



Published in final edited form as:

Chemistry. 2013 October 4; 19(41): 13847–13858. doi:10.1002/chem.201302389.

Improved Synthesis of Capuramycin and Its Analogs

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Abstract

Capuramycin and its congeners have been considered 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 due to difficulty in selective chemical modifications of the desired position(s) of the natural product with biologically interesting functional groups. We have developed efficient syntheses of capuramycin and its analogs using new protecting groups, which are derived from the chiral (chloro-4-methoxyphenyl) (chlorophenyl) methanols, for the uridine ureido nitrogen and primary alcohol. The chiral non-racemic (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, whose (*S*)-configuration isomer plays a significant role in improving the mycobactericidal activity of capuramycin.

Introduction

The emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (Mtb) seriously threatens tuberculosis (TB) control and prevention efforts.^[1] Moreover, people who are HIV-AIDS patients are susceptible to TB infection.^[2] There are significant problems associated with treatment of AIDS and Mtb co-infected patients. Rifampicin and isoniazid [a key component of the DOTS (Directly Observed Treatment, Short-course) therapy] induce the cytochrome P450 3A4 enzyme in liver which shows significant interactions with protease inhibitors for HIV infections.^[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 are significant needs and interests in developing new TB drugs. However, over the last 40 years, only bedaquiline (SirturoTM), an ATP synthase inhibitor, was approved for the treatment of MDR-Mtb infections as a monotherapeutic agent in 2012.^[5] The ultimate goal of the development of the treatment of MDR-Mtb strains is to find novel antibacterial agents which 1) interfere with unexploited bacterial molecular targets, 2) can shorten a TB drug regimen (one-month to three-month regimen), 3) can apply to combination TB chemotherapy, and 4) do not interfere with 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

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem>.

extensively studied.^[6] Thus, the enzymes associated with the early PG biosynthesis enzymes [MurA, B, C, D, E, and F, *MraY* (phospho-MurNAc-pentapeptide 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 (Park's nucleotide) to 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 analogs 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 time frame for effective anti-TB chemotherapy. Therefore, capuramycin and its congeners have been considered important lead molecules for the development of a new drug for MDR-*Mtb* infections.

Since discovery of capuramycin as a specific spectrum antimycobacterial agent, extensive SAR studies of capuramycins have been limited because of difficulty in modifying the complex natural product at the desired position(s) with a wide range of functional groups. Accordingly, it is essential to establish a concise and convergent synthesis of capuramycin that is amenable to synthesis of analogs 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 13 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 to small to medium scale, several steps are not ideal for the synthesis of a large amount of capuramycin and its analogs for *in vivo* studies using rodents.

α -Mannosylation of **5** with the thioglycoside **6** requires the diluted conditions (0.05 M) and long reaction time (12–16 h). Selective deacetylation at the 6''-position of **7a** have to be stopped at around 30–70% conversion in order 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 *via* heterogeneous conditions often yields the over-reduced product of which the C5–C6 double bond of the uracil moiety was saturated.^[19] Recently, we identified a new capuramycin analog UT-01309 (**2**) possessing (*S*)-3-amino-1,4-benzodiazepine-2-one [(*S*)-**13**], which showed an improved antimycobacterial activity (2.5 μ g/mL vs 12.0 μ g/mL for **1** against *M. tuberculosis*).^[20] Significantly, UT-01309 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 μ g/mL concentrations (*vide infra*). Thus, we are very interested in *in vivo* evaluation of **2** in comparison with capuramycin (**1**) and other related molecules. Herein, we report improved synthesis of capuramycin (**1**) and its analog UT-01309 (**2**) *via* 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 Discussions

Our synthetic strategy to improve the syntheses of capuramycin (**1**) and capuramycin analog, 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 trichloroacetimidatephenyl) methoxymethyl [monomethoxydiphenylmethoxymethyl (MDPM)] for *primary* alcohols and ureido nitrogens, respectively.^[21] These protecting groups showed a significant relative stability against a wide variety of conditions utilized for the syntheses of natural and unnatural products. However, the MTPM and MDPM protecting groups can conveniently be deprotected by using 30% TFA in CH₂Cl₂. 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 capuramycin analogs (Scheme 2). (*S*)-3-Amino-1,4-benzodiazepin-2-one [(*S*)-**13**] is an important functional group to improve antimycobacterial activity of capuramycin. For our SAR studies of capuramycin analogs, it is desirable to have a versatile resolution protocol of *racemic* amino acids which are not available commercially. We expected that the optically pure carbonate (*S*)-**14**, derived from the unsymmetrical (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol, can resolve a diastereomixture of the carbamates *via* convenient chromatography and can readily be deprotected under mild conditions.^[22]

Synthesis of (2*S*)-uridyl-hydroxyacetonitrile **10** and mannosyl donor imidate **11**

MDPM and MTPM groups have significant advantages over the other ordinal protecting groups for the syntheses of capuramycin analogs in that these new protecting groups 1) are stable to a wide variety of acids, 2) are not susceptible to hydrogenation conditions, and 3) can be deprotected efficiently by solvolytic cleavage with 30% TFA at room temperature within 2 h without addition of a cation scavenger.^[21] We synthesized over 10 gram of MDPMCl (**16**) and MTPM-imidate (**22**) according to the established procedures.²¹ The uridine ureido nitrogen was protected with MDPMCl (**16**) in the presence of 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 *via* a SnCl₂-mediated methylation condition to yield the desired mono-methyl derivative in 60% yield.^[23] Selective chloroacetylation of the *primary* alcohol of the diol was performed with ClCH₂CO₂H, EDCl, NaHCO₃, and glyceracetone-Oxyrna (**17**) in 5% H₂O-CH₃CN to give rise to **18** in 98% yield.^[24] The regiochemistry of **18** was unequivocally determined by extensive ¹H-NMR decoupling studies and the 2D NOESY experiments.^[25] Albeit the ordinal esterification conditions (e.g. ClCH₂CO₂H, DCC, DMAP in CH₂Cl₂ or ClCH₂COCl, pyridine in CH₂Cl₂) provided a mixture of **18** and the over-reaction product, we did not observe the formation of *secondary* alcohol ester under the conditions applied to the synthesis of **18**. Acetylation of the *secondary* alcohol of **18** followed by the removal of the chloroacetyl group with thiourea in MeOH afforded **19** in 95% overall yield.^[26] The *primary* alcohol of **19** was oxidized under Pfitzner-Moffatt conditions (DCC, Cl₂CHCO₂H, DMSO-CH₂Cl₂) to provide the corresponding aldehyde **20**, which was utilized without purification.^[27] We have extensively studied cyanohydrin formation reactions of the uridyl-aldehyde derivatives using TMSCN.^[28] In all cases, Lewis acid-promoted trimethylsilylcyanations of the uridyl-aldehydes furnished a mixture of the TMS-protected cyanohydrins in favor of undesired (*R*)-configuration products (e.g. **21**) in low yields. Lewis base-catalyzed trimethylsilylcyanations (e.g. Ph₃PO, NMO, BABCO, cinchona alkaloids) did not provide the products due to the fact that the uridyl-aldehydes were not stable against Lewis and Brønsted bases. In previous studies we observed that the Ti-mediated conditions gave the desired (*S*)-configuration cyanohydrin as the major product with satisfactory yield.^[18] Similarly, TMSCN addition of **20** with 10 mol% of Ti(O*i*Pr)₄ in CH₂Cl₂-H₂O (1%) provided a mixture of **10** and **21** in 90% yield with the **10/21** ratio of 1.5–2.0:1 after desilylation.^[29] In our recent studies, we found that trimethylsilylcyanation reaction of **20** with 1,3-bis(2-(dimethylamino)ethyl)thiourea also gave a mixture of **10** and **21** with compatible selectivity and yield to the reaction with Ti(O*i*Pr)₄ in CH₂Cl₂-H₂O (1%). Moreover, we observed that

hydrocyanation of **20** with BzCN in DMSO-H₂O 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 high-yield conversion, we decided to scale-up the conversion of **19** to **10** with this condition and the undesired stereochemistry of **21** was inverted *via* a modified Mitsunobu reaction [DIAD, TPP, ClCH₂CO₂H, pyridine (1:1:1:1)]. The chloroacetyl group of the ester was selectively deprotected 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 process of the inversion (**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 of **22** was selectively deprotected with [tBu₂SnCl(OH)]₂^[31] and the generated alcohol was protected with MTPM-imidate **23** in the presence of 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 the cyanohydrin **10** with **11**

In our previous capuramycin synthesis, we have screened an effective promoter to catalyze the thioglycoside **6** for the mannosylation of **5** (Scheme 1). We found that α -selective mannosylation of **5** with **6** was achieved *via* the combination of NIS and AgBF₄ in CH₂Cl₂ (at 0.05 μ M concentrations).^{[18],[33]} Interestingly, the NIS/AgBF₄ 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. The orthoester **25** could be distinguished from **7a** in ¹H-NMR spectra of the crude reaction mixture; **25** showed a characteristic chemical shift of 1.78 ppm (CH₃).^[34] All triflate ion associated-glycosylations with **6** (e.g. NIS/TfOH or NBS/TfOH) yielded a mixture of α - and β -mannosides.^[35] Under the NIS/AgBF₄ promoted conditions, mannosylation of the MDPM-protected **10** with the thioglycoside **26** did not provide the desired product **12**. The acceptor **10** was stable under the NIS/AgBF₄ conditions, however, the thioglycoside **26** was completely consumed to form the complex mixtures. Albeit 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 BF₃•OEt₂-catalyzed mannosylation of **10** with the imidate **11** afforded 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 conditions of NIS/AgBF₄. We confirmed that mannosylations of **10** with **11** were reproducible at any concentration between 0.1–0.5 M and applied to a gram scale synthesis of **12**.

Resolution of *racemic* 3-amino-1,4-benzodiazepine-2-one

We 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**] (*vide supra*). In order to synthesize enough quantities of UT-01309 (**2**) for *in vivo* studies, it was desirable to establish an efficient resolution method of *racemic* 3-amino-1,4-benzodiazepine-2-one [(\pm)-**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. respiratory syncytial virus), resolution methods of *racemic* 3-amino-1,4-benzodiazepine-2-one [(\pm)-**13**] have been reported by several groups.^[37] However, most reported protocols provide separations of the diastereomers formed by amide-forming reactions with optically active amino acids, and only a few reports have demonstrated the resolution of (\pm)-**13** with readily cleavable chiral agents. Sherrill et al. reported the resolution of **13** with the *p*-nitrophenyl carbonate of (*R*)- α -methyl benzyl

alcohol. In their procedure, the carbamate auxiliary was cleaved with HBr (gas) in CH₂Cl₂ and the generated by-product, (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 absolute configuration of amino acids (Scheme 5).^[21c] Carbamate formation of (±)-**13** with (*S*)-**14** was achieved by using *i*Pr₂NEt in a mixture of acetone and H₂O (3/1). Gratifyingly, the generated diastereomers could be purified by silica gel chromatography to afford **28** and **29** in 98% yield (approximately 49% each). As shown in Figure 2, we have reported that the absolute configurations 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 ¹H-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 ¹H-NMR, the chemical shifts of **29** should appear identical to those of the antipode of **29** (*ent*-**29**) (Figure 2). Thus, the $\Delta\delta(S-R)$ value of the *N*^α protons of **28** and *ent*-**29** should determine the absolute stereochemistry of **28**. The $\Delta\delta(N^{\alpha}_{28}-N^{\alpha}_{29})$ value was +0.03 and thus the absolute stereochemistry of **28** was assigned to be L-configuration (*R* for 3-amino-1,4-benzodiazepine-2-one) as shown in Scheme 5. The diastereomeric excesses (*des*) 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 20% TFA in CH₂Cl₂ to afford (*S*)-**13** and (*R*)-**13** in >95% yields. The chiral auxiliary was recovered as racemic trifluoroacetate **30** in quantitative yield. The absolute configurations of (*S*)-**13** and (*R*)-**13** were unequivocally confirmed by the comparison of optical rotations of those with the reported values for (*S*)-**13** and (*R*)-**13**.^[37c]

Syntheses of capuramycin and UT-01309

We have 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 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 scheme required only three times of purifications by chromatography in the total number of synthetic steps (Scheme 6). The cyano group of **12** was hydrated using InCl₃-aldoxime in toluene, furnishing the corresponding *primary* amide.^[39] Without further purification, the *primary* amide was subjected to simultaneous deprotections of the MDPM and MPTM groups with 30% TFA in CH₂Cl₂ to afford **8** in greater than 95% overall yield for two steps. We could achieve the synthesis of over 1 gram of **8** *via* the new protecting group strategy summarized in Schemes 3, 4, 5 and 6. The conversions of **8** to capuramycin (**1**) and UT-01309 (**2**) were carried out *via* the previously reported procedures except for the amide-forming reactions.^[18] Oxidation-elimination reactions of **8** using SO₃·pyridine in a biphasic solvent system (DMSO/Et₃N = 3/1) provided the α,β-unsaturated aldehyde **31**.^[40] The aldehyde **31** was oxidized to the corresponding carboxylic acid **32** by Pinnick oxidation (NaClO₂, 2-methyl-2-butene).^[41] The resulting crude carboxylic acid was coupled with (*S*)-aminocaprolactam (**33**) using an amide forming reaction in water media [glyceroacetone-Oxyrna (**17**), EDCI, NaHCO₃ in H₂O] to yield **33** in 80–85% overall yield from **8**.^[42] In our previous synthesis of **1**, HOAt (1-hydroxy-7-azabenzotriazole) was used as a peptide-coupling additive to couple the segments **32** and **33**. HOAt and some other by-products generated in the coupling conditions (EDCI, HOAt, NMM (*N*-methylmorpholine) in DMF) were difficult to separate from the desired product by a standard column chromatography. On the contrary, in the glyceroacetone-Oxyrna (**17**) / EDCI-mediated coupling reaction, simple basic and acidic aqueous work-up 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-H₂O provided capuramycin (**1**) in greater than

95% yield. Similarly, UT-01309 (**2**) was synthesized using (*S*)-**13** instead of **33** in the synthesis of **1** (Scheme 6). The purity of synthetic products, **1** and **2** were determined to be >99% by reverse-phase HPLC analyses.

***In vitro* biological evaluation of UT-01309**

UT-01309 (**2**) was identified by cell-based assays of a small optimized library of capuramycin analogs. *In vitro* biological activities of **2** synthesized here were evaluated against *Mtb* *MraY* (IC₅₀) and a series of bacteria including *Mycobacterium spp.* The IC₅₀ value of **2** against *Mtb* *MraY* was 5.5 nM (**1**: IC₅₀ 18 nM against *Mtb* *MraY*). UT-01309 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 concentrations. UT-01309 showed bactericidal activities specific to *Mycobacterium spp.* UT-01309 killed *M. tuberculosis* (H37Rv) completely at 2.5 µg/mL concentrations whereas capuramycin required 12.0 µg/mL. UT-01309 showed the MIC value of 6.5 µg/mL against *M. smegmatis*. Significantly, UT-01309 is active against drug-resistant *M. tuberculosis* (e.g. *M. tuberculosis* H37Rv INHr and *M. tuberculosis* H37Rv RFPPr), and did not exhibit cytotoxicity against Vero monkey kidney cells and HepG2 human hepatoblastoma cells even at 250 µg/mL concentrations.

Conclusion

In summary, we present an improved synthesis of capuramycin (**1**) and its analog UT-01309 (**2**), a promising investigational drug lead for MDR-*Mycobacterium tuberculosis* infections. MDPM and MPTM protecting groups for the uridine ureido nitrogen and primary alcohol could improve the overall efficiency of syntheses of **1** and **2**. The synthetic scheme reported here enables us to synthesize gram-quantities of the key intermediate **8** for the syntheses of a series of capuramycin analogs; **8** could be synthesized in 9 steps from uridine (**15**) in 32% overall yield. In addition, we have demonstrated an 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 *in vitro* biological activity of capuramycin. We will evaluate UT-01309 (**2**) *in vivo* using an infected mouse model and study toxicity and 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 (Et₂O) were distilled from sodium benzophenone ketyl under an argon atmosphere prior to use. Methylene Chloride (CH₂Cl₂), acetonitrile (CH₃CN), benzene, toluene and triethylamine (Et₃N) were distilled from calcium hydride under an Argon atmosphere. Flash 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 60F₂₅₄) visualizing at 254 nm, or developed with ceric ammonium molybdate or anisaldehyde solutions by heating on a hot plate. ¹H-NMR spectral data were obtained using 400, and 500 MHz instruments. ¹³C-NMR spectral data were obtained using 100 and 125 MHz instruments. For all NMR spectra, δ values are given in ppm and *J* values in Hz.

(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 procedure previously reported.^{7a} To a

stirred solution of (2,6-dichloro-4-methoxyphenyl)-(2,4,6-trichlorophenyl)-methoxymethyl methyl sulfide (11.18 g, 25.0 mmol) in CH₂Cl₂ (63.0 mL) was added sulfuryl chloride (2.0 mL, 25.0 mmol) at rt. The reaction mixture was stirred for 1 h and all volatiles were evaporated to provide the crude product as oil which was pure enough for the next reaction (10.45 g, 96%). ¹H NMR (400 MHz, CDCl₃): δ= 7.33 (s, 2H), 6.88 (s, 2H), 6.77 (s, 1H), 5.57 (q, *J* = 6.4 Hz, 2H), 3.80 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ= 159.6, 136.8, 136.6, 134.4, 131.7, 129.7, 124.3, 115.6, 80.1, 55.8; IR: ν = 3473, 1445, 1309 cm⁻¹; elemental analysis calcd (%) for C₁₅H₁₀Cl₆O₂: C, 41.42; H, 2.32; Cl, 48.91. Found: C, 41.81; H, 2.41; Cl, 48.97.

3-[(2,6-Dichloro-4-methoxy-phenyl)-(2,4,6-trichloro-phenyl)-methoxymethyl]-1-(3,4-dihydroxy-5-hydroxymethyl-tetrahydro-furan-2-yl)-1H-pyrimidine-2,4-dione(9)—To a stirred solution of uridine (10.98 g, 45.0 mmol) in DMF (120 mL) at 0 °C, DBU (9.0 mL, 60.0 mmol) and **16** (13.08 g, 30.0 mmol) were added. 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 chromatography with CHCl₃/MeOH (95:5) to afford **9** as an oil (17.62 g, 95%). *R*_f = 0.3 (10% MeOH/CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ= 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 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): 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; IR: ν = 3435, 1719, 1665, 1440, 1081 cm⁻¹; HRMS (ESI⁺) *m/z* calcd for C₂₄H₂₂C₁₅N₂O₈: 640.9819; found: 640.9825.

Synthesis of 18—To a stirred solution of **9** (12.8 g, 20.0 mmol) in DMF (300 mL) was added SnCl₂ (1.91 g, 10.0 mmol). The reaction mixture was heated to 50 °C followed by addition of CH₂N₂ (150 mL, 60.0 mmol, 0.4 M in Et₂O). After 1h, all volatiles were evaporated *in vacuo*. The selectivity ratio and yield of the mono-methyl ethers were determined by ¹H-NMR analyses of the crude mixture to be 3:2 ratio in favor of the desired product. The crude product was dissolved in 5% H₂O/MeCN (1.0 mL). Glyceroacetone-Oxyma **17** (6.7 g, 30.0 mmol), EDCI (5.7 g, 30.0 mmol), chloroacetic acid (3.72 g, 40.0 mmol), and NaHCO₃ (10.1 g, 120.0 mmol) were added to the reaction mixture. After 3 h, the reaction was quenched with aq. NaHCO₃. The aqueous layer was extracted with EtOAc (2x). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to yield the desired ester **18** (8.6 g, 59% over two steps) as a colorless liquid. *R*_f = 0.3 (30% hexanes/AcOEt); ¹H NMR (500 MHz, CDCl₃): 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), 5.50-5.46 (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 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 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; IR: ν = 3442, 1711, 1660, 1445, 1309, 1070 cm⁻¹; HRMS (ESI⁺) *m/z* calcd for C₂₇H₂₄C₆N₂NaO₉: 754.9481; found 754.9484.

Synthesis of 19—The ester **18** above was dissolved in pyridine/Ac₂O (2:1, 200 mL) and stirred at rt. Upon completion, all volatiles 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. The reaction mixture was stirred at 50 °C for 4 h and cooled to rt. All volatiles were evaporated *in vacuo*. Purification by silica gel column chromatography with hexanes/AcOEt (1:1) yielded the desired product **19** as an oil (7.8 g, 95% over two steps). *R*_f = 0.4 (30% hexanes/AcOEt); ¹H NMR (500 MHz, CDCl₃): 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 (bs, 2H), 5.44

(bs, 1H), 4.18 (bs, 1H), 4.11 (bs, 1H), 4.00 (d, $J = 11.5$ Hz, 1H), 3.80 (s, 1H), 3.77 (s, 3H), 3.41 (s, 3H), 2.25 (bs, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.5, 162.6, 159.3, 151.4, 140.3, 136.7, 134.0, 132.6, 129.5, 125.3, 115.5, 102.3, 91.4, 83.0, 80.9, 77.8, 70.1, 69.2, 61.3, 59.0, 55.7, 20.8$; IR: $\nu = 3445, 1719, 1665, 1440, 1302, 1081$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{27}\text{H}_{25}\text{Cl}_5\text{N}_2\text{NaO}_9$: 720.9871; found 720.9875.

Synthesis of 10—To a stirred solution of **19** (5.75 g, 8.0 mmol) in $\text{CH}_2\text{Cl}_2/\text{DMSO}$ (1:1, 80 mL) at 0 °C was added DCC (4.0 g, 20.0 mmol) and dichloroacetic acid (1.02 g, 8.0 mmol). After 1 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with NaHCO_3 (aq.). 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. To a stirred solution of the crude aldehyde in $\text{DMSO}/\text{H}_2\text{O}$ (4/1, 80 mL) was added BzCN (1.58 g, 12.0 mmol). After being stirred for 12 h at rt, NaHCO_3 (aq.) was added followed by AcOEt. The aqueous layer was extracted with EtOAc (2x). The combined organic extracts were dried over Na_2SO_4 and concentrated. The resulting crude material was purified by silica gel chromatography with AcOEt/hexanes (2:3) to give **10** (3.7 g, 63%) and **21** (1.88 g, 32%). Data for **10**: $R_f = 0.4$ (60% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.31$ (d, $J = 7.5$ Hz, 2H), 6.84 (d, $J = 10.0$ Hz, 2H), 6.56 (s, 1H), 5.83 (dd, $J = 5.5$ Hz, 1H), 5.58 (m, 1H), 5.40 (bs, 1H), 5.34 (bs, 1H), 5.23 (bs, 1H), 4.67 (d, $J = 11.0$ Hz, 1H), 4.55 (bs, 1H), 4.35 (s, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.2, 162.2, 159.4, 151.7, 142.2, 136.7, 134.2, 132.3, 129.6, 124.9, 117.2, 115.6, 103.1, 95.1, 84.2, 78.5, 70.4, 69.3, 61.7, 59.3, 55.8, 43.1, 21.9$; IR: $\nu = 3378, 1755, 1724, 1676, 1463, 1238$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{28}\text{H}_{24}\text{Cl}_5\text{N}_3\text{NaO}_9$: 745.9823; found 745.9826. Data for **21**: $R_f = 0.45$ (60% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.31$ (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, 0.5H), 5.57 (m, 2.5H), 5.49 (m, 0.5H), 5.42 (m, 0.5H), 4.77 (m, 1H), 4.71 (bs, 0.5H), 4.49 (bs, 0.5H), 4.36–4.29 (m, 2H), 3.77 (s, 3H), 3.45 (s, 1.5H), 3.43 (s, 1.5H), 2.19 (s, 1.5H); 2.16 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.9, 162.7, 159.4, 151.4, 140.0, 136.7, 134.1, 132.3, 129.5, 125.1, 117.3, 115.5, 102.7, 83.6, 81.1, 77.9, 73.5, 61.4, 59.4, 55.7, 42.4, 23.4$; IR: $\nu = 3378, 1755, 1724, 1676, 1463, 1238$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{28}\text{H}_{24}\text{Cl}_5\text{N}_3\text{NaO}_9$: 745.9823; found 745.9826.

Synthesis of 10 via a Mitsunobu reaction—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) was added DIAD (22.0 mg, 0.10 mmol). After 4 h at rt, all volatiles were removed *in vacuo* and the crude ester was purified by silica gel chromatography. To a stirred solution of the ester in MeOH (2 mL), thiourea (38.0 mg, 0.50 mmol) was added and the reaction mixture was heated to 50 °C. After 4 h at 50 °C, the reaction was cooled down to rt and MeOH was evaporated *in vacuo*. The residue was purified by silica gel chromatography with hexanes/AcOEt (1:1) to give **10** (68.0 mg, 90%) as a colorless oil. This reaction was performed for **21** (1.5 g, 2.01 mmol).

Synthesis of 26—To a stirred solution of **6** (9.0 g, 20.0 mmol) in MeOH (200 mL), was added the $[\text{tBu}_2\text{SnCl}(\text{OH})_2]$ (0.58 g, 1.0 mmol). 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. To the free alcohol in CH_2Cl_2 (400 mL) at 0 °C was added the imidate **23**^{7b} (11.9 g, 24.0 mmol) and TMSOTf (1.0 mL, 12.0 mmol) was added. After 2 h at 0 °C, the reaction mixture was quenched with aq. sat. NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extracts was washed with brine, dried over Na_2SO_4 and evaporated. Purification of the crude material by silica gel chromatography afforded **26** (13.7 g, 92% over two steps) as a colorless liquid. $R_f = 0.5$ (30% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.83$ (dd, $J = 8.5$ Hz, 1H), 7.37 (m,

2H), 7.18 (dd, $J = 7.5$ 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), 5.39-5.23 (m, 3H), 4.63-4.55 (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, 1.5H), 2.13 (s, 1.5H), 2.07 (s, 1.5H), 2.01 (s, 1.5H), 2.00 (s, 1.5H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.9, 159.5, 137.5, 137.2, 136.4, 133.4, 132.7, 132.4, 131.7, 131.6, 129.9, 129.8, 129.0, 126.1, 125.5, 125.0, 115.2, 86.0, 76.1, 71.2, 70.4, 69.7, 69.4, 68.2, 67.1, 55.7, 25.7$; IR: $\nu = 3050, 1742, 1613, 1481$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{33}\text{H}_{32}\text{Cl}_4\text{NaO}_9\text{S}$: 769.0389; found 769.0387.

Synthesis of 24—To a stirred solution of **22** (13.2 g, 30.0 mmol) in MeOH (300 mL) was added the $[\text{Bu}_2\text{SnCl}(\text{OH})_2]$ catalyst (0.87 g, 1.5 mmol). Upon completion, the reaction mixture was concentrated *in vacuo* and filtered through a silica gel plug and concentrated to yield the free alcohol in 100% yield. To a stirred solution of the *primary* alcohol (12.0 g, 30.0 mmol) and the imidate **23**^{7b} (16.3 g, 33.0 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added TMSOTf (1.0 mL, 6.0 mmol) dropwise. After being stirred for 2 h, the reaction mixture was quenched with aq. sat. NaHCO_3 . The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extract was washed with brine and dried over Na_2SO_4 . The evaporation of all volatiles *in vacuo* gave the crude product which was purified by silica gel chromatography to afford **24** (21.9 g, 98%) as a colorless liquid. $R_f = 0.5$ (30% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): $\delta = 7.91$ (m, 1H), 7.35-7.18 (m, 7H), 6.85 (s, 2H), 6.23 (d, $J = 6.5$ Hz, 1H), 5.40-5.31 (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), 3.69-3.56 (m, 2H), 2.13 (s, 1.5H), 2.10 (s, 1.5H), 1.99 (s, 1.5H), 1.98 (s, 1.5H), 1.96 (s, 1.5H), 1.95 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.1, 170.0, 169.9, 169.7, 159.5, 137.4, 137.2, 136.4, 133.5, 132.5, 131.6, 129.1, 128.5, 128.2, 126.1, 125.6, 125.1, 115.2, 96.4, 96.0, 76.9, 70.4, 69.7, 69.3, 69.0, 68.4, 67.6, 66.9, 60.4, 55.7, 20.8$; IR: $\nu = 3055, 1744, 1615, 1484$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{33}\text{H}_{32}\text{Cl}_4\text{NaO}_{10}$: 753.0618; found 753.0615.

Synthesis of 11—To a stirred solution of **24** (10.8 g, 15.0 mmol) in MeOH (600 mL) was added Pd/C (4.5 g, 10 wt %) under N_2 . H_2 gas was introduced *via* double-folded balloon and the reaction mixture was stirred for 4h under H_2 . Upon completion, the solution was filtered through Celite and eluted with AcOEt. 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). Upon completion, all volatiles were evaporated *in vacuo*. Purification by silica gel chromatography afforded the desired product **11** as colorless oil (11.2 g, 95%). $R_f = 0.7$ (30% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): $\delta = 8.71$ (s, 1H), 7.87 (dd, $J = 1\text{H}$) 7.28-7.23 (m, 2H), 6.83 (s, 2H), 6.26 (d, $J = 8.5$ Hz, 1H), 6.19 (s, 1H), 5.48-5.40 (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 (s, 1.5H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.9, 169.8, 169.4, 159.7, 159.5, 137.3, 136.4, 133.4, 132.3, 131.6, 131.4, 129.0, 128.8, 126.1, 126.1, 125.8, 125.4, 125.0, 115.2, 94.6, 94.3, 90.6, 76.5, 75.8, 72.8, 71.8, 69.0, 68.2, 68.0, 67.1, 66.0, 55.8, 55.6, 20.7$; IR: $\nu = 3050, 1755, 1680, 1622, 1480$ cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{28}\text{H}_{26}\text{Cl}_7\text{N NaO}_{10}$: 805.9245; found 805.9249.

Synthesis of 12—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) was added MS 3 Å (10.0 g). The reaction was stirred for 30 min. at rt. The reaction mixture was cooled to -5 °C, followed by dropwise addition of $\text{BF}_3 \cdot \text{OEt}_2$ (1.48 mL, 12.0 mmol). After being stirred for 3 h at -5 °C, the reaction was quenched with NaHCO_3 (aq.). The reaction mixture was passed through 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 chromatography afforded **12** (4.04 g, 75%) as an oil. $R_f = 0.45$

(60% AcOEt/hexanes); ^1H NMR (500 MHz, CDCl_3): δ = 7.98 (dd, J = 21 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 (bs, 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 (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, 80.173.1, 72.1, 71.8, 68.9, 68.1, 65.7, 63.5, 59.2, 55.8, 29.7, 20.6; IR: ν = 3338, 2921, 2250, 1737, 1669, 1465, 1221 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{54}\text{H}_{48}\text{Cl}_9\text{N}_3\text{NaO}_{18}$: 1367.9968; found 1367.9975.

Synthesis of 8—To a stirred solution of **12** (2.42 g, 1.8 mmol) in toluene (180 mL) was added InCl_3 (0.4 g, 1.8 mmol) and acetaldoxime (0.67 mL, 10.8 mmol). The reaction mixture was heated at 70 °C for 4 h. Upon completion, the reaction was cooled to rt and all volatiles 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 chromatography to afford the product **8** as an amorphous solid (1.1 g, 96% over two steps). R_f = 0.3 (95% $\text{CHCl}_3/\text{MeOH}$); $[\alpha]_{\text{D}}^{20}$ = +75 (c = 0.4 in MeOH); ^1H 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 (bs, 1H), 3.64–3.58 (m, 3H), 3.40 (s, 3H), 2.13 (s, 6H), 2.04 (s, 3H), 2.00 (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; IR: ν = 3413, 1710, 1680, 1223, 1066 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{25}\text{H}_{33}\text{N}_3\text{NaO}_{16}$: 654.1753; found 654.1746.

(2-Oxo-5-phenyl-2, 3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-carbamic acid (2,6-dichloro-4-methoxy-phenyl)-(2,4-dichloro-phenyl)-methyl ester (28, 29)—*Racemic* 3-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one [(±)-**13**] was synthesized according the reported procedure.¹⁴ To a stirred solution of (±)-**13** (25.0 mg, 0.10 mmol) in acetone/ H_2O (3:1, 3 mL) at rt was added (*S*)-(2,6-dichloro-4-methoxyphenyl)-(2,4-dichlorophenyl)-methyl-*N*-succinimidyl carbonate (*S*)-**14** (58.0 mg, 0.20 mmol) and *i*Pr₂NEt (70.0 μL , 0.40 mmol). Upon completion after 4h, the reaction mixture was concentrated *in vacuo* to remove acetone. The crude material was partitioned between AcOEt (5 mL) and HCl (1 N, 5 mL). The water phase was extracted with AcOEt (2x). The combined organic extracts was dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by silica gel 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 gram of *rac*-**13** to provide **28** (1.24 g). **Data for 28**: R_f = 0.34 (95% $\text{CHCl}_3/\text{MeOH}$); $[\alpha]_{\text{D}}^{20}$ = +77 (c = 0.2 in MeOH); ^1H NMR (400 MHz, CD_3OD): δ = 7.55–7.49 (m, 5H), 7.45 (m, 2H), 7.36 (m, 4H), 7.25–7.14 (m, 3H), 6.91 (s, 2H), 6.71 (m, 1H), 5.38 (d, J = 8.8 Hz, 1H), 3.82 (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; IR: ν = 3441, 1936, 1711, 1413, 1354, 1222, 1150 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{30}\text{H}_{21}\text{Cl}_4\text{N}_3\text{NaO}_4$: 652.0154; found 652.0150; HPLC: retention time, 8.5 min (*des* >99%). **Data for 29**: R_f = 0.30 (95% $\text{CHCl}_3/\text{MeOH}$); $[\alpha]_{\text{D}}^{20}$ = +181 (c = 0.2 in MeOH); ^1H 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 (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; IR: $\tilde{\nu}$ = 3441, 1936, 1711, 1413, 1354, 1222, 1150 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{30}\text{H}_{21}\text{Cl}_4\text{N}_3\text{NaO}_4$: 652.0154; found 652.0151; HPLC: retention time, 8.0 min (*des* >99%).

(S)-3-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one [(S)-13]—The 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 NaHCO_3 (aq.) and $\text{CHCl}_3/\text{MeOH}$ (10:1). The aqueous layer was back extracted with $\text{CHCl}_3/\text{MeOH}$ (10:1). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude material by silica gel chromatography afforded the desired product (S)-**13** (12.0 mg, 95%) as an amorphous solid and the byproduct ester **29** (24.0 mg, 100%) as an oil. Data for (S)-**13**: $[\alpha]_{\text{D}}^{20} = -220$ ($c = 0.2$ in CH_2Cl_2); ^1H NMR (400 MHz, DMSO- d_6): δ = 10.74 (bs, 1H), 7.64 (m, 1H), 7.50 (m, 5H), 7.33 (m, 2H), 7.25 (m, 1H), 4.29 (s, 1H), 2.60 (bs, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): 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; IR: $\tilde{\nu}$ = 3389, 2935, 1688, 1519, 1251, 1081 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{NaO}$: 274.0956; found 274.0958. Data for **30**: $R_f = 0.6$ (95% hexanes/AcOEt); ^1H NMR (500 MHz, CDCl_3): δ = 7.70 (s, 1H), 7.46 (s, 1H), 7.25 (s, 2H), 6.94 (s, 2H), 3.83 (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; IR: $\tilde{\nu}$ = 1721, 1438, 1410, 1325 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{16}\text{H}_9\text{Cl}_4\text{F}_3\text{NaO}_3$: 470.9126; found 470.9124.

Synthesis of 35—To a vigorously stirred solution of the alcohol **8** (0.20 g, 0.32 mmol) in dry DMSO (10 mL) and dry Et_3N (5 mL) was added a solution of $\text{SO}_3 \cdot \text{Py}$ (0.252 g, 1.60 mmol) in dry DMSO (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 volatiles were removed by evaporation *in vacuo* to give the crude aldehyde **31** which was used without purification in the next step. 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 was added 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). After 1 h at rt, the reaction mixture was extracted with AcOEt, then $\text{CHCl}_3/\text{MeOH}$ (10:1). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude acid **32**. 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) was added EDCI (90.0 mg, 0.48 mmol), glyceracetone-Oxyma **17** (0.114 g, 0.48 mmol) and NaHCO_3 (0.102 g, 1.20 mmol) sequentially. After 4 h at rt, all volatiles were evaporated and the resulting slurry was partitioned between AcOEt and NaHCO_3 (aq.), the aqueous layer was extracted with AcOEt (3x). 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 chromatography to afford **35** (66.7 mg, 85% from **8**) as an amorphous solid. $[\alpha]_{\text{D}}^{20} = +99$ ($c = 0.2$ in MeOH); ^1H NMR (500 MHz, CD_3OD): δ = 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 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 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; IR: $\tilde{\nu}$ = 3389, 2935, 1688, 1519, 1251, 1081 cm^{-1} ; HRMS (ESI⁺) m/z calcd for $\text{C}_{38}\text{H}_{38}\text{N}_6\text{NaO}_{15}$: 841.2293; found 841.2296.

Synthesis of UT-01309 (2)—To a stirred solution of **34** (13.0 mg, 16.0 μmol) in THF/ H_2O (10:1, 0.4 mL) at 0 °C was added LiOH (0.08 mL, 1 M in H_2O). After being stirred for 1 h at 0 °C, the reaction mixture was quenched with THF/AcOH (10:1, 0.08 mL). All

volatiles were evaporated *in vacuo*. Purification by silica gel PTLC (MeOH/CHCl₃, 1:2) afforded **2** (10.60 mg, 95%) as an amorphous solid. $R_f = 0.4$ (70% CHCl₃/MeOH); $[\alpha]_D^{20} = +85$ ($c = 0.1$ in MeOH); ¹H NMR (500 MHz, CD₃OD): $\delta = 7.88$ (d, $J = 8.5$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.41 (m, 3H), 7.33 (m, 2H), 7.26-7.17 (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), 4.3 (m, 1H), 3.89 (t, $J = 5.5$ Hz, 1H), 3.74 (t, $J = 4.0$ Hz, 1H), 3.40 (s, 3H); ¹³C NMR (100 MHz, CD₃OD): $\delta = 179.1, 173.8, 166.3, 164.9, 152.3, 142.0, 140.0, 133.6, 132.2, 131.9, 131.0, 129.4, 128.6, 124.8, 122.7, 102.7, 100.7, 91.1, 83.6, 80.0, 76.3, 75.8, 74.1, 72.7, 71.5, 70.6, 68.3, 62.8, 58.4$; IR: $\nu = 3411, 2933, 1696, 1515, 1279$ cm⁻¹; HRMS (ESI⁺) m/z calcd for C₃₂H₃₂N₆NaO₁₂: 715.1976; found 715.1972.

Synthesis of 34—To a stirred solution of the acid **32** (55.0 mg, 96.0 μ mol) and **32** (31.0 mg, 192.0 μ mol) in H₂O (1.0 mL) was added EDCI (90.0 mg, 0.48 mmol), glyceracetone-Oxya **17** (0.114 g, 0.48 mmol) and NaHCO₃ (0.102 g, 1.20 mmol) sequentially. After being stirred for 4 h at rt, all volatiles were evaporated and the resulting slurry was partitioned between EtOAc and aq. NaHCO₃, the aqueous layer was extracted with AcOEt (3x). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give the crude product. For data collections, a portion was purified by silica gel chromatography to afford **34** as an amorphous solid (57.0 mg, 85% from **8**). $[\alpha]_D^{20} = +103$ ($c = 0.3$ in CHCl₃); ¹H NMR (500 MHz, CDCl₃): $\delta = 9.72$ (broad, 1H), 7.96 (d, $J = 6.8$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.39 (broad, 1H), 7.20 (broad, 1H), 6.23 (broad, 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), 5.32-5.26 (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 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 176.1, 170.3, 170.2, 170.12, 170.08, 169.03, 169.00, 163.5, 159.1, 150.8, 144.5, 140.6, 104.1, 103.8, 98.0, 82.0, 73.3, 65.2, 63.1, 59.1, 52.0, 42.4, 31.6, 28.8, 20.95, 20.88, 20.83$; IR: $\nu = 3379, 2930, 1691, 1509, 1250, 1070$ cm⁻¹; HRMS (ESI⁺) m/z calcd for C₂₉H₈N₅NaO₁₅: 718.2178; found 718.2186.

Synthesis of Capuramycin (1)—To a stirred solution of **34** (11.0 mg, 16.0 μ mol) in THF/H₂O (10:1, 0.4 mL) at 0 °C was added LiOH (0.08 mL, 1 M in H₂O). After being stirred for 1 h at 0 °C, the reaction mixture was quenched with THF/AcOH (10:1, 0.08 mL). All volatiles were evaporated *in vacuo*. Purification by silica gel PTLC (MeOH/CHCl₃, 1:2) afforded the desired product **1** (8.60 mg, 95%) as an amorphous solid. $R_f = 0.4$ (70% CHCl₃/MeOH); $[\alpha]_D^{20} = +98$ ($c = 0.1$ in H₂O); ¹H NMR (400 MHz, CD₃OD): $\delta = 7.71$ (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), 1.94-1.57 (m, 6H), 1.32 (m, 2H). ¹³C NMR (100 MHz, D₂O): $\delta = 176.3, 173.0, 166.1, 161.4, 151.2, 141.5, 141.0, 109.4, 101.8, 99.3, 90.1, 81.6, 78.1, 75.5, 71.9, 64.7, 61.7, 57.8, 52.2, 41.4, 30.3, 27.3$; IR: $\nu = 3411, 2933, 1696, 1515, 1279$ cm⁻¹; HRMS (ESI⁺) m/z calcd for C₂₃H₃₁N₅NaO₁₂: 592.1867; found 592.1864.

Acknowledgments

The National Institutes of Health is greatly acknowledged for financial support of this work (AI084411). We also thank University of Tennessee for generous financial support. NMR data were obtained on instruments supported by the NIH Shared Instrumentation Grant.

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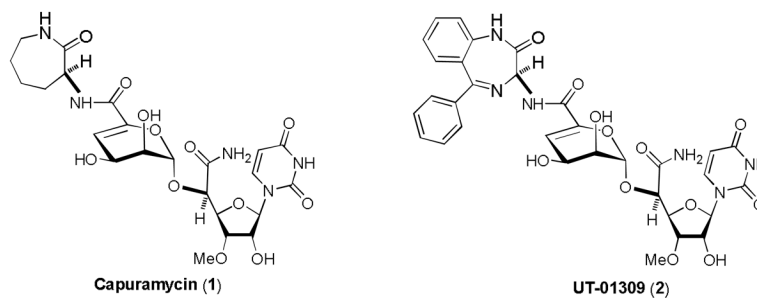


Figure 1.
Structures of Capuramycin (1) and UT-01309 (2).

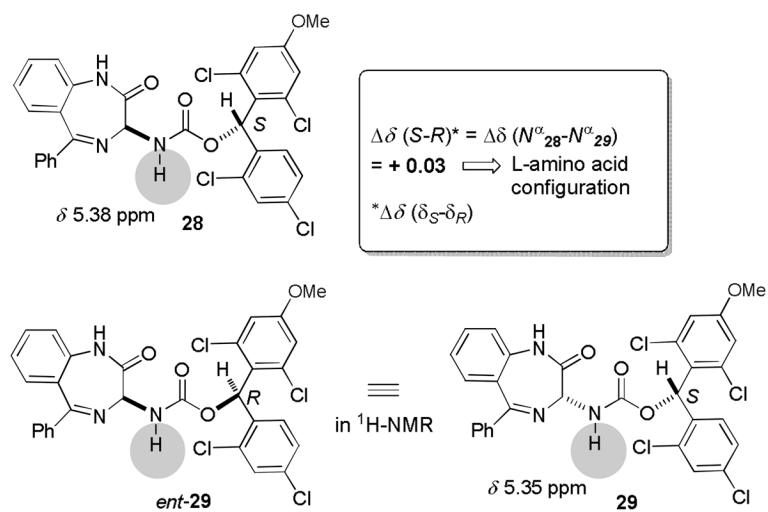
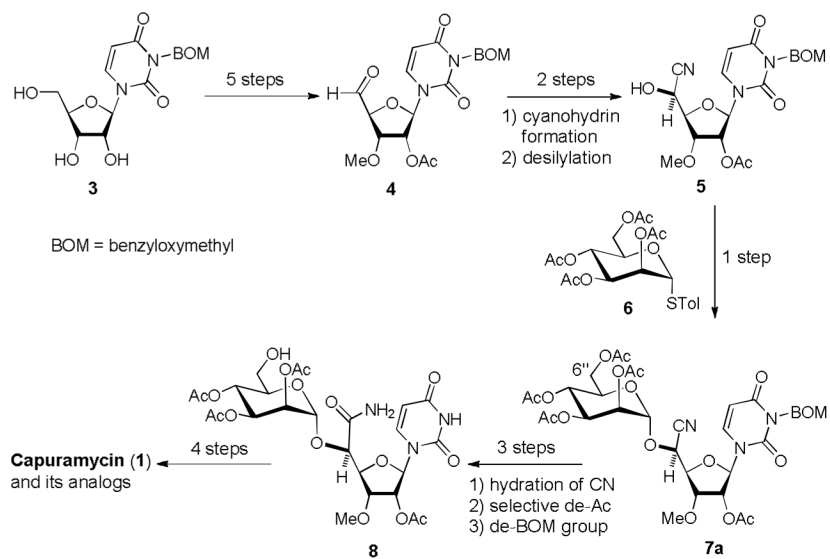
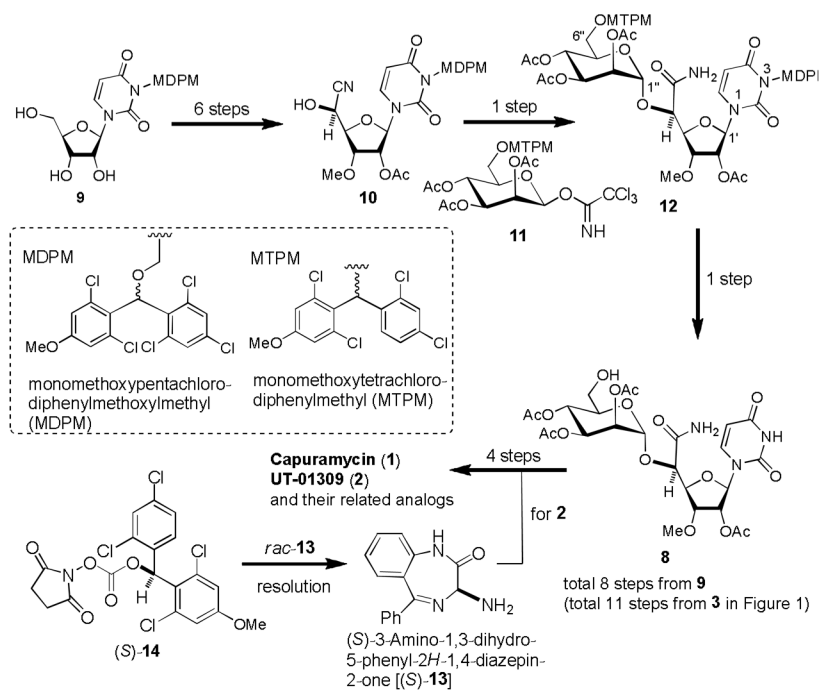


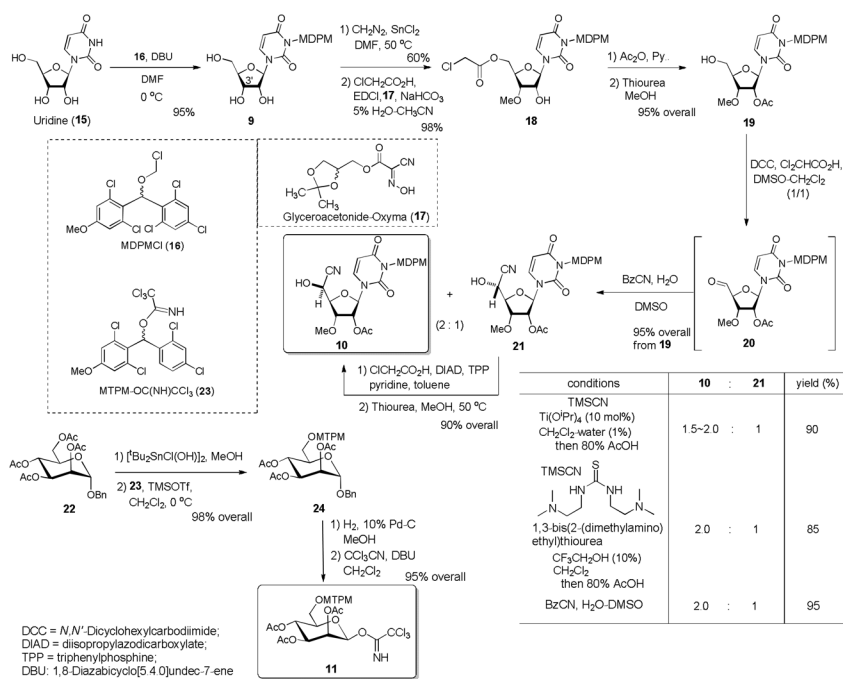
Figure 2.
Absolute configurations of 28 and 29.



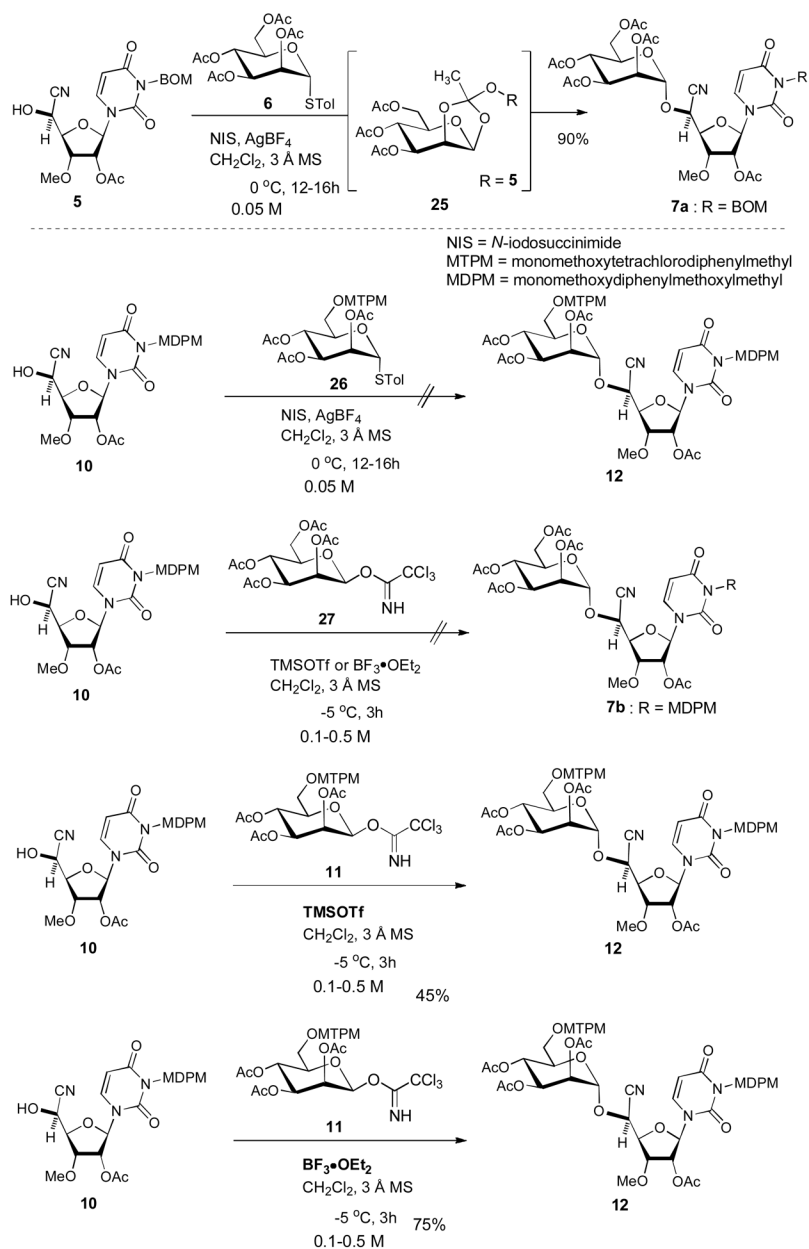
Scheme 1.
Previously reported syntheses of capuramycin.



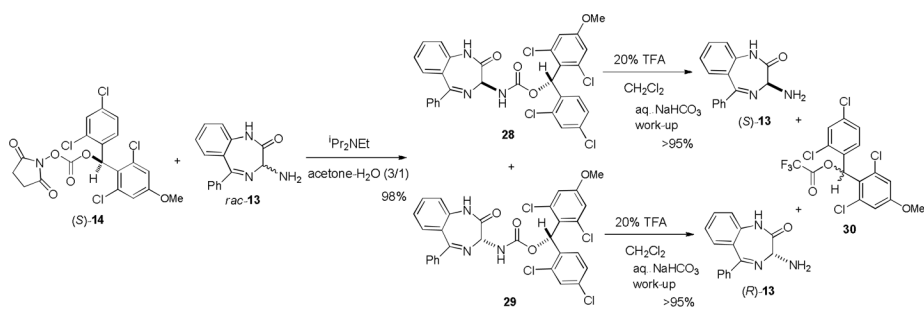
Scheme 2.
Improved synthetic strategy for capuramycin analogs.



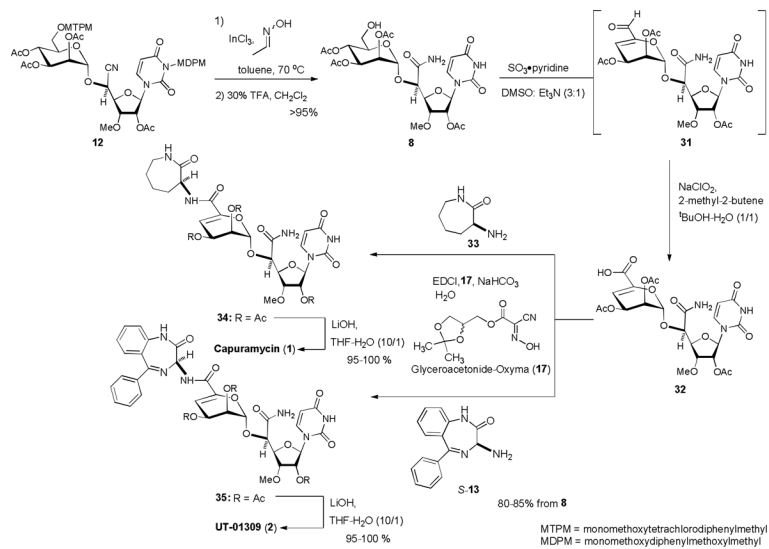
Scheme 3.
Syntheses of the glycosyl donor 10 and acceptor 11.



Scheme 4.
Mannosylation of the cyanohydrins.



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



Scheme 6.
Synthesis of capuramycin and UT-01309.