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Total synthesis of malayamycin A and analogues

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Abstract—The total synthesis of the bicyclic *C*-nucleoside malayamycin A is described starting with D-ribonolactone. A new method was developed to obtain preparatively important quantities of β-pseudouridine, which was used as an intermediate. The synthesis of a carba *N*-nucleoside analogue of malayamycin A is also described.

1. Introduction

Nucleosides are traditionally associated with the fascinating chemistry and biology of DNA and RNA.[1] Indeed, the intricate three-dimensional arrays of *N*-nucleotidic sequences in DNA constitute the basis of the alphabet of life that is responsible for all the vital processes.[2] Nature has also produced a group of *N*-nucleosides with potent chemotherapeutic activities, which have been the source of extensive chemical modification.[3] In this regard, several antitumor, antiviral, and antibiotic nucleosides are known. In contrast, *C*-nucleosides[4] constitute a smaller subgroup of carbon-linked anomeric heterocycles that nature has also provided with much less exploited potential for biological activities.[5] Pseudouridine, a constituent of various RNAs,[6,7] was the first naturally occurring 5-uracilyl β-D-*C*-ribofuranoside.[8] Its biosynthesis continues to elicit proposals for fascinating pathways.[9] Curiously, pseudouridine isolated from beer has shown antimutagenic properties against *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine.[10]

A unique example of bicyclic *C*-nucleoside having antifungal and antibiotic properties was reported by Sakata and co-workers in 1977.[11] Degradative and spectroscopic work[12] revealed the structures of ezomycin B_2 and ezomycin C_2 as constrained pseudouridine-type *C*-nucleoside disaccharides (Fig. 1). The perhydrofuropyran motif was also revealed in the structures of *N*-nucleosides such as ezomycin A1,[13] miharamycin,[14] and octosyl acid A.[15] Quantamycin[16] is a structure-based bicyclic synthetic hybrid of lincomycin

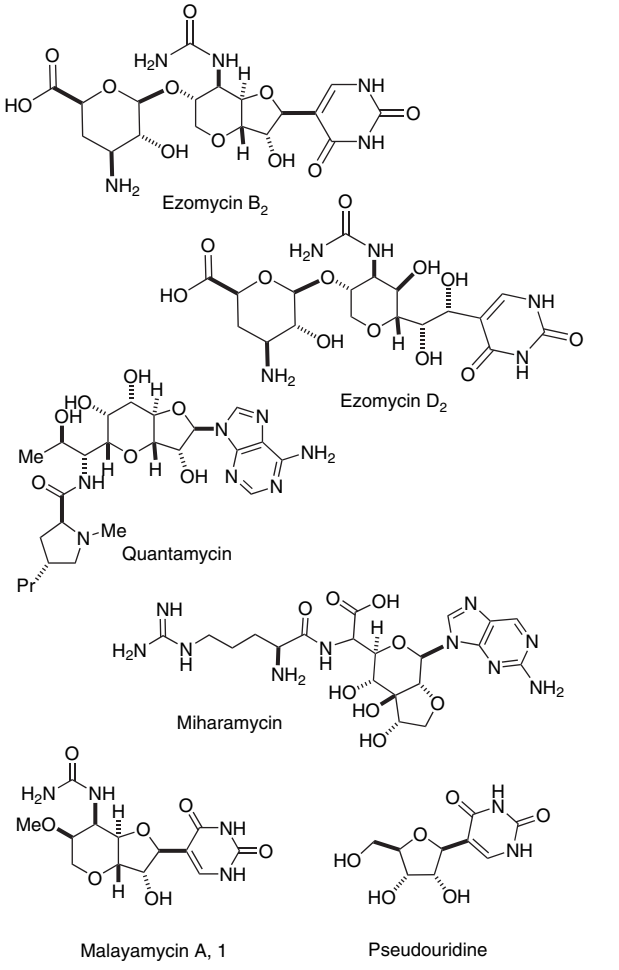

Figure 1. Structures of perhydrofuropyran *C*-nucleosides and β-pseudouridine.

Keywords: *C*-Nucleoside; Thioglycoside; Ring closure metathesis; Perhydrofuropyran.
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and a natural 'starter' nucleotide involved in the process of protein biosynthesis. The field of naturally occurring *C*-nucleosides lay dormant for nearly 25 years before the discovery of a new member by a group at the Syngenta Crop Protection Laboratories in Jeallott's Hill, UK.[17] Malayamycin A (**1**) was isolated from the soil organism *Streptomyces malaysiensis*, and its structure was proposed by detailed NMR studies and by degradation (Fig. 1). As in the case of ezomycin B_2 and pseudouridine, malayamycin A was found to be unstable under strongly acidic and basic conditions. In contrast to the ezomycins that exhibit antifungal and antibiotic activities,[11] malayamycin A is a potent fungicide.[17] The perhydrofuropyran motif in **1**, which is also common to the ezomycins and octosyl acid A, has different functionality and differs by the absence of a carboxylic acid and a disaccharide unit. Recently, the proposed structure and absolute stereochemistry of **1**[17] were confirmed by a stereocontrolled total synthesis.[18] Herein we give details of various aspects of this synthesis, as well as the preparation of semi-synthetic analogues intended to probe the importance of some functional groups. The total synthesis of *N*-malayamycin A and related purine and pyrimidine nucleosides was recently reported.[19]

2. The synthesis plan

As previously remarked,[18] the synthesis plan for **1** has to consider several challenges that include as follows: (a) the stereocontrolled formation of the anomeric *C*-5-uracilyl bond, (b) the construction of a trans-fused bicylic perhydrofuropyran ring, and (c) incorporation of usable functionality to achieve the desired stereochemical arrangement.

The disconnection shown in Figure 2 capitalizes on the formation of an enantiopure unsaturated *C*-pyrimidinyl perhydrofuropyran via a ring closure metathesis of a pseudouridine precursor that would be prepared from D-ribonolactone **2**. Although the first phase of the synthesis had precedents (see below), a main challenge was the stereo- and regio-

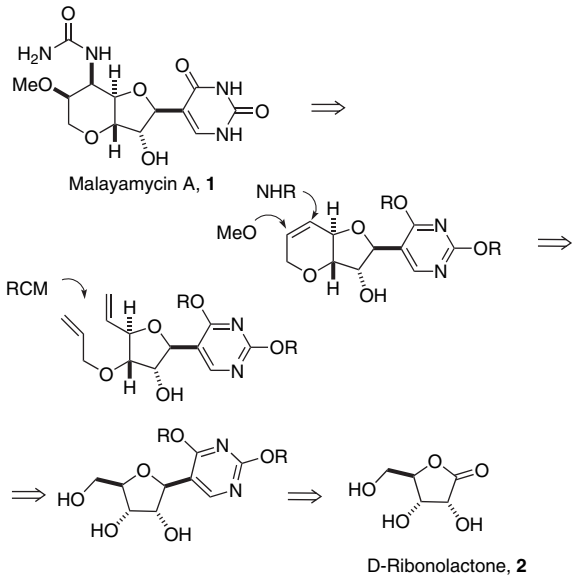


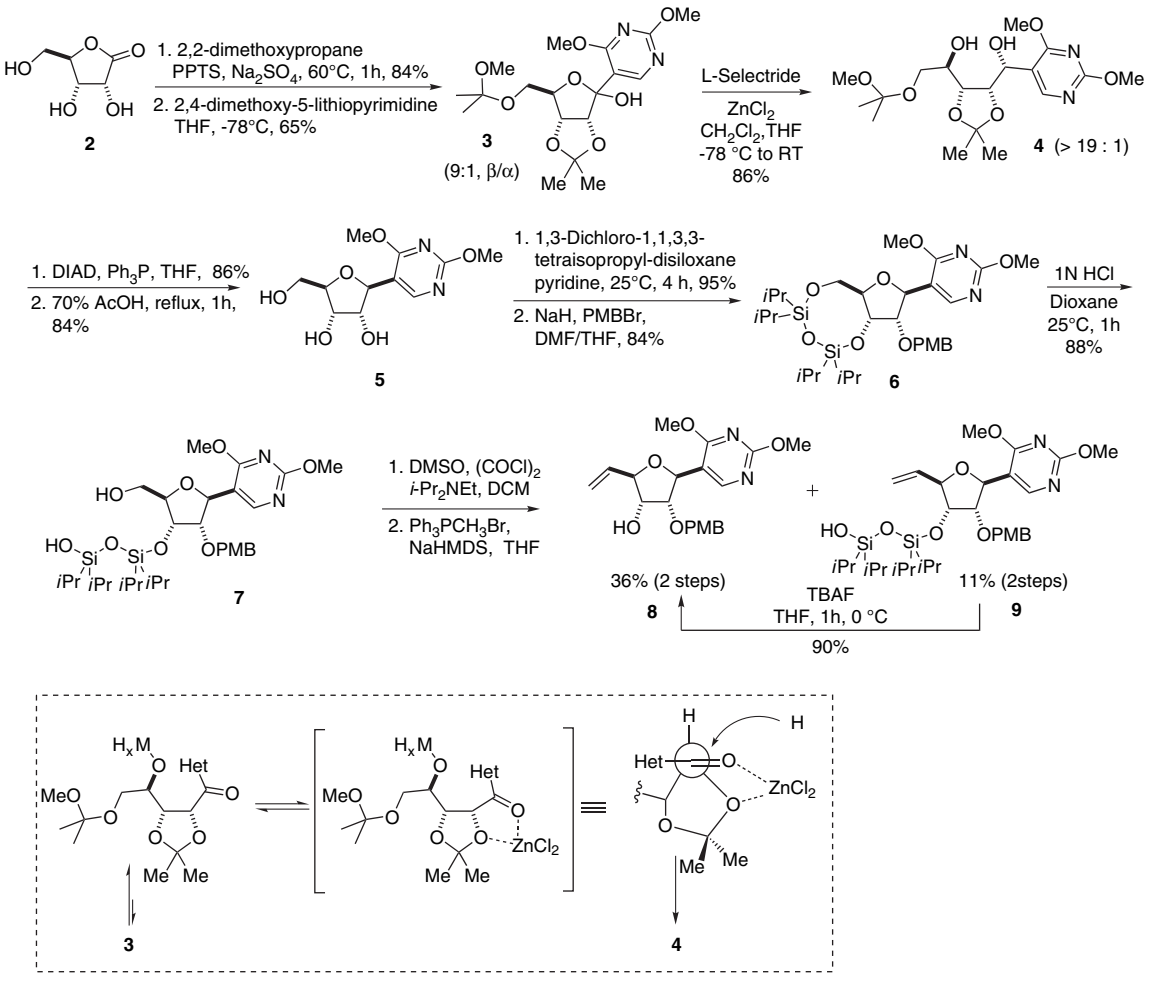
Figure 2. Disconnective analysis of malayamycin A.

controlled introduction of a vicinally disposed *cis*-amino alcohol. In considering pseudouridine as a starting material, we would already resolve the *C*-nucleoside issue. The prohibitive cost of pseudouridine was an initial deterrent that was soon dismissed with the knowledge that a number of total syntheses have been reported over the years.[20] The most recent of these[20a] offered a preparatively viable protocol, although a mixture of anomers was obtained. The need to start with a relatively large amount of **2** instigated the search for a highly stereocontrolled synthesis of **1** and its α-anomer from a common precursor. In our synthetic approach to a new synthesis of pseudouridine,[21] we used a 5-(2,4-dimethoxypyrimidinyl) β-D-ribofuranose as an intermediate.[22]

3. Results and discussion

The readily available D-ribonolactone **2** was treated with 2,2-dimethoxypropane in refluxing CH_2Cl_2 in the presence of PPTS and excess Na_2SO_4 to give the corresponding mixed acetal, which was surprisingly stable to chromatographic purification. In the absence of Na_2SO_4 the bis-acetal lactone was obtained in 40% yield only.[23] Addition of 5-lithio 2,4-dimethoxypyridine[20b] to the protected lactone at −78 °C led to a 75% yield of a mixture of anomers **3** in an α/β ratio of 1:9. Treatment with L-Selectride in the presence of $ZnCl_2$ in a mixture of CH_2Cl_2/THF led to the alcohol **4** as a major isomer in 86% yield on a 1–5 mmol scale. However, on a larger scale (22 mmol), the yield was 54%. Reduction with $NaBH_4$ in MeOH gave a 1:1 mixture of diastereomers. The quasi-exclusive stereocontrolled reduction to the D-*allo* alcohol **4** can be explained by the initial coordination of an intermediate alkoxy ketone followed by *Si*-face-selective hydride attack from the bulky reagent (Scheme 1).[21] Interestingly, the epimeric D-*altro* alcohol, a precursor to α-pseudouridine was the major product in the absence of $ZnCl_2$.[21] Similar observations have been reported in a related case.[24] Treatment of **4** under Mitsunobu conditions led, via a site-selective intramolecular cycloetherification, to the corresponding 1,4-anhydro-D-ribitol *C*-nucleoside.[25] Removal of the acetonide in the presence of 70% acetic acid gave 5-(2,4-dimethoxypyrimidinyl) β-D-ribofuranose **5** in excellent overall yield. The original pseudouridine synthesis involved the corresponding 2,4-dibutoxypyridine as intermediate in order to facilitate the final deprotection step without anomerization.[21] In the case of **1**, however, the more robust dimethoxypyrimidine analogue was used.

With **5** in hand, we devised a protecting group selection protocol that would allow preferential manipulation of the triol system. Thus, the 3′,5′-diol could be protected as the disiloxane acetal, and the 2′-hydroxyl group was treated with PMBBr to give **6** in an 86% overall yield for the two steps. Quite unexpectedly, the disiloxane was selectively cleaved with 1 N HCl in dioxane, exposing the primary alcohol in **7**. Moreover, the primary alcohol could be oxidized to the aldehyde under Swern conditions and the latter converted to the 5′-*C*-vinyl intermediate **8** and its monosilylated derivative **9**, which could be transformed to **8** in the presence of TBAF as expected. Thus, the disiloxane served a dual purpose as a protective group in three operationally different reactions. Allylation of **8** under standard conditions afforded



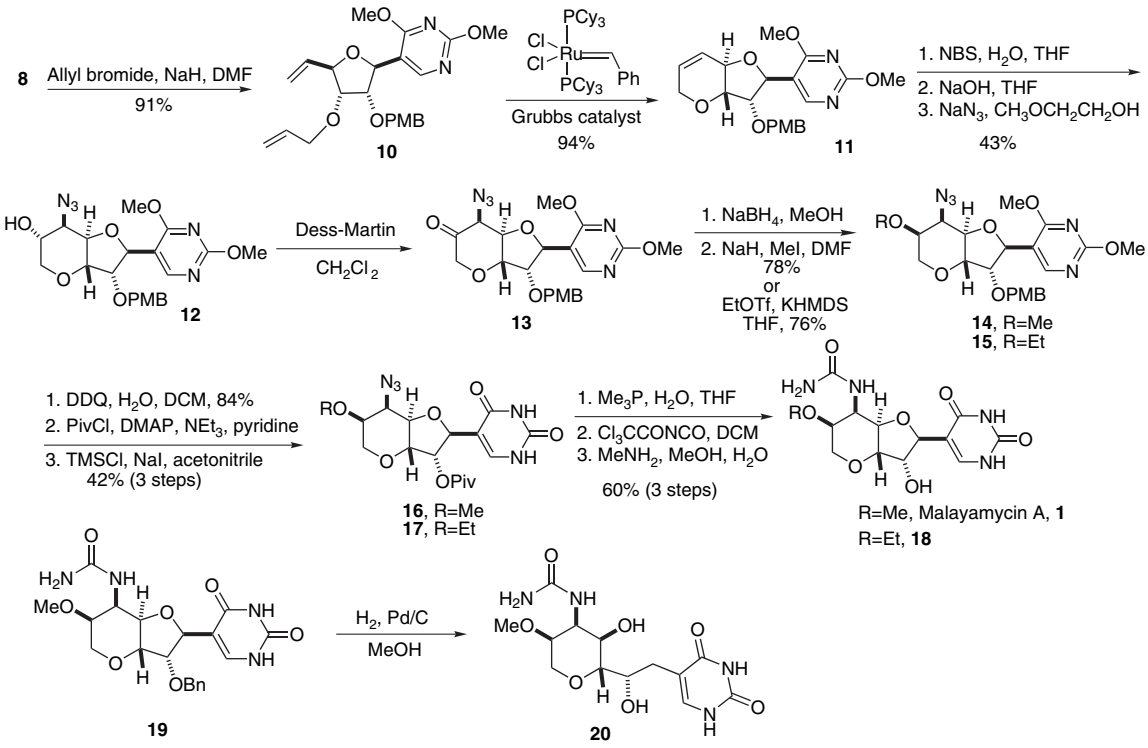
Scheme 1.

10, which was subjected to the Grubbs ring closure metathesis reaction (Scheme 2).[26] In the presence of 5 mol % first generation catalyst[27] and a concentration of 0.05 M, smooth cyclization took place to afford an 89% yield of crystalline product **11**. The reaction could be scaled up to 2 g without appreciable loss in efficiency.[28] It is of interest that in an analogous RCM cyclization of 1,2-*O*-isopropylidene-3-*O*-allyl-5-*C*-vinyl-α-D-ribofuranose to afford a tricyclic intermediate, there was a significant improvement in yield when the concentration was 0.01 M (92%)[19] compared to 0.02 M (63%).[28]

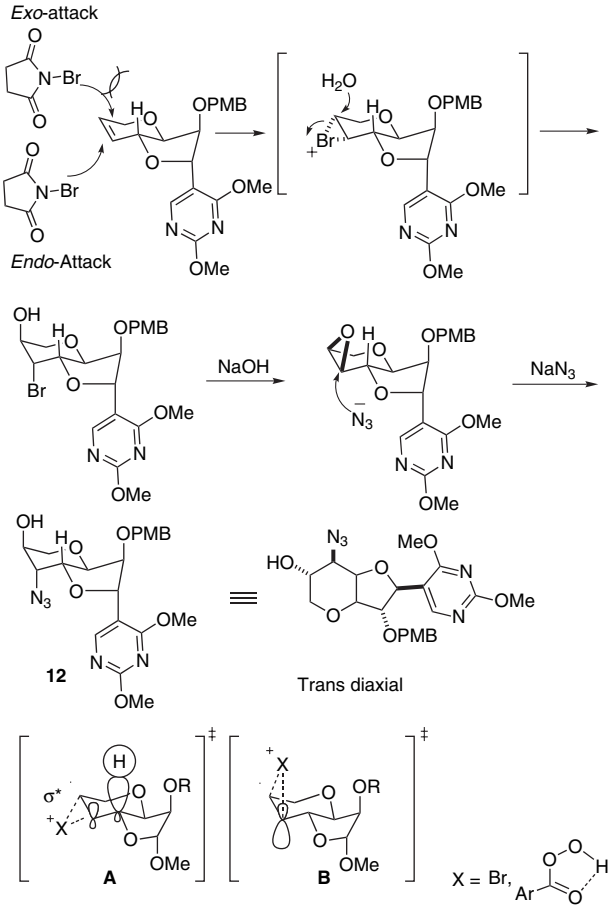
Our initial efforts to introduce an amino function relied on an epoxidation of **11** with mCPBA followed by ring opening with sodium azide. However, this protocol led to a regioisomeric azide.[18] We adopted a different route involving initial treatment with NBS in aqueous THF,[29] which led to the corresponding diaxial bromohydrin via the epibromonium ion (Scheme 3). Base-catalyzed epoxide formation followed by treatment with sodium azide in refluxing methoxyethanol afforded the trans diaxial azido alcohol **12** as a major product (5:1 ratio). The preference for the *endo*-attack of NBS is not clear, although there are precedents for related reactions.[30] It is possible that the *endo*-bromohydrin may benefit from a favorable electron-donation from the C–H σ bond[31] with the developing antibonding orbital in the transition state model A, compared to B. The same rationale can be advanced for the corresponding *endo*-epoxide when mCPBA is used even in the presence of steric bulk.

Oxidation of **12** with the Dess–Martin reagent[32] afforded **13**, without evidence of partial racemization of the pseudoaxial azide group (Scheme 2). Reduction with $NaBH_4$ in MeOH followed by methylation gave **14** in excellent overall yield. In order to probe the spatial importance of the ether group, we also prepared the ethyl ether **15** by treatment of the alcohol with ethyl triflate and KHMDS.

In an earlier version of the synthesis we had reached intermediate **19** having a benzyl ether instead of PMB (Scheme 2). However, when we attempted to remove the benzyl ether in the penultimate step, we were dismayed to find that a second hydrogenolysis had taken place resulting in ring opening of the ribosyl moiety to give **20**. This led us to use the PMB group instead. Model studies showed that the PMB group would not be stable to TMSCl and NaI required to generate the pyrimidinone from the dimethoxy precursor **14**. Thus, a protective group adjustment was needed. Cleavage of the PMB with DDQ proceeded smoothly and the resulting alcohol was esterified as a pivalate, which proved to be stable to the demethoxylation in the presence of TMSCl and NaI (Scheme 2). The methyl and ethyl ethers **16** and **17** were thus obtained in good overall yield. Reduction of the azide under Staudinger conditions,[33] followed by formation of the



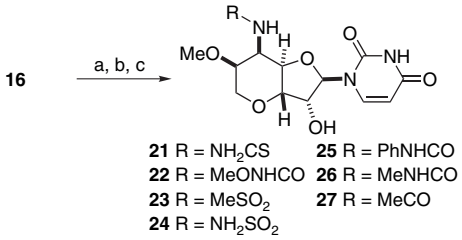
Scheme 2.



Scheme 3.

trichloroacetyl urea,[34] and deprotection with methylamine[35] afforded malayamycin A **1** and its 6-*O*-ethyl analogue **18**. Synthetic **1** was found to be identical to the natural sample in all respects including fungicidal activity. The ethyl ether analogue, however, was considerably less effective.

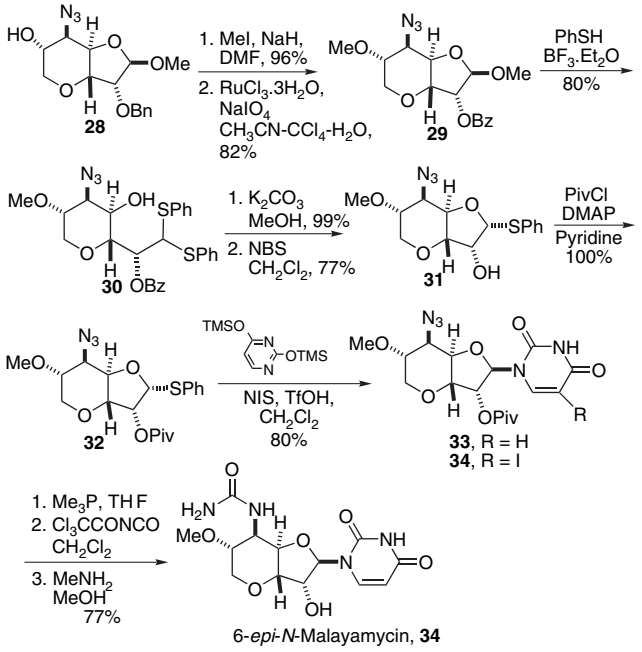
With the azide intermediate **16** in hand, we deemed it appropriate to introduce diversity at the original urea site, hoping to gain some information regarding the nature of the functional groups and activity. Thus, we prepared a series of analogues **21**–**27** ranging from ureas to sulfonamides, to carbamates, and to a simple acetamide (Scheme 4). Unfortunately, these and related modifications resulted in loss of fungicidal activity.



Scheme 4. Reagents and conditions: (a) Me_3P, THF–H_2O; (b) BzNCS, CH_2Cl_2 for **21**; carbonyl diimidazole, CH_2Cl_2, then $MeONH_2 \cdot HCl$, Et_3N, CH_2Cl_2 for **22**; $MeSO_2Cl$, pyridine for **23**; FmocNHSO$_2$Cl, pyridine, then piperidine, DMF for **24**; PhNCO, CH_2Cl_2 for **25**; MeNCO, CH_2Cl_2 for **26**; 40% v/v $MeNH_2$, MeOH for **27**; (c) 40% v/v $MeNH_2$, MeOH for **21**, 56%; **22**, 45%; **23**, 46%; **24**, 22%; **25**, 27%; **26**, 46%; Ac_2O, $NaHCO_3$, MeOH for **27**, 30%.

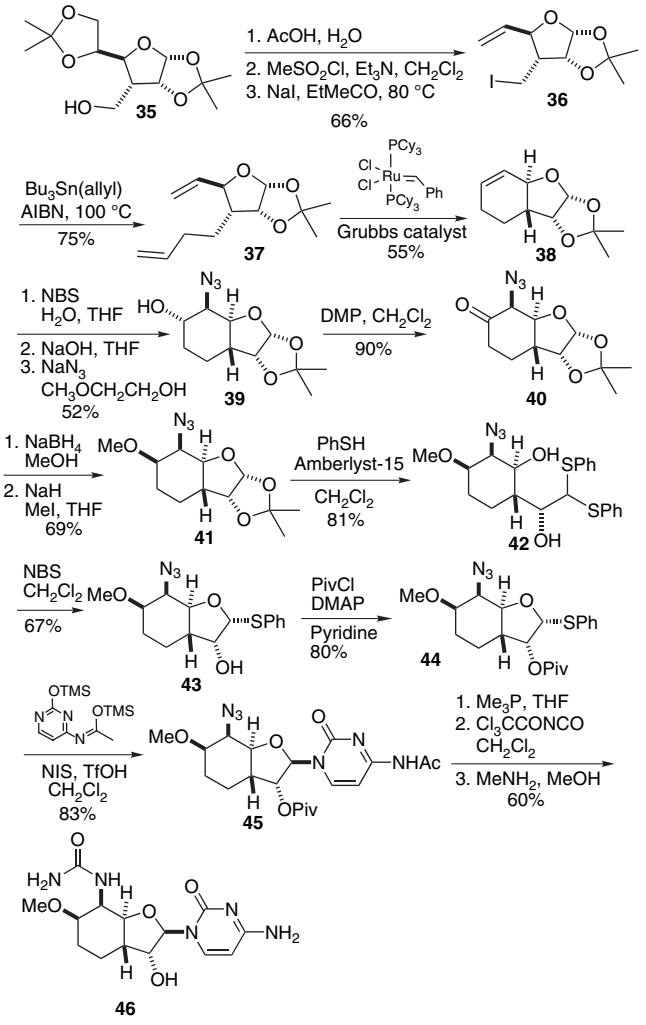
To further establish an SAR, we developed a strategy to do functional and structural modifications on *N*-malayamycin, which could be easily obtained from D-ribose or D-glucose.[19]

The known intermediate **28**[19] was methylated and the product was subjected to an oxidative transformation of the benzyl ether to the benzoate **29** in excellent overall yield[36] (Scheme 5). Treatment with benzenethiol in the presence of BF_3-etherate gave the diphenyl dithioacetal **30**, which was converted to the phenyl thioglycoside **31** as previously described.[19,37] Protection as the pivalate ester **32** and *N*-glycoside formation[19,34,38] via neighboring group participation, gave the 1′,2′-*trans*-bicyclic nucleoside **33** in excellent overall yield accompanied by a small amount of the 5-iodonucleoside **34**. Finally, Staudinger reduction of **33** and manipulation of the amine as described above gave 6′-*epi*-*N*-malayamycin **34**, which had diminished fungicidal activity compared to **1**. Thus, epimerization at C_6 was not tolerated.



Scheme 5.

To probe the tolerance of *N*-malayamycin for deep-seated structural modifications, we embarked on the preparation of the *N*-cytosinyl carba analogue **46** in which the tetrahydro-2*H*-pyran ring was replaced by a cyclohexane (Scheme 6). The synthesis started from the known and easily accessible **35**.[39] Regioselective removal of the 5′,6′-isopropylidene group followed by per-mesylation of the crude triol intermediate and treatment with NaI in ethylmethyl ketone at 80 °C triggered the concomitant formation of a terminal olefin and a primary iodide in 66% yield. Allylation of **36**, under free radical conditions was best performed in neat allyltributyltin in the presence of AIBN, to give **37** in 75% yield. In the presence of 5 mol % of first generation Grubbs catalyst[27] and a concentration of 0.05 M, cyclization took place to afford the volatile tricyclic olefin **38** in 55% yield. Application of the bromohydrin-epoxidation and azide opening protocol, followed by inversion of the C_6–OH stereocenter and O-methylation, led to **41** in 32% yield for six steps. Cleavage of the acetal with concomitant dithioacetal formation in **41** was most efficiently done with benzenethiol in the presence of Amberlyst-15 suspended in CH_2Cl_2 to give the corresponding product **42** in 81% yield. Thioglycoside formation in the presence of NBS followed by pivaloylation proceeded in good overall yield to deliver **44**. N-Glycosidation and subsequent functional group manipulations proceeded uneventfully to give the final *N*-cytosinyl nucleoside **46**. Surprisingly, the seemingly benign replacement of a tetrahydro-2*H*-pyranyl by a cyclohexyl moiety resulted in a complete loss of fungicidal activity.



Scheme 6.

4. Experimental

4.1. General procedure

Solvents were distilled under positive pressure of dry argon before using and dried by standard methods: toluene, THF, and ether from sodium/benzophenone ketyl; CH_2Cl_2 from calcium hydride. All commercially available reagents were used without further purification. All non-aqueous reactions were performed under argon atmosphere with oven-dried glassware. NMR (^1H, ^{13}C, COSY, NOESY) spectra were recorded on AV-400 and ARX-400 spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. High-resolution mass spectra were recorded using fast atom bombardment (FAB), (TOF CI+). Melting points are uncorrected. Optical rotations were recorded in a 1 dm cell

at ambient temperature with a sodium lamp (wavelength of 589 nm). Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by ultraviolet light and/or by staining with ceric ammonium molybdate or potassium permanganate. Chromatographic purifications were performed on a column with 230–400 mesh silica gel with the indicated solvent system.

4.1.1. (3a*R*, 4*R*/*S*, 6*R*, 6a*R*)-4-(2′,4′-Dimethoxypyrimidin-5′-yl)-6-(1″-methoxy-1″-methyl-ethoxymethyl)-2,2-dimethyltetrahydro-furo[3,4-*d*][1,3]dioxol-4-ol (3). To a mixture of (+)-D-ribonolactone **2** (6.7 g, 45 mmol) and pyridinium *p*-toluenesulfonate (0.84 g, 3.3 mmol) in 2,2-dimethoxypropane (167 mL) in 500 mL round-bottomed flask was added anhydrous Na_2SO_4 (67 g, 0.47 mol) at room temperature under argon atmosphere. The mixture was stirred at 60 °C with a condenser for 1 h, then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel column to afford the protected lactone (10 g, 38.1 mmol, 84%) as a colorless solid; mp 92–94 °C; $[\alpha]_D$ −45.9 (*c* 0.44, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.31 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 3.14 (s, 3H), 3.52 (d, 1H, *J*=9.0 Hz), 3.75 (d, 1H, *J*=8.44 Hz), 4.7 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 24.1, 25.0, 26.0, 28.0, 62.2, 78.5, 80.4, 83.9, 103.7, 114.8, 172.2, 173.4; MS (ESI): 261.5 [M+H].

To a solution of 5-bromo-2,4-dimethoxy-pyrimidine (5.7 g, 26 mmol) in 200 mL dry THF was added *t*-butyllithium (1.7 M in hexanes) (31.8 mL, 54 mmol) at −78 °C under argon atmosphere. After stirring for 30 min, a solution of protected lactone (5.2 g, 20 mmol) in 100 mL dry THF was added to this mixture via cannula. The mixture was stirred for 1.5 h at −78 °C, and then quenched by addition of brine (100 mL). The mixture was warmed to room temperature and extracted with EtOAc (200 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 4:1) afforded **3** as a white solid (5.2 g, 13 mmol, 65%); mp 39–41 °C; $[\alpha]_D$ −56.9 (*c* 0.55, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (m, 6H), 1.43 (s, 4H), 3.30 (s, 3H), 3.62 (d, 2H, *J*=6.8 Hz), 3.91 (s, 3H), 4.1 (s, 3H), 4.29 (m, 2H), 4.35 (t, 1H, *J*=5.83 Hz), 4.9 (m, 2H), 8.44 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 24.5, 25.1, 26.9, 54.8, 55.8, 64.3, 85.0, 87.3, 88.4, 102.0, 107.3, 114.6, 116.9, 158.2, 166.8, 171.2; MS (ESI): 401.1 [M+H].

4.1.2. (1*R*, 4″*R*, 5″*S*)-2-(2′-Methoxypropan-2′-yloxy)-1-(5″-[(*R*)-hydroxy(2‴,4‴-dimethoxypyrimidin-5‴-yl-methyl)-2″,2″-dimethyl-1″,3″-dioxolan-4″-yl] ethanol (4). To a solution of **3** (22 g, 55 mmol) in 2 L CH_2Cl_2 was added slowly a solution of $ZnCl_2$ (1 M in Et_2O) (74.8 mL, 74.8 mmol) at −78 °C under argon atmosphere. After stirring for 30 min, L-Selectride (1 M in THF) (190 mL, 0.19 mol) was added slowly to this solution. The mixture was warmed slowly to room temperature and stirred overnight. The reaction was quenched by adding MeOH (50 mL), and then H_2O (25 mL), 30% H_2O_2 (25 mL), 6 M NaOH (25 mL). The mixture was extracted with CH_2Cl_2 (400 mL×3). The combined organic layer was washed with satd $NaHCO_3$ sodium bicarbonate and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 2:1) afforded **4** as a crystalline solid (12 g, 30 mmol, 54%); mp 35–37 °C; $[\alpha]_D$ −115.6 (*c* 1, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 1.31 (s, 3H), 1.40 (s, 6H), 1.60 (s, 3H), 3.29 (s, 3H), 3.48 (m, 1H), 3.52 (m, 1H), 4.11 (s, 6H), 4.35 (m, 3H), 5.40 (s, 1H), 8.41 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 24.8 (2), 25.5, 26.8 (2), 54.7, 55.3, 64.4, 65.5, 70.1, 77.9, 79.4, 101.4, 109.8, 117.1, 158.5, 165.8, 169.1; MS (ESI): 403.1 [M+H].

4.1.3. (2*S*, 3*S*, 4*R*, 5*R*)-2-(2,4-Dimethoxy-pyrimidin-5-yl)-5-hydroxymethyl-tetrahydro-furan-3,4-diol (5). To a solution of **4** (12 g, 30 mmol) in THF (1.2 L) was added Ph_3P (15.6 g, 59.4 mmol) at 0 °C under argon atmosphere. Diisopropyl azadicarbonate (12 mL, 59.4 mmol) was added, and the mixture was stirred overnight and concentrated. The residue was purified by flash chromatography on silica gel column (2:1 hexanes/EtOAc) to afford the bis-acetal as a colorless oil (10 g, 26.4 mmol, 86%). R_f=0.27 (1:1 hexanes/EtOAc); $[\alpha]_D$ −3.4 (*c* 0.9, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 1.34 (s, 9H), 1.60 (s, 3H), 3.19 (s, 3H), 3.54 (dd, 1H, *J*=15.0, *J*=3.9 Hz), 3.63 (dd, 1H, *J*=14.3, *J*=3.5 Hz), 3.94 (s, 3H), 4.07 (s, 3H), 4.18 (m, 1H), 4.72 (s, 2H), 5.01 (s, 1H), 8.32 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 24.3 (2), 26.0, 28.1 (2), 54.1, 55.1, 63.1, 82.2, 83.4, 85.0, 87.1, 102.3, 114.9, 115.0, 158.5, 167.3, 170.1; MS (ESI): 386.1 [M+H].

The bis-acetal was then treated with 70% AcOH (300 mL) at reflux for 2 h. The mixture was then brought to room temperature and concentrated to give a yellow oil. The oil was diluted in water (150 mL) and evaporated (repeated two times). It was then diluted in MeOH (150 mL) and evaporated (repeated two times). The residue was purified by flash chromatography on silica gel column (10:1 EtOAc/MeOH) to afford the product **5** as a white solid (6.0 g, 22 mmol, 84%); mp 128–130 °C; $[\alpha]_D$ +10.0 (*c* 0.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 3.68 (dd, 1H, *J*=7.42, *J*=4.62 Hz), 3.81 (dd, 1H, *J*=8.88, *J*=3.2 Hz), 3.90 (m, 1H), 3.95 (s, 4H), 4.05 (s, 4H), 4.80 (s, 1H), 8.39 (s, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 54.6, 55.3, 62.9, 75.1, 76.9, 80.0, 85.0, 114.9, 157.8, 166.3, 170.2; MS (ESI): 273.3 [M+H].

4.1.4. (2*S*, 3*S*, 4*R*, 5*R*)-2,4-Dimethoxy-5-[5,5,7,7-tetraisopropyl-3-(4-methoxy-benzyloxy)-tetrahydro-1,4,6,8-tetraoxa-5,7-disila-cyclopentacycloocten-2-yl]-pyrimidine (6). Compound **5** (1.10 g, 4.04 mmol) was dissolved in dry pyridine (42 mL) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.42 mL, 4.44 mmol) was added dropwise at room temperature in a 100 mL round-bottomed flask. The colorless mixture was stirred at room temperature for 4 h under argon and then concentrated (*T*<45 °C). The white solid was diluted with Et_2O (50 mL), then with water (50 mL), the two phases were separated, the aqueous phase was extracted with Et_2O (3×50 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the colorless oil was purified by flash chromatography (eluant, 3:1 hexanes/EtOAc) to afford the mono-alcohol as a colorless oil (1.97 g, 3.83 mmol, 95%). R_f=0.21 (3:1 hexanes/EtOAc), $[\alpha]_D$ −1.31 (*c* 1.45, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (m, 28H), 2.91 (s, 1H), 3.95 (s, 3H), 4.0 (s, 3H),

4.12 (m, 4H), 4.35 (m, 1H), 4.95 (s, 1H), 8.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 12.6, 12.9, 13.2, 16.8, 16.9, 17.1, 53.6, 53.9, 54.6, 54.7, 60.2, 61.4, 71.1, 75.2, 75.3, 79.9, 79.9, 80.9, 113.2, 156.5, 164.9, 168.0; MS (ESI): 515.7 [M+H].

In a 25 mL flame-dried round-bottomed flask, NaH (135 mg, 3.4 mmol, 60% in mineral oil) was washed with dry hexane (15 mL) under argon atmosphere. After removal of hexane, dry DMF (1.5 mL) was added to NaH and the white heterogeneous mixture was cooled to 0 °C. The mono-alcohol (1.25 g, 2.43 mmol) was dissolved in dry THF (5 mL), added to NaH in DMF at 0 °C, and the mixture was stirred for 10 min at 25 °C after which PMBBr (3.2 mL, 4.13 mmol, 1.3 M in toluene) was added dropwise. The white heterogeneous mixture was stirred for 15 h and then quenched with water (5 mL), and then diluted with Et_2O (15 mL). The two phases were separated, the aqueous phase was extracted with Et_2O (3×10 mL), and the combined organic phase was washed with brine, dried with Na_2SO_4, and concentrated to give an oil. Purification by flash chromatography (eluant, 3:1 hexanes/EtOAc) gave **6** as a colorless oil (1.3 g, 2.05 mmol, 84%). R_f=0.34 (3:1 hexanes/EtOAc). $[\alpha]_D$ −5.9 (*c* 5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (m, 28H), 3.80 (s, 3H), 3.96 (s, 6H), 4.00 (dd, 1H, *J*=17.0, *J*=3.1 Hz), 4.10 (m, 2H), 4.20 (d, 1H, *J*=4.47 Hz), 4.29 (m, 1H), 4.66 (d, 1H, *J*=11.9 Hz), 4.85 (d, 1H, *J*=11.9 Hz), 5.04 (s, 1H), 6.85 (d, 2H, *J*=6.77 Hz), 7.30 (d, 2H, *J*=8.6 Hz), 8.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 12.5, 13.3, 13.7, 14.2, 16.9, 17.2, 53.7, 53.8, 54.5, 54.6, 55.1, 55.2, 60.1, 70.1, 71.6, 78.6, 78.7, 80.2, 81.5, 81.6, 113.5, 113.9, 128.9, 130.5, 156.3, 158.9, 164.7, 167.3; MS (ESI): 635.4 [M+H].

4.1.5. (2*S*, 3*S*, 4*R*, 5*R*)-2,4-Dimethoxy-5-[5,5,7,7-tetraisopropyl-3-(4-methoxy-benzyloxy)-tetrahydro-1,4,6,8-tetraoxa-5,7-disila-cyclopen-tacycloocten-2-yl]-pyrimidine (7). Compound **6** (1.12 g, 1.77 mmol) was dissolved in dioxane (38 mL) followed by the addition of 1 N HCl (19 mL) and the mixture was stirred at room temperature for 1 h. The colorless mixture was quenched with Et_3N (4.2 mL, 30 mmol) and diluted with water (38 mL). The organic phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic phase was dried with Na_2SO_4. After concentration, the colorless oil was purified by flash chromatography (eluant, 1:1 hexanes/EtOAc) to afford **7** as a white solid (1.01 g, 1,55 mmol, 88%). R_f=0.29 (1:1 hexanes/EtOAc); mp 62–65 °C; $[\alpha]_D$ −6.23 (*c* 0.69, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (m, 28H), 3.75 (s, 3H), 3.90 (s, 4H), 4.01 (s, 4H), 4.04 (m, 1H), 4.10 (m, 1H), 4.61 (m, 3H), 5.01 (d, 1H, *J*=4.26 Hz), 6.79 (d, 2H, *J*=8.65 Hz), 7.14 (d, 2H, *J*=8.66 Hz), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.59, 13.3, 13.4, 13.5, 14.3, 14.8, 16.5, 17.2, 53.7, 53.8, 54.7, 54.8, 55.0, 55.1, 60.2, 69.9, 71.7, 78.3, 78.4, 81.6, 82.8, 112.9, 113.5, 129.4, 129.6, 157.3, 159.1, 164.8, 167.8; MS (ESI): 653.4 [M+H].

4.1.6. (2*S*, 3*S*, 4*R*, 5*R*)-5-(2,4-Dimethoxy-pyrimidin-5-yl)-4-(4-methoxy-benzyloxy)-2-vinyl-tetrahydro-furan-3-ol (8). In a 25 mL flame-dried round-bottomed flask, dry CH_2Cl_2 (6.5 mL) and dry DMSO (0.63 mL, 8.87 mmol) were added under argon atmosphere. Mixture was cooled to −78 °C and oxalyl chloride (0.37 mL, 4.29 mmol) was added dropwise. The colorless mixture was stirred at −78 °C for 15 min and **7** (935 mg, 1.43 mmol) dissolved in dry CH_2Cl_2 (8.5 mL) was added and stirred at −78 °C for 45 min. ^{i}Pr$_2$NEt (1.99 mL, 11.44 mmol) was added and mixture was stirred at −30 °C for 1 h 30 min. It was then quenched with satd NH_4Cl. (15 mL), diluted with Et_2O (15 mL) and with water (15 mL). The organic phase was separated and concentrated. It was then dissolved in Et_2O (50 mL) and hexane (50 mL), then washed with water (5×20 mL), brine (1×20 mL), and dried over Na_2SO_4. A pale yellow oil was obtained after concentration of the organic phase.

In a 100 mL round-bottomed flask, Ph_3PCH_3Br (1.02 g, 2.86 mmol) was put in suspension in dry THF (29 mL) and cooled to 0 °C. NaHMDS (2.86 mL, 2.86 mmol, 1 M in THF) was added and the yellow mixture was stirred at 0 °C for 1 h. The above obtained aldehyde (930 mg, 1.43 mmol) in dry THF (25 mL) was added to the ylide at −40 °C and stirred for 2 h. After stirring at 0 °C for 16 h, the orange-brown mixture was quenched with satd NH_4Cl and the aqueous phase was extracted with Et_2O (3×40 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to give an orange oil. Purification by flash chromatography (eluant, 1:1 hexanes/EtOAc) afforded compound **9** (204 mg, 0.31 mmol, 11%) as an oil and the desired product **8** as a white solid (200 mg, 0.51 mmol, 36% (two steps)). R_f=0.28 (1:1 hexanes/EtOAc), mp 74 °C; $[\alpha]_D$ +23.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 1H), 3.80 (s, 3H), 3.87 (m, 1H), 3.93 (dd, 1H, *J*=5.5, *J*=2.8 Hz,), 3.98 (s, 3H), 4.00 (s, 3H), 4.24 (dd, 1H, *J*=7.5, *J*=6.5 Hz), 4.53 (d, 1H, *J*=11.3 Hz),, 4.70 (d, 1H, *J*=11.3 Hz), 5.05 (d, 1H, *J*=2.6 Hz), 5.28 (d, 1H, *J*=10.0 Hz), 5.44 (d, 1H, *J*=17.1 Hz), 5.9–6.05 (m, 1H), 6.86 (d, 2H, *J*=8.6 Hz), 7.22 (d, 2H, *J*=8.6 Hz), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.2, 55.1, 56.0, 57.8, 72.3, 74.6, 82.5, 84.1, 113.1, 114.8, 117.5, 128.2, 130.1, 136.1, 156.3, 159.1, 165.0, 167.2; MS (ESI): 411.4 [M+Na]. Compound **9** (204 mg) was treated with TBAF in THF (1 h, 0 °C) to give **8** (108 mg, 0.28 mmol, 90%).

4.1.7. (2*S*, 3*S*, 4*R*, 5*R*)-4-Allyloxy-2-(2′,4′-dimethoxypyrimidin-5′-yl)-3-(*p*-methoxy-benzyloxy)-5-vinyl-tetrahydrofuran (10). To a solution of **8** (2.5 g, 6.44 mmol) in 30 mL dry DMF was added sodium hydride (0.387 g, 9.66 mmol) at 0 °C under argon atmosphere. After stirring for 10 min, allyl bromide (0.817 mL, 9.66 mmol) was added to this mixture. The mixture was stirred overnight and quenched by adding $NaHCO_3$. The mixture was extracted with EtOAc (200 mL×3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 4:1) afforded **10** as a colorless oil (2.5 g, 5.84 mmol, 91%); $[\alpha]_D$ +37.7 (*c* 0.97, CHCl3), IR (thin film) ν 2956, 1603, 1571, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (dd, 1H, *J*=7.5, *J*=4.8 Hz), 3.77 (s, 3H, –OMe), 3.92 (m, 3H), 3.97 (s, 6H, 2×–OMe), 4.52 (t, 1H, *J*=7.5 Hz), 4.59 (d, 1H, *J*=11.9 Hz), 4.65 (d, 1H, *J*=11.9 Hz), 5.15–5.3 (m, 5H), 5.45 (d, 1H, *J*=17.1 Hz), 5.75–6.0 (m, 2H), 6.82 (d, 2H, *J*=8.6 Hz), 7.23 (d, 2H, *J*=8.6 Hz), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.8, 54.7, 55.1, 71.2 (2C), 78.1, 79.4, 80.8, 81.3, 113.5, 113.5, 117.3, 117.9, 129.3,

129.7, 134.1, 135.9, 156.3, 159.1, 164.8, 167.9; MS (FAB) 429.2 ($M+H^+$); HRMS (FAB) calcd for $C_{23}H_{29}N_2O_6$ 429.2025; found 429.2045.

4.1.8. (2*S*, 3*S*, 3a*R*, 7a*R*)-2-(2′,4′-Dimethoxy-pyrimidin-5′-yl)-3-(*p*-methoxy-benzyloxy)-3,3a,5,7a-tetrahydro-2*H*-furo[3,2-*b*]pyran (11). To a solution of **10** (2.5 g, 5.84 mmol) in 1.2 L dry degassed CH_2Cl_2 was added the first generation Grubbs catalyst (240 mg, 0.29 mmol) at room temperature under argon atmosphere. The mixture was refluxed for 5 h and concentrated. The residue was purified by flash chromatography on silica gel column (hexanes/EtOAc, 4:1) to afford the bicyclic product **11** as a white solid (2.2 g, 5.5 mmol, 94%); mp. 80 °C, $[\alpha]_D$ −33.2 (*c* 1.1, $CHCl_3$), IR (thin film) ν 2956, 1603, 1602, 1575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.42 (dd, 1H, *J*=8.9, *J*=4.5 Hz), 3.77 (s, 3H, –OMe), 3.93 (m, 1H), 3.95 (s, 3H, –OMe), 3.96 (s, 3H, –OMe), 4.40 (m, 2H), 4.54 (m, 1H), 4.65 (d, 1H, *J*=11.9 Hz), 4.74 (d, 1H, *J*=11.9 Hz), 5.11 (m, 1H), 5.69 (d, 1H, *J*=10.3 Hz), 6.28 (d, 1H, *J*=9.7 Hz), 6.85 (d, 2H, *J*=8.7 Hz), 7.28 (d, 2H, *J*=8.7 Hz), 8.18 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 54.7, 55.1, 68.6, 71.3, 71.6, 78.8, 79.5, 81.7, 113.4, 113.6, 127.1, 127.4, 129.1, 130.0, 156.1, 159.1, 164.8, 167.6; HRMS (MAB) calcd for $C_{21}H_{25}N_2O_6$ ($M+H^+$) 401.1710; found 401.1699.

4.1.9. (2*S*, 3*S*, 3a*R*, 6*R*, 7*R*, 7a*R*)-7-Azido-2-(2′,4′-dimethoxy-pyrimidin-5′-yl)-6-hydroxyl-3-(*p*-methoxy-benzyloxy)-hexahydro-2*H*-furo[3,2-*b*]pyran (12). To a solution of **11** (1.0 g, 2.5 mmol) in 60 mL THF and 60 mL H_2O was added NBS (0.53 g, 2.95 mmol) at room temperature. The mixture was stirred for 1.5 h and quenched by adding 100 mL H_2O containing 2 g $Na_2S_2O_3$. The mixture was extracted with EtOAc (100 mL×3), the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was dissolved in 200 mL THF and 1 N NaOH (33 mL). The solution was refluxed for 1 h and cooled to room temperature, then extracted with EtOAc (200 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The intermediate epoxide was dissolved in 150 mL methoxyethanol. The solution was refluxed for 1 h, cooled to room temperature, then poured into 200 mL brine, and extracted with EtOAc (100 mL×3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 3:1) afforded the *trans*-azido alcohol **12** as a white solid (500 mg, 1.1 mmol, 43%); mp 119 °C; $[\alpha]_D$ +93.1 (*c* 0.98, $CHCl_3$), IR (thin film) ν 3400, 2915, 2105 (N3), 1604, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (br s, 1H, OH), 3.58 (dd, 1H, *J*=10.0, 4.7 Hz), 3.68 (m, 1H), 3.73 (d, 1H, *J*=12.7 Hz), 3.78 (s, 3H, –OMe), 3.89 (m, 2H), 3.97 (s, 6H, 2×–OMe), 4.33 (m, 2H), 4.67 (s, 2H), 5.10 (m, 1H), 6.86 (d, 2H, *J*=8.7 Hz), 7.27 (d, 2H, *J*=8.7 Hz), 8.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 54.8, 55.1, 61.6, 68.3, 69.3, 71.4, 73.3, 74.2, 79.8, 80.3, 113.3, 113.7, 129.2, 129.7, 155.8, 159.2, 164.8, 167.4; HRMS (FAB) calcd for $C_{21}H_{26}N_5O_7$ ($M+H^+$) 460.1832; found 460.1842.

4.1.10. (2*S*, 3*S*, 3a*R*, 7*R*, 7a*R*)7-Azido-2-(2,4-dimethoxy-pyrimidin-5-yl)-3-(4-methoxy-benzyloxy)-tetrahydro-furo[3,2-*b*]pyran-6-one(13). To a solution of **12** (1.0 g, 2.2 mmol) in 50 mL anhydrous CH_2Cl_2 was added Dess–Martin periodinane (2.22 g, 7.0 mmol) at room temperature under argon atmosphere. The mixture was stirred for 4 h and quenched by adding satd $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (30 mL). The mixture was stirred for 30 min, extracted with EtOAc (200 mL×3), the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. Compound **13** was used immediately in the next step without any purification.

4.1.11. (2*S*, 3*S*, 3a*R*, 6*S*, 7*R*, 7a*R*)-7-Azido-2-(2′, 4′-dimethoxy-pyrimidin-5′-yl)-6-methoxy-3-(*p*-methoxy-benzyloxy)-hexahydro-2*H*-furo[3,2-*b*]pyran (14). Compound **13** was dissolved in 40 mL MeOH and $NaBH_4$ (840 mg, 22.7 mmol) was added to this mixture. After stirring for 1 h, the mixture was concentrated at room temperature. The residue was dissolved in 200 mL EtOAc and washed with H_2O (50 mL×3), brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was dissolved in 20 mL anhydrous DMF and NaH (131 mg, 3.27 mmol) was added at 0 °C under argon atmosphere. The resulting mixture was stirred for 10 min, iodomethane (0.638 mL, 99 mmol) was added, and the mixture was stirred overnight. After adding satd $NaHCO_3$ (30 mL), the mixture was extracted with EtOAc (50 mL×3), the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 4:1) afforded **14** as a white solid (800 mg, 1.7 mmol, 78%); mp 89 °C; $[\alpha]_D$ +60.6 (*c* 0.88, $CHCl_3$), IR (thin film) ν 2913, 2105 (N_3), 1602, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H, –OMe), 3.61 (m, 2H), 3.75 (m, 1H), 3.76 (s, 3H, –OMe), 3.85 (d, 1H, *J*=4.63 Hz), 3.96 (s, 3H, –OMe), 3.97 (s, 3H, –OMe), 4.01 (dd, 1H, *J*=10.04, *J*=2.91 Hz), 4.67 (m, 3H), 5.16 (s, 1H), 6.86 (d, 2H, *J*=8.6 Hz), 7.26 (d, 2H, *J*=8.6 Hz), 8.44 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 53.9, 54.8, 55.1, 57.1, 57.4, 59.7, 65.7, 71.2, 74.0, 75.0, 76.4, 78.9, 81.5, 113.3, 113.7, 129.7, 156.0, 159.1, 164.9, 167.2; HRMS (FAB) calcd for $C_{22}H_{28}N_5O_7$ ($M+H^+$) 474.1988; found 474.2002.

The corresponding 6-ethoxy analogue **15** was similarly prepared (76%); $[\alpha]_D$ +68 (0.6, $CHCl_3$); MS (FAB): 488.2 ($M+H^+$).

4.1.12. (2*S*, 3*S*, 3a*R*, 6*S*, 7*R*, 7a*R*)-7-Azido-2-(2′,4′-dioxo-1′,2′,3′,4′-tetrahydro–pyrimidin-5′-yl)-6-methoxy-3-pivaloyloxy)-hexahydro-2*H*-furo[3,2-*b*]pyran (16). To a solution of **14** (800 mg, 1.69 mmol) in 20 mL CH_2Cl_2 and 1 mL H_2O was added DDQ (1.18 g, 5.2 mmol) at room temperature. The mixture was stirred for 6 h and quenched by adding satd $NaHCO_3$ (200 mL). The mixture was extracted with CH_2Cl_2 (50 mL×4). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel column (EtOAc) to afford the alcohol as a colorless oil (580 mg, 1.65 mmol, 97%); $[\alpha]_D$ +93 (*c* 0.3, $CHCl_3$); IR (thin film) ν 3540, 2920, 2105, 1603, 1574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, OMe), 3.57 (ddd, 1H, *J*=10.4, *J*=4.85, *J*=2.91 Hz), 3.65 (t, 1H, *J*=10.4 Hz), 3.76 (dd, 1H, *J*=9.8, *J*=4.64 Hz), 3.94 (m, 2H), 3.98 (m, 4H, –OMe), 4.02 (s, 3H, –OMe), 4.10 (d, 1H, *J*=4.6 Hz),

4.67 (m, 2H), 5.06 (s, 1H), 8.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.1, 54.8, 57.4, 59.4, 65.7, 73.0, 73.7, 74.7, 76.3, 83.5, 112.9, 155.8, 164.4, 167.6; HRMS (FAB) calcd for $C_{14}H_{20}N_5O_6$ ($M+H^+$) 353.1335; found 353.1341.

The alcohol (580 mg, 1.64 mmol) was dissolved in 30 mL anhydrous pyridine, and DMAP (122 mg, 1 mmol) and pivaloyl chloride (0.4 mL, 3.32 mmol) were added at room temperature under argon atmosphere. The mixture was stirred overnight, concentrated, and the residue was purified by flash chromatography on silica gel column (hexanes/EtOAc, 4:1) to afford the pivalate ester as a colorless oil (650 mg, 1.49 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H, –OPiv), 3.47 (s, 3H, $-OCH_3$), 3.53 (m, 1H), 3.56 (t, 1H, J=10.2 Hz), 3.79 (dd, 1H, J=10.2, J=2.6 Hz), 3.90 (ddd, 2H, J=10.5, J=5.2, J=2.8 Hz), 3.97 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 4.67 (s, 1H), 5.05 (s, 1H), 5.27 (d, 1H, J=3.7 Hz), 8.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 39.3, 54.5, 55.2, 57.9, 59.5, 66.2, 73.4, 73.8, 75.7, 76.1, 76.7, 77.0, 81.8, 112.8, 156.5, 165.7, 168.1, 177.5; MS (FAB): 438.2 ($M+H^+$).

To a solution of the pivalate ester (650 mg, 1.49 mmol) in 27 mL dry MeCN were added NaI (740 mg, 5.22 mmol) and TMSCl (565 mg, 5.22 mmol) at room temperature under argon atmosphere. The mixture was stirred for 24 h and quenched by adding 10% sodium metabisulfite (10 mL) and satd $NaHCO_3$ (10 mL). The mixture was stirred for 10 min and extracted with EtOAc (30 mL×3), the combined organic layer was washed with brine (35 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel column (hexanes/EtOAc, 1:1) afforded **16** as a colorless oil (214 mg, 35%). Starting material (150 mg) and non-demethylated intermediate (145 mg, 34%) were recovered. The latter could be recycled as described above. For **16**, $[\alpha]_D$ +100.75 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22, (s, 9H, –OPiv), 3.46 (s, 3H, –OMe), 3.47 (ddd, 1H, J=10.7, J=2.9, J=4.0 Hz), 3.59 (t, 1H, J=10.7 Hz), 3.75 (dd, 1H, J=10.0, J=2.7 Hz), 3.86 (m, 2H), 4.65 (s, 1H), 4.91 (s, 1H), 5.31 (d, 1H, J=4.7 Hz), 7.55 (s, 1H), 10.00 (br, 2H, 2×NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 38.7, 57.4, 59.1, 65.6, 72.6, 72.8, 75.2, 76.4, 80.9, 111.6, 138.8, 152.2, 162.5, 171.1; HRMS (FAB) calcd for $C_17H_{24}N_5O_7$ ($M+H^+$) 410.1675; found 410.1693.

4.1.13. Malayamycin A (1). Compound **16** (32 mg, 0.076 mmol) was dissolved in dry THF (6 mL) and argon was bubbled in the solution for 10 min. Water (6 mL) and PMe_3 (88 mL, 1 M solution in toluene, 0.088 mmol) were added. After 5 min at room temperature, the solution was refluxed for 30 min, then concentrated and held under vacuum for 1 h. It was then dissolved in dry CH_2Cl_2 (8 mL) and trichloroacetylisocyanate (10 mL, 0.082 mmol) was added. After 30 min, the solution was concentrated. The oily residue was dissolved in MeOH (2 mL), 40% $MeNH_2$ in water (4 mL) was added and the solution was stirred for 52 h. Concentration gave a solid that was purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to give pure malayamycin A as a white solid (16 mg), 60%; mp 158 °C (dec) $[\alpha]_D$ +120 (*c* 0.19, MeOH); (authentic sample $[\alpha]_D$ +126 (*c* 0.36, MeOH)). ^{1}H NMR (D_2O, 400 MHz) identical to the authentic sample δ 3.30 (s, 3H, OMe), 3.38 (t, 1H, J=10.7, H-7ax′.), 3.51 (dd, 1H, J=10.7, J=5.1 Hz, H-3′), 3.69 (ddd, 1H, J=5.2, J=3.5, J=10.7 Hz, H-6′), 3.85 (dd, 1H, J=3.5, J=11.8 Hz, H-7eq′), 3.93 (dd, 1H, J=10.7, J=5.4 Hz, H-6′), 4.16 (d, 1H, J=2.1 Hz, H-2′), 4.74 (s, 1H, H-1′), 4.82 (s, 1H, H-5′), 7.24 (s, 1H, H-6). ^{13}C NMR (100 MHz, D_2O) δ 48.1, 57.3, 66.4, 73.2, 75.0, 76.6, 85.2, 113.8, 141.2, 154.8, 163.1, 167.5, 179.8. HRMS (FAB) MH+ calcd 342.1176; found 342.1181.

4.1.14. (2*R*, 3*R*, 3a*R*, 6*R*, 7*R*, 7a*R*)-7-Azido-3-benzyloxy-2,6-dimethoxy-hexahydrofuro[3,2-*b*]pyran (29). To a solution of **28** (600 mg, 1.9 mmol) in 30 mL dry DMF were added NaH (60% dispersion in mineral oil) (200 mg, 5.0 mmol) and MeI (0.5 mL, 8.0 mmol) at 0 °C under argon atmosphere. After stirring overnight, the reaction was quenched by adding satd $NaHCO_3$ and extracted with EtOAc (30 mL×4). The combined organic layer was washed with satd $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica chromatography (hexanes/EtOAc, 10:1) afforded the product as colorless oil (600 mg, 1.8 mmol, 96%); $[\alpha]_D$ −16.0 (*c* 1.36, $CHCl_3$); IR (neat): 2960, 2098, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.22 (m, 1H, H-6); 3.38 (s, 3H, –OMe); 3.41 (s, 3H, –OMe); 3.64 (d, 1H, J=12.8 Hz, H-5); 3.86 (dd, 1H, J=10.0, 4.2 Hz, H-3a); 3.95 (d, 1H, J=4.2 Hz, H-2); 4.03 (d, 1H, J=12.8 Hz, H-5); 4.40 (d, 1H, J=3.0 Hz, H-7); 4.45 (dd, 1H, J=10.0, J=3.1 Hz, H-7a); 4.62 (d, 1H, J=12.2 Hz, $PhCH_2$–); 4.84 (d, 1H, J=12.2 Hz, $PhCH_2$–); 4.86 (s, 1H, H-2); 7.26–7.38 (m, 5H, Ph–); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 56.1, 57.7, 59.3, 66.9, 72.7, 74.8, 75.1, 77.8, 79.8, 128.1, 128.2, 128.8, 138.4. FABMS *m*/*z* (relative intensity): 335 (M^+, 15), 275, 184 (100). HRMS (FAB) calcd for $C_{16}H_{21}N_3O_5$ (M^+) 335.1481; found 335.1481.

To a solution of benzyl ether (590 mg, 1.84 mmol) in 25 mL CCl_4–MeCN–H_2O (1:1:1.5) were added $RuCl_3\cdot 3H_2O$ (87.5 mg, 0.35 mmol) and $NaIO_4$ (464 mg, 2.2 mmol) at 16 °C under argon atmosphere, and then 1.2 g of $NaIO_4$ was added in portions over 24 h. After stirring over 24 h, the reaction was quenched by adding 3 mL isopropanol. The mixture was extracted with CH_2Cl_2 (50 mL×3) and the combined organic layer was washed with satd $NaHCO_3$ and brine, filtered, and concentrated. Purification by flash silica chromatography (hexanes/EtOAc, 10:1) afforded benzoate **29** (500 mg, 1.43 mmol, 82%); $[\alpha]_D$ +0.78 (*c* 1.15, $CHCl_3$); IR (neat, cm^{-1}): 2916, 2103, 1727, 1452, 1269, 1199, 1115, ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.22 (m, 1H, H-6); 3.36 (s, 3H, –OMe); 3.47 (s, 3H, –OMe); 3.65 (d, 1H, J=12.9 Hz, H-5); 4.0 (d, 1H, J=12.9 Hz, H-5); 4.03 (dd, 1H, J=10.0, J=4.4 Hz, H-8); 4.40 (m, 2H, H-7 and H-9); 5.03 (s, 1H, H-2); 5.40 (d, 1H, J=4.4 Hz, H-3), 7.42–8.05 (m, 5H, Ph–). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 56.4, 57.7, 59.5, 66.7, 72.6, 75.0, 75.5, 77.9, 107.6, 128.8, 129.6, 130.4, 133.7, 170.0. FABMS *m*/*z* (relative intensity): 349 (M^+, 10).

4.1.15. (1′*R*, 2*R*, 3*R*, 4*S*, 5*R*)-4-Azido-2-(1′-benzoyloxy-2′,2′-bisphenylsulfanylethyl)-3-hydroxyl-5-methoxy-tetrahydropyran (30). To a solution of **29** (390 mg, 1.1 mmol) in 10 mL dry CH_2Cl_2 was added benzenethiol (490 mg, 4.5 mmol), then $BF_3\cdot Et_2O$ (0.17 mL, 1.34 mmol) at

−78 °C under argon atmosphere. The mixture was stirred for 3 h, warmed to 0 °C, and quenched by adding satd $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (30 mL×3), and the combined organic layer was washed with satd $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica chromatography (hexanes/EtOAc, 5:1) afforded the dithioacetal **30** as a colorless oil (473 mg, 0.88 mmol, 80%); $[\alpha]_D$ +41.0 (*c* 0.56, $CHCl_3$); IR (neat): λ 2918, 2109, 1723, 1439, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.54 (d, 1H, *J*=5.6 Hz, –OH); 3.35 (s, 3H, –OMe); 3.40 (m, 1H, H-5); 3.49 (dd, 1H, *J*=12.5, *J*=3.5 Hz, H-6), 3.56 (dd, 1H, *J*=12.5, *J*=2.4 Hz, H-6); 3.94 (t, 1H, *J*=4.2 Hz, H-4); 4.07 (m, 1H, H-3); 4.18 (t, 1H, *J*=7.6 Hz, H-7), 4.95 (d, 1H, *J*=2.5 Hz, H-2′); 5.73 (dd, 1H, *J*=7.6, *J*=2.5 Hz, H-1′); 7.25–8.08 (m, 15H, Ph–); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 57.1, 61.5, 62.3, 63.6, 67.9, 74.6, 74.7, 76.7, 127.7, 128.3, 128.33, 128.9, 129.0, 129.3, 130.1, 132.3, 133.3, 133.7, 134.5, 166.2; FABMS *m*/*z* (relative intensity): 537 (M+, 3), 428 (M^+−PhS, 16); HRMS (FAB) calcd for $C_{27}H_{28}N_3O_5S_2$ ($M+H^+$) 538.1470; found 538.1453.

4.1.16. (2*R*, 3*R*, 3a*S*, 6*R*, 7*R*, 7a*R*)-7-Azido-6-methoxy-2-phenylsulfanyl-hexahydrofuro[3,2-*b*]pyran-3-ol (31). To a solution of **30** (420 mg, 0.78 mmol) in 10 mL MeOH was added anhydrous K_2CO_3 (5 mg) at room temperature and the mixture was stirred for 30 min. The mixture was evaporated under vacuum and the residue was purified by flash silica chromatography (hexanes/EtOAc, 3:1) to afford diol as a colorless oil (335 mg, 0.77 mmol). To a solution of above diol in 10 mL dry CH_2Cl_2 was added NBS (205 mg, 1.16 mmol) at room temperature under argon atmosphere. After stirring for 30 min, the reaction was quenched by adding satd $Na_2S_2O_3$ (10 mL), and the mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layer was washed with satd $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica chromatography (hexanes/EtOAc, 10:1) afforded alcohol as a colorless oil (190 mg, 0.59 mmol, 77%); $[\alpha]_D$ +150.5 (*c* 0.54, $CHCl_3$); IR (neat): 3402, 2918, 2103, 1584, 1482, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 2.59 (d, 1H, *J*=2.0 Hz, –OH); 3.31 (dd, 1H, *J*=2.4, *J*=1.3 Hz, H-6); 3.73 (m, 1H, H-7); 3.78 (dd, 1H, *J*=12.9, *J*=1.6 Hz, H-5); 4.06 (d, 1H, *J*=12.9 Hz, H-5); 4.46 (m, 2H, H-3a and H-7a), 4.58 (m, 1H, H-3); 5.77 (d, 1H, *J*=4.0 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 57.6, 58.7, 66.7, 70.6, 70.61, 73.4, 74.7, 92.8, 127.3, 129.4, 130.8, 132.5; FABMS *m*/*z* (relative intensity): 323 (M^+, 25); HRMS (FAB) calcd for $C_{14}H_{18}N_3O_4S$ ($M+H^+$) 324.1018; found 324.1012.

To a solution of **31** (170 mg, 0.53 mmol) in 5 mL dry pyridine was added DMAP (200 mg), then pivaloyl chloride (0.2 mL) at room temperature under argon atmosphere. The mixture was stirred overnight and pyridine was removed under reduced pressure. The residue was dissolved with 50 mL CH_2Cl_2, washed with satd $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica chromatography (hexanes/EtOAc, 5:1) afforded the pivalate ester **31** as a colorless oil (214 mg, 0.53 mmol, quant.); $[\alpha]_D$ +149.6 (*c* 0.51, $CHCl_3$); IR (neat): 2977, 2931, 2104, 1742, 1480, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.30 (s, 9H, PivO–); 3.28 (m, 1H, H-6); 3.37 (s, 3H, –OMe); 3.63 (d, 1H, *J*=12.0 Hz, H-5), 3.73 (d, 1H, *J* =10.0, *J*=4.3 Hz, H-3a); 3.98 (d, 1H, *J*=12.0 Hz, H-5); 4.42 (m, 2H, H-7 and H-7a); 5.69 (t, 1H, *J*=4.3 Hz, H-3); 5.82 (d. 1H, *J*=4.3 Hz, H-2), 7.24–7.51 (m, 5H, Ph–); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 26.9, 39.2, 56.6, 58.5, 65.0, 70.5, 73.5, 73.6, 76.9, 89.9, 126.9, 128.9, 130.5, 134.8, 176.8; FABMS *m*/*z*: 408 (M+H^+, 20), 298 (M^+−PhS, 100); HRMS (FAB) calcd for $C_{19}H_{26}N_3O_5S$ ($M+H^+$) 408.1593; found 408.1601.

4.1.17. (2*R*, 3*R*, 3a*R*, 6*R*, 7*R*, 7a*R*)-7-Azido-2-(2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-6-methoxy-3-pivaloyl-oxy-hexahydrofuro[3,2-*b*]pyran and (2*R*, 3*R*, 3a*R*, 6*R*, 7*R*, 7a*R*)-7-azido-2-(5′-iodo-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro [3,2-*b*]pyran (32, 33). To a solution of **31** (41 mg, 0.1 mmol), bis-TMS-uracil (40 mg, 0.16 mmol) and NIS (45 mg, 0.2 mmol) in 4 mL dry CH_2Cl_2 was added TfOH (10 μL) over several minutes. After stirring for 5 h, the mixture was quenched by adding satd $Na_2S_2O_3$, and extracted with CH_2Cl_2 (30 mL×3). The combined organic layer was washed with satd $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica chromatography (CH_2Cl_2/MeOH, 10:1) afforded the **32** (20 mg) and iodonucleoside **33** (8 mg) as colorless oils, the combined yield was 80% based on recovered starting material (10 mg). For **32**: $[\alpha]_D$ +114.5 (*c* 1.6, $CHCl_3$); IR (neat): 2971, 2106, 1695, 1458, 1147 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.25 (s, 9H, PivO–); 3.39 (m, 1H, H-6); 3.40 (s, 3H, –OMe); 3.68 (d, 1H, *J*=13.4 Hz, H-5); 3.80 (dd, 1H, *J*=9.8, *J*=5.1 Hz, H-7a); 4.08 (d, 1H, *J*=13.4 Hz, H-5); 4.21 (dd, 1H, *J*=9.8, *J*=3.0 Hz, H-3a); 4.45 (m, 1H, H-7); 5.30 (d, 1H, *J*=3.0 Hz, H-3); 5.79 (d, 1H, *J*=8.1 Hz, H-5′); 5.85 (s, 1H, H-1); 7.44 (d, 1H, *J*=8.1 Hz, H-6′); 8.29 (s, 1H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 26.9, 38.8, 56.8, 59.2, 65.2, 71.9, 73.0, 74.4, 76.6, 89.6, 102.9, 139.4, 149.4, 162.5, 176.9; FABMS *m*/*z* (relative intensity): 410 (M+H^+, 10), 391 (M^+−H_2O, 16), 298 (M^+−uracilyl, 16); HRMS (FAB) calcd for $C_{17}H_{24}N_5O_7$ ($M+H^+$) 410.1675; found 410.1662. For **33**: $[\alpha]_D$ +123.4 (*c* 0.87, $CHCl_3$); IR (neat): 2978, 2104, 1691, 1611, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 1.25 (s, 9H, PivO–); 3.40 (s, 3H, –OMe); 3.42 (m, 1H, H-6); 3.72 (d, 1H, *J*=13.1 Hz, H-5); 3.79 (dd, 1H, *J*=10.1, 5.0 Hz, H-3a); 4.08 (d, 1H, *J*=13.1, H-5); 4.25 (dd, 1H, *J*=10.1, *J*=2.4 Hz, H-7a); 4.47 (s, 1H, H-7); 5.36 (d, 1H, *J*=5.0 Hz, H-3); 5.80 (s, 1H, H-2); 8.03 (s, 1H, H-6′); 8.59 (s, 1H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 27.5, 39.4, 57.4, 59.9, 65.8, 68.8, 72.2, 73.4, 75.4, 77.3, 90.3, 144.7, 149.5, 159.8, 177.2; FABMS *m*/*z* (relative intensity): 536 (M+H^+, 10), 298 (M^+−iodouracilyl, 26); HRMS (FAB) calcd for $C_{17}H_{23}N_5O_7I$ (M^+) 536.0642; found 536.0664.

4.1.18. (2*R*, 3*R*, 3a*S*, 6*S*, 7*R*, 7a*R*)-[2-(2′,4′-Dioxo-3′,4′-dihyro-2*H*-pyrimidin-1′-yl)-3-hydroxyl-6-methoxy-hexahydrofuro[3,2-*b*]pyran-7-yl]-urea (6-*epi*-*N*-malayamycin) (34). To a solution of **32** (37 mg, 0.09 mmol) in 4 mL anhydrous THF was added Me_3P (1 M in toluene) (250 μL, 0.25 mmol) at room temperature under argon atmosphere. After stirring for 30 min, 10 μL of H_2O was added, and the resulting mixture was refluxed for 40 min, then evaporated. The residue was dried under reduced

pressure (1 mmHg) for 1.5 h and dissolved in 2 mL dry CH_2Cl_2. To this solution was added trichloroacetylisocyanate (20 μL) at room temperature under argon atmosphere. After stirring for 60 min, CH_2Cl_2 was removed and the residue was dissolved with MeOH (3 mL) and 40% $MeNH_2$ in H_2O (3 mL), and stirred over 3 days. The mixture was evaporated and purified by flash silica chromatography (CH_2Cl_2/MeOH, 9:1) to afford 6-*epi*-*N*-malayamycin **34** as a white solid (25 mg, 0.073 mmol, 77%); $[\alpha]_D$ +30.0 (*c* 0.45, MeOH); ^{1}H NMR (400 MHz, CD_3OD, ppm): δ 3.39 (m, 1H, H-6′); 3.44 (s, 1H, –OMe); 3.59 (dd, 1H, *J*=10.7, *J*=5.2 Hz, H-3a); 3.79 (d, 1H, *J*=13.2 Hz, H-5); 4.12 (d, 1H, *J*=13.2 Hz, H-5); 4.22 (dd, 1H, *J*=10.7, *J*=4.2 Hz, H-7a); 4.31 (d, 1H, *J*=5.2 Hz, H-3); 4.65 (m, 1H, H-7); 5.62 (s, 1H, H-2); 5.70 (d, 1H, *J*=8.1 Hz, H-5′); 7.62 (d, 1H, *J*=8.1 Hz, H-6′); ^{13}C NMR (100 MHz, CD_3OD, ppm) δ 48.7, 56.4, 66.6, 72.6, 73.5, 74.1, 78.7, 93.8, 101.7, 141.7, 150.9, 160.6, 165.2; FABMS *m*/*z* 343 ($M+H^+$); HRMS (FAB) calcd for $C_{13}H_{19}N_4O_7$ ($M+H^+$) 343.1253; found 343.1284.

4.1.19. (3a*R*, 5*R*, 6*R*, 6a*R*)-Dihydro-6-(iodomethyl)-2,2-dimethyl-5-vinyl-5*H*-furo[2,3-*d*][1,3]dioxole (36). A solution of **35**[39] (10 g, 36.5 mmol) in AcOH/H_2O 75:25 v/v (70 mL) was kept at room temperature for 15 h, and then concentrated in vacuo at 30 °C to afford the triol as a colorless oil, which did not require further purification. R_f=0.27 (100:3 AcOEt/MeOH).

To a solution of the above triol, triethylamine (21 mL, 151 mmol) and DMAP (400 mg, 3.27 mmol) in CH_2Cl_2 (45 mL) at −20 °C under an argon atmosphere was added dropwise methanesulfonic chloride (10 mL, 129 mmol) (strongly exothermic). The reaction mixture was stirred at room temperature for 1 h. Aq satd $NaHCO_3$ (50 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash silica gel chromatography (hexanes/EtOAc 7:3) afforded the intermediate trimesylate as a colorless oil (13.8 g, 81% for two steps). R_f=0.42 (8:3 AcOEt/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (d, 1H, *J*=3.6 Hz), 4.92 (td, 1H, *J*=6.4, *J*=2.7 Hz), 4.79 (dd, 1H, *J*=4.1, *J*=3.6 Hz), 4.57 (dd, 1H, *J*=11.9, *J*=2.7 Hz), 4.53–4.45 (m, 2H), 4.41 (dd, 1H, *J*=11.9, *J*=6.4 Hz), 4.18–4.10 (m, 1H), 3.18 (s, 3H), 3.09 (s, 3H), 3.08 (s, 3H), 2.65–2.52 (m, 1H), 1.52 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 105.2, 80.4, 78.6, 77.2, 67.6, 65.8, 46.6, 39.0, 37.7, 37.2, 26.9, 26.4.

A solution of the above trimesylate (9.5 g, 20.3 mmol) in ethylmethyl ketone (80 mL) was treated with NaI (15.2 g, 101 mmol). The resulting suspension was refluxed for 15 h, whereas a dark-brown coloration corresponding to the formation of iodine developed gradually. The reaction mixture cooled down to room temperature was treated with satd $Na_2S_2O_3$ (200 mL). After stirring for 15 min, *t*-butyl methyl ether (200 mL) was added and the phases were separated. The aqueous layer was extracted with *t*-butyl methyl ether (100 mL×2). The organic extracts were combined, washed with brine (100 mL×2), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash silica gel chromatography (hexanes/EtOAc 9:1) afforded the diene **36** as a yellowish oil (5.2 g, 82%). R_f=0.68 (7:3 AcOEt/hexanes); $[\alpha]_D$ +14.1 (*c* 1.11 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, 1H, *J*=3.7 Hz), 5.76 (ddd, 1H, *J*=17.8, *J*=10.5, *J*=7.8 Hz), 5.35 (d, 1H, *J*=17.8 Hz), 5.29 (d, 1H, *J*=10.5 Hz), 4.72 (app. t, 1H, *J*=4.1 Hz), 4.10 (dd, 1H, *J*=10.0, *J*=7.8 Hz), 3.25 (dd, 1H, *J*=11.9, *J*=9.6 Hz), 3.06 (dd, 1H, *J*=9.6, *J*=3.7 Hz), 2.14 (ddt, 1H, *J*=11.9, *J*=10.0, *J*=4.1 Hz), 1.54 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 119.2, 111.7, 103.9, 81.2, 81.1. 53.4, 26.4, 26.1, −2.9; HRMS calcd for $C_{10}H_{16}IO_3$ $[M+H]^+$ 311.0144; found 311.0146.

4.1.20. (3a*R*, 5*R*, 6*R*, 6a*R*)-6-(But-3-enyl)-dihydro-2,2-dimethyl-5-vinyl-5*H*-furo[2,3-*d*][1,3]dioxole (37). A mixture of **36** (3.0 g, 9.7 mmol), allyltributyltin (54 mL, 174 mmol) and AIBN (159 mg, 0.97 mmol) under an argon atmosphere was heated at 100 °C for 1 h. An additional portion of AIBN (159 mg, 0.97 mmol) was then added and the reaction mixture was heated for 1 h. The product was isolated by two successive flash silica gel chromatography (CH_2Cl_2), which afforded 1.86 g of **37** (75%) as a colorless oil. R_f=0.52 (3:1.5:0.5 toluene/hexanes/AcOEt); $[\alpha]_D$ +26.4 (*c* 1.10 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.76 (m, 1H), 5.80 (d, 1H, *J*=3.7 Hz), 5.73 (ddd, 1H, *J*=17.4, *J*=10.5, *J*=7.8 Hz), 5.31 (ddd, 1H, *J*=10.5, *J*=1.8, *J*=0.9 Hz), 5.03 (dm, 1H, *J*=17.4 Hz), 4.97 (dm, 1H, *J*=10.5 Hz), 4.13 (app. t, 1H, *J*=3.7 Hz), 2.35–2.19 (m, 1H) 2.18–2.02 (m, 1H), 1.76–1.63 (m, 2H), 1.52 (s, 3H), 1.47–1.35 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 136.0, 118.5, 114.9, 111.4, 105.0, 83.1, 80.7, 49.1, 31.8, 26.7, 26.6, 23.3.

4.1.21. (3a*R*, 4a*R*, 8a*R*, 8b*R*)-7,8,8a,8b-Tetrahydro-2,2-dimethyl-4a*H*-benzofuro[2,3-*d*][1,3]dioxole (38). A solution of **37** (7.0 g, 31.2 mmol) and Grubbs first generation catalyst (1.28 g, 1.56 mmol) in CH_2Cl_2 (620 mL) saturated with argon was refluxed under a slight flow of argon for 2 h. The reaction mixture was concentrated at 400 mbar without heating. Purification of the residue by flash silica gel chromatography (CH_2Cl_2) afforded 3.37 g of **38** (55%) as a brown oil, which is volatile. R_f=0.38 (3:1.5:0.5 toluene/hexanes/AcOEt); $[\alpha]_D$ −14.1 (*c* 1.01 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dm, 1H, *J*=10.5 Hz), 5.90 (d, 1H, *J*=3.7 Hz), 5.64 (ddd, 1H, *J*=10.5, *J*=6.4, *J*=3.2 Hz), 4.62 (app. t, 1H, *J*=3.7 Hz), 4.34–4.25 (m, 1H), 2.30–2.19 (m, 2H), 2.03–1.92 (m, 1H), 1.85–1.68 (m, 1H), 1.65–1.51 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.7, 127.3, 111.5, 106.6, 80.0, 75.9, 47.0, 30.9, 26.1, 25.9, 19.6; HRMS calcd for $C_{11}H_{17}O_3$ $[M+H]^+$ 197.1178; found 197.1176.

4.1.22. (3a*R*, 4a*S*, 5*R*, 6*S*, 8a*R*, 8b*R*)-5-Azido-hexahydro-2,2-dimethyl-4a*H*-benzofuro[2,3-*d*][1,3]dioxol-6-ol (39). To a solution of **38** (2.80 g, 14.3 mmol) in THF–H_2O (1:1 v/v, 340 mL) at room temperature was added NBS (4.82 g, 27.1 mmol). The mixture was stirred at room temperature for 2 h and then diluted with aq satd $Na_2S_2O_3$ (100 mL) and extracted with EtOAc (100 mL×3). The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated in vacuo. The resulting brown oil was engaged in the next reaction. R_f=0.68 (AcOEt).

A solution of the above residue in THF (240 mL) was treated with aq 1 N NaOH (120 mL) and then refluxed for 1 h. The

mixture was poured into H_2O (120 mL) and extracted with EtOAc (150 mL×2). The combined organic layer was washed with brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo to give a brown oil, which was engaged in the next reaction. R_f=0.60 (AcOEt).

The above material was dissolved in 2-methoxyethanol (300 mL) and sodium azide (13.9 g, 214 mmol) was added. The mixture was heated at 130 °C for 2 h, diluted with brine (300 mL), and extracted with EtOAc (100 mL×3). The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes/EtOAc 2:1) to afford 1.9 g of azide **39** (52%) as an orange oil. R_f=0.24 (2:1 hexanes/AcOEt); $[\alpha]_D$ −7.5 (*c* 0.80 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (d, 1H, *J*=3.7 Hz), 4.60 (app. t, 1H, *J*=3.7 Hz), 4.22–4.15 (m, 2H), 4.09–4.05 (br m, 1H), 2.10 (d, 1H, *J*=3.7 Hz), 1.89–1.79 (m, 1H), 1.79–1.63 (m, 4H), 1.52 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.0, 105.3, 80.2, 76.8, 69.3, 62.3, 42.1, 28.0, 26.3, 26.0, 18.3; HRMS calcd for $C_{11}H_{18}N_3O_4$ $[M+H]^+$ 256.1297; found 256.1299.

4.1.23. (3a*R*, 4a*S*, 5*S*, 8a*R*, 8b*R*)-5-Azido-tetrahydro-2,2-dimethyl-7*H*-benzofuro[2,3-*d*][1,3]dioxol-6(8b*H*)-one (40). To a solution of **39** (1.80 g, 7.05 mmol) in CH_2Cl_2 (32 mL) at room temperature was added Dess–Martin periodinane (3.59 g, 8.46 mmol). The mixture was stirred for 2.5 h. Aq satd $NaHCO_3$ (50 mL) and $Na_2S_2O_3$ (50 mL) were added sequentially. The mixture was stirred for 20 min and the phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash silica gel chromatography (hexanes/EtOAc, 4:1) afforded the product **40** as a colorless oil (1.6 g, 90%). R_f=0.25 (4:1 hexanes/AcOEt); $[\alpha]_D$ +12.4 (*c* 0.95 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (d, 1H, *J*=3.7 Hz), 4.65 (app. t, 1H, *J*=3.7 Hz), 4.35 (d, 1H, *J*=3.7 Hz), 3.88 (dd, 1H, *J*=11.0, 3.7 Hz), 2.60 (ddd, 1H, *J*=15.0, *J*=13.2, *J*=7.3 Hz), 2.38 (ddm, 1H, *J*=15.1, *J*=5.0 Hz), 2.37–2.24 (m, 1H), 2.06–1.96 (m, 1H), 1.65 (ddd, 1H, *J*=26.0, *J*=13.2, *J*=5.0 Hz), 1.48 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 112.5, 106.8, 79.4, 79.2, 68.4, 41.0, 36.2, 26.3, 26.0, 18.8; HRMS calcd for $C_{11}H_{16}N_3O_4$ $[M+H]^+$ 254.1141; found 254.1144.

4.1.24. (3a*R*, 4a*S*, 5*R*, 6*R*, 8a*R*, 8b*R*)-5-Azido-hexahydro-6-methoxy-2,2-dimethyl-4a*H*-benzofuro[2,3-*d*][1,3]dioxole (41). To a solution of **40** (3.4 g, 13.4 mmol) in MeOH (68 mL) at 0 °C was added $NaBH_4$ (761 mg, 20.1 mmol). The resulting mixture was stirred at room temperature for 3 h, and then concentrated in vacuo without heating. The residue was taken up with EtOAc (30 mL) and washed with water (30 mL). The aqueous layer was extracted with EtOAc (30 mL×2). The organic extracts were combined, dried over $MgSO_4$, and concentrated in vacuo to afford a crude oil that did not require further purification. R_f=0.13 (4:1 hexanes/AcOEt).

To a solution of the above alcohol in THF (20 mL) at 0 °C under an argon atmosphere was added NaH (60% suspension, 1.07 g, 26.7 mmol). After stirring for 1 h at 0 °C, MeI (1.71 mL, 27.5 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and was quenched by adding satd NH_4Cl (50 mL). The mixture was extracted with EtOAc (30 mL×2). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash silica gel chromatography (hexanes/EtOAc, 4:1) to afford **41** (2.5 g, 69%) as a colorless oil, which crystallized upon conservation at 4 °C. R_f=0.32 (4:1 hexanes/AcOEt); $[\alpha]_D$ +16.1 (*c* 0.86 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, 1H, *J*=3.2 Hz), 4.54 (app. t, 1H, *J*=3.7 Hz), 4.45 (br app. t, 1H, *J*=2.7 Hz), 3.63 (dd, 1H, *J*=11.0, *J*=2.7 Hz), 3.41 (s, 3H), 3.32 (ddd, 1H, *J*=11.4, *J*=4.6, *J*=3.2 Hz), 1.97–1.75 (two m, 3H), 1.58 (ddd, 1H, *J*=24.7, *J*=12.8, *J*=4.1 Hz), 1.48 (s, 3H), 1.41–1.23 (1H, obscured by CH_3), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.9, 106.4, 79.9, 79.5, 78.5, 60.0, 56.6, 41.7, 26.3, 26.0, 25.9, 14.1; HRMS calcd for $C_{12}H_{20}N_3O_4$ $[M+H]^+$ 270.1454; found 270.1460.

4.1.25. (1*S*, 2*S*, 3*R*, 6*R*)-2-Azido-6-((*R*)-1-hydroxy-2,2-bis(phenylthio)ethyl-3-methoxycyclohexanol (42). To a solution of **41** (1.00 g, 3.71 mmol) in CH_2Cl_2 (22 mL) at 5 °C, PhSH (1.73 mL, 16.9 mmol) was added followed by Amberlyst-15 (1.0 g). The mixture was stirred at 5 °C for 3.5 h and at room temperature for 2 h before being filtrated and concentrated. Purification of the crude product by flash silica gel chromatography (hexanes/EtOAc, 4:1) afforded the product **42** as a colorless oil (1.30 g, 81%). R_f=0.10 (4:1 hexanes/AcOEt); $[\alpha]_D$ −18.5 (*c* 1.15 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.50 (m, 2H), 7.43–7.29 (m, 8H), 4.61 (d, 1H, *J*=3.2 Hz), 4.23 (d, 1H, *J*=3.7 Hz), 4.15 (br app. t, 1H, *J*=3.7 Hz), 3.88 (d, 1H, *J*=2.3 Hz), 3.70 (app. dt, 1H, *J*=8.2, *J*=2.7 Hz), 3.64 (app. dt, 1H, *J*=10.0, *J*=3.2 Hz), 3.38 (s, 3H), 3.16 (ddd, 1H, *J*=11.4, *J*=4.6, *J*=2.7 Hz), 2.40–2.25 (m, 1H), 1.78–1.65 (m, 1H), 0.84–0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5, 133.3, 133.0, 132.6, 129.4, 129.2, 128.5, 128.1, 79.0, 77.2, 74.5, 64.8, 64.3, 56.3, 39.6, 24.4, 23.4; HRMS calcd for $C_{21}H_{25}N_3O_3S_2Na$ $[M+Na]^+$ 454.1235; found 454.1239.

4.1.26. (2*R*, 3*R*, 3a*S*, 6*R*, 7*R*, 7a*S*)-7-Azido-octahydro-6-methoxy-2-(phenylthio)benzofuran-3-ol (43). To a solution of **42** (1.00 g, 2.32 mmol) in CH_2Cl_2 (58 mL) at 0 °C, NBS (615 mg, 3.46 mmol) was added and the mixture was stirred at 0 °C for 1 h. A saturated solution of $Na_2S_2O_3$ (50 mL) was added and the solution was stirred at room temperature until it became colorless. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (25 mL×2). The combined organic phase was washed with brine (50 mL), dried with $MgSO_4$, filtrated, and concentrated. Flash silica gel chromatography (hexanes/EtOAc, 6:4) afforded the product **43** as pale yellowish oil (499 mg, 67%). R_f=0.46 (1:1 hexanes/AcOEt); $[\alpha]_D$ −12.1 (*c* 1.09 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.48 (m, 2H), 7.38–7.22 (m, 8H), 5.74 (d, 1H, *J*=3.7 Hz), 4.52 (br app. t, 1H, *J*=2.7 Hz), 4.44 (app. t, 1H, *J*=4.1 Hz), 3.95 (dd, 1H, *J*=11.4, *J*=2.7 Hz), 3.44 (s, 3H), 3.33 (ddd, 1H, *J*=11.4, *J*=4.6, *J*=3.2 Hz), 2.33 (d, 1H, *J*=3.2 Hz), 2.10 (app. tt, 1H, *J*=11.4, *J*=4.1 Hz), 1.92 (dm, 1H, *J*=12.3 Hz), 1.88–1.77 (m, 1H), 1.63 (ddd, 1H, *J*=12.8, *J*=11.4, *J*=4.1 Hz), 1.53–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 131.1, 129.1, 127.2, 95.4, 79.8, 79.6, 72.8, 60.3, 56.7, 42.2, 25.8, 19.1; HRMS calcd for $C_{15}H_{20}N_3O_3S$ $[M+H]^+$ 322.1225; found 322.1229.

4.1.27. (2*R*, 3*R*, 3a*R*, 6*R*, 7*R*, 7a*S*)-7-Azido-octahydro-6-methoxy-2-(phenylthio)benzofuran-3-yl pivalate (44). To the alcohol **43** (360 mg, 1.12 mmol) in pyridine (6.5 mL), DMAP (684 mg, 5.60 mmol) and pivaloyl chloride (1.38 mL, 11.2 mmol) was added and the mixture was stirred at 50 °C for 4 h. Aq satd $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added and the two phases were separated. The organic phase was washed with NH_4Cl (10 mL) and brine (10 mL×2), dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude residue by flash silica gel chromatography (EtOAc) afforded the product **44** as pale yellowish oil (363 mg, 80%). R_f=0.77 (1:1 hexanes/AcOEt); $[\alpha]_D$ −12.1 (*c* 1.09 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.47 (m, 1H), 7.35–7.20 (m, 4H), 5.83 (d, 1H, *J*=4.1 Hz), 5.65 (app. t, 1H, *J*=4.6 Hz), 4.44 (br app. t, 1H, *J*=2.7 Hz), 3.87 (dd, 1H, *J*=11.4, *J*=2.7 Hz), 3.43 (s, 3H), 3.32 (ddd, 1H, *J*=11.4, *J*=4.6, *J*=3.2 Hz), 2.22 (app. tt, 1H, *J*=11.9, *J*=4.1 Hz), 1.96–1.85 (m, 1H), 1.85–1.74 (m, 1H), 1.69–1.53 (m, 1H), 1.30 (s, 9H), 1.16–0.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 135.3, 131.1, 129.1, 127.2, 95.4, 83.1, 79.6, 72.8, 60.3, 56.7, 42.2, 19.5, 27.4, 25.8, 19.5; HRMS calcd for $C_{20}H_{28}N_3O_4S$ $[M+H]^+$ 406.1801; found 406.1803.

4.1.28. (2*R*, 3*R*, 3a*R*, 6*R*, 7*R*, 7a*S*)-2-(4′-Acetylamino-2′-oxo-2*H*-pyrimidin-1′-yl)-7-azido-octahydro-6-methoxy-benzofuran-3-yl pivalate (45). To a solution of **44** (180 mg, 0.43 mmol), *N*-4-acetyl bis-*O*-TMS cytosine (316 mg, 1.06 mmol) and NIS (238 mg, 1.06 mmol) in CH_2Cl_2 (3.0 mL) at room temperature, TfOH (92 μL, 1.06 mmol) was added portionwise over a period of 20 min. The mixture was stirred at room temperature for 6 h, which was followed by the addition of a saturated solution of $Na_2S_2O_3$ (3 mL) and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (6 mL×2), the organic layer was washed with aq satd $NaHCO_3$ (6 mL), and dried with $MgSO_4$. After concentration, the crude product was purified by flash silica gel chromatography (EtOAc/MeOH, 99:1) to afford the product **45** as pale yellowish oil (160 mg, 83%). R_f=0.35 (100:2 AcOEt/MeOH); $[\alpha]_D$ +6.5 (*c* 1.10 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.18 (br s, 1H), 8.31 (d, 1H, *J*=7.8 Hz), 7.46 (d, 1H, *J*=7.8 Hz), 5.94 (s, 1H), 5.23 (d, 1H, *J*=4.6 Hz), 4.60 (br app. t, 1H, *J*=2.7 Hz), 3.74 (dd, 1H, *J*=11.9, *J*=2.7 Hz), 3.44 (s, 3H), 3.39 (ddd, 1H, *J*=11.4, *J*=4.6, *J*=2.7 Hz), 2.26 (s, 3H), 2.12–1.99 (m, 1H), 1.99–1.88 (m, 1H), 1.87–1.55 (m, 1H), 1.73–1.55 (m, 1H), 1.23 (s, 9H), 1.04–0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 171.1, 163.0, 154.7, 144.2, 96.6, 91.9, 81.4, 76.6, 67.9, 60.3, 56.8, 38.9, 38.5, 30.3, 27.2, 25.6, 24.8, 19.1; MS (ESI) 449 $[M+H]^+$.

4.1.29. (2*R*, 3*R*, 3a*S*, 6*R*, 7*R*, 7a*S*)-[2-(4′-Amino-2′-oxo-2*H*-pyrimidin-1′-yl)-octahydro-3-hydroxy-6-methoxy-benzofuran-7-yl]urea (46). The azide **45** (100 mg, 0.22 mmol) was dissolved in dry THF (6.6 mL) and argon was bubbled in the solution for 10 min. Water (17 μL) and Me_3P (0.66 mL, 1 M solution in toluene, 0.66 mmol) were added. After 5 min at room temperature, the solution was refluxed for 30 min, then concentrated, and kept in vacuo for 1 h. The residue was then dissolved in dry CH_2Cl_2 (6.6 mL) and trichloroacetylisocyanate (30 μL, 0.25 mmol) was added. After 1 h at room temperature, the solution was concentrated. The oily residue was dissolved in MeOH (6.6 mL), 40% $MeNH_2$ in water (6.6 mL) was added and the solution was stirred for 30 h. Concentration gave a solid, which was purified successively by flash silica gel chromatography (CH_2Cl_2/MeOH/25% aq NH_3, 10:3:0.3) and reverse phase HPLC (LiChrospher 100 RP 18, CH_3CN 0–100% gradient) to give **46** as a colorless crystalline solid (45 mg, 0.0233 mmol, 60%). R_f=0.18 (10:3:0.3 CH_2Cl_2/MeOH/NH_3 aq 25%); mp 278–288 °C (decomposition); $[\alpha]_D$ +8.1 (*c* 0.56 in $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 7.85 (d, 1H, *J*=7.8 Hz), 5.83 (d, 1H, *J*=7.8 Hz), 5.62 (s, 1H), 5.94–4.86 (br m, 1H), 4.09 (d, 1H, *J*=4.6 Hz), 3.92 (dd, 1H, *J*=11.0, *J*=3.0 Hz), 3.47–3.40 (m, 1H), 3.37 (s, 3H), 1.95–1.89 (br m, 1H), 1.78–1.71 (m, 1H), 1.63–1.53 (br m, 1H), 1.52–1.38 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 167.9, 162.5, 158.4, 142.0, 96.0, 95.2, 83.7, 79.1, 76.8, 56.5, 49.5, 40.5, 27.9, 19.5; HRMS calcd for $C_{14}H_{22}N_5O_5$ $[M+H]^+$ 340.1621; found 340.1624.

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