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Structure-Based Organic Synthesis of a Tricyclic *N*-Malayamycin Analogue

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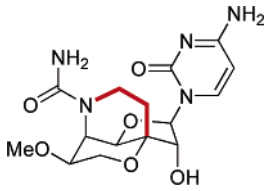

The solid-state structure of crystalline malayamycin A reveals a urea substituent that bisects the plane of the chairlike tetrahydropyran subunit. On the basis of this topological feature, we synthesized a tricyclic *N*-nucleoside analogue in which an ethano bridge linked the urea NH group with the ring junction of the bicyclic tetrahydrofuropyran unit.

Introduction

Naturally occurring purine and pyrimidine nucleosides have been the cornerstones of the chemistry and biology of nature's genetic code since the beginning of creation.[1] *N*- and *C*-nucleosides with nontraditional heterocyclic as well as sugar components have also been found outside the DNA/RNA world.[2] Some of these have been endowed with impressive chemotherapeutic properties as anticancer, antiviral, and anti-infective agents in medical practice for decades.[3]

A select group of *N*- and *C*-pyrimidine nucleosides contains a bicyclic perhydrofuropyran "sugar" moiety rather than the more commonly encountered monocyclic pentofuranosyl or hexopyranosyl residues. For example, ezomycin A_2[4] **1** and octosyl acid A[5] **2** are representatives of such bicyclic *N*-nucleosides, while ezomycin B_2[6] **3** is a *C*-nucleoside equivalent (Figure 1). The ezomycins have been reported to exhibit antifungal and antibiotic activities.[6] Quantamycin **4**, an unnatural synthetic analogue of lincomycin, was designed as a potential antibacterial agent.[7] Some years ago, scientists at the Syngenta Crop Protection Laboratories in Jealott's Hill, U.K., isolated a new *C*-nucleoside from the soil organism *Streptomyces malaysiensis*, which they named malayamycin A (**5**).[8] The gross structure of **5** was based on detailed NMR studies and degradation work. The proposed structure and stereochemical identity of **5** were recently confirmed by a total synthesis.[9] Except for the commonly shared perhydrofuropyran core, the presence of a urea group, and the 5-substituted pyrimidinone units, the nature of functional groups and appendages in **5** were different from those in ezomycin B_2. Furthermore, **5** exhibited

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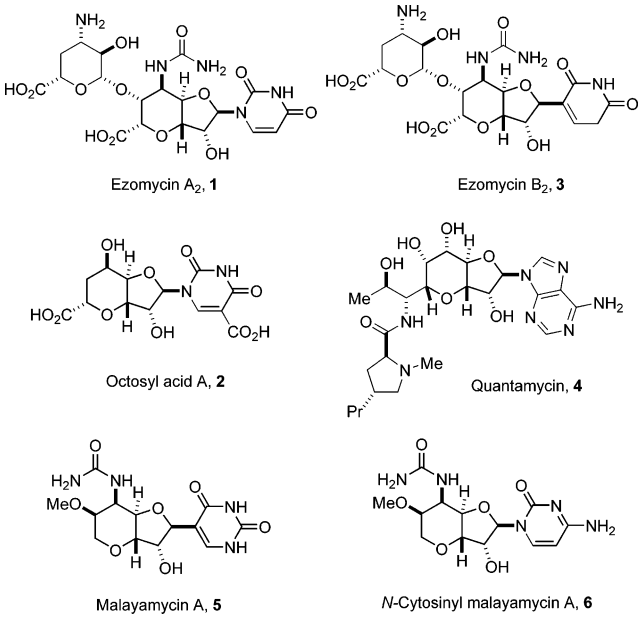

FIGURE 1. Natural (**1**, **2**, **3**, and **5**) and unnatural (**4** and **6**) perhydrofuropyranyl *N*- and *C*-nucleosides.

potent fungicidal activity,[8] which instigated efforts toward the synthesis of *N*-purinyl and *N*-pyrimidinyl analogues.[10] Indeed, a total synthesis of *N*-cytosinyl malayamycin A (**6**) revealed fungicidal activity at least equivalent to **5** (Figure 1).[10]

In the course of our synthetic efforts, we obtained X-ray quality crystals of **5** from water after slow evaporation. The three-dimensional solid-state structure as seen in the ORTEP diagram of one of the hydrated crystals revealed several interesting topological features (Figure 2). Most prominent was the orthogonal orientation of the axial C_5 urea group which bisects the plane of the chairlike tetrahydropyran ring of the bicyclic system, with the N−H group pointing "inward". Previous functional group modifications[10] have delineated the importance of stereochemistry as well as substitution to maintain fungicidal activity in this series. We therefore utilized the three-dimensional functional characteristics shown in the crystal structure of **5** to derive a tricyclic analogue **7** in which the axially oriented urea group was connected to C_3 (malayamycin A numbering) by an ethano bridge. Preliminary superposition of a modeled and minimized structure over the X-ray structure of **5** showed excellent congruence. Thus, we embarked on the synthesis of the proposed tricyclic analogue as part of a program dealing with structure-based organic synthesis.[11] In this approach, structural data available from bioactive natural products are used in the design and synthesis of unnatural congeners.[12]

Interestingly, such an approach was used many years ago in our de novo conception and synthesis of quantamycin **4**, a hybrid structure intended to simulate recognition of the peptidyl amino acid transfer step by a modified lincomycin.[7,13,14] The advent of X-ray crystal structures of complexes involving synthetic compounds with relevant enzymes has popularized so-called structure-based design in the quest for new therapeutic lead compounds.[12] Application of these notions to three-dimensional structural information in conjunction with bioactive conformations of natural products, alone or complexed with biological macromolecules such as enzymes[15] and RNA,[16] provides a powerful tool to explore synthetic chemistry in new directions.[11]

Synthesis Plan

Clearly, a major challenge in the synthesis of **7** was the elaboration of the *N*−*C* ethano bridge in a stereocontrolled manner. In the disconnection illustrated in Scheme 1, we chose to first create the more demanding *C*-bridgehead tether and subsequently to engage it in aza-ring formation (Scheme 1). The allylic ether, readily available from diacetone-D-glucose, would be an appropriate substrate for a ring-closure metathesis reaction[17] to generate the bicyclic core system. Following a stereo- and regiocontrolled functionalization of the double bond to give the *cis*-amino alcohol, the tether would be engaged in an intramolecular nucleophilic attack by the nitrogen to give the tricyclic core structure. Alternatively, the amino group in the tether could be the nucleophile. Elaboration of the acetal via anomeric activation, introduction of the cytosine, and functional group adjustments would afford the intended target **7**.

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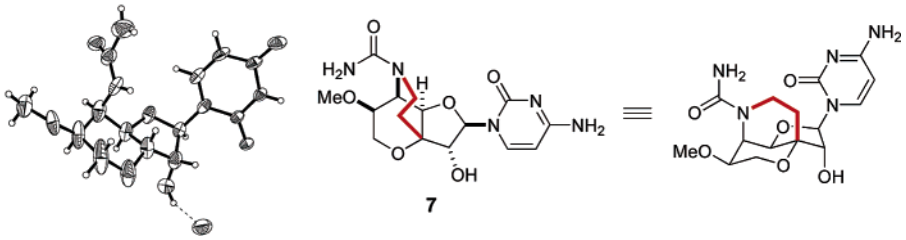
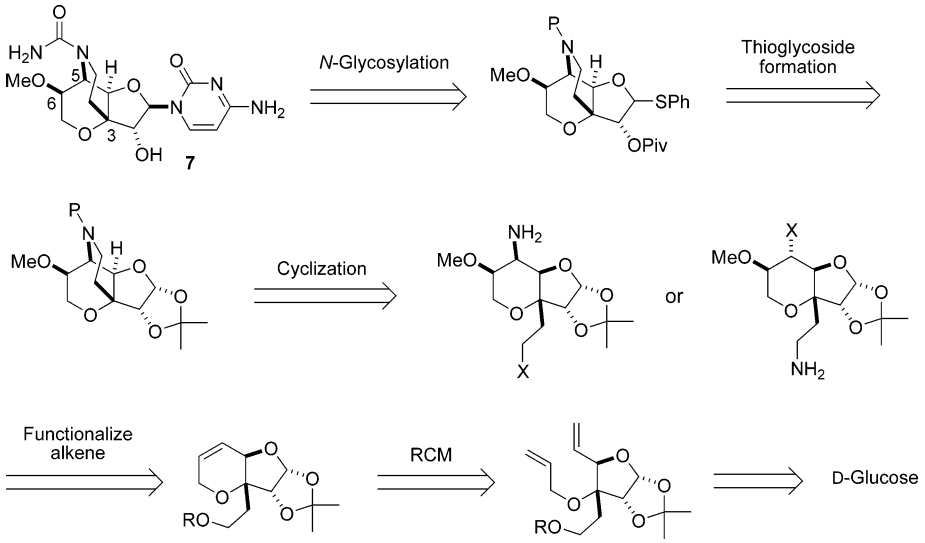


FIGURE 2. ORTEP diagram of malayamycin A hydrate and a tricyclic *N*-cytosinyl malayamycin A.

SCHEME 1. Disconnective Analysis



Although the essentials of this proposed route were previously accomplished in the synthesis of *N*-malayamycin A analogues,[10] we were not in a position to ensure safe passage to **7**, being cognizant of the influence of steric effects and the uncertainty of ring strain in the elaboration of the acetal functionality in a bridged tricyclic ring system.

Results

Oxidation of diacetone-D-glucose **8** and treatment of the resulting ketone with allylmagnesium bromide gave the known[18] *C*-allyl product **9** in 77% overall yield (Scheme 2). Ozonolysis followed by treatment of the ozonide with $NaBH_4$ in MeOH gave a cyclic alkoxyborane **10**, which necessitated treatment with ammonia in MeOH at 75 °C before the desired diol **11** could be liberated. Although *O*-benzylation of the primary hydroxyl group of **11** took place at room temperature in the presence of NaH in DMF, *O*-allylation of the tertiary hydroxyl group in **12** required heating at 100 °C in THF containing HMPA to give **13** in 97% yield. The distal acetonide of **13** was selectively cleaved, and the diol **14**, after bis-mesylation, was subjected to a Finklestein-type elimination[19] to give olefin **15**. Ring-closure metathesis employing Grubbs first-generation catalyst[20] led to the tethered bicyclic core **16** in 93% yield.

We then attempted to introduce the vicinal azido alcohol groups by first epoxidizing **16** to the α-epoxide **17** with *m*-CPBA, followed by opening with azide ion to the intended **18**. However, this sequence was abandoned because of the poor yield of epoxidation and the reluctance of the epoxide to open with azide ion, no doubt due to a sterically impeded path caused by the benzyloxyethyl tether (Scheme 3). An alternative approach involved the cis-dihydroxylation of **16** in the presence of OsO_4 and NMO in aqueous acetone. The diol **19** (dr > 100:1) was easily separable from traces of the minor diastereoisomeric diol by column chromatography on silica gel. The configuration of **19** was established by nOe experiments. Mesylation of the diol **19** with 1.1 equiv of mesyl chloride at −78 °C afforded the monomesylate **20** selectively, most likely due to the pseudoequatorial disposition of the C_5 alcohol. The mesylate **20** was recovered unchanged when treated with NaN_3, even after prolonged periods of reflux in 2-methoxyethanol. Alternatively, treatment of **19** under Mitsunobu conditions with diphenylphosphoryl azide was also unsuccessful.

At this juncture, we reversed the order of bond-forming events leading to the desired aza-tricyclic system. Thus, diol **19** was debenzylated by catalytic hydrogenation, and the product was converted to the bis-tosylate **21** in 71% yield (Scheme 4). As expected, the pseudoaxial hydroxyl group at C_6 in **21** remained free after bis-tosylation. The position of the tosylate in **21** was confirmed via oxidation of the alcohol by the Dess−Martin periodinane reagent[21] in CH_2Cl_2 to the corresponding ketone, and the latter compound was analyzed by ^1H NMR. Treatment of **21** with NaN_3 in DMF at 90 °C led to smooth and selective displacement of the primary tosylate to give **22** in 96% yield. We were now poised to effect an intramolecular ring closure

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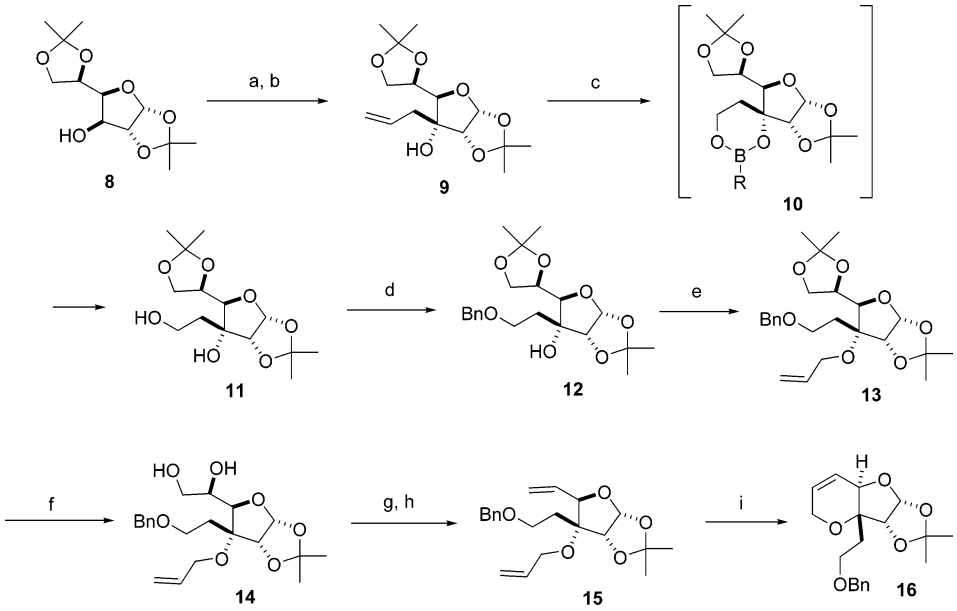
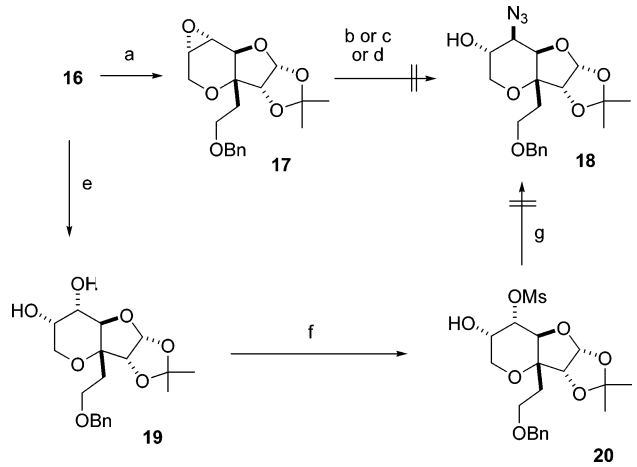
SCHEME 2. Synthesis of the Bicyclic Core[a]



[a] Reagents and conditions: (a) CrO_3, pyridine, Ac_2O, CH_2Cl_2, 0 °C to rt; (b) allylmagnesium bromide, THF, −10 °C to rt, 77% (two steps); (c) O_3, CH_2Cl_2, −78 °C then $NaBH_4$, MeOH, −78 °C to 75 °C, NH_3, rt to 75 °C then AcOH, rt, 59 to 84%; (d) NaH, BnBr, THF, 0 °C to rt, 88%; (e) NaH, allyl bromide, HMPA, THF, 100 °C, 97%; (f) 85% AcOH/H_2O, rt, 88%; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaI, DMA, 100 °C, 83% (two steps); (i) 5 mol % Grubbs first-generation catalyst, CH_2Cl_2, rt, 93%.

SCHEME 3[a]



[a] Reagents and conditions: (a) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, rt, 19%; (b) NaN_3, CH_2OCH_2OMe, 130 °C; (c) NaN_3, NH_4Cl, MeCN/H_2O, 130 °C; (d) NaN_3, NH_4Cl, CH_2OCH_2OMe, 130 °C; (e) 5 mol % OsO_4, NMO, acetone/H_2O, rt, 92%, dr > 100:1; (f) MsCl, Et_3N, CH_2Cl_2, −78 °C, 45%; (g) NaN_3, CH_2OCH_2OMe, 155 °C.

from the azide extremity of the tether, after reduction to the primary amine, onto the C_5 tosylate group. In the event, reduction of the azide group in **22** in the presence of Pd black containing pyridine in EtOH, followed by heating in MeCN containing Et_3N, effected ring closure to the aza-tricyclic system **23**.

Before proceeding with the elaboration of the acetal into an anomerically activatable group, we had to select an appropriate *N*-protecting group that would be resistant to the acidic conditions required to cleave the 1,2-acetonide group and for the nucleobase coupling step, yet removable once the nucleosidic linkage was established. Initially, the 9-fluorenylmethyloxycarbonyl (Fmoc) protecting group was chosen. Addition of FmocCl and pyridine to a solution of **23** in acetonitrile provided **24** in good overall yield. We were now in a position to "invert" the C_6 hydroxyl group and to *O*-methylate. To do so, we first oxidized the alcohol in **24** to the ketone **25** using the Dess−Martin periodinane reagent. Reduction with $NaBH_4$ in MeOH/CH_2Cl_2 was highly stereoselective giving the "inverted" alcohol **26** in good yield (the epimer was not observed). Being wary of forming a cyclic carbamate during *O*-methylation of **26** under basic conditions, we examined a number of acidic conditions for the *O*-methylation of **26**, such as CH_2N_2/silica gel,[22] Me_2SO_4/$NaHCO_3$,[23] and $Me_3O^+BF_4^-$/proton sponge.[24] Unfortunately, all of these attempts were unsuccessful, and the use of MeI and Ag_2O in MeCN[25] resulted in the deprotection of the Fmoc group to give **27**. The trichloroethoxycarbonyl (Troc) group was then utilized due to its higher tolerance of basic conditions. However, exposure of **29**, which was synthesized in a manner analogous to that of **26**, to MeI and Ag_2O in acetonitrile led to the cyclic carbamate **30**.

It was clear that a far more robust protecting group would be required for the successful *O*-methylation of the C_6 alcohol. Accordingly, we opted for the *t*-butylsulfonyl (Bus) group, originally reported by Sun and Weinreb[26] and subsequently used in isolated instances only.[27] Treatment of **23** with *t*-butylsulfinyl chloride, followed by oxidation with *m*-CPBA, gave the desired *N*-Bus derivative **31** (Scheme 5). The oxidation−reduction sequence was repeated as before, and the alcohol **32** was

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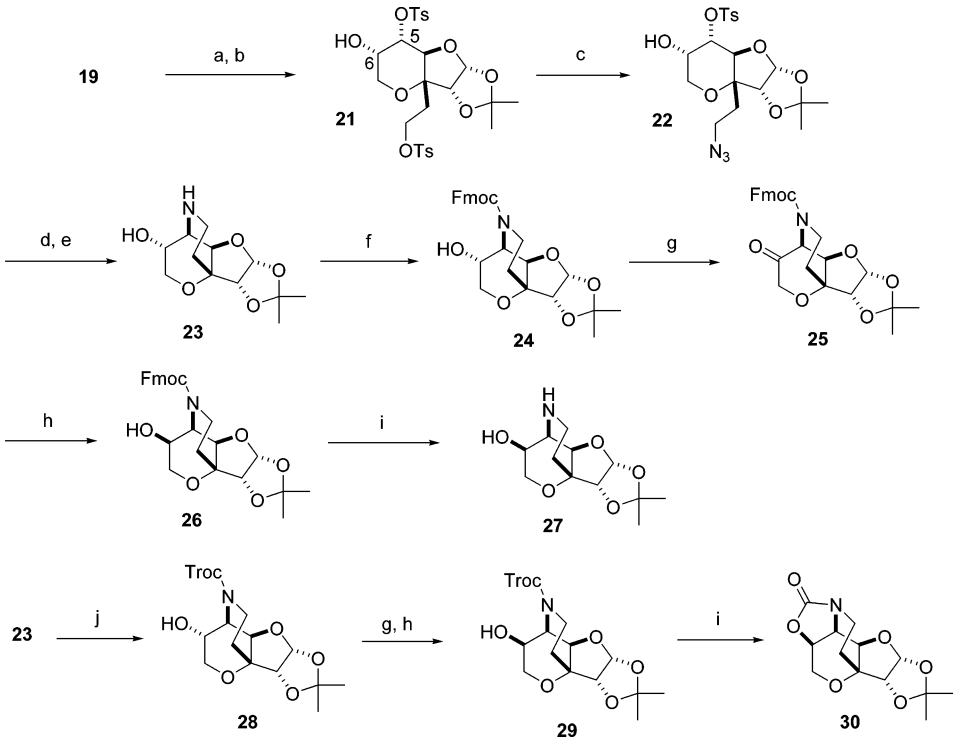
SCHEME 4[a]



[a] Reagents and conditions: (a) $Pd(OH)_2$, H_2 (1 atms), EtOAc, rt; (b) TsCl, pyridine, −20 °C, 71% (two steps); (c) NaN_3, DMF, 90 °C, 96%; (d) Pd black, H_2 (1 atm), pyridine, EtOH, rt; (e) Et_3N, MeCN, 95 °C; (f) FmocCl, pyridine, MeCN, rt, 50% (three steps); (g) Dess−Martin periodinane, CH_2Cl_2, rt; (h) $NaBH_4$, MeOH/CH_2Cl_2, rt, 66% for **26**, 89% for **29** (two steps); (i) Ag_2O, MeI, MeCN, rt; (j) TrocCl, pyridine, MeCN, rt, 45% (three steps).

methylated under standard Williamson conditions to give the methyl ether **33**.

Previous reports from our laboratory[7,9,10b,28] and the Knapp group[29] had shown the utility of γ-hydroxy dialkyl dithioacetals as intermediates for the synthesis of the alkyl thioglycosides, en route to nucleosidic bond formation in monocyclic as well as bicyclic systems. The feasibility of the same chemistry in the case of the bridged tricycle **33** as a precursor required some exploration. The mildest condition to effect acetal cleavage and formation of a diphenyldithioacetal was treatment of **33** with benzenethiol and Amberlyst-15 (H^+) as a suspension in CH_2Cl_2.[10] The diphenyldithioacetal **34** was then treated with NBS in CH_2Cl_2 at 0 °C to effect cycloetherification,[28] affording **35** in 71% yield. A trace amount of a byproduct which may have been the β-anomer (not shown) was not isolated or characterized. Protection of the alcohol in **35** as the pivalate ester **36** gave X-ray quality crystalline material. As seen in the ORTEP diagram,[30] all the anticipated bond-forming sequences had taken place with the correct stereo- and regiochemistries. We continued the synthesis with the crystalline pivalate **36**, relying on its ability to direct anomeric substitution through neighboring group participation. The penultimate steps in the synthesis involved activation of the thioglycoside **36** with NIS/TfOH[29,31] and nucleophilic attack by the bis-TMS derivative of *N*-acetylcytosine to give **37** as a crystalline compound. Single-crystal X-ray analysis[32] confirmed the 1,2-trans-disposition of the *N*-cytosinyl moiety. Finally, cleavage of the *N*-Bus group could be effected with TfOH in CH_2Cl_2 containing anisole. Subsequent installation of the urea group as previously reported[9,10] and deprotection gave the intended tricyclic *N*-cytosinyl malayamycin A, **7**, as an amorphous, colorless solid. The synthesis of **7** was achieved starting with diacetone-D-glucose over 27 steps in an overall yield of 1.5%.

Discussion

The failure of nucleophilic attack by the azide ion, even under forcing conditions, of the epoxide **17** (or the mesylate **20**) is not surprising. It can be argued that the azide ion would have to approach the mesylate **20**, for example, from a trajectory that is sterically challenged. Furthermore, the required overlap with the σ^* C−O bond would be inaccessible in a chair conformation as in A (Figure 3). A boat conformer, B, would better expose the σ^* C−O orbital to the incoming charged nucleophile, although the benzyloxyethyl tether would still be an impediment. The intramolecular cyclization of the amine derived from **22** in MeCN at 90 °C diminishes the energetic penalty of a sterically impeded bimolecular attack by azide ion. A suprafacial trajectory of attack by the tethered aminoethyl group finds the requisite angle to effectively overlap with the σ^* orbital of the now axially disposed tosylate in **22**, presumably in a boat conformer, as shown in C (Figure 3).

(28) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129.

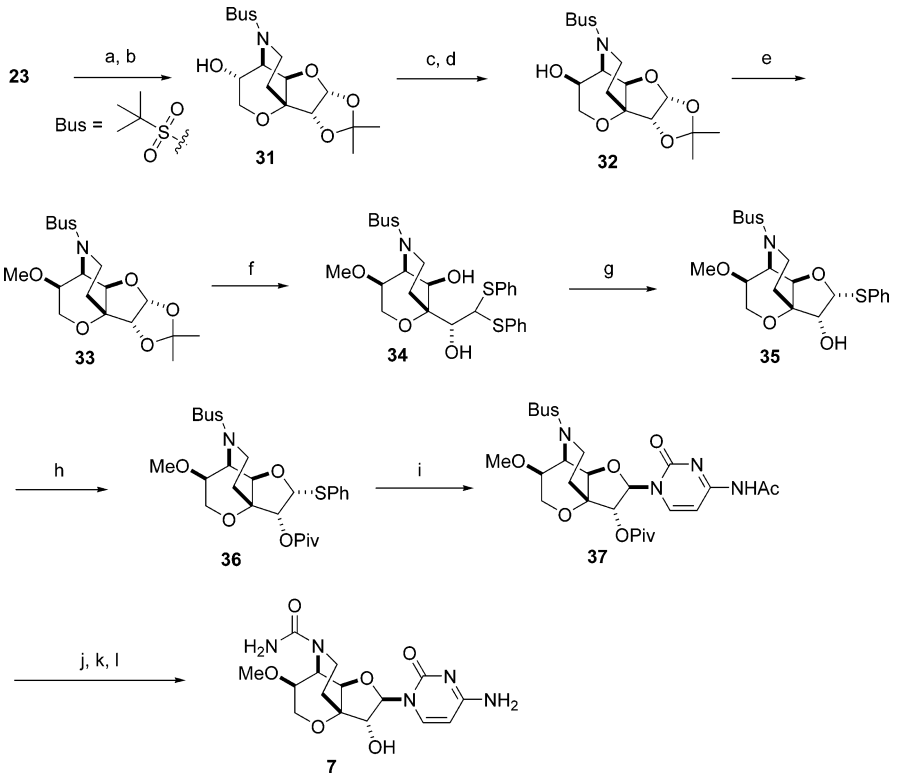
(29) (a) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Triller, R.; Nandau, S. R. *J. Org. Chem.* **1994**, *59*, 946. (b) Knapp, S.; Shieh, W.-C. *Tetrahedron Lett.* **1991**, *32*, 3627.

(30) For an ORTEP diagram of compound **36**, see Supporting Information S64.

(31) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.

(32) For an ORTEP diagram of compound **37**, see Supporting Information S73.

SCHEME 5[a]



[a] Reagents and conditions: (a) *t*-Butylsulfinyl chloride, Et_3N, rt; (b) *m*-CPBA, CH_2Cl_2, rt, 51% (four steps); (c) Dess−Martin periodinane, CH_2Cl_2, rt; (d) $NaBH_4$, CH_2Cl_2/MeOH, rt; (e) NaH, MeI, THF, rt, 98% (three steps); (f) PhSH, Amberlyst-15, CH_2Cl_2, rt, 80%; (g) NBS, CH_2Cl_2, 0 °C, 71%; (h) PivCl, DMAP, CH_2Cl_2/pyridine, rt, 81%; (i) 4-(*N*-trimethylsilyl)-acetamido-2-(trimethylsilyloxy)-pyrimidine, NIS, TfOH, CH_2Cl_2, rt, 52% (based on recovered starting material); (j) TfOH, anisole, CH_2Cl_2, rt; (k) $Cl_3C(O)NCO$, pyridine, rt; (l) $MeNH_2$, MeOH/H_2O, rt, 52% (three steps).

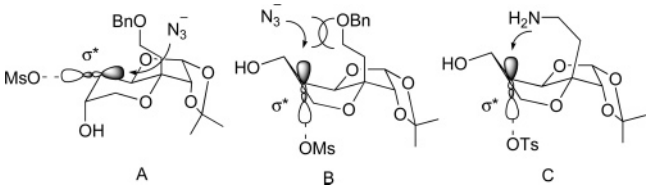


FIGURE 3. Inaccessible (A and B) approaches of an intermolecular nucleophile and the proposed boat conformation (C) allowing intramolecular cyclization.

Anomeric activation through oxocarbenium ion intermediates is at the core of glycoside and nucleoside chemistry.[2,33] The ease of cycloetherification in going from the diphenyldithioacetal **34** to thioglycoside **35** deserves comment (Figure 4). This type of reactivity was at the basis of our early construction of nucleosides of perhydrofuropyrans.[28] It was thought, however, that extension to a bridged, trans-fused dioxabicyclic precursor such as **35** would present additional torsional strain in the transition state involving intramolecular attack of the hydroxyl group onto the phenylthionium ion. This reaction is best done in the absence of an ester-protecting group next to the dithioacetal group because of its participating ability.[10b] It is possible that transient α-phenylthio epoxides may also be present (not shown). The successful cyclization to **35** in good yield is therefore remarkable.

Thioglycosides are well-known precursors to *O*-glycosides proceeding by activation with thiophilic reagents.[31] In spite of precedents in the synthesis of bicyclic *N*-malayamycin A and related analogues,[10] it is noteworthy that the formation of the nucleosidic bond in the tricycle **37** takes place in spite of the strained nature of the intermediates. Generation of the oxocarbenium ion A (Figure 4) must be followed by participation of the neighboring pivalate to the planar 1,2-dioxolenium ion B which imposes a fourth ring in the system. Attack of the pyrimidine base takes place in an anti-fashion to give the observed 1,2-trans-stereochemistry in **37**. Direct *β*-attack of the pyrimidine base on the oxocarbenium ion A is also possible. The apparent spatial tolerance of the axially disposed syn-aza-bridge with a bulkyl *N*-Bus group to the incoming *O*-silylated pyrimidine is certainly a felicitous result, in spite of the modest yield of this step.

Clearly, much remains to be learned from the chemistry of thionium and oxonium ions in these polycyclic systems in particular.[33,34]

(33) See pertinent chapters in: (a) *The Organic Chemistry of Sugars*; Levy, D. E., Fugedi, P., Eds.; CRC Press: Boca Raton, FL, 2006. (b) *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sanaÿ, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (c) *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997. (d) *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood Academic: Amsterdam, 1996.

(34) For insightful work on the reactivity and stereochemistry of oxocarbenium ions, see: (a) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879. (c) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521. (d) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169. (e) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893.

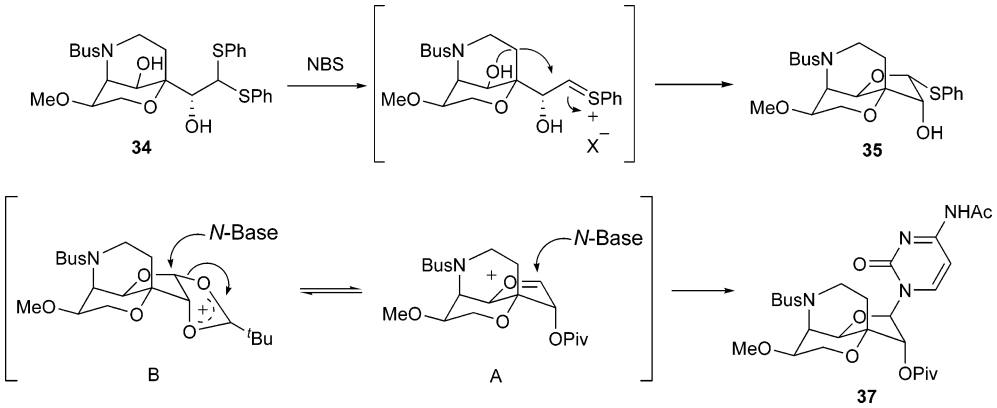


FIGURE 4. Activation at the anomeric center-thioglycoside and *N*-nucleoside formation.

Conclusion

We have conceived and synthesized a tricyclic analogue of *N*-malayamycin A in a stereocontrolled manner, based on the solid-state X-ray crystal structure of the parent malayamycin A. Topological information gleaned from the structure led to the choice of an ethano bridge tethering the proximal urea nitrogen atom with C_3 at the junction of the perhydrofuropyran ring system. Intramolecular cyclization from an amino terminal group on the tether was successfully performed onto a tosylate as a leaving group, possibly passing through a boatlike conformation to allow for better access to a σ^* orbital.

The utility of thionium and oxocarbenium ion intermediates in the construction of the tricyclic nucleoside highlights the successful completion of the synthesis. Unfortunately, preliminary testing of **7** as a fungicide did not show any activity, which may reflect a truly delicate balance between structure, function, and donor−acceptor interactions of the urea group in malayamycin A and its analogues in the presence of biological receptors and requisite enzymes. The possible role of the urea group in a preformed bioactive conformation of malayamycin A is presently under study.

Experimental Section

1,2:5,6-Di-*O*-isopropylidene-3-*C*-allyl-D-allofuranose (9). To a dry flask was charged CrO_3 (6.46 g, 64.6 mmol), under Ar atmosphere, containing anhydrous CH_2Cl_2 (110 mL), which was cooled to 0 °C. Anhydrous pyridine (11.8 mL, 11.5 g, 146 mmol) and Ac_2O (7.0 mL, 7.56 g, 74.0 mmol) were added followed by diacetone-D-glucose (10.0 g, 38.4 mmol), which was added portionwise over 30 min. After being stirred for 30 min, the reaction was brought to room temperature, and after a further 2 h the black solution was poured into EtOAc (ca. 400 mL). The mixture was filtered through silica washed with EtOAc. All the solvents were removed, and the residue was pumped overnight.

The crude oil was dissolved in anhydrous THF (120 mL) and added slowly to allylmagnesium bromide (1 M in Et_2O, 80 mL) at −10 °C. After the addition, the reaction was allowed to warm to room temperature and was stirred for 3 h. The reaction was then poured into ice/water (ca. 250 mL), and the majority of the solvent was evaporated in vacuo. The pH of the solution was taken to pH 7, with a solution of AcOH in Et_2O, and the products were extracted with Et_2O (3 × 200 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 85:15), which gave the product **9** (8.45 g, 28.2 mmol, 77%) as a colorless solid, and recrystallized from EtOAc/hexanes. R_f = 0.77 (hexanes/ethyl acetate, 1:1); mp 108−110; lit.[18] 124 °C; $[\alpha]^{25}_D$ +42.4 (*c* 1.40, $CHCl_3$); lit.[18] $[\alpha]^{25}_D$ +42.8 (*c* 3.0, $CHCl_3$); IR (neat) ν 3474, 1374, 1073; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.01 (m, 1H), 5.69 (d, J = 3.7, 1H), 5.18 (m, 2H), 4.38 (d, J = 3.8, 1H), 4.16 (m, 2H), 3.93 (ddd, J = 9.3, 5.7, 4.2, 1H), 3.83 (d, J = 8.2, 1H), 2.67 (ddt, J = 14.4, 5.8, 1.5, 2H), 2.20 (dd, J = 14.5, 8.7, 1H), 1.61 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 132.5, 118.7, 112.3, 109.5, 103.4, 81.9, 81.1, 78.5, 73.0, 67.8, 36.6, 26.53, 26.52, 26.2, 25.1; LRMS (ESI) 301 (10%) $[M + H]^+$.

3-*C*-(2-Hydroxyethyl)-1,2:5,6-di-*O*-isopropylidene-D-allofuranose (11). The alkene **9** (1.50 g, 5.00 mol) was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C. Ozone was bubbled through the solution until an excess was present. The excess ozone was removed by sparging O_2 through the solution, after which $NaBH_4$ (454 mg, 12.0 mmol) and MeOH (25 mL) were added. The reaction was brought to room temperature and then refluxed for 1.5 h. After being cooled to room temperature, $NH_{3(g)}$ was bubbled through the solution for 30 min, followed by refluxing for a period of 8 h. The reaction was finally cooled and taken to pH 8 using MeOH/AcOH solution. The solvents were evaporated, and the material was purified by flash chromatography (7:3 to 1:9, hexanes/ethyl acetate) to provide **11** (1.27 g, 4.2 mmol, 84%) as a colorless solid. R_f = 0.13 (1:1, hexanes/ethyl acetate); mp 85 °C; $[\alpha]^{25}_D$ +22.7 (*c* 0.67, $CHCl_3$); IR (neat) ν 3539, 3452, 1388; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.72 (d, J = 3.8, 1H), 4.56 (d, J = 3.9, 1H), 4.13 (m, 2H), 3.95 (m, 3H), 3.77 (d, J = 7.9, 1H), 2.75 (br s, 2H), 2.16 (ddd, J = 14.8, 8.1, 4.6, 1H), 1.61 (s, 3H), 1.58 (m, 1H), 1.46 (s, 3H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 112.2, 109.3, 103.1, 81.9, 80.8, 79.4, 72.8, 67.4, 58.0, 32.6, 26.26, 26.27, 26.0, 24.9; HRMS (ESI) calcd for $C_{14}H_{24}O_7Na$ [M + Na] 327.1414, found 327.1408

3-*C*-(2-Benzyloxyethyl)-1,2:5,6-di-*O*-isopropylidene-D-allofuranose (12). A solution of **11** (5.34 g, 17.6 mmol) in anhydrous THF (65 mL) was cooled to 0 °C under an Ar atmosphere. NaH (60% dispersion in mineral oil, 850 mg, 21.3 mmol) was added portionwise and stirred for 1 h at 0 °C. BnBr (2.93 mL, 4.21 g, 24.6 mmol) was added dropwise, stirred for 30 min at 0 °C, then warmed to room temperature, and stirred for 3 days. A saturated solution of NH_4Cl (50 mL) was added slowly, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 60 mL), and the organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residual material was purified by flash chromatography (85:15, hexanes/EtOAc), which yielded **12** (6.12 g, 15.5 mmol, 88%) as a colorless solid. R_f = 0.16 (4:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +19.7 (*c* 0.58, $CHCl_3$); IR (neat) ν 3480, 1386, 1373; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 5.70 (d, J = 3.7, 1H), 4.69 (d, J = 3.7, 1H), 4.56 (d, J = 12.7, 1H), 4.52 (d, J = 12.6, 1H), 4.13 (m, 2H), 3.92 (dd, J = 11.4, 8.4, 1H), 3.85 (m, 2H), 3.76 (dt, J = 9.4, 5.7, 1H), 2.89 (br s, 1H), 2.14 (ddd, J = 14.6, 5.6, 5.6, 1H), 1.78 (ddd, J = 14.6, 7.4, 5.6, 1H), 1.61 (s, 3H), 1.47 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ (ppm) 137.7, 128.1, 127.4, 127.7, 112.1, 109.3, 103.2, 81.8, 81.0, 78.6, 72.93, 72.90, 67.6, 65.4, 31.1, 26.35, 26.33, 26.0, 24.9; HRMS (ESI) calcd for $C_{21}H_{30}O_7Na$ [M + Na] 417.1884, found 417.1882.

3-*O*-Allyl-3-*C*-(2-benzyloxyethyl)-1,2:5,6-di-*O*-isopropylidene-D-allofuranose (13). To a solution of **12** (7.75 g 19.7 mmol) in anhydrous THF (110 mL), under Ar atmosphere, was added NaH (60% dispersion, 1.25 g, 31.3 mmol) portionwise. The reaction was heated to gentle reflux for 2 h and then cooled to room temperature when HMPA (12 mL) was added, followed by allyl bromide (3.60 mL, 4.98 g, 41.2 mmol). The reaction was refluxed at 95 °C for 1.5 h and cooled to room temperature, and H_2O (100 mL) was added. The products were extracted with Et_2O (3 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography (4:1, hexanes/ethyl acetate) to provide **13** (8.33 g, 19.1 mmol, 97%) as pale yellow oil. $R_f = 0.25$ (4:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +41.0 (*c* 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 5H), 5.93 (ddt, *J* = 17.2, 10.4, 5.2, 1H), 5.62 (d, *J* = 3.5, 1H), 5.30 (dtd, *J* = 17.2, 3.6, 1.7, 1H), 5.13 (dtd, *J* = 10.4, 3.4, 1.5, 1H), 4.62 (d, *J* = 3.5, 1H), 4.52 (s, 2H), 4.32 (dt, *J* = 5.2, 1.6, 1H), 4.19 (dt, *J* = 5.1, 1.6, 1H), 4.04−4.17 (m, 3H), 3.92 (dd, *J* = 8.0, 5.6, 1H), 3.74 (m, 2H), 2.18 (dt, *J* = 14.8, 6.6, 1H), 1.89 (dt, *J* = 14.8, 6.9, 1H), 1.59 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8, 135.0, 128.1, 127.34, 127.29, 115.2, 112.3, 109.2, 102.8, 83.2, 83.1, 80.9, 72.8, 72.6, 68.1, 65.8, 65.2, 30.4, 26.6, 26.13, 26.12, 25.0; HRMS (ESI) calcd for $C_{24}H_{34}O_7Na$ [M + Na] 457.2197, found 457.2194.

3-*O*-Allyl-3-*C*-(2-benzyloxyethyl)-1,2-*O*-isopropylidene-D-allofuranose (14). Compound **13** (9.91 g, 22.8 mmol) was stirred in AcOH/H_2O (85:15 v/v, 100 mL) for 48 h at room temperature. A saturated solution of $NaHCO_3$ (200 mL) was added slowly, and the reaction was neutralized carefully with solid $NaHCO_3$. The products were extracted with Et_2O (3 × 250 mL), dried (Na_2SO_4), filtered, and concentrated, and the crude material was purified by flash chromatography (7:3 to 1:1, hexanes/ethyl acetate), which gave **14** (7.90 g, 20.1 mmol, 88%) as a pale yellow oil. $R_f = 0.36$ (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +47.6 (*c* 0.53, $CHCl_3$); IR (neat) ν 3436; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (m, 5H), 5.90 (m, 1H), 5.66 (d, *J* = 3.6, 1H), 5.24 (ddt, *J* = 17.2, 3.3, 1.6, 1H), 5.14 (ddt, *J* = 10.5, 3.0, 1.4, 1H), 4.59 (d, *J* = 3.6, 1H), 4.53 (d, *J* = 11.8, 1H), 4.50 (d, *J* = 11.8, 1H), 4.25 (ddt, *J* = 12.1, 5.0, 1.6, 1H), 4.15 (ddt, *J* = 12.1, 5.5, 1.4, 1H), 4.07 (d, *J* = 9.0, 1H), 3.85 (m, 2H), 3.69 (m, 3H), 2.90 (br s, 1H), 2.20 (dt, *J* = 15.0, 6.9, 1H), 1.89 (dt, *J* = 14.8, 6.9, 1H), 1.80 (br s, 1H), 1.59 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.4, 134.2, 128.1, 127.5, 127.4, 116.1, 112.5, 103.6, 84.0, 82.1, 78.3, 72.9, 69.3, 66.5, 65.1, 64.3, 30.9, 26.4, 26.1; LRMS (ESI) 395 (25%) $[M + H]^+$.

(3a*R*,5*S*,6*R*,6a*R*)-6-Allyloxy-6-(2-benzyloxyethyl)-2,2-dimethyl-5-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole (15). A solution of **14** (7.90 g, 20.1 mmol) in anhydrous CH_2Cl_2 (110 mL), under an Ar atmosphere, was cooled to 0 °C. Et_3N (7.10 mL, 5.13 g, 50.3 mmol) was added, and the temperature of the solution was allowed to equilibrate before MsCl (3.40 mL, 5.03 g, 43.9 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h, then H_2O (55 mL) was added, and the reaction was stirred for a further 10 min at this temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organics were combined, dried (Na_2SO_4), filtered, and concentrated.

The oily residue was dissolved in anhydrous dimethylacetamide (110 mL), and NaI (19.6 g, 131 mmol) was added. The reaction was heated to 100 °C for 6 h and then cooled to room temperature, and a saturated solution of $Na_2S_2O_3$ (100 mL) was poured into the reaction mixture. Stirring was continued until the color had disappeared, then H_2O (100 mL) was added, and the products were extracted with Et_2O (3 × 200 mL), dried (Na_2SO_4), and filtered. After evaporation of the solvents in vacuo, the residue was purified by flash chromatography (9:1, hexanes/ethyl acetate), which gave **15** (5.97 g, 16.6 mmol, 83%) as a very pale yellow oil. $R_f = 0.91$ (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +41.2 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 5.91 (ddt, *J* = 17.2, 10.4, 5.3, 1H), 5.82 (ddd, *J* = 16.7, 10.7, 5.8, 1H), 5.72 (d, *J* = 3.7, 1H), 5.46 (dt, *J* = 17.3, 1.7, 1H), 5.28 (m, 2H), 5.15 (ddd, *J* = 10.4, 3.2, 1.7, 1H), 4.64 (m, 1H), 4.58 (d, *J* = 3.7, 1H), 4.50 (s, 2H), 4.14 (dt, *J* = 5.4, 1.5, 2H), 3.64 (dt, *J* = 6.8, 1.2, 2H), 2.07 (dt, *J* = 14.8, 6.8, 1H), 1.80 (dt, *J* = 14.9, 6.7, 1H), 1.60 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.8, 134.7, 132.1, 128.1, 127.32, 127.26, 118.2, 115.8, 112.2, 103.1, 83.7, 82.3, 81.1, 72.7, 65.5, 65.1, 30.2, 26.5, 26.1; HRMS (ESI) calcd for $C_{21}H_{28}O_5Na$ [M + Na] 383.1829, found 383.1819.

(3a*R*,3b*S*,7a*S*,8a*R*)-3b-(2-Benzyloxyethyl)-2,2-dimethyl-3a,5,-7a,8a-tetrahydro-3b*H*-1,3,4,8-tetraoxacyclopenta[*a*]indene (16). A solution of **15** (5.97 g, 16.6 mmol) in anhydrous CH_2Cl_2 (2.1 L) was degassed, and an Ar atmosphere was applied. Grubbs first-generation catalyst (4 mol %, 0.66 mmol, 542 mg) was added, and the reaction was stirred overnight at room temperature. EtOAc (100 mL) was then added, and the reaction was filtered through silica washing with CH_2Cl_2/EtOAc (9:1). The solvents were removed, and the oily residue was purified by flash chromatography (4:1, hexanes/ethyl acetate) to yield **16** (5.18 g, 15.6 mmol, 93%) as a viscous, pale brown oil. $R_f = 0.74$ (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ −5.6 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (m, 5H), 6.18 (m, 1H), 5.83 (d, *J* = 3.4, 1H), 5.66 (ddd, *J* = 10.5, 5.5, 2.5, 1H), 4.82 (dd, *J* = 3.5, 0.8, 1H), 4.68 (m, 1H), 4.57 (d, *J* = 11.8, 1H), 4.52 (d, *J* = 11.8, 1H), 4.42 (ddd, *J* = 17.9, 5.4, 2.6, 1H), 4.22 (ddt, *J* = 17.9, 3.7, 2.5, 1H), 3.78 (ddd, *J* = 9.6, 6.9, 5.8, 1H), 3.68 (m, 1H), 2.18 (dt, *J* = 15.6, 5.5, 1H), 1.62 (s, 3H), 1.44 (ddd, *J* = 15.6, 7.9, 6.2, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.9, 128.0, 127.2, 125.7, 123.9, 112.6, 105.6, 79.0, 78.4, 77.4, 72.8, 72.5, 65.5, 64.5, 27.4, 25.8, 25.5; HRMS (ESI) calcd for $C_{19}H_{24}O_5Na$ [M + Na] 355.1516, found 355.1507.

(3a*R*,3b*R*,6*S*,7*S*,7a*S*,8a*R*)-3b-(2-Benzyloxyethyl)-2,2-dimethylhexahydro-1,3,4,8-tetraoxacyclopenta[*a*]indene-6,7-diol (19). To a solution of **16** (5.18 g, 15.6 mmol) in acetone/H_2O (8:1, 130 mL) were added 4-methylmorpholine *N*-oxide (3.67 g, 31.3 mmol) and then 2.5 wt % solution of OsO_4 in ^{t}BuOH (9.78 mL, ca. 3.5 mol %) at room temperature. After 2.5 h, a saturated solution of $Na_2S_2O_3$ (100 mL) was added, and the solution was stirred overnight. The majority of the acetone was removed in vacuo, and the black solution was extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (9:1, ethyl acetate/hexanes) to yield **19** (5.28 g, 14.4 mmol, 92%) as an off-white foam and >100:1 mixture of diastereoisomers, the minor, of which, was not characterized. $R_f =$ 0.33 (ethyl acetate); $[\alpha]^{25}_D$ +59.7 (*c* 1.7, $CHCl_3$); IR (neat) ν 3446, 2250; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (m, 5H), 5.79 (d, *J* = 3.4, 1H), 4.69 (d, *J* = 3.5, 1H), 4.56 (d, *J* = 11.7, 1H), 4.51 (d, *J* = 11.7, 1H), 4.23 (d, *J* = 10.5, 1H), 4.11 (m, 2H), 4.01 (m, 1H), 3.85 (dd, *J* = 13.5, 2.0, 1H), 3.72 (dt, *J* = 9.5, 6.9, 1H), 3.64 (ddd, *J* = 9.6, 7.1, 5.4, 1H), 2.50 (br s, 1H), 2.20 (dt, *J* = 15.5, 5.4, 1H), 1.85 (br s, 1H), 1.63 (s, 3H), 1.47 (dt, *J* = 15.5, 7.1, 1H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.6, 128.1, 127.4, 127.3, 113.3, 104.4, 80.7, 79.7, 75.1, 73.0, 68.6, 67.7, 66.8, 64.6, 25.8, 25.7, 25.4; HRMS (ESI) calcd for $C_{19}H_{27}O_7$ [M + H] 367.1751, found 367.1768.

Bis-*p*-toluenesulfonate Ester 21. Compound **19** (364 mg, 0.99 mmol) was dissolved in EtOAc (10 mL), and $Pd(OH)_2$/C 20 wt % (40 mg) was added. The suspension was degassed, and an H_2 atmosphere was applied (1 atm). The reaction was stirred at room temperature for 2 h, and then the suspension was filtered and washed with hot EtOAc and then warm MeOH. The solution was concentrated in vacuo to provide a colorless solid.

The crude material was dissolved in anhydrous pyridine (9 mL) and cooled to −20 °C. TsCl (850 mg, 4.46 mmol) was added in three portions with 3-h intervals, and the reaction was stirred at −20 °C overnight. MeOH was then added, the reaction was stirred

for 10 min, and the solvents were removed in vacuo. The residue was dissolved in H_2O (20 mL) and extracted with Et_2O (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography (3:2 to 1:1, hexanes/ethyl acetate) to yield **21** (414 mg, 0.71 mmol, 71%) as a colorless foam. R_f = 0.22 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +32.1 (*c* 0.43, $CHCl_3$); IR (neat) ν 3525, 1598, 1358, 1176; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84 (d, *J* = 8.4, 2H), 7.80 (d, *J* = 8.4, 2H), 7.39 (d, *J* = 7.9, 2H), 7.37 (d, *J* = 7.9, 2H), 5.64 (d, *J* = 3.5, 1H), 4.79 (dd, *J* = 11.5, 3.5, 1H), 4.39 (d, *J* = 11.5, 1H), 4.37 (d, *J* = 3.5, 1H), 4.28 (m, 1H), 4.15 (m, 2H), 4.08 (dd, *J* = 13.6, 1.3, 1H), 3.70 (dd, *J* = 13.5, 1.9, 1H), 2.54 (br s, 1H), 2.49 (s, 6H), 2.23 (m, 1H), 1.58 (s, 3H), 1.54 (m, 1H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.1, 145.0, 132.5, 132.2, 129.7, 129.6, 127.6, 127.5, 113.7, 104.1, 81.3, 79.1, 77.5, 71.4, 67.6, 66.7, 64.6, 25.7, 25.6, 25.1, 21.4, 21.3; LRMS (ESI) 585 (100%) $[M + H]^+$.

Azide 22. Compound **21** (414 mg, 0.71 mmol) was dissolved in anhydrous DMF (10 mL), and NaN_3 (46 mg, 0.71 mmol) was added before the reaction was heated to 90 °C. After 50 min, LC−MS indicated consumption of starting material, and therefore the solution was cooled to room temperature and diluted with brine (15 mL). The product was extracted with EtOAc (3 × 15 mL), and the combined organics were washed with H_2O (2 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (1:1, hexanes/ethyl acetate) to yield **22** (311 mg, 0.68 mmol, 96%) as a colorless foam. R_f = 0.34 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +43.5 (*c* 0.95, $CHCl_3$); IR (neat) ν 3503, 2102; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, *J* = 8.3, 2H), 7.38 (d, *J* = 8.0, 2H), 5.70 (d, *J* = 3.5, 1H), 4.89 (dd, *J* = 11.5, 3.5, 1H), 4.53 (d, *J* = 3.5, 1H), 4.43 (d, *J* = 11.6, 1H), 4.33 (m, 1H), 4.14 (dd, *J* = 13.5, 1.3, 1H), 3.81 (dd, *J* = 13.5, 2.0, 1H), 3.47 (m, 2H), 2.48 (s, 3H), 2.10 (m, 2H), 1.60 (s, 3H), 1.33 (s, 3H), 1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.0, 132.6, 129.5, 127.6, 113.7, 104.2, 81.5, 79.2, 77.6, 71.5, 67.8, 66.6, 45.2, 25.8, 25.7, 24.9, 21.4; HRMS (ESI) calcd for $C_{19}H_{25}N_3O_8$-SNa [M + Na] 478.1255, found 478.1247.

***N*-9-Fluorenylmethylcarbamate 24.** To a solution of **22** (100 mg, 0.22 mmol) in EtOH/pyridine (99:1, 5.5 mL) was added Pd black (16 mg), and the suspension was degassed, and an H_2 atmosphere (1 atm) was applied. After being stirred at room temperature for 1.5 h, the suspension was filtered and washed with warm MeOH/pyridine (99:1), and the solution was concentrated and dried on the pump overnight.

The crude material was dissolved in MeCN (6 mL) with Et_3N (90 μL, 66 mg, 0.66 mmol), and the reaction was refluxed (95 °C) for 24 h. The solution was then cooled to 0 °C, and pyridine (18 μL, 17 mg, 0.22 mmol) and FmocCl (63 mg, 0.24 mmol) were added. After 3 h, LC−MS indicated the consumption of the amine, and the solvents were removed in vacuo. The brown residue was dissolved in 0.2 M HCl (5 mL), and the products were extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (1:1 to 7:3, ethyl acetate/hexanes) to yield **24** (54 mg, 0.11 mmol, 50%) as a colorless foam. R_f = 0.16 (1:1, ethyl acetate/hexanes); $[\alpha]^{25}_D$ 10.6 (*c* 1.8, $CHCl_3$); IR (neat) ν 3449, 1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (m, 2H), 7.58 (m, 2H), 7.30−7.46 (m, 4H), 5.76 (d, *J* = 3.3, 0.4H), 5.72 (d, *J* = 3.3, 0.6H), 4.67 (dd, *J* = 10.7, 5.2, 0.4H), 4.63 (dd, *J* = 10.7, 4.7, 0.6H), 4.55 (m, 1.4H), 4.45 (dd, *J* = 10.8, 6.2, 0.4H), 4.33 (d, *J* = 3.1, 0.6H), 4.31 (d, *J* = 0.4H), 4.25 (m, 1.6H), 4.23 (m, 1H), 3.90 (m, 1.4H), 3.70 (d, *J* = 13.6, 0.6H), 3.43 (m, 2H), 3.28 (br s, 0.6H), 2.75 (m, 1H), 1.64 (s, 1.2H), 1.61 (s, 1.8H), 1.38 (s, 1.2H), 1.35 (s, 1.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 149.1, 148.6, 137.1, 138.0, 137.9, 137.7, 135.8, 135.58, 135.54, 135.4, 123.2, 123.0, 122.8, 122.6, 122.45, 122.40, 120.6, 120.4, 120.3, 115.88, 115.85, 115.80, 115.7, 110.7, 110.6, 101.6, 81.9, 76.6, 73.5, 73.4, 70.0, 68.4, 68.9, 67.5, 66.8, 56.4, 54.4, 54.1, 49.1, 49.0, 40.0, 39.8, 31.2, 31.0, 29.8, 29.5; HRMS (ESI) calcd for $C_{27}H_{30}NO_7$ [M + H] 480.2017, found 480.2020.

Alcohol 26. To a solution of **24** (26 mg, 0.054 mmol) in dry CH_2Cl_2 (1 mL) was added Dess−Martin peridodinane (34 mg, 0.081 mmol) at room temperature. After 2.5 h, a saturated solution of $Na_2S_2O_3$ (2 mL) was added, and the reaction was stirred for 30 min. The products were extracted with CH_2Cl_2 (3 × 3 mL), and the combined organics were washed with a saturated solution of $NaHCO_3$ (2 × 4 mL), dried (Na_2SO_4), filtered, and concentrated.

The residue was dissolved in CH_2Cl_2/MeOH (1:1, 1 mL) at room temperature, and to the stirred solution was added $NaBH_4$ (4 mg, 0.11 mmol). After 30 min, a saturated solution of NH_4Cl (2 mL) was added, and the reaction was stirred for 10 min. The layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL), after which the organics were combined, dried ($MgSO_4$), and filtered, and the solvent was removed. The solid residue was purified by flash chromatography (3:2, ethyl acetate/hexanes) to yield **26** (17 mg, 0.035 mmol, 66%) as a colorless solid. R_f = 0.19 (1:1, ethyl acetate/hexanes); mp 90−93 °C; $[\alpha]^{25}_D$ −3.4 (*c* 0.85, $CHCl_3$); IR (neat) ν 3432, 1694; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.79 (d, *J* = 7.6, 2H), 7.59 (d, *J* = 7.4, 2H), 7.44 (t, *J* = 7.3, 2H), 7.34 (t, *J* = 7.3, 2H), 5.81 (d, *J* = 3.0, 0.7H), 5.77 (br s, 0.3H), 4.91 (s, 0.7H), 4.55 (m, 1.3H), 4.43 (dd, *J* = 10.4, 6.7, 0.7H), 4.34 (d, *J* = 2.9, 0.7H), 4.27 (t, *J* = 6.5, 1H), 4.15 (br s, 0.3H), 3.85−4.25 (m, 3.7H), 3.80 (br s, 0.3H), 3.53−3.74 (m, 2.0H), 3.44 (m, 0.3H), 2.20 (m, 0.7H), 1.95 (m, 0.3H), 1.63 (m, 4H), 1.39 (s, 2.1H), 1.35 (s, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.8, 143.3, 143.2, 141.0, 127.5, 127.0, 126.8, 124.7, 124.5, 124.2, 124.1, 119.7, 114.2, 105.2, 82.1, 81.3, 70.8, 76.9, 73.1, 72.2, 68.5, 67.8, 67.3, 66.8, 64.4, 52.8, 46.8, 38.8, 37.5, 28.4, 26.8, 26.2, 26.0, 25.7; HRMS (ESI) calcd for $C_{16}H_{28}NO_7S$ [M + H] 378.1581, found 378.1576.

***N*-Trichloroethylcarbamate 28.** To a solution of **22** (100 mg, 0.22 mmol) in EtOH/pyridine (99:1, 5.5 mL) was added Pd black (17 mg), the suspension was degassed, and an H_2 atmosphere (1 atm) was applied. After being stirred at room temperature for 2 h, the suspension was filtered and washed with warm MeOH/pyridine (99:1), and the solution was concentrated and dried on the pump overnight. The crude material was dissolved in MeCN (6 mL) with Et_3N (90 μL, 66 mg, 0.66 mmol), and the reaction was refluxed (95 °C) for 24 h. The solution was then cooled to 0 °C, and pyridine (23 μL, 23 mg, 0.29 mmol) and TrocCl (56 mg, 36 μL, 0.24 mmol) were added. After 3 h, LC−MS indicated the consumption of the amine, and the solvents were removed in vacuo. The brown residue was dissolved in 0.2 M HCl (5 mL), and the products were extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by flash chromatography (1:1, ethyl acetate/hexanes) to yield **28** (43 mg, 0.10 mmol, 45%) as a colorless solid. R_f = 0.49 (7:3, ethyl acetate/hexanes); mp >175 °C dec; $[\alpha]^{25}_D$ +5.5 (*c* 1.0, $CHCl_3$); IR (neat) ν 3461, 1713; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.80 (d, *J* = 3.2, 0.5H), 4.78 (d, *J* = 3.4, 0.5H), 4.93 (d, *J* = 11.9, 0.5H), 4.83 (d, *J* = 11.9, 0.5H), 4.53−4.68 (m, 3H), 4.37 (d, *J* = 3.3, 0.5H), 4.35 (d, *J* = 3.6, 0.5H), 4.05−4.25 (m, 2H), 3.95 (d, *J* = 2.2, 0.5H), 3.92 (d, *J* = 2.8, 0.5H), 3.60−3.80 (m, 2H), 2.80 (br s, 0.4H), 2.40 (br s, 0.5H), 2.20 (m, 1H), 1.65 (s, 3H), 1.63 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.5, 146.9, 110.84, 110.79, 101.7, 93.2, 81.9, 81.8, 76.5, 74.7, 74.6, 73.6, 70.0, 69.9, 68.5, 66.8, 66.6, 54.1, 53.9, 41.0, 39.9, 31.1, 30.9, 29.9, 29.5; HRMS (ESI) calcd for $C_{15}H_{21}$-Cl_3NO_7 [M + H] 432.0378, found 432.0384.

Alcohol 29. To a solution of **28** (26 mg, 0.060 mmol) in dry CH_2Cl_2 (1 mL) was added Dess−Martin peridodinane (39 mg, 0.092 mmol) at room temperature. After 2.5 h, a saturated solution of $Na_2S_2O_3$ (2 mL) was added, and the reaction was stirred for 20 min. The products were extracted with CH_2Cl_2 (3 × 3 mL), and the combined organics were washed with a saturated solution of $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated.

The residue was dissolved in CH_2Cl_2/MeOH (1:1, 1 mL) at room temperature, and to the stirred solution was added $NaBH_4$ (4 mg, 0.11 mmol). After 30 min, a saturated solution of NH_4Cl (2 mL) was added, and the reaction was stirred for 10 min. The layers were separated. The aqueous layer was extracted with EtOAc (3

× 4 mL), after which the organics were combined, dried ($MgSO_4$), and filtered, and the solvent was removed. The solid residue was purified by flash chromatography (1:1, ethyl acetate/hexanes) to yield **29** (23 mg, 0.053 mmol, 89%) as a colorless, glassy solid. R_f = 0.50 (7:3, ethyl acetate/hexanes); $[\alpha]^{25}_D$ −8.0 (*c* 1.2, $CHCl_3$); IR (neat) ν 3460, 1613; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.82 (s, 0.4H), 5.81 (s, 0.6H), 4.9− 5.05 (m, 1.4H), 4.85 (d, *J* = 11.9, 0.6H), 4.71 (d, *J* = 11.9, 0.6H), 4.63 (d, *J* = 12.0, 0.4H), 4.33 (d, *J* = 3.0, 0.6H), 4.28 (d, *J* = 2.7, 0.4H), 3.98−4.23 (m, 3.4H), 3.95 (d, *J* = 2.4, 0.4H), 3.78 (m, 2.4H), 3.59 (m, 0.4H), 3.43 (br s, 0.6H), 2.21 (m, 1H), 1.69 (m, 1H), 1.64 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.8, 114.1, 113.8, 105.5, 105.3, 94.8, 82.9, 81.4, 76.8, 75.2, 74.9, 73.0, 72.7, 67.9, 67.1, 66.4, 65.0, 52.9, 52.3, 38.3, 38.0, 27.9, 26.8, 26.1, 26.0, 25.7, 25.6; HRMS (ESI) calcd for $C_{16}H_{28}NO_7S$ [M + H] 378.1581, found 378.1576.

***N*-*tert*-Butylsulfamate 31.** To a solution of **22** (200 mg, 0.44 mmol) in EtOH/pyridine (99:1, 10 mL) was added Pd black (25 mg), the suspension was degassed, and an H_2 atmosphere (1 atm) was applied. After being stirred at room temperature for 1.5 h, the suspension was filtered and washed with warm MeOH/pyridine (99:1), and the solution was concentrated and dried on the pump overnight.

The crude material was dissolved in MeCN (10 mL) with Et_3N (180 μL, 133 mg, 1.31 mmol), and the reaction was refluxed overnight (95 °C). When LC−MS showed the disappearance of starting material, the reaction was cooled to room temperature, and Et_3N (310 μL, 223 mg, 2.20 mmol) and then a 1.0 M solution of *tert*-butylsulfinyl chloride in CH_2Cl_2 (480 μL, 0.48 mmol) were added. After 4 h, H_2O (10 mL) was added to the reaction, and the majority of the MeCN was removed in vacuo. The product was extracted with EtOAc (3 × 7 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through silica to remove Et_3N and washed with EtOAc/MeOH (95:5). The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (5 mL), to which *m*-CPBA (75 mg, 0.43 mmol) was added. After being stirred for 1.5 h at room temperature, a saturated solution of Na_2SO_3 (5 mL) was decanted into the reaction, and stirring was continued for a further 30 min. The layers were separated, and the organic layer was washed with a saturated solution of $NaHCO_3$ (2 × 5 mL) and dried (Na_2SO_4). After filtration and concentration, the crude material was purified by flash chromatography (7:3, ethyl acetate/hexanes) to yield **31** (85 mg, 0.23 mmol, 51%) as a colorless solid. R_f = 0.54 (ethyl acetate); mp >175 °C dec; $[\alpha]^{25}_D$ −16.2 (*c* 1.18, $CHCl_3$); IR (neat) ν 3482, 2254, 1314; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.80 (d, *J* = 3.4, 1H), 4.49 (d, *J* = 3.3, 1H), 4.30 (m, 4H), 3.95 (dd, *J* = 13.1, 3.0, 1H), 3.58 (m, 2H), 2.07 (br s, 1H), 1.86 (m, 1H), 1.65 (s, 3H), 1.63 (m, 1H), 1.43 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 113.6, 104.6, 81.6, 73.2, 70.8, 69.3, 68.6, 61.9, 56.3, 40.9, 27.6, 26.0, 25.7, 23.9; HRMS (ESI) calcd for $C_{16}H_{28}NO_7S$ [M + H] 378.1581, found 378.1576.

***O*-Methyl Ether 33.** To a solution of **31** (121 mg, 0.32 mmol) in dry CH_2Cl_2 (6 mL) was added Dess−Martin peridodinane (191 mg, 0.45 mmol) at room temperature. After 1 h, a saturated solution of $Na_2S_2O_3$ (6 mL) was added, and the reaction was stirred for 20 min. The products were extracted with CH_2Cl_2 (3 × 5 mL), and the combined organics were washed with a saturated solution of $NaHCO_3$ (2 × 6 mL), dried (Na_2SO_4), filtered, and concentrated.

The residue was dissolved in CH_2Cl_2/MeOH (1:1, 6 mL) at room temperature, and to the stirred solution was added $NaBH_4$ (19 mg, 0.33 mmol). After 30 min, a saturated solution of NH_4Cl (7 mL) was added, and the reaction was stirred for 10 min. The layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), after which the organics were combined, dried ($MgSO_4$), and filtered, and the solvent was removed.

The solid residue, **32**, was dissolved in anhydrous THF (6 mL), to which NaH (60% dispersion in mineral oil, 28 mg, 0.70 mmol) was added at room temperature. After being stirred for 20 min, MeI (56 μL, 127 mg, 0.90 mmol) was added, and the reaction was stirred overnight. The reaction was then poured into a saturated solution of NH_4Cl (6 mL), and the products were extracted with Et_2O (3 × 10 mL), which was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (1:1, ethyl acetate/hexanes) to yield **33** (122 mg, 0.31 mmol, 95%, average of three runs) as a colorless foam. R_f = 0.29 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +6.5 (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.85 (d, *J* = 3.3, 1H), 4.71 (br s, 1H), 4.20 (m, 2H), 3.89 (br s, 2H), 3.66 (br s, 3H), 3.53 (s, 3H), 1.88 (br s, 1H), 1.73 (m, 1H), 1.62 (s, 3H), 1.42 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 113.4, 105.4, 81.1, 75.1, 72.8, 71.2, 67.8, 61.6, 58.3, 51.5, 42.3, 27.7, 26.0, 25.6, 23.9; HRMS (ESI) calcd for $C_{17}H_{30}NO_7S$ [M + H] 392.1738, found 392.1735.

Diphenyldithioacetal 34. Compound **33** (112 mg, 0.29 mmol) was dissolved into anhydrous CH_2Cl_2 (6 mL) under an Ar atmosphere, then PhSH (300 μL, 318 mg, 2.90 mmol) was added, followed by Amberlyst-15 (280 mg), which was added in two portions in a 24-h interval. The reaction was stirred at room temperature for 60 h. After this time, a saturated solution of $NaHCO_3$ (8 mL) was poured into the reaction vessel and stirred for 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by flash chromatography (65:35, hexanes/ethyl acetate) to yield **34** (129 mg, 0.23 mmol, 80%) as a colorless foam. R_f = 0.41 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +29.5 (*c* 1.29, $CHCl_3$); IR (neat) ν 3451, 2250, 1307; ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm) 7.44 (m, 4H), 7.28 (m, 6H), 5.00 (d, *J* = 1.8, 1H), 4.33 (m, 1H), 4.05 (d, *J* = 1.7, 1H), 3.95 (m, 3H), 3.67 (d, *J* = 2.4, 1H), 3.58 (m, 3H), 3.42 (s, 3H), 2.41 (ddd, *J* = 14.5, 13.1, 8.0, 1H), 2.10 (dd, *J* = 14.6, 4.3, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 134.7, 134.1, 131.2, 130.8, 128.7, 128.6, 127.1, 127.0, 78.5, 75.2, 72.5, 67.3, 64.3, 61.8, 58.7, 57.6, 54.8, 42.7, 26.4, 24.0; HRMS (ESI) calcd for $C_{26}H_{35}NO_6S_3Na$ [M + Na] 576.1519, found 576.1512.

Thioglycoside 35. A solution of **34** (125 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and NBS (62 mg, 0.35 mmol) was added. After being stirred at 0 °C for 30 min, a saturated solution of $Na_2S_2O_3$ (15 mL) was added, and the biphasic mixture was stirred until colorless. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organics were combined, dried (Na_2SO_4), and filtered, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (1:1, hexanes/ethyl acetate) to yield **35** (72 mg, 0.16 mmol, 71%) as a colorless foam. R_f = 0.20 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +170.8 (*c* 0.72, $CHCl_3$); IR (neat) ν 3467, 2433, 1315; ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm) 7.53 (dd, *J* = 8.2, 1.3, 2H), 7.28 (m, 3H), 5.75 (d, *J* = 4.3, 1H), 4.78 (m, 1H), 4.20 (dd, *J* = 12.2, 8.1, 1H), 4.08 (d, *J* = 4.4, 1H), 3.98 (m, 2H), 3.68 (br s, 3H), 3.53 (s, 3H), 2.92 (s, 1H), 1.83 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 135.2, 130.5, 128.7, 128.5, 126.7, 93.3, 76.9, 75.1, 74.4, 72.2, 70.5, 68.1, 58.3, 51.5, 42.1, 27.6, 23.9; HRMS (ESI) calcd for $C_{20}H_{30}NO_6S_2$ [M + H] 444.1509, found 444.1500.

***O*-Pivaloyl Ester 36.** To a solution of **35** (72 mg, 0.16 mmol) and DMAP (90 mg, 0.74 mmol) in anhydrous CH_2Cl_2/pyridine (2:1, 2 mL) was added PivCl (300 μL, 294 mg, 2.44 mmol) under an Ar atmosphere at room temperature. After 5 h, the solvents were removed in vacuo (without heating), and the residue was dissolved in CH_2Cl_2 (6 mL), which was washed sequentially with 0.1 M HCl (2 × 3 mL) and H_2O (3 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (4:1, hexanes/ethyl acetate) to yield **36** (70 mg, 0.13 mmol, 81%) as a colorless foam and recrystallized by slow evaporation of $CHCl_3$. R_f = 0.68 (1:1, hexanes/ethyl acetate); $[\alpha]^{25}_D$ +118.2 (*c* 0.45, $CHCl_3$); IR (neat) ν 2255, 1742, 1481, 1317; ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm) 7.54 (m, 2H), 7.30 (m, 3H), 5.84 (d, *J* = 4.9, 1H), 5.24 (d, *J* = 4.3, 1H), 4.76 (br s, 1H), 4.09 (m, 1H), 3.95 (m, 2H), 3.65 (m, 3H), 3.54 (s, 3H), 1.83 (m, 2H), 1.43 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.3, 134.6,

130.8, 128.5, 127.0, 91.1, 75.2, 74.0, 72.0, 67.8, 65.5, 61.6, 58.2, 51.3, 42.1, 38.9, 26.8, 23.9, 14.9; LRMS (ESI) 528 (85%) $[M + H]^+$.

***N*-Nucleoside 37.** A solution of **36** (24 mg, 0.046 mmol) in dry CH_2Cl_2 (0.7 mL) was added to a solution of bis-silylated *N*-acetylcytosine[10b] (0.32 mmol of crude material) in dry CH_2Cl_2 (0.5 mL) under an Ar atmosphere at room temperature. NIS (41 mg, dried by lypophilization overnight) was added, followed immediately by triflic acid (5 μL, 8 mg, 0.055 mmol). Triflic acid (3 μL, 5 mg, 0.034 mmol) was added in two portions at 24-h intervals, and after 4 days the reaction was quenched with a saturated solution of $Na_2S_2O_3$ (3 mL) and a saturated solution of $NaHCO_3$ (2 mL) and stirred for 30 min. The products were extracted with EtOAc (4 × 6 mL), dried ($MgSO_4$), filtered, and concentrated. Flash chromatography of the crude material (4:1 to 1:4, hexanes/ethyl acetate) gave recovered starting material (10 mg, 0.019 mmol) and **37** (8 mg, 0.014 mmol, 52% based on recovered starting material) as a colorless solid. The crude product was recrystallized from EtOAc/hexanes. $R_f = 0.32$ (ethyl acetate); mp >210 °C dec; $[\alpha]^{25}_D$ +91.4 (*c* 0.35, EtOAc); ^{1}H NMR 400 MHz, $CDCl_3$) δ (ppm) 9.16 (br s, 1H), 8.53 (br s, 1H), 7.52 (d, $J = 7.4$, 1H), 5.86 (s, 1H), 4.90 (br s, 1H), 4.87 (s, 1H), 4.16 (dd, $J = 12.1$, 7.6, 1H), 4.05 (m, 1H), 3.82 (m, 3H), 3.60 (m, 1H), 3.48 (s, 3H), 2.25 (s, 3H), 1.83 (m, 1H), 1.52 (m, 1H),1.46 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 177.4, 172.5, 164.0, 156.9, 144.9, 97.2, 93.4, 78.5, 75.0, 74.2, 71.6, 68.3, 67.8, 62.5, 58.4, 53.3, 39.2, 28.9, 27.0, 25.9, 24.1; LRMS (ESI) 571 (100%) $[M + H]^+$.

Tricyclic *N*-Malayamycin A (7). The sulfonamide **37** (15 mg, 0.026 mmol) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) under an Ar atmosphere. Anisole (43 μL, 43 mg, 0.39 mmol) and then triflic acid (8 μL, 14 mg, 0.10 mmol) were added, and the reaction was stirred at room temperature until LC−MS showed the disappearance of starting material. Trichloroacetyl isocyanate (13 μL, 20 mg, 1.04 mmol) and then anhydrous pyridine (7.5 μL, 7 mg, 0.093 mmol) were added, and the reaction was stirred at room temperature until LC−MS showed full conversion of the amine to the protected urea. At this point, the solvents were removed in vacuo (without heating), and the solid residue was stirred in 40 wt % $MeNH_2$ in H_2O/MeOH (3:1, 0.9 mL). After 24 h, 40 wt % $MeNH_2$ in H_2O solution (0.10 mL) was added, and the reaction was stirred for a further 48 h. The reaction was lypophilized, and the crude material was purified by preparative TLC (3:2, $CHCl_3$/MeOH) to yield **7** (5 mg, 0.014 mmol, 52%) as a colorless solid. $R_f = 0.22$ (75:25, $CHCl_3$/MeOH); $[\alpha]^{25}_D$ +25.8 (*c* 0.06, MeOH); ^{1}H NMR (400 MHz, D_2O) δ (ppm) 7.53 (d, $J = 7.5$, 1H), 5.88 (d, $J = 7.6$, 1H), 5.48 (s, 1H), 5.28 (br s, 1H), 4.07 (dd, $J = 10.2$, 5.6, 1H), 3.92 (d, $J = 2.7$, 1H), 3.79 (m, 3H), 3.55 (br s, 1H), 3.39 (br s, 1H), 3.32 (s, 3H), 1.79 (dd, $J = 16.2$, 6.1, 1H), 1.34 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 166.3, 161.0, 156.7, 139.4, 95.3, 94.4, 78.0, 75.3, 73.5, 71.1, 66.9, 56.6, 39.8, 36.3, 27.3; HRMS (ESI) calcd for $C_{15}H_{22}N_5O_6$ $[M + H]$ 368.1565, found 368.1573.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **9**, **11**−**19**, **21**, **22**, **24**, **26**, **28**, **29**, **31**, **33**−**37**, and **7** and X-ray crystallographic data for compounds **5**, **36**, and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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