **11** could be achieved at high concentrations in short reaction times compared to the mannosylation of **5** with **6** under the NIS/$AgBF_4$ conditions. We confirmed that mannosylation of **10** with **11** was reproducible at any concentration between 0.1–0.5 M and could be applied to a gram-scale synthesis of **12**.

Resolution of racemic 3-amino-1,4-benzodiazepine-2-one: We have previously identified that in vitro antimycobacterial activity of capuramycin (**1**) was improved by the replacement of the (*S*)-3-aminoazepan-2-one moiety of **1** with (*S*)-3-amino-1,4-benzodiazepine-2-one [(*S*)-**13**] (see above). To synthesize sufficient quantities of UT-01309 (**2**) for in vivo studies, it was desirable to establish an efficient resolution method for racemic 3-amino-1,4-benzodiazepine-2-one [(±)-**13**]. Due to the fact that 3-amino-1,4-benzodiazepine-2-ones are important building blocks[36] for the development of several therapeutic areas (e.g., to combat the respiratory syncytial virus), resolution methods for racemic 3-amino-1,4-benzodiazepine-2-one [(±)-**13**] have been reported by several groups.[37] However, most reported protocols provide separation of the diastereomers formed by amide-forming reactions with optically active amino acids, and only a few reports have demonstrated the resolution of (±)-**13** with readily cleavable chiral agents. Sherrill et al. reported the resolution of **13** by use of the *para*-nitrophenyl carbonate of (*R*)-α-methyl benzyl alcohol. In their procedure, the carbamate auxiliary was cleaved with HBr (gas) in CH_2Cl_2 and the generated byproduct, (1-bromoethyl)benzene, needed to be removed by recrystallization.[38]

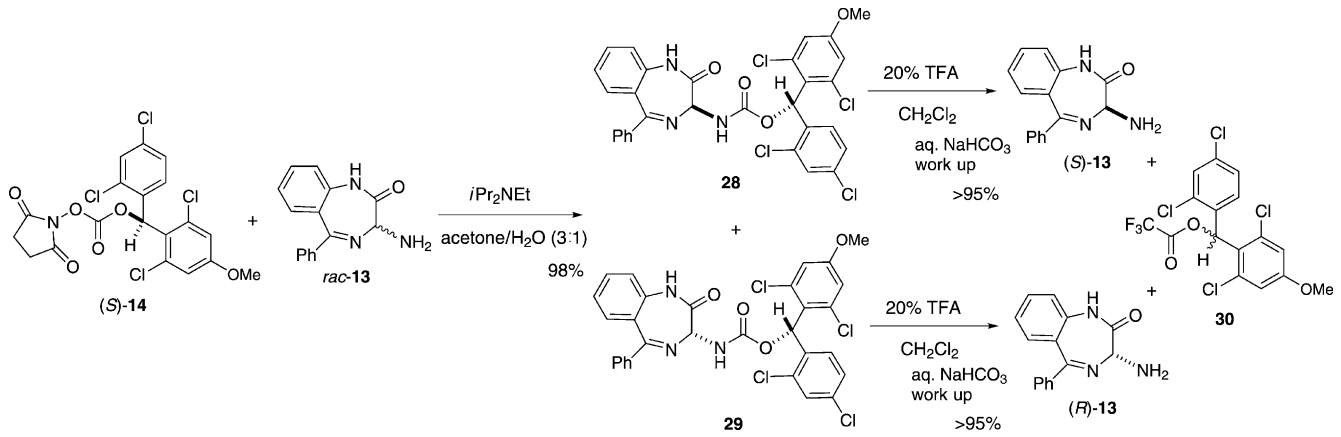
We envisioned the resolution of (±)-**13** with the chiral carbonate (*S*)-**14**, which was originally developed as a new chiral derivatizing agent for determination of the absolute configuration of amino acids (Scheme 5).[21c] Carbamate formation between (±)-**13** and (*S*)-**14** was achieved by using $i\mathrm{Pr_2NEt}$ in a mixture of acetone and H_2O (3:1). Gratifyingly, the generated diastereomers could be purified by silica gel column chromatography to afford **28** and **29** in 98% yield (approximately 49% each). As shown in Figure 2, we have reported that the absolute configuration of a wide range of amino acids can be determined by only analyzing the carbamate nitrogen protons of (*S*)-**14** and (*R*)-**14** derivatives in ^{1}H NMR spectra. In all cases, the nitrogen protons of carbamates derived from L-amino acids and (*S*)-**14** were shifted downfield relative to those obtained with L-amino acid–(*R*)-**14** derivatives.[22] In ^{1}H NMR spectra, the chemical shifts of **29** should be identical to those of the antipode of **29** (*ent*-**29**) (Figure 2). Thus, the $\Delta\delta(S\text{–}R)$ value of the N^α protons of **28** and *ent*-**29** should determine the absolute stereochemistry of **28**. The $\Delta\delta(N^\alpha_{\mathbf{28}}\text{–}N^\alpha_{\mathbf{29}})$ value was +0.03 and thus the absolute stereochemistry of **28** was assigned to be the L-configuration (*S* for 3-amino-1,4-benzodiazepine-2-one) as shown in Scheme 5. The diastereomeric excesses (*de* values) of purified **28** and **29** were determined by HPLC to be >99.0%. Removal of the carbamate auxiliaries of **28** and **29** was achieved by use of 20% TFA in CH_2Cl_2, to afford (*S*)-**13** and (*R*)-**13** in >95% yield. The chiral auxiliary was recovered as the racemic trifluoroacetate **30** in quantitative yield. The absolute configurations of (*S*)-**13** and (*R*)-**13** were unequivocally confirmed by the comparison of optical rotations with the reported values for (*S*)-**13** and (*R*)-**13**.[37c]

Syntheses of capuramycin and UT-01309 (2): We have previously reported the synthesis of capuramycin (**1**) from **7** in 7 steps (Scheme 1).[18] The use of MDPM and MPTM protecting groups for the uridine ureido nitrogen and primary alcohol could, however, significantly improve the synthesis of **8**. As summarized in Scheme 6, capuramycin (**1**) and UT-01309 (**2**) were synthesized in 6 steps from **12**. The improved method required purifications by chromatography for only three of the total number of synthetic steps (Scheme 6). The cyano group in **12** was hydrated by using $InCl_3$–aldoxime in toluene, furnishing the corresponding primary amide.[39] Without further purification, the primary amide was subjected to simultaneous removal of the MDPM and MPTM groups with TFA (30%) in CH_2Cl_2, to afford **8** in >95% overall yield for the two steps. We could achieve the synthesis of over 1 g of **8** through the new protecting-group strat-



Scheme 4. Mannosylation of the cyanohydrins.

egy summarized in Schemes 3, 4, 5, and 6. The conversions of **8** to capuramycin (**1**) and UT-01309 (**2**) were carried out through the previously reported procedures except for the amide-forming reactions.[18] Oxidation–elimination reactions of **8** by using SO_3·pyridine in a biphasic solvent system (DMSO/Et_3N, 3:1) provided the α,β-unsaturated aldehyde **31**.[40] Aldehyde **31** was then oxidized to the corresponding carboxylic acid (**32**) by Pinnick oxidation ($NaClO_2$, 2-methyl-2-butene).[41] The resulting crude carboxylic acid was coupled with (*S*)-aminocaprolactam (**33**) by using an amide forming reaction in water media [glyceroacetonide–Oxyma (**17**), EDCI, $NaHCO_3$ in H_2O] to yield **33** in 80–85% overall yield from **8**.[42] In our previous synthesis of **1**, 1-hydroxy-7-azabezotriazole (HOAt) was used as the peptide-coupling



Scheme 5. Resolution of *rac*-3-amino-1,4-benzodiazepine-2-one.

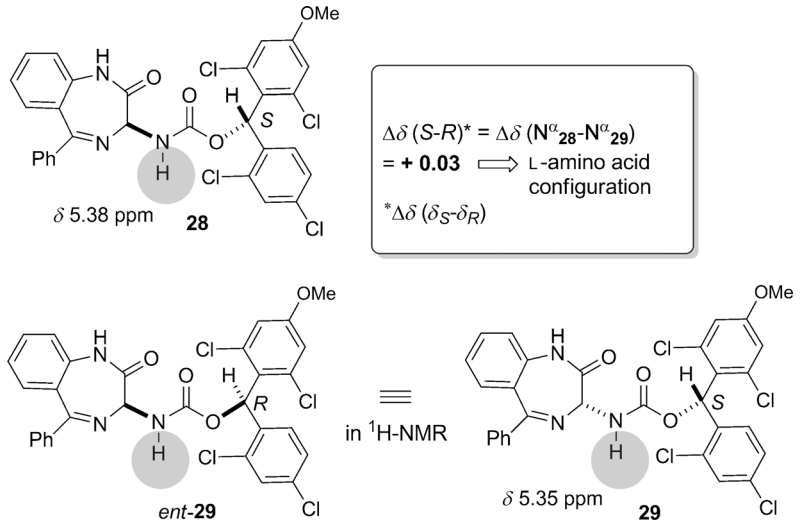


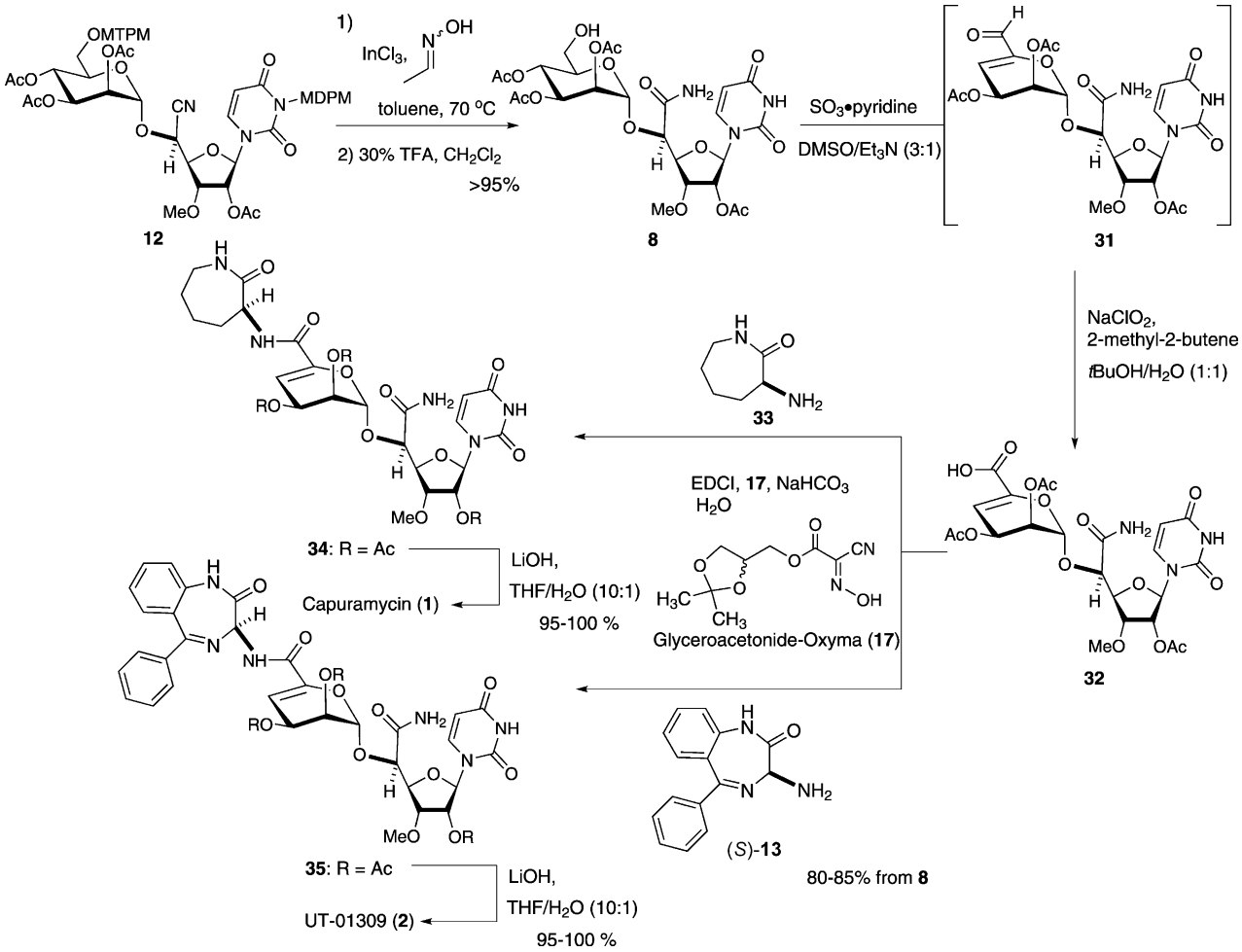
Figure 2. Absolute configurations of **28** and **29**.

additive to couple the segments **32** and **33**. HOAt and some other byproducts generated under the coupling-reaction conditions [EDCI, HOAt, *N*-methylmorpholine (NMM) in DMF] were difficult to separate from the desired product by standard column chromatography. In contrast, in the glyceroacetonide–Oxyma (**17**)/EDCI-mediated coupling reaction, simple basic and acidic aqueous workup procedures could remove all reagents utilized in the reactions, to afford the coupling product **34** in high yield with excellent purity. Saponification of **34** by using LiOH in THF/H_2O provided capuramycin (**1**) in greater than 95% yield. Similarly, UT-01309 (**2**) was synthesized by the same process, but by using (*S*)-**13** instead of **33** (Scheme 6). The purities of synthetic products **1** and **2** were determined to be >99% by reverse-phase HPLC analyses.

The in vitro biological evaluation of UT-01309 (2): UT-01309 (**2**) was identified by cell-based assays of a small optimized library of capuramycin analogues. The in vitro biological activities of **2** synthesized herein were evaluated against *Mtb* MraY (IC_{50} values) and a series of bacteria including *Mycobacterium spp*. The IC_{50} value of **2** against *Mtb* MraY was 5.5 nM (**1**: IC_{50} = 18 nM against *Mtb* MraY). UT-01309 (**2**) did not exhibit growth inhibitory activity against a series of Gram-positive and -negative bacteria, including *S. aureus*, *E. faecalis*, *E. coli*, *K. pneumonia*, and *P. aeruginosa*, even at 400 μg mL^{-1} concentrations. UT-01309 (**2**) showed bactericidal activities specific to *Mycobacterium spp*. UT-01309 (**2**) killed *M. tuberculosis* (H37Rv) completely at 2.5 μg mL^{-1} concentrations, whereas capuramycin required 12.0 μg mL^{-1}. UT-01309 (**2**) showed a minimum inhibitory concentration (MIC) of 6.5 μg mL^{-1} against *M. smegmatis*. Significantly, UT-01309 (**2**) is active against drug-resistant *M. tuberculosis* (e.g., *M. tuberculosis* H37Rv INHr and *M. tuberculosis* H37Rv RFPr), and did not exhibit cytotoxicity against Vero monkey kidney cells and HepG2 human hepatoblastoma cells, even at 250 μg mL^{-1} concentrations.

Conclusion

We present an improved synthesis of capuramycin (**1**) and its analogue UT-01309 (**2**), a promising investigational drug lead for MDR-*Mycobacterium tuberculosis* infections. MDPM and MPTM protecting groups for the uridine ureido nitrogen atom and primary alcohol improved the overall efficiency of the syntheses of **1** and **2**. The synthetic scheme reported herein enables us to synthesize gram quantities of the key intermediate **8** for the synthesis of a series of capuramycin analogues; **8** could be synthesized in 9 steps from uridine (**15**) in 32% overall yield. In addition, we have demon-



Scheme 6. Synthesis of capuramycin and UT-01309 (**2**).

strated efficient resolution of racemic 3-amino-1,4-benzodiazepine-2-one [(±)-**13**] with the chiral carbonate (*S*)-**14** to yield (*S*)-**13**, an important building block to improve the in vitro biological activity of capuramycin. We will evaluate UT-01309 (**2**) in vivo by using an infected-mouse model and study the toxicity and pharmacokinetics and pharmacodynamics (PK/PD) profile of **2**; these data will be reported elsewhere.

Experimental Section

General: All reagents and solvents were of commercial grade and were used as received, without further purification, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under an argon atmosphere prior to use. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), benzene, toluene, and triethylamine (Et_3N) were distilled from calcium hydride under an argon atmosphere. Flash column chromatography was performed with Whatman silica gel (Purasil 60 Å, 230–400 Mesh). Analytical thin-layer chromatography was performed with 0.25 mm coated commercial silica gel plates (EMD, Silica Gel $60F_{254}$) visualizing at 254 nm, or developed with ceric ammonium molybdate or anisaldehyde solutions by heating on a hot plate. ^{1}H NMR spectral data were obtained by using 400 and 500 MHz instruments. ^{13}C NMR spectral data were obtained by using 100 and 125 MHz instruments.

(2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxy methyl chloride (16): (2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxymethyl methyl sulfide was synthesized according to the previously reported procedure.[7a] Sulfuryl chloride (2.0 mL, 25.0 mmol) was added to a stirred solution of (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxymethyl methyl sulfide (11.18 g, 25.0 mmol) in CH_2Cl_2 (63.0 mL) at RT. The reaction mixture was stirred for 1 h and all volatile compounds were evaporated to provide the crude product as an oil that was pure enough for the next reaction (10.45 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (s, 2H), 6.88 (s, 2H), 6.77 (s, 1H), 5.57 (q, $J = 6.4$ Hz, 2H), 3.80 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 159.6, 136.8, 136.6, 134.4, 131.7, 129.7, 124.3, 115.6, 80.1, 55.8 ppm; IR: $\tilde{\nu} = 3473$, 1445, 1309 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{10}C_{16}O_2$: C 41.42, H 2.32, Cl 48.91; found: C 41.81, H 2.41, Cl 48.97.

3-[(2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxymethyl]-1-(3,4-dihydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (9): DBU (9.0 mL, 60.0 mmol) and **16** (13.08 g, 30.0 mmol) were added to a stirred solution of uridine (10.98 g, 45.0 mmol) in DMF (120 mL) at 0 °C. After 1 h at 0 °C, the reaction was quenched by addition of MeOH (24 mL). All volatiles were evaporated in vacuo and the crude product was purified by silica gel column chromatography with $CHCl_3$/MeOH (95:5) to afford **9** as an oil (17.62 g, 95%). $R_f = 0.3$ (10% MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J = 6.8$ Hz, 1H), 7.30 (d, $J = 3.6$ Hz, 2H), 6.83 (d, $J = 4.8$ Hz, 2H), 6.57 (s, 1H), 5.77 (d, $J =$ 8.4 Hz, 1H), 5.59 (m, 3H), 4.32 (m, 2H), 4.24 (s, 1H), 3.97 (d, $J =$

12.0 Hz, 1H), 3.90 (s, 1H), 3.83 (m, 1H), 3.78 (s, 3H), 3.05 (s, 1H), 2.20 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.9, 159.4, 151.9, 140.1, 136.7, 134.1, 132.5, 129.5, 125.2, 115.5, 101.6, 93.2, 85.7, 77.9, 74.8, 70.4, 69.1, 61.7, 55.7, 36.6, 31.5 ppm; IR: $\tilde{\nu}$=3435, 1719, 1665, 1440, 1081 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{24}H_{22}C_{l5}N_2O_8$: 640.9819; found: 640.9825.

Synthesis of 18: $SnCl_2$ (1.91 g, 10.0 mmol) was added to a stirred solution of **9** (12.8 g, 20.0 mmol) in DMF (300 mL). The reaction mixture was heated to 50°C followed by addition of CH_2N_2 (150 mL, 60.0 mmol, 0.4 M in Et_2O). After 1 h, all volatile compounds were evaporated in vacuo. The selectivity ratio and yield of the monomethyl ethers were determined, by ^{1}H NMR analyses of the crude mixture, to be a 3:2 ratio in favor of the desired product. The crude product was dissolved in 5% H_2O/MeCN (1.0 mL). Glyceroacetonide–Oxyma (**17**; 6.7 g, 30.0 mmol), EDCI (5.7 g, 30.0 mmol), chloroacetatic acid (3.72 g, 40.0 mmol), and $NaHCO_3$ (10.1 g, 120.0 mmol) were added to the reaction mixture. After 3 h, the reaction was quenched with aqueous $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield the desired ester **18** as a colorless liquid (8.6 g, 59% over the two steps). R_f=0.3 (30% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29 (d, *J*=7.5 Hz, 1H), 7.20 (s, 2H), 6.76, (s, 2H), 6.50 (s, 1H), 5.71 (d, *J*=7.5 Hz, 1H), 5.48 (m, 3H), 4.45 (m, 1H), 4.34 (m, 2H), 4.15 (m, 1H), 4.04 (m, 2H), 3.96 (m, 1H), 3.71 (s, 3H), 3.42 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.9, 162.7, 159.3, 151.2, 140.3, 136.7, 134.0, 132.6, 129.5, 125.3, 115.5, 102.1, 79.7, 78.9, 77.8, 72.7, 69.2, 65.0, 58.9, 55.7, 40.6 ppm; IR: $\tilde{\nu}$=3442, 1711, 1660, 1445, 1309, 1070 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{27}H_{24}C_6N_2NaO_9$: 754.9481; found: 754.9484.

Synthesis of 19: Ester **18** was dissolved in pyridine/Ac_2O (2:1, 200 mL) and stirred at RT. Upon completion, all volatile compounds were evaporated in vacuo to afford the desired acetate. The crude material was dissolved in MeOH (200 mL) and thiourea (3.8 g, 50.0 mmol) was added to the mixture. The reaction mixture was stirred at 50°C for 4 h and cooled to RT. All volatile compounds were evaporated in vacuo. Purification by silica gel column chromatography with hexanes/EtOAc (1:1) yielded the desired product **19** as an oil (7.8 g, 95% over the two steps). R_f=0.4 (30% hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.48 (d, *J*=7.5 Hz, 1H), 7.30 (s, 2H), 6.83 (s, 2H), 6.57 (s, 1H), 5.77 (d, *J*=7.5 Hz, 1H), 5.66 (s, 1H), 5.57 (brs, 2H), 5.44 (brs, 1H), 4.18 (brs, 1H), 4.11 (brs, 1H), 4.00 (d, *J*=11.5 Hz, 1H), 3.80 (s, 1H), 3.77 (s, 3H), 3.41 (s, 3H), 2.25 (brs, 1H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 162.6, 159.3, 151.4, 140.3, 136.7, 134.0, 132.6, 129.5, 125.3, 115.5, 102.3, 91.4, 83.0, 80.9, 77.8, 70.1, 69.2, 61.3, 59.0, 55.7, 20.8 ppm; IR: $\tilde{\nu}$=3445, 1719, 1665, 1440, 1302, 1081 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{27}H_{25}Cl_5N_2NaO_9$: 720.9871; found: 720.9875.

Synthesis of 10: DCC (4.0 g, 20.0 mmol) and dichloroacetic acid (1.02 g, 8.0 mmol) were added to a stirred solution of **19** (5.75 g, 8.0 mmol) in CH_2Cl_2/DMSO (1:1, 80 mL) at 0°C. After 1 h at 0°C, the reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with aqueous $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the crude aldehyde, which was used directly in the next step after passing through a SiO_2 pad. BzCN (1.58 g, 12.0 mmol) was added to a stirred solution of the crude aldehyde in DMSO/H_2O (4:1, 80 mL). After being stirred for 12 h at RT, aqueous $NaHCO_3$ was added, followed by EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated. The resulting crude material was purified by silica gel column chromatography with EtOAc/hexanes (2:3) to give **10** (3.7 g, 63%) and **21** (1.88 g, 32%).

Data for ***10***: R_f=0.4 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31 (d, *J*=7.5 Hz, 2H), 6.84 (d, *J*=10.0 Hz, 2H), 6.56 (s, 1H), 5.83 (dd, *J*=5.5, 6.0 Hz, 1H), 5.58 (m, 1H), 5.40 (brs, 1H), 5.34 (brs, 1H), 5.23 (brs, 1H), 4.67 (d, *J*=11.0 Hz, 1H), 4.55 (brs, 1H), 4.35 (s, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 2.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2, 162.2, 159.4, 151.7, 142.2, 136.7, 134.2, 132.3, 129.6, 124.9, 117.2, 115.6, 103.1, 95.1, 84.2, 78.5, 70.4, 69.3, 61.7, 59.3, 55.8, 43.1, 21.9 ppm; IR: $\tilde{\nu}$=3378, 1755, 1724, 1676, 1463, 1238 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{28}H_{24}Cl_5N_3NaO_9$: 745.9823; found: 745.9826.

Data for ***21***: R_f=0.45 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.31 (d, *J*=5.5 Hz, 2H), 6.83 (s, 2H), 6.55 (m, 1H), 5.81 (dd, *J*=4.5 Hz, 1H), 5.69 (m, 1H), 5.57 (m, 2H), 5.42 (m, 1H), 4.77 (m, 1H), 4.71 (brs, 1H), 4.49 (brs, 1H), 4.33 (m, 2H), 3.77 (s, 3H), 3.45 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.9, 162.7, 159.4, 151.4, 140.0, 136.7, 134.1, 132.3, 129.5, 125.1, 117.3, 115.5, 102.7, 83.6, 81.1, 77.9, 73.5, 61.4, 59.4, 55.7, 42.4, 23.4 ppm; IR: $\tilde{\nu}$=3378, 1755, 1724, 1676, 1463, 1238 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{28}H_{24}Cl_5N_3NaO_9$: 745.9823; found: 745.9826.

Synthesis of 10 through a Mitsunobu reaction: DIAD (22.0 mg, 0.10 mmol) was added to a stirred solution of **21** (72.0 mg, 0.10 mmol), $ClCH_2COOH$ (10.0 mg, 0.10 mmol), Ph_3P (26.0 mg, 0.10 mmol), and pyridine (8.0 μL, 0.10 mmol) in toluene (1 mL). After 4 h at RT, all volatile compounds were removed in vacuo and the crude ester was purified by silica gel column chromatography. Thiourea (38.0 mg, 0.50 mmol) was added to a stirred solution of the ester in MeOH (2 mL), and the reaction mixture was heated to 50°C. After 4 h at 50°C, the reaction was cooled to RT and MeOH was evaporated in vacuo. The residue was purified by silica gel column chromatography with hexanes/EtOAc (1:1) to give **10** as a colorless oil (68.0 mg, 90%). This reaction was also performed for 1.5 g (2.01 mmol) of **21**.

Synthesis of 26: [{tBu$_2$SnCl(OH)}$_2$] (0.58 g, 1.0 mmol) was added to a stirred solution of **6** (9.0 g, 20.0 mmol) in MeOH (200 mL). Upon completion, the reaction mixture was concentrated in vacuo and filtered through a silica gel plug and concentrated to yield the free alcohol in quantitative yield. Imidate **23**[7b] (11.9 g, 24.0 mmol) and then TMSOTf (1.0 mL, 12.0 mmol) were added to the free alcohol in CH_2Cl_2 (400 mL) at 0°C. After 2 h at 0°C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated. Purification of the crude material by silica gel column chromatography afforded **26** as a colorless liquid (13.7 g, 92% over the two steps). R_f=0.5 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.83 (dd, *J*=8.5 Hz, *J*=25.5 Hz, 1H), 7.37 (m, 2H), 7.18 (dd, *J*=7.5 Hz, *J*=15.0 Hz, 1H), 7.00 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=5.5 Hz, 2H), 6.21 (s, 0.5H), 6.15 (s, 0.5H), 5.47 (s, 1H), 5.31 (m, 3H), 4.59 (m, 1H), 3.78 (d, *J*=6.5 Hz, 3H), 3.64 (m, 1H), 3.57 (d, *J*=9.5 Hz, 1H), 2.32 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.97 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.9, 159.5, 137.5, 137.2, 136.4, 133.4, 132.7, 132.4, 131.7, 131.6, 129.9, 129.8, 129.0, 126.1, 125.5, 125.0, 115.2, 86.0, 76.1, 71.2, 70.4, 69.7, 69.4, 68.2, 67.1, 55.7, 25.7 ppm; IR: $\tilde{\nu}$=3050, 1742, 1613, 1481 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{33}H_{32}Cl_4NaO_9S$: 769.0389; found: 769.0387.

Synthesis of 24: [{tBu$_2$SnCl(OH)}$_2$] (0.87 g, 1.5 mmol) was added to a stirred solution of **22** (13.2 g, 30.0 mmol) in MeOH (300 mL). Upon completion, the reaction mixture was concentrated in vacuo, filtered through a silica gel plug and concentrated to yield the free alcohol in 100% yield. TMSOTf (1.0 mL, 6.0 mmol) was added dropwise to a stirred solution of the primary alcohol (12.0 g, 30.0 mmol) and imidate **23**[7b] (16.3 g, 33.0 mmol) in CH_2Cl_2 (300 mL) at 0°C. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with brine and dried over Na_2SO_4. The evaporation of all volatile compounds in vacuo gave the crude product, which was purified by silica gel column chromatography to afford **24** as a colorless liquid (21.9 g, 98%). R_f=0.5 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.91 (m, 1H), 7.27 (m, 7H), 6.85 (s, 2H), 6.23 (d, *J*=6.5 Hz, 1H), 5.36 (m, 2H), 5.27 (s, 1H), 5.22 (m, 1H), 4.85 (d, *J*=7.5 Hz, 1H), 4.71 (m, 1H), 4.52 (d, *J*=11.5 Hz, 1H), 4.06 (m, 1H), 3.80 (s, 3H), 3.63 (m, 2H), 2.13 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 170.0, 169.9, 169.7, 159.5, 137.4, 137.2, 136.4, 133.5, 132.5, 131.6, 129.1, 128.5, 128.2, 126.1, 125.6, 125.1, 115.2, 96.4, 96.0, 76.9, 70.4, 69.7, 69.3, 69.0, 68.4, 67.6, 66.9, 60.4, 55.7, 20.8 ppm; IR: $\tilde{\nu}$=3055, 1744, 1615, 1484 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{33}H_{32}Cl_4NaO_{10}$: 753.0618; found: 753.0615.

Synthesis of 11: Pd/C (4.5 g, 10 wt%) was added to a stirred solution of **24** (10.8 g, 15.0 mmol) in MeOH (600 mL) under N_2. H_2 gas was introduced through a double-folded balloon and the reaction mixture was stir-

red for 4 h under H_2. Upon completion, the solution was filtered through Celite and eluted with EtOAc. The organic solvent was evaporated to form the crude product, which was used directly without further purification. The crude product was dissolved in dry CH_2Cl_2, followed by the addition of CCl_3CN (15.0 mL) and DBU (0.45 mL). The mixture was stirred for 2 h. Upon completion, all volatile compounds were evaporated in vacuo. Purification by silica gel column chromatography afforded the desired product **11** as a colorless oil (11.2 g, 95%). R_f=0.7 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.71 (s, 1H), 7.87 (dd, J=7.5, 10.0 Hz, 1H), 7.26 (m, 2H), 6.83 (s, 2H), 6.26 (d, J=8.5 Hz, 1H), 6.19 (s, 1H), 5.44 (m, 3H), 4.23 (m, 1H), 3.78 (s, 3H), 3.74 (m, 1H), 3.64 (m, 1H), 2.18 (s, 1.5H), 2.16 (s, 1.5H), 2.01 (s, 3H), 1.97 (s, 1.5H), 1.94 ppm (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.9, 169.8, 169.4, 159.7, 159.5, 137.3, 136.4, 133.4, 132.3, 131.6, 131.4, 129.0, 128.8, 126.1, 125.8, 125.4, 125.0, 115.2, 94.6, 94.3, 90.6, 76.5, 75.8, 72.8, 71.8, 69.0, 68.2, 68.0, 67.1, 66.0, 55.8, 55.6, 20.7 ppm; IR: $\tilde{\nu}$=3050, 1755, 1680, 1622, 1480 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{28}H_{26}Cl_7NNaO_{10}$: 805.9245; found: 805.9249.

Synthesis of 12: Molecular sieves (MS; 3 Å, 10.0 g) were added to a stirred solution of **10** (2.90 g, 4.0 mmol) and **11** (6.26 g, 8.0 mmol) in dry CH_2Cl_2 (50 mL). The reaction was stirred for 30 min at RT. The reaction mixture was cooled to −5 °C, followed by dropwise addition of BF_3·OEt_2 (1.48 mL, 12.0 mmol). After being stirred for 3 h at −5 °C, the reaction was quenched with aqueous $NaHCO_3$. The reaction mixture was passed through a SiO_2 pad and eluted with CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography afforded **12** as an oil (4.04 g, 75%). R_f=0.45 (60% EtOAc/hexanes); ^{1}H NMR (500 MHz,$CDCl_3$): δ=7.98 (dd, J=21, 7.0 Hz, 1H), 7.30 (s, 4H), 7.25 (s, 1H), 6.84 (s, 4H), 6.56 (s, 1H), 6.27 (s, 0.5H), 6.17 (s, 0.5H), 5.94 (d, J=7.5 Hz, 1H), 5.88 (m, 1H), 5.58 (m, 3H), 5.39 (brs, 1H), 5.25 (d, J=10.5 Hz, 1H), 5.22 (s, 1H), 5.00 (d, J=20.5 Hz, 1H), 4.60 (m, 1H), 4.38 (s, 1H), 4.19 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.66 (m, 1H), 3.45 (s, 3H), 2.20 (s, 3H), 2.18 (s, 1.5H), 2.16 (s, 1.5H), 2.11 (s, 1.5H), 2.06 (s, 1.5H), 2.02 (s, 3H), 1.97 (s, 1.5H), 1.96 ppm (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 169.6, 162.3, 159.6, 149.8, 137.1, 136.9, 135.8, 134.4, 133.9, 133.0, 131.7, 131.1, 129.7, 129.3, 126.3, 125.1, 124.3, 115.4, 114.7, 103.8, 95.9, 89.7, 89.3, 80.9, 80.1, 73.1, 72.1, 71.8, 68.9, 68.1, 65.7, 63.5, 59.2, 55.8, 29.7, 20.6 ppm; IR: $\tilde{\nu}$=3338, 2921, 2250, 1737, 1669, 1465, 1221 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{54}H_{48}Cl_9N_3NaO_{18}$: 1367.9968; found: 1367.9975.

Synthesis of 8: $InCl_3$ (0.4 g, 1.8 mmol) and acetaldoxime (0.67 mL, 10.8 mmol) was added to a stirred solution of **12** (2.42 g, 1.8 mmol) in toluene (180 mL). The reaction mixture was heated at 70 °C for 4 h. Upon completion, the reaction was cooled to RT and all volatile compounds were evaporated. The crude material was passed through a short SiO_2 pad. The amide was dissolved in TFA/CH_2Cl_2 (1:2, 75 mL) and stirring was continued for 1 h at RT. The reaction mixture was concentrated in vacuo. The crude product was purified by silica gel column chromatography to afford **8** as an amorphous solid (1.1 g, 96% over the two steps). R_f=0.3 (95% $CHCl_3$/MeOH); $[\alpha]_D^{20}$=+75 (c=0.4 in MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ=7.83 (d, J=8.0 Hz, 1H), 5.98 (d, J=1.5 Hz, 1H), 5.91 (d, J=8.5 Hz, 1H), 5.52 (s, 1H), 5.40 (t, J=5.0 Hz, 1H), 5.28 (m, 2H), 5.01 (s, 1H), 4.49 (d, J=3.0 Hz, 1H), 4.40 (m, 1H), 4.20 (t, J= 4.0 Hz, 1H), 3.91, (brs, 1H), 3.61 (m, 3H), 3.40 (s, 3H), 2.13 (s, 6H), 2.04 (s, 3H), 2.00 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ=172.8, 172.0, 171.7, 171.6, 166.3, 152.2, 142.1, 103.9, 98.2, 89.4, 83.8, 79.4, 76.7, 75.2, 73.9, 71.1, 70.5, 67.2, 62.0, 59.4, 20.8, 20.6 ppm; IR: $\tilde{\nu}$=3413, 1710, 1680, 1223, 1066 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{25}H_{33}N_3NaO_{16}$: 654.1753; found: 654.1746.

(2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)carbamic acid (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methyl ester (28, 29): Racemic 3-amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one [(±)-**13**] was synthesized by following the reported procedure.[14] (*S*)-(2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenylmethyl-*N*-succinimidyl carbonate [(*S*)-**14**; 58.0 mg, 0.20 mmol] and *i*Pr_2NEt (70.0 μL, 0.40 mmol) were added to a stirred solution of (±)-**13** (25.0 mg, 0.10 mmol) in acetone/H_2O (3:1, 3 mL) at RT. Upon completion after 4 h, the reaction mixture was concentrated in vacuo to remove acetone. The crude material was partitioned between EtOAc (5 mL) and HCl (1 N, 5 mL). The water phase was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/acetone, 1:3) afforded the desired diastereomers **28** and **29** as an amorphous solid (31.0 mg each, 98% total yield). This reaction was performed with 1 g of *rac*-**13** to provide **28** (1.24 g).

*Data for **28***: R_f=0.34 (95% $CHCl_3$/MeOH); $[\alpha]_D^{20}$=+77 (c=0.2 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=7.52 (m, 5H), 7.45 (m, 2H), 7.36 (m, 4H), 7.20 (m, 3H), 6.91 (s, 2H), 6.71 (m, 1H), 5.38 (d, J= 8.8 Hz, 1H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 168.2, 160.0, 154.9, 138.6, 137.4, 134.5, 133.6, 132.4, 131.6, 130.9, 130.1, 129.9, 128.5, 127.9, 126.7, 125.1, 124.5, 121.6, 115.5, 71.9, 69.5, 56.0 ppm; IR: $\tilde{\nu}$=3441, 1936, 1711, 1413, 1354, 1222, 1150 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{30}H_{21}Cl_4N_3NaO_4$: 652.0154; found: 652.0150; HPLC: retention time, 8.5 min (de>99%).

*Data for **29***: R_f=0.30 (95% $CHCl_3$/MeOH); $[\alpha]_D^{20}$=+181 (c=0.2 in MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=7.48 (d, J=16.8 Hz, 1H), 7.46 (m, 4H), 7.40 (m, 1H), 7.38 (m, 5H), 7.20 (m, 2H), 7.12 (m, 1H), 6.86 (s, 2H), 6.82 (m, 1H), 5.35 (d, J=8.0 Hz, 1H), 3.78 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.6, 168.1, 159.7, 154.7, 138.4, 137.2, 134.4, 133.4, 132.2, 131.5, 130.7, 129.9, 129.7, 128.3, 127.7, 126.4, 124.8, 124.3, 121.3, 115.3, 71.7, 69.0, 55.7 ppm; IR: $\tilde{\nu}$=3441, 1936, 1711, 1413, 1354, 1222, 1150 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{30}H_{21}Cl_4N_3NaO_4$: 652.0154; found: 652.0151; HPLC: retention time, 8.0 min (de>99%).

(*S*)-3-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one [(*S*)-13]: Carbamate **28** (30.0 mg, 0.05 mmol) was dissolved in TFA/CH_2Cl_2 (1:4, 2 mL) under N_2. After 1 h at RT, the reaction mixture was concentrated in vacuo. The residue was partitioned between aqueous $NaHCO_3$ and $CHCl_3$/MeOH (10:1). The aqueous layer was back extracted with $CHCl_3$/MeOH (10:1). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude material by silica gel column chromatography afforded the desired product (*S*)-**13** as an amorphous solid (12.0 mg, 95%) and the byproduct ester **30** as an oil (24.0 mg, 100%).

*Data for (S)-**13***: $[\alpha]_D^{20}$=−220 (c=0.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, [D_6]DMSO): δ=10.74 (brs, 1H), 7.64 (m, 1H), 7.50 (m, 5H), 7.33 (m, 2H), 7.25 (m, 1H), 4.29 (s, 1H), 2.60 ppm (brs, 2H); ^{13}C NMR (100 MHz, [D_6]DMSO): δ=170.5, 164.7, 138.8, 138.6, 131.6, 130.1, 129.3, 128.2, 126.6, 122.8, 121.2, 70.4 ppm; IR: $\tilde{\nu}$=3389, 2935, 1688, 1519, 1251, 1081 cm^{-1}; HRMS (ESI$^+$): m/z calcd for $C_{15}H_{13}N_3NaO$: 274.0956; found: 274.0958.

*Data for **30***: R_f=0.6 (95% hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl3): δ=7.70 (s, 1H), 7.46 (s, 1H), 7.25 (s, 2H), 6.94 (s, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.0, 160.5, 136.8, 135.8, 134.7, 130.9, 126.9, 122.1, 115.6, 74.3, 55.9 ppm; IR: $\tilde{\nu}$=1721, 1438, 1410, 1325 cm^{-1}; HRMS (ESI+): m/z calcd for $C_{16}H_9Cl_4F_3NaO_3$: 470.9126; found: 470.9124.

Synthesis of 35: A solution of SO_3·pyridine (0.252 g, 1.60 mmol) in dry DMSO (5 mL) was added to a vigorously stirred solution of alcohol **8** (0.20 g, 0.32 mmol) in dry DMSO (10 mL) and dry Et_3N (5 mL) at 20 °C under N_2. After 1 h at RT, the reaction mixture was quenched with water (0.1 mL). The DMSO and all volatile compounds were removed by evaporation in vacuo to give the crude aldehyde **31**, which was used without purification in the next step. A solution of NaH_2PO_4 (11.0 mg, 0.10 mmol) and $NaClO_2$ (9.0 mg 0.10 mmol) in H_2O (0.8 mL) was added to a vigorously stirred solution of crude aldehyde **31** in *t*BuOH (0.8 mL) and 2-methyl-2-butene (0.60 mL) at RT. After 1 h at RT, the reaction mixture was extracted with EtOAc, then $CHCl_3$/MeOH (10:1). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the crude acid **32**. EDCI (90.0 mg, 0.48 mmol), glyceroacetonide–Oxyma (**17**, 0.114 g, 0.48 mmol), and $NaHCO_3$ (0.102 g, 1.20 mmol) were sequentially added to a stirred solution of the crude acid **32** (55.0 mg, 96.0 μmol) and (*S*)-**13** (48.0 mg, 192.0 μmol) in DMF/H_2O (2:1, 3 mL). After 4 h at RT, all volatile compounds were evaporated and the resulting slurry was partitioned between EtOAc and aqueous $NaHCO_3$. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in

vacuo to give the crude product, which was purified by silica gel column chromatography, to afford **35** as an amorphous solid (66.7 mg, 85% from **8**). $[\alpha]_D^{20} = +99$ ($c = 0.2$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta =$ 7.91 (s, 1H), 7.86 (m, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 7.53 (m, 2H), 7.43 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 5.98 (s, 2H), 5.96 (s, 1H), 5.50 (s, 1H), 5.41 (s, 1H), 5.09 (m, 1H), 4.97 (m, 1H), 4.74 (m, 2H), 4.37 (s, 1H), 4.18 (m, 1H), 3.89 (m, 2H), 3.76 (m, 2H), 3.44 (s, 1H), 3.41 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 172.3, 171.6, 169.3, 166.1, 152.1, 141.5, 140.1, 133.4, 132.1, 131.8, 130.9, 129.4, 128.7, 124.7, 122.5, 104.0, 98.1, 88.7, 82.3, 82.9, 79.5, 76.7, 75.9, 73.5, 71.8, 70.9, 70.4, 65.1, 62.2, 59.5, 20.6 ppm; IR: $\tilde{\nu} = 3389$, 2935, 1688, 1519, 1251, 1081 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{38}H_{38}N_6NaO_{15}$: 841.2293; found: 841.2296.

Synthesis of UT-01309 (2): LiOH (0.08 mL, 1 M in H_2O) was added to a stirred solution of **34** (13.0 mg, 16.0 μmol) in THF/H_2O (10:1, 0.4 mL) at 0°C. After being stirred for 1 h at 0°C, the reaction mixture was quenched with THF/AcOH (10:1, 0.08 mL). All volatile compounds were evaporated in vacuo. Purification by silica gel PTLC (MeOH/$CHCl_3$, 1:2) afforded **2** as an amorphous solid (10.60 mg, 95%). $R_f = 0.4$ (70% $CHCl_3$/MeOH); $[\alpha]_D^{20} = +85$ ($c = 0.1$ in MeOH); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.88$ (d, $J = 8.5$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.41 (m, 3H), 7.33 (m, 2H), 7.22 (m, 3H), 6.00 (d, $J = 4.0$ Hz, 1H), 5.81 (d, $J = 3.0$, 1H), 5.64 (d, $J = 8.5$ Hz, 1H), 5.33 (s, 1H), 5.19 (d, $J = 6.0$ Hz, 1H), 4.67 (s, 1H), 4.43 (d, $J = 6.5$ Hz, 1H), 4.35 (d, $J = 5.5$ Hz, 1H), 4.30 (m, 1H), 3.89 (t, $J = 5.5$ Hz, 1H), 3.74 (t, $J = 4.0$ Hz, 1H), 3.40 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 179.1$, 173.8, 166.3, 164.9, 152.3, 142.0, 140.0, 133.6, 132.2, 131.9, 131.0, 129.4, 128.6, 124.8, 122.7, 102.7, 100.7, 91.1, 83.6, 80.0, 76.3, 75.8, 74.1, 72.7, 71.5, 70.6, 68.3, 62.8, 58.4 ppm; IR: $\tilde{\nu} =$ 3411, 2933, 1696, 1515, 1279 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{32}H_{32}N_6NaO_{12}$: 715.1976; found: 715.1972.

Synthesis of 34: EDCI (90.0 mg, 0.48 mmol), glyceroacetonide–Oxyma (**17**, 0.114 g, 0.48 mmol), and $NaHCO_3$ (0.102 g, 1.20 mmol) was sequentially added to a stirred solution of the acid **32** (55.0 mg, 96.0 μmol) and **33** (31.0 mg, 192.0 μmol) in H_2O (1.0 mL). After being stirred for 4 h at RT, all volatile compounds were evaporated and the resulting slurry was partitioned between EtOAc and aqueous $NaHCO_3$. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give the crude product. For data collection, a portion was purified by silica gel column chromatography to afford **34** as an amorphous solid (57.0 mg, 85% from **8**). $[\alpha]_D^{20} = +103$ ($c = 0.3$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.72$ (brs, 1H), 7.96 (d, $J = 6.8$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.39 (brs, 1H), 7.20 (brs, 1H), 6.23 (brs, 1H), 6.05 (d, $J = 3.2$ Hz, 1H), 5.80 (s, 1H), 5.69 (t, $J = 3.6$ Hz, 1H), 5.49 (s, 1H), 5.29 (m, 2H), 4.61 (dd, $J = 7.2$, 10.8 Hz, 1H), 4.55 (s, 1H), 4.39 (d, $J = 5.6$ Hz,1H), 4.01 (s, 1H), 3.30 (s, 2H), 3.25 (s, 3H), 2.11 (s, 6H), 2.06 (s, 3H), 1.86 (m, 2H), 1.60 (m, 3H), 1.40 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.1$, 170.3, 170.2, 170.12, 170.08, 169.03, 169.00, 163.5, 159.1, 150.8, 144.5, 140.6, 104.1, 103.8, 98.0, 82.0, 73.3, 65.2, 63.1, 59.1, 52.0, 42.4, 31.6, 28.8, 20.95, 20.88, 20.83 ppm; IR: $\tilde{\nu} = 3379$, 2930, 1691, 1509, 1250, 1070 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{29}H_8N_5NaO_{15}$: 718.2178; found: 718.2186.

Synthesis of capuramycin (1): LiOH (0.08 mL, 1 M in H_2O) was added to a stirred solution of **34** (11.0 mg, 16.0 μmol) in THF/H_2O (10:1, 0.4 mL) at 0°C. After being stirred for 1 h at 0°C, the reaction mixture was quenched with THF/AcOH (10:1, 0.08 mL). All volatile compounds were evaporated in vacuo. Purification by silica gel PTLC (MeOH/$CHCl_3$, 1:2) afforded the desired product **1** as an amorphous solid (8.60 mg, 95%). $R_f = 0.4$ (70% $CHCl_3$/MeOH); $[\alpha]_D^{20} = +98$ ($c = 0.1$ in H_2O); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.71$ (d, $J = 8.0$ Hz, 1H), 5.97 (s, 1H), 5.82 (d, $J = 8.0$ Hz, 1H), 5.73 (s, 1H), 5.35 (s, 1H), 4.59 (d, $J = 11.2$ Hz, 2H), 4.47 (s, 1H), 4.44 (d, $J = 4.8$ Hz, 1H), 4.34 (s, 1H), 4.15 (s, 1H), 3.71 (t, $J =$ 4.8 Hz, 1H), 3.26 (s, 3H), 1.97 (m, 6H), 1.32 ppm (m, 2H). ^{13}C NMR (100 MHz, D_2O): $\delta = 176.3$, 173.0, 166.1, 161.4, 151.2, 141.5, 141.0, 109.4, 101.8, 99.3, 90.1, 81.6, 78.1, 75.5, 71.9, 64.7, 61.7, 57.8, 52.2, 41.4, 30.3, 27.3 ppm; IR: $\tilde{\nu} = 3411$, 2933, 1696, 1515, 1279 cm^{-1}; HRMS (ESI$^+$): *m/z* calcd for $C_{23}H_{31}N_5NaO_{12}$: 592.1867; found: 592.1864.

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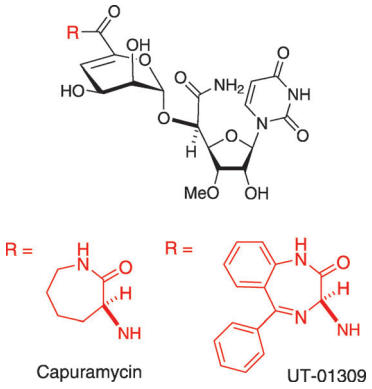
Battling TB: Capuramycin and its congeners (see scheme) are considered to be important lead molecules for the development of a new drug for multidrug-resistant *Mycobacterium tuberculosis* infections. Efficient synthesis of capuramycin and its analogues by using new protecting groups for the uridine ureido nitrogen and primary alcohol was accomplished.



Capuramycin UT-01309

Total Synthesis

*Y. Wang, S. Siricilla, B. A. Aleiwi, M. Kurosu** ..... ▮▮▮▮–▮▮▮▮

Improved Synthesis of Capuramycin and Its Analogues