JOC*Article*

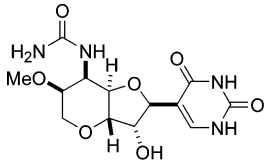
Total Synthesis of *N*-Malayamycin A and Related Bicyclic Purine and Pyrimidine Nucleosides

Stephen Hanessian,* Guobin Huang, Caroline Chenel, Roger Machaalani, and Olivier Loiseleur†

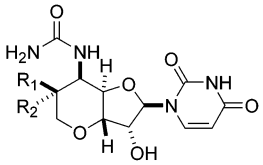
Department of Chemistry, Université de Montréal, C. P. 6128, Succ. Centre-Ville, Montréal, P. Q., Canada H3C 3J7, and Syngenta Crop Protection AG, WRO 1060.5.04, Schwarzwaldaller, CH-4002 Basel, Switzerland

stephen.hanessian@umontreal.ca

Received April 12, 2005



Malayamycin A



N-Malayamycin A and analogues;
R_1 = OMe; R_2 = Me; R_1= F; R_2 = H.
R_1 = OMe; R_2 = H

Methods are described for the total synthesis of bicyclic perhydrofuropyran nucleosides as *N*-analogues of the naturally occurring malayamycin A. Formation of the *N*-nucleosides relied on the activation of thioglycosides, proceeding via sulfonium intermediates. Ring closure metathesis was used in two approaches to build the bicyclic dioxa heterocycle. Another approach relied on the use of a sugar precursor and cyclization to the bicyclic thioglycoside.

Introduction

The phenomenal advances in the chemistry and biology of purine and pyrimidine ribonucleosides over the past few decades have unraveled many of life's mysteries, culminating with the deciphering of the genetic code. Nature has also been a generous provider of a rich source of non-DNA/RNA related nucleosides, possessing fascinating structures and impressive chemotherapeutic effects.[1] Indeed, some of the most potent anticancer and antiviral agents of clinical importance are nucleosides.[2] Extensive efforts have been made over the years toward the development of synthetic or semisynthetic analogues to broaden the biological profile and potential toxic effects of certain naturally occurring nucleosides.[3]

There are a handful of *N*- and *C*-nucleosides in which the "sugar" part consists of a bicyclic perhydrofuropyran rather than the commonly encountered monocyclic pentofuranosyl and hexofuranosyl subunits.[4] Ezomycin A_2, **1**,[5] and octosyl acid A, **2**,[6] are examples of bicyclic uracilyl nucleosides with reported antifungal activity (Figure 1). Quantamycin **3**[7] is an example of a "man-made" hybrid analogue of lincomycin, which was designed to mimic the natural *f*-Met *t*-RNA starter unit during ribosomal protein synthesis. Ezomycin B_2, **4**,[8] is the *C*-nucleoside counterpart of ezomycin A_2. The most recent entry in the small arsenal of bicyclic *C*-nucleosides is malayamycin A, **5**, a potent fungicide which was isolated from the soil organism *Streptomyces malaysiensis* by a group at the Syngenta Crop Protection Laboratories in Jealott's Hill U.K.[9] The structure and absolute configuration of malayamycin A was recently confirmed by total synthesis.[10]

† Syngenta Crop Protection AG.

(1) For pertinent reviews, see (a) Ichikawa, S.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 3895. (b) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859. (c) Isono, K. *Pharm. Ther.* **1991**, *52*, 264.

(2) (a) Walker, M. P.; Appleby, T. C.; Zhong, W.; Lau, j. Y. N.; Hong, Z. *Antiviral Chem. Chemother.* **2003**, *14*, 1. (b) Mansour, T.; Storer, R. *Curr. Pharm. Design* **1997**, *3*, 227.

(3) Gao, H.; Mitra, A. K. *Synthesis* **2000**, 329.

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

(5) (a) Sakata, K.; Bakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1973**, *37*, 697. (b) Sakata, K.; Sakurai, A.; Tamura, S. *Agric. Biol. Chem.* **1975**, *39*, 885; 3141.

(6) For the total synthesis of octosyl acid, see: (a) Danishefsky, S.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486. (b) Hanessian, S.; Kloss, J.; Sugawara, T. *J. Am. Chem. Soc.* **1986**, *108*, 2758. For isolation, see: (c) Isono, K.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc*. **1975**, *97*, 043.

(7) Hanessian, S.; Sato, K.; Liak, T. J.; Danh, N.; Dixit, D. M.; Cheney, B. V. *J. Am. Chem. Soc*. **1984**, *106*, 6114.

(8) Sakata, K.; Sakurai, A. Tamura, S. *Tetrahedron Lett*. **1975**, 3191.

(9) Benner, J. P.; Boehlendorf, B. G. H.; Kips, M. R.; Lambert, N. E. P.; Luck, R.; Molleyres, L.-P.; Neff, S.; Schuez, T. C.; Stanley, P. D. WO 03/062242, CAN 139:132519.

10.1021/jo050727b CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/21/2005

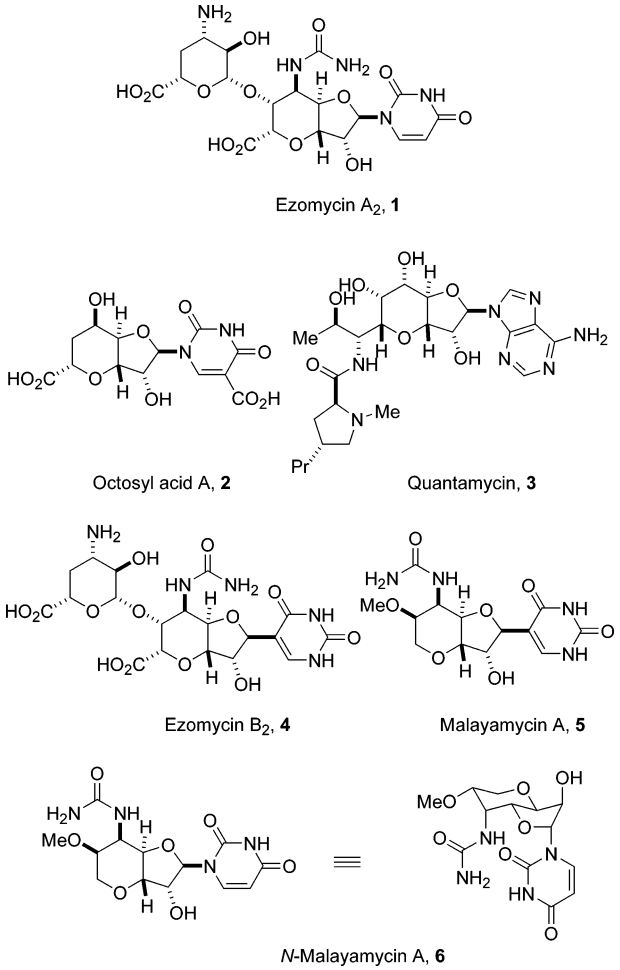


FIGURE 1. Structures of *N*- and *C*-bicyclic nucleosides.

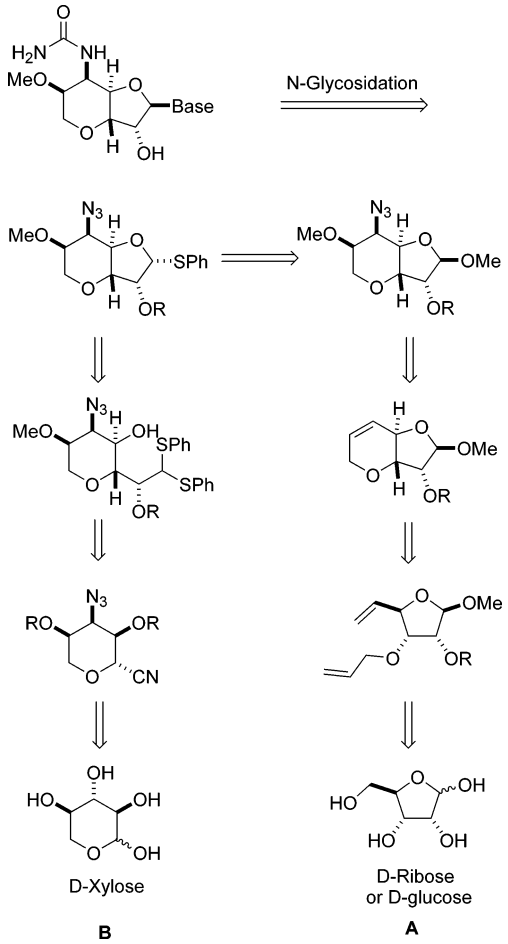


FIGURE 2. Disconnective analyses.

Although ezomycin B_2 and malayamycin A share the common "nucleoside" portion, there are notable differences in the nature and stereochemistries of the functional groups present in the six-membered tetrahydropyran subunit (Figure 1).

By analogy to the naturally occurring *N*- and *C*-ezomycins, it was of interest to consider a total synthesis of *N*-malayamycin A, **6,** and related purine and pyrimidine congeners. The availability of such analogues with modified heterocyclic aglycones would also provide an opportunity to test their biological activities, since the corresponding *C*-malayamycins are presently not available. We therefore set out to develop methods for the stereocontrolled construction of the bicyclic core,[11] allowing for flexibility of anomeric diversity. Toward that goal, we intended to synthesize the *N*-malayamycins with 1-uracilyl, 1-cytosinyl, 1-thyminyl, 9-adeninyl, and 9-hypoxanthinyl heterocyclic aglycones.

We chose two approaches that would converge to a common precursor. In the first, ring closure metathesis[12] of an appropriate diene prepared from D-ribose would generate the unsaturated perhydrofuropyran, which would undergo site-selective functionalization to install the *syn*-disposed azido and alcohol groups (Figure 2A). In an alternative disconnection we would build the azido intermediate from D-xylose and elaborate the bicyclic system via a glycosyl nitrile (Figure 2B). An anomeric phenylthio group would then be used to introduce the heterocyclic aglycones en route to the intended targets. We have previously exploited the activation of thioglycosides with thiophilic agents as a means to prepare quantamycin and other bicyclic nucleosides.[4,7,13] A major challenge however, was to maintain the integrity of the *trans*-fused and relatively strained bicyclic core during the exchange of a thiophenyl group to a purine or pyrimidine moiety.

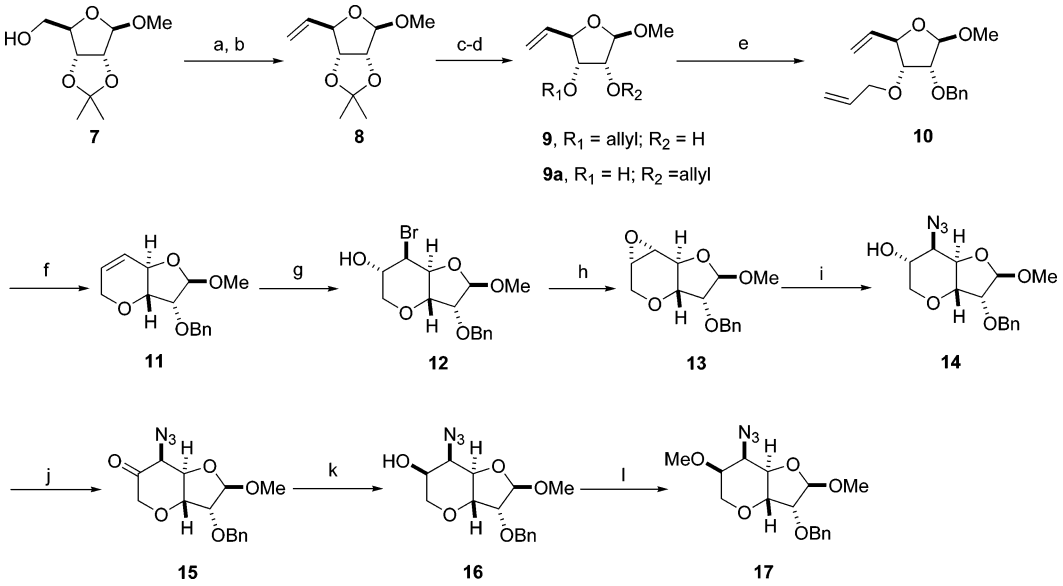
(10) Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G. *Org. Lett*. **2003**, *5*, 4277.

(11) For the synthesis of related bicyclic fused compounds, see: (a) Ravn, J.; Nielsen, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 985. (b) Oh, J.; Lee, C. R.; Chun, K. H. *Tetrahedron Lett.* **2001**, *42*, 4879. (c) Leeuwenburgh, M. A.; Kulker, C.; Dugnster, H. I.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. *Tetrahedron* **1999**, *55*, 8253. (d) Meur, R.; Grüschow, S.; Leumann, C. *Helv. Chim. Acta* **1999**, *82*, 1813. (e) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. *Synlett* **1997**, 1263. (f) Nicolaou, K. C.; Postema, H. D.; Claiborne, C. I. *J. Am. Chem. Soc*. **1996**, *118*, 1565. (g) Clark, J. S. Kettle, J. G.; *Tetrahedron Lett*. **1997**, *38*, 127. (h) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun*. **1998**, 1041. (i) Delgado, M.; Martin, J. D. *Tetrahedron Lett*. **1997**, *38*, 6299. (j) Peris, E.; Cavé, A.; Estornell, E.; Zafra,-Polo, M. C.; Frigadère, B.; Cortes, D.; Bermejó, A. *Tetrahedron* **2002**, *58*, 1335.

(12) For pertinent reviews, see: (a) Grubbs, R.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371. (c) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, H. H. *Chem. Commun*. **1998**, 1315. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed*. **1997**, *36*, 2036.

(13) For related methods, see: (a) Knapp, S.; Shieh, W.-C. *Tetrahedron Lett*. **1991**, *32*, 3627. (b) Knapp, S.; Shih, W.-C.; Jaramillo, C.; Triller, R. V.; Nandau, S. R. *J. Org. Chem*. **1994**, *59*, 946.

SCHEME 1[a]



[a] Reagents and conditions: (a) IBX, MeCN, reflux, 2 h, 92%, or CrO_3, pyridine, CH_2Cl_2, rt, 30min, 70%; (b) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, −78 °C, 3 h, 85%; (c) catalytic TsOH, MeOH, reflux, 24 h, 83%; (d) allyl bromide, Bu_2SnO, Bu_4N+I, 4Å MS, MeCN, reflux, 5 h 58%; (e) BnBr, NaH, DMF, rt, overnight, 91%; (f) $Cl_2RuCHPh(PCy_3)_2$ (5% mol), CH_2Cl_2 (c = 0.01 M), reflux, 8 h, 68%; (g) NBS, THF/H_2O (1:1), rt, 2 h; (h) 1 N NaOH, THF, reflux, 1 h; (i) NaN_3, 2-methoxyethanol, 126 °C, 53% in 3 steps; (j) Dess−Martin periodinane, CH_2Cl_2, rt, 2.5 h; (k) $NaBH_4$, MeOH, 0 °C, 1 h; (l) MeI, NaH, DMF, rt, overnight, 81% in 3 steps.

Results

The readily available acetonide **7**[14] was converted to the 5-vinyl derivative, **8**, via oxidation to the aldehyde and Wittig olefination (Scheme 1).[15] Selective acetal cleavage to **9** and treatment with dibutyltin oxide and allyl bromide[16] gave the desired regioisomer **9** (58%) and the 2-*O*-allyl analogue **9a**, which could be easily separated by chromatography. Treatment of **9** with benzyl bromide under usual alkylation conditions gave **10** in quantitative yield. Reversing the order of alkylation by first treatment with dibutyltin oxide and benzyl bromide gave a 1:1 mixture of both regioisomers.

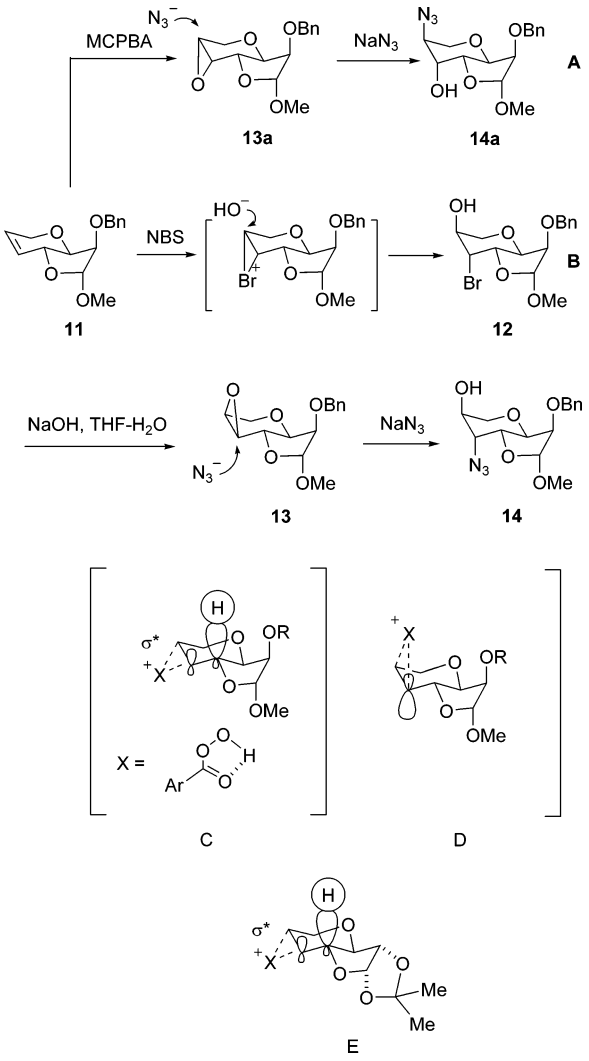
With the two olefin appendages in place, we proceeded with the ring closure metathesis reaction using the Grubbs first generation catalyst[12,17] to give the bicyclic intermediate **11** in 68% yield. Treatment of **11** with NBS in aqueous THF followed by NaOH[18] gave the epoxide **13**. Subsequent opening with sodium azide in 2-methoxyethanol afforded the desired regioisomeric azide **14** in good overall yield. Inversion of configuration was achieved by oxidation with the Dess−Martin periodinane reagent[19] to **15**. Reduction with $NaBH_4$, and methylation gave the fully functionalized perhydrofuropyran subunit **17**.

Initially, we had explored a direct epoxidation route to **13** (Scheme 2A). Thus, treatment of **11** with mCPBA[20] gave **13a**, which underwent a *trans*-diaxial opening with azide ion to give the regioisomeric **14a**.[10] Evidently, epoxidation had occurred from the least hindered face of the endocyclic double bond, possibly due to the proximal *O*-benzyl ether. This preference has precedence[21,22] and can also be rationalized by considering the favorable electron-donating ability of the C−H σ bond with the developing antibonding orbital in the transition state model C leading to the observed epoxide (Scheme 2).[23] Approach of the peracid from the opposite side as depicted in D would not benefit from the same stereoelectronic effect. The transition state model in the epoxidation of the tricyclic acetonide analogue E, in which an impeding benzyl ether is absent, also takes place from the same side as in **11** (Scheme 2, see below). Likewise, treatment with NBS in aqueous THF gave the α-orientated epibromonium ion, which underwent *trans*-diaxial attack by hydroxide ion leading to the diaxial bromohydrin **12**. Subsequent treatment with base generated the correct regioisomeric epoxide **13** (Scheme 2B).

The stereocontrolled introduction of various purine and pyrimidine heterocycles at the anomeric position en route to *N*-malayamycin and analogues presented certain challenges. We had previously shown that related bicyclic phenylthio glycosides could be converted to adenine nucleosides simply by activation with bromine and addition of adenine in DMF.[4,7] Activation of the phenylthio group via a sulfonium intermediate followed by direct attack of adenine or by participation of a 2′-benzoate had

(14) Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem*. **1966**, 3, 485.
(15) Butterworth: R. F.; Hanessian, S. *Can. J. Chem.* **1971**, *49*, 2755.
(16) For a review, see: David, S.; Hanessian, S. *Tetrahedron* **1985**, 41, 643.
(17) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100.
(18) (a) Bannard, R. A. B.; Casselman, A. A.; Hawkins, L. R. *Can. J. Chem*. **1965**, *43*, 2398. (b) Bannard, R. A. B.; Casselman, A. A.; Langstaff, E. J.; Moir, R. Y. *Can. J. Chem.* **1968**, *46*, 35.
(19) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277. for a review, see: Moriarty, R. M. *Org. React*. **1999**, *54*, 273.
(20) For a review, see: Krow, G. R. *Org. React*. **1993**, *43*, 251.
(21) Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem*. **2003**, 68, 7219.
(22) (a) Hussain, N.; Leonard, J. *Tetrahedron Lett*. **1987**, *28*, 4871. (b) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett*. **1985**, *26*, 4895. (c) Leeper, F. J.; Howard, S. *Tetrahedron Lett*. **1995**, *36*, 2335.
(23) Cieplak, A. S. *J. Am. Chem. Soc*. **1981**, *103*, 4540.

SCHEME 2



led to an anomeric mixture of bicyclic nucleosides. Knapp[13] has also shown that similar activation was possible using NIS and triflic acid[24] in the synthesis of the bicyclic unit of ezomycin A_1.

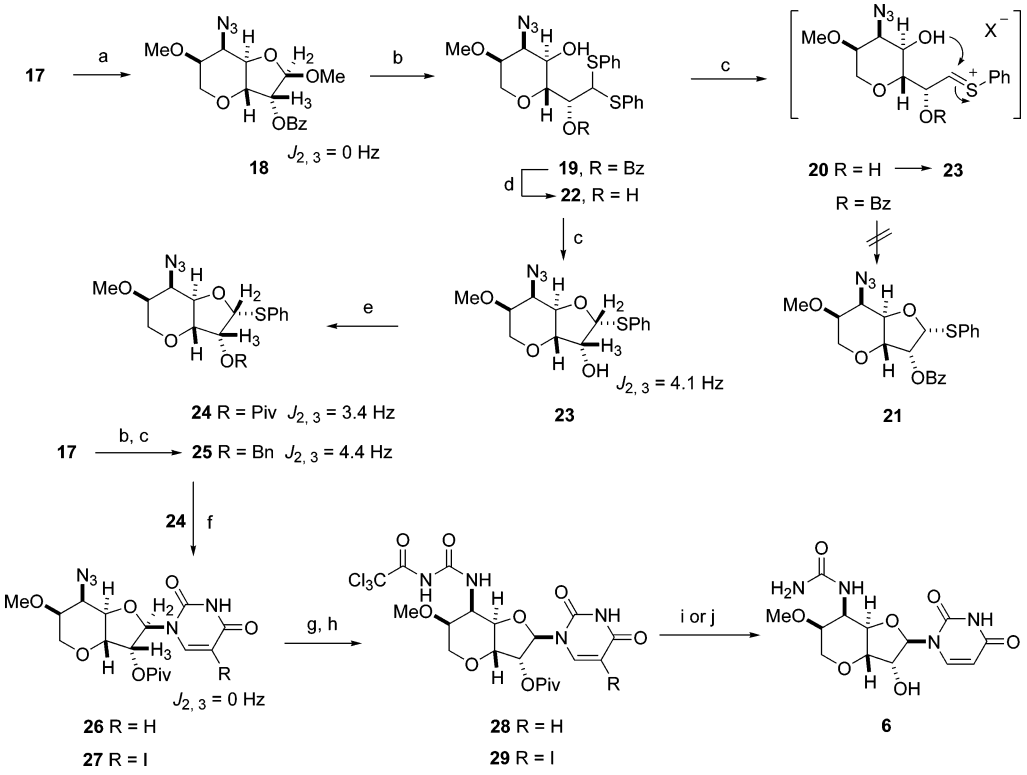
We first explored the reactivity of a diphenyldithioacetal intermediate in a synthesis of the intermediate phenylthio glycoside (Scheme 3). To secure a 1′,2′-*trans* relationship of the intended nucleosides, we relied on a neighboring group participation by the C_2'-benzoate. Thus, treatment of **17** with $RuCl_3/NaIO_4$[25] gave the desired benzoate **18** in 80% yield. The diphenyldithioacetal **19** was easily obtained from **18** by treatment with benzene thiol and $BF_3{\cdot}Et_2O$.[26] Treatment of **19** with NBS did not lead to the desired bicyclic thioglycoside **21** presumably because of concomitant participation of the neighboring benzoate, at the intermediate *S*-phenylthionium ion **20** stage, and subsequent degradation. However, cyclization of the free C_2' OH analogue **22** in the presence of NBS gave directly the bicyclic α-phenylthioglycoside **23** in 76% yield. Formation of the *O*-benzyl analogue **25** from **17** was also achieved under the same conditions. It is of interest that the *trans*-fused bicyclic perhydrofuropyran thioglycosides **23** and **25** are obtained in good yields and in anomerically pure form from their respective acyclic *S*-phenylthionium precursor **20**. Most likely, this must take place by a π-face selective approach of the tetrahydropyranyl C-3 hydroxyl group.[4,7,13] Although initial epoxide formation from **20** and opening with inversion cannot be excluded in the case of **23**, the high yield cyclization of *O*-benzyl **17** to **25** favors the direct attack on the thionium intermediate. To ensure a stereocontrolled introduction of the uracil unit, we chose to protect C_2' as the pivalate **24** rather than to rebenzoylate. Activation of the phenylthio group with NIS and triflic acid in the presence of 2, 4-trimethysiloxypyrimidine[13] led to **26** in 62% yield as the only detectable anomer, as a result of pivalate participation.[27] This reaction was accompanied by the formation of the 5-iodo uracil nucleoside **27**, which could be separated by chromatography.[28] Reduction of the azido group in **26** and **27** under Staudinger conditions,[29] followed by treatment with trichloroacetyl isocyanate[13b] gave the corresponding ureas **28** and **29**. Cleavage of the trichloroacetyl and pivaloyl groups from **28** with methylamine[30] gave *N*-malayamycin A **6,** as an amorphous colorless solid. Catalytic hydrogenation to remove the iodo group in **29** and subsequent urea formation also gave **6**. Using the same protocol, the thioglycoside **24** was transformed individually into the thymine **30**, cytosine **31**, adenine **32**, and inosine **33** nucleosides (Scheme 4). Elaboration of functional groups as described above, gave *N*-malayamycin nucleoside analogues **34**−**37**.

An alternative synthesis of the dithioacetal precursor **19** is shown in Scheme 5. The readily available 3-azido analogue **38**, prepared from D-xylose in four steps,[31] was treated with aqueous acetic acid followed by esterification with benzoyl chloride to give the corresponding benzoylated analogue **39** in excellent yield. Activation of the anomeric benzoate in the presence of $BF_3{\cdot}Et_2O$ in $MeNO_2$ and treatment with TMSCN[32] afforded 3-azido-2,4-di-*O*-benzyl-β-D-ribofuranosyl nitrile **40** and its α-anomer in a ratio of >4:1 and a 73% combined yield. Treatment with trimethylaluminum and *N*,*O*-dimethylhydroxylamine[33] gave the Weinreb amide **41** in 68% yield after separation of the α-anomer. Dibal-H reduction led to the primary alcohol which was oxidized with the Dess−Martin periodinane[19] reagent to the aldehyde **42**.

Treatment of **42** with the lithium anion derived from bis(phenylthio)methane led to a 2:1 mixture of epimeric alcohols, which was enriched in the desired *R*-isomer **43**

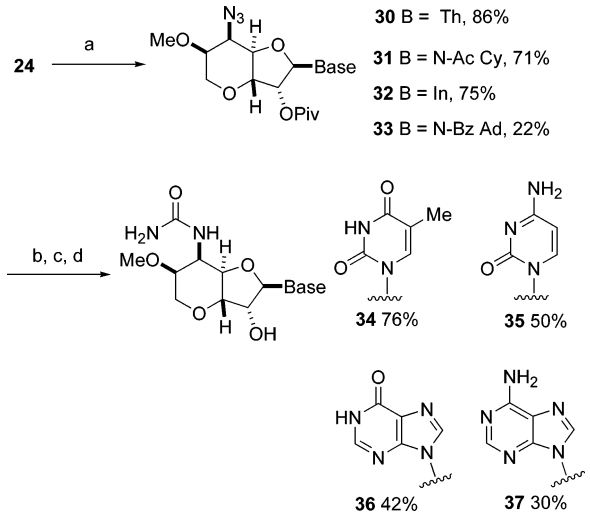
(24) Veeneman, G. h.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett*. **1990**, *31*, 1331.
(25) (a) Tamura, J.; Koike, S.; Shimadate, T. *J. Carbohydr. Chem*. **1991**, *11*, 531. (b) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett*. **1983**, *24*, 3829. (c) Kim, B. M.; Sharpless, C. B. *Tetrahedron Lett*. **1989**, *30*, 655.
(26) Furneaux, R. H.; Martin, B.; Rendle, P. M.; Taylor, C. M. *Carbohydr. Res*. **2002**, *337*, 1999.
(27) Sato, S.; Nonomura, S.; Nakano, T.; Ito, Y.; Ogano, T. *Tetrahedron Lett*. **1988**, *29*, 4097.
(28) See, for example: Robins, M. J.; Barr, P. J.; Giziewicz, J. *Can. J. Chem*. **1982**, *60*, 554.
(29) (a) Vaultier, M.; Knouz, N.; Carrie, R. *Tetrahedron Lett*. **1983**, *24*, 763. (b) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
(30) Griffin, B. E.; Jarman, M.; Reese, C. B. *Tetrahedron* **1968**, *24*, 639.
(31) McDevitt, J. P.; Lansbury, P. T. *J. Am. Chem. Soc*. **1996**, *118*, 3818.
(32) Brunel, F. M.; Leduc, A.-M.; Mashuta, M. S.; Taylor, K. G.; Spatola, A. F. *Lett. Pept. Sci.* **2002**, *9*, 111.
(33) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815. (b) Barha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, 4271.

SCHEME 3[a]



[a] Reagents and conditions: (a) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, MeCN/CCl_4/H_2O (1:1:1.5), 16 °C, 24 h, 80%; (b) PhSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −78°C, 3 h, 97% for **19**, or 91% for **25**; (c) NBS, CH_2Cl_2, 0 °C, 20 min, 76% for **23**, or 80% for **25** ; (d) K_2CO_3, MeOH, rt, 30 min, 93%; (e) PivCl, DMAP, pyridine, rt, overnight, 100%; (f) *O*,*O*′-bis(trimethylsilyl)uracil, NIS, trifluoromethanesulfonic acid, CH_2Cl_2, rt, 4 h, 62% for **26**, 24% for **27**; (g) Me_3P, THF/H_2O, reflux, 60 min; (h) trichloroacetyl isocyanate, CH_2Cl_2, rt, 2 h; (i) 40% w/v $MeNH_2$, MeOH, rt, 3 days, 50% in 3 steps from **26**; (j) 10% palladium-on-carbon, H_2, Et_3N, 60 psi, rt, 24 h, then 40% w/v $MeNH_2$, MeOH, rt, 3 days, 45% in 3 steps from **27**.

SCHEME 4[a]



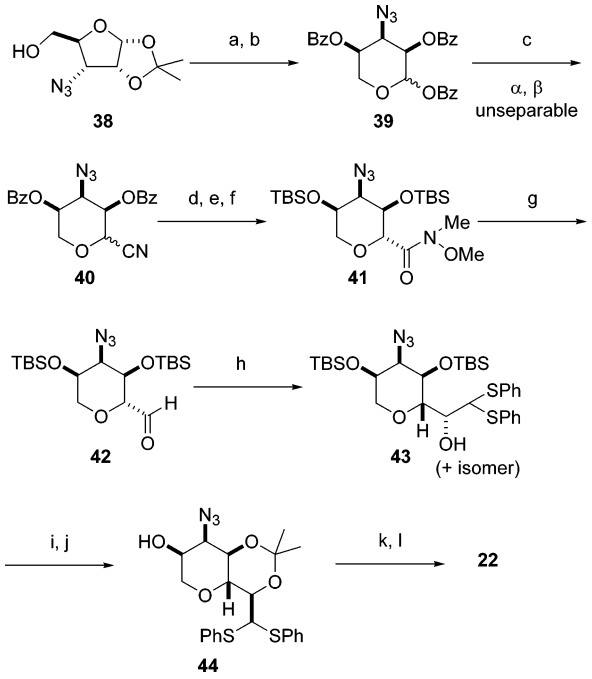
[a] Reagents and conditions: (a) *O*,*O*′-bis(trimethylsilyl)thymine, N^4-acetyl-*O*,N^4-bis(trimethylsilyl)cytosine, *O*,N^9-bis(trimethylsilyl) hypoxanthine, or N^6-benzoyl-*N*,$^6N^9$-bis(trimethylsilyl) adenine, NIS, TfOH, CH_2Cl_2; (b) Me_3P, THF/H_2O, reflux; (c) trichloroacetyl isocyanate, CH_2Cl_2; (d) 40% w/v $MeNH_2$, MeOH.

after chromatographic separation. To differentiate the three hydroxyl groups in **43**, it was treated in sequence with *n*-Bu_4NF and then with 2-methoxypropene in the presence of pTSA to afford the cyclic acetal **44**. Methylation and mild acid hydrolysis led to **22**, identical with a sample prepared via the RCM route.

In an effort to study the functional importance of the methyl ether, we sought another route to bicyclic intermediates that would be amenable to diversification. Starting with the readily available D-glucose, a six-step sequence has been reported to give intermediate **45** in 70% overall yield[11c] (Scheme 6). Ring closure metathesis of **45** using the Grubbs first generation catalyst gave the tricyclic olefin **46** in 92% yield. In their studies of the application of the Grubbs RCM reaction to carbohydrates, van Boom and co-workers[11c] reported a 63% yield for the formation of **46** at a substrate concentration of 0.02 M in order to avoid dimerization. Quite independently, we had performed the same cyclization at a concentration of 0.01 M and a catalyst loading of 5 mol %. On a 2 g scale the yield was consistently over 90%. Clearly, a higher dilution appears to be beneficial in the RCM cyclizations of relatively strained tricyclics such as **46**. Application of the bromohydrin-epoxidation and azide opening protocol as described for **11** led to **47** in 57% yield for three steps.

Oxidation with the Dess−Martin periodinane reagent,[19] followed by treatment of the ketone with MeMgBr in THF at −78 °C, led to the corresponding tertiary alcohol, as the only detectable isomer, albeit in modest overall yield. Methylation gave **48**, whose stereochemistry was ascertained by ^{1}H NMR (COSY, NOESY).[34] The ketone intermediate resulting from the oxidation of **47**

SCHEME 5[a]

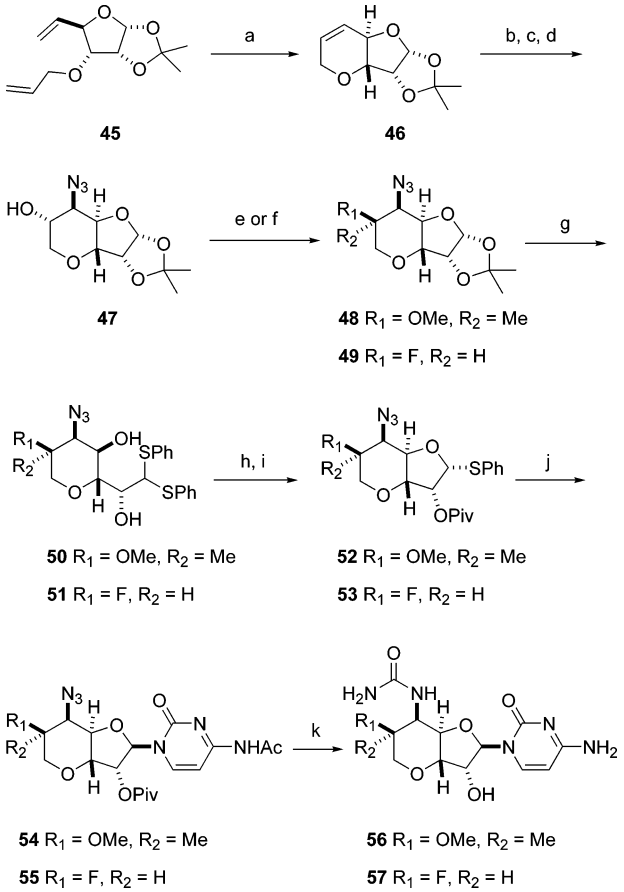


[a] Reagents and conditions: (a) AcOH/H_2O (1/1), 100 °C, 85%; (b) BzCl, Et_3N, DMAP, DCM, 97%; (c) TMSCN, TMSOTf, $MeNO_2$, 73%, β/α 4:1; (d) (i) NaOMe 0.1 equiv, MeOH, 1 h, (ii) NaOH 5 M/MeOH (1/1), 50 °C, 2 h, (iii) TMSCl, MeOH, 75% over three steps; (e) TBDMSCl, imid., DCM, 95%; (f) $AlMe_3$, HCl.HN(Me)OMe, 68%; (g) (i) DIBALH, toluene, −78 °C, 2 h, (ii) Dess−Martin periodinane, $NaHCO_3$(s), DCM, 2 h; (h) $(PhS)_2CH_2$, BuLi, −78 °C, 30 min, 75% over three steps, (*R*)/(*S*) 2:1; (i) TBAF, 4Å MS, THF, 92%; (j) PTSA, Na_2SO_4, 2-methoxypropene, DCM, 91%; (k) NaH 1.5 equiv, MeI 1.2 equiv, 0 °C, 93%; (l) PTSA, MeOH, 100%.

was prone to epimerization of the axially disposed azide group. It was used without purification, hence the low overall yield of **48**. Treatment of **47** with DAST[35] gave the inverted fluoride **49** in modest yield. The reaction was accompanied by the formation of baseline material, and attempts to increase the yields were not successful. Cleavage of the acetal with concomitant dithioacetal formation in **48** and **49** was most efficiently done with benzenethiol in the presence of Amberlyst-15 suspended in CH_2Cl_2[36] to give the corresponding products **50** and **51** in 80% and 85% yields, respectively. Thioglycoside formation in the presence of NBS followed by pivaloylation proceeded in good overall yield to give **52** and **53** (72% and 69%, respectively). In this series we chose to prepare the corresponding *N*-cytosinyl analogues. Application of the same protocol for the synthesis of **31** (Scheme 4) proceeded smoothly to give **54** and **55** which were individually transformed into the C_6 modified analogues **56** and **57** (Scheme 6).

In conclusion, we have described the total synthesis of *N*-malayamycin A and related pyrimidine and purine nucleosides using three approaches. The key carbocyclization step to bicyclic perhydrofuropyran intermediates in two of the approaches involved a Grubbs ring closure metathesis reaction that proceeded in excellent yield.

SCHEME 6[a]



[a] Reagents and conditions: (a) $Cl_2RuCHPh(PCy_3)_2$ (5% mol), CH_2Cl_2 (c = 0.01 M), reflux, 3 h, 92%; (b) NBS, THF/H_2O (1:1), rt, 2 h; (c) 1 N NaOH, THF, reflux, 1 h; (d) NaN_3, 2-methoxyethanol, 126 °C, 1 h, 57% in 3 steps; (e) (i) Dess−Martin periodinane, CH_2Cl_2, rt, 2.5 h, (ii) MeMgBr, THF, −78 °C, 1 h, 18% in 2 steps, (iii) MeI, NaH, DMF, rt, 2 h, 75% for **48**; (f) DAST, CH_2Cl_2, −78 °C to rt, 30% for **49**; (g) PhSH, Amberlyst-15, CH_2Cl_2, 80% for **50**, 85% for **51**; (h) NBS, CH_2Cl_2; (i) PivCl, DMAP, pyridine, 72% for **52**, 69% for **53** in 2 steps; (j) N^4-acetyl-*O*-trimethylsilylcytosine, NIS, trifluoromethanesulfonic acid, CH_2Cl_2, rt, 4 h, 66% for **54**, 70% for **55**; (k) (i) Me_3P, THF/H_2O, reflux, 60 min, (ii) trichloroacetyl isocyanate, CH_2Cl_2, rt, 2 h, (iii) 40% w/v $MeNH_2$, MeOH, rt, 3 days, 9% for **56**, 30% for **57** in 3 steps.

Regioselective functionalization of the bicyclic olefins was achieved through stereocontrolled epoxidation and diaxial opening with azide ion. The formation of bicyclic *N*-nucleosides was achieved with a variety of purine and pyrimidine bases, and new analogues substituted in the dihydropyran unit were synthesized from a common intermediate. Further aspects of the chemistry and biological properties of these unique class of bicyclic *C*- and *N*-nucleosides related to malayamycin A will be reported in due course.

Experimental Section

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-ribo-hex-5-enofuranoside (8). To a suspension of methyltriphenylphosphonium bromide (12.9 g, 36 mmol) in 350 mL of anhydrous THF was added dropwise 14.4 mL of BuLi (2.5 M solution in hexanes, 36 mmol) at −78 °C under argon atmosphere. After addition was completed, the resulting mixture was stirred at 0 °C for 30 min and then cooled to −78 °C again. A solution of

(34) See Supporting Information.
(35) For a review, see: Hudlicky, M. *Org. React.* **1988**, *35*, 513.
(36) Loiseleur, O.; Vifian, T. Syngenta Crop Protection, Basel, Switzerland; unpublished results.

aldehyde (6.06 g, 30 mmol) obtained from the oxidation of **7**[15] in 60 mL of anhydrous THF was added to this solution over 30 min. The mixture was warmed to room temperature, stirred for 3 h at this temperature, then quenched by adding saturated NH_4Cl (400 mL). The mixture was extracted with Et_2O (200 mL × 3), and the combined organic layer was washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 10:1) afforded product **8** (5.1 g, 85%) as a colorless oil: $[\alpha]_D$ −57.6° (*c* 1.15, $CHCl_3$); IR (thin film) ν 2989, 2939, 1461, 1425, 1373, 1211, 1105, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (s, 3H, $-CH_3$), 1.48 (s, 3H, $-CH_3$), 3.33 (s, 3H, −OMe), 4.64 (m, 3H), 4.97 (s, 1H), 5.14 (d, 1H, J = 10.3 Hz), 5.25 (d, 1H, J = 16.7 Hz), 5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.4, 26.9, 54.5, 84.39, 85.4, 88.3, 109.1, 112.2, 117.2, 137.5; HRMS (FAB) calcd for $C_{10}H_{17}O_4$ $[M + H]^+$ 201.1127, found 201.1126.

Methyl 3-*O*-Allyl-5,6-dideoxy-β-D-ribo-hex-5-enofuranoside (9). A mixture of **8** (4.5 g, 22.5 mmol) and TsOH (0.5 g) in dry MeOH (500 mL) was refluxed for 24 h, pyridine (0.5 mL) was added, and the mixture was concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 2:1) afforded a mixture of α and β diols (3.0 g, 83%) as a colorless oil with a 1:7 ratio: $[\alpha]_D$ −24.2° (*c* 2.18, $CHCl_3$); IR (thin film) ν 3402, 2936, 1646, 1426, 1196, 1124, 1030, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.38 (br, 2H, −OH × 2), 3.40 (s, 3H, −OMe), 4.14 (m, 1H, H-2), 4.17 (m 1H, H-4), 4.33 (t, 1H, J = 6.8 Hz, H-3), 4.87 (s, 1H, H-1), 5.21 (d, 1H, J = 12.8 Hz), 5.36 (d, 1H, J = 17.1 Hz), 5.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.2, 75.2, 75.3, 85.2, 107.9, 117.4, 136.9; HRMS (FAB) calcd for $C_7H_{12}O_4$ $[M^+]$ 160.0736, found 160.0734.

To a solution of the above diol (2.62 g, 16.4 mmol) in 200 mL of dry MeCN were added Bu_2SnO (4.9 g, 19.7 mmol), *n*-Bu_4NI (4.84 g, 13.1 mmol), allyl bromide (1.42 g, 16.4 mmol), and 4Å molecular sieves (17.0 g) at room temperature under argon atmosphere. The mixture was refluxed for 5 h, and solvent was removed by evaporation. To the residue were added Et_2O (200 mL) and H_2O (200 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (100 mL × 2), and the combined organic layer was washed with saturated $NaHCO_3$, brine, then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 10:1) afforded the product **9** (1.9 g, 58%) as a colorless oil: $[\alpha]_D$ +82.5° (*c* 0.2, $CHCl_3$); IR (thin film) ν 3557, 3083, 2987, 2918, 2850, 1733, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.74 (d, 1H, J = 8.9 Hz, −OH), 3.41 (s, 3H, −OMe), 3.61 (dd, 1H, J = 7.0, 3.7 Hz), 4.17 (m, 3H, H-2 and $-CH_2O-$), 4.44 (t, 1H, J = 5.1 Hz, H-4), 4.91 (d, 1H, J = 4.6 Hz, H-1), 5.2−5.4 (m, 4H, CH_2=CH−), 5.80−5.95 (m, 2H, H-5 and CH_2=C*H*−); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.5, 71.1, 72.2, 79.4, 82.9, 102.4, 116.8, 117.7, 134.1, 135.7.

Methyl 3-*O*-allyl-2-*O*-benzyl-5,6-dideoxy-β-D-ribo-hex-5-enofuranoside (10). To a solution of alcohol **9** (1.9 g, 9.5 mmol) in 40 mL of dry DMF were added NaH (60% dispersion in mineral oil) (750 mg, 18.8 mmol) and BnBr (1.93 g, 11.3 mmol) at 0 °C under argon atmosphere. After stirring overnight, the reaction was quenched by adding saturated $NaHCO_3$ (100 mL), and the mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$, brine, then dried over anhydrous Na_2SO_4, filtered, concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 10:1) afforded **10** (2.5 g, 91%) as a colorless oil: $[\alpha]_D$ +8.8° (*c* 0.5, $CHCl_3$); IR (thin film) ν 3402, 2936, 1646, 1426, 1196, 1124, 1030, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.37 (s, 3H, −OMe), 3.87 (m, 2H, H-2 and H-3), 4.00 (m, 2H), 4.52 (t, 1H, J = 3 Hz), 4.65 (d, 1H, J = 11.0 Hz, $PhCH_2-$), 4.72 (d, 1H, J = 11.0 Hz, $PhCH_2-$), 4.91 (s, 1H), 5.1−5.2 (m, 4H), 5.87 (m, 2H), 7.2−7.4 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.5, 72.0, 72.8, 80.2, 82.3, 82.5, 106.6, 117.9, 128.2, 128.4, 128.8, 134.8, 138.1, 138.2; HRMS (FAB) calcd for $C_{17}H_{22}O_4$ $[M^+]$ 290.1518, found 290.1518.

(2*R*,3*R*,3a*R*,7a*R*)-3-Benzyloxy-2-methoxy-3,3a,5,7a-tetrahydro-2*H*-furo[3,2-*b*]pyran (11). To a solution of **10** (1.0 g, 3.66 mmol) in 366 mL of dry degassed CH_2Cl_2 was added 5 mol % Grubbs catalyst $[Cl_2RuCHPh(PCy_3)_2]$ (150 mg, 0.18 mmol) under argon atmosphere at room temperature, and the mixture was heated to reflux for 8 h until the starting material disappeared. The mixture was concentrated and the residue was purified by flash silica gel chromatography (hexane/ethyl acetate, 5:1) to afford **11** (650 mg, 68%) as a colorless oil: $[\alpha]_D$ −49.7° (*c* 0.3, $CHCl_3$); IR (thin film) ν 2933, 1730, 1454, 1367, 1100, 1027, 926, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.38 (s, 3H, −OMe), 3.57 (dd, 1H, J = 8.9, 4.3 Hz), 3.94 (d, 1H, J = 4.3 Hz), 4.43 (m, 2H), 4.54 (d, 1H, J = 8.9 Hz), 4.64 (d, 1H, J = 12.0 Hz, $PhCH_2-$), 4.84 (d, 1H, J = 12.0 Hz, $PhCH_2-$), 4.95 (s, 1H), 5.66 (m, 1H), 6.24 (d, 1H, J = 10.3 Hz), 7.29−7.39 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.8, 68.6, 71.3, 72.0, 78.3, 79.6, 109.3, 126.6, 127.5, 127.6, 127.7, 128.3, 137.7; HRMS (FAB) calcd for $C_{15}H_{18}O_4$ $[M^+]$ 262.1205, found 262.1202.

(2*R*,3*R*,3a*R*,6*R*,7*R*,7a*R*)-7-Azido-3-benzyloxy-2-methoxy-hexahydro-furo[3,2-*b*]pyran-6-ol (14). To a solution of **11** (464 mg, 1.77 mmol) in 20 mL of THF/H_2O (1:1) was added *N*-bromosuccinimide (550 mg, 3.1 mmol) at room temperature. The mixture was stirred vigorously for 1.5 h, poured into 20 mL H_2O containing 1.0 g $Na_2S_2O_3$ and extracted with EtOAc (50 mL ×3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford crude product **12**, which was engaged in the next reaction.

To a solution of **12** in 25 mL of THF was added 1 N NaOH (13 mL). The solution was refluxed for 1 h, poured into 50 mL of H_2O, and extracted with EtOAc (60 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to afford **13** as a crude oil.

This product was dissolved in 100 mL of 2-methoxyethanol, 2.56 g (39.3 mmol) of sodium azide was added, and the mixture was heated to 126 °C for 2 h. The mixture was poured into 200 mL of saturated brine and extracted with EtOAc (60 mL × 4), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 4:1) to afford azide **14** (300 mg) as a white powder: yield 53%; mp 120−122 °C; $[\alpha]_D$ −3.05° (*c* 1.8, $CHCl_3$); IR (thin film) ν 3067, 2911, 2101, 1454, 1124, 1061, 1022, 903 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.3 (d, 1H, J = 6.9 Hz, −OH), 3.39 (s, 3H, −OMe), 3.70 (m, 1H, H-6), 3.77−3.90 (m, 3H, H-5 and H-3a), 3.96 (d, 1H, J = 4.3 Hz, H-3), 4.29 (m, 1H, H-7), 4.46 (dd, 1H, J = 10.3, 3.2 Hz, H-7a), 4.65 (d, 1H, J = 12.0 Hz, $PhCH_2-$), 4.79 (d, 1H, J = 12.0 Hz, $PhCH_2-$), 4.90 (s, 1H, H-2), 7.3−7.39 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.2, 61.4, 69.0, 70.3, 72.7, 74.7, 74.8, 91.1, 107.6, 128.2, 128.4, 128.9, 137.9; HRMS (FAB) calcd for $C_{15}H_{19}N_3O_4$ $[M^+]$ 321.1325, found 321.1323.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-3-benzyloxy-2,6-dimethoxy-hexahydrofuro[3,2-*b*]pyran (17). To a solution of **14** (300 mg, 0.93 mmol) in 200 mL of dry CH_2Cl_2 was added Dess−Martin periodinane reagent (1.5 g, 3.54 mmol) at room temperature under argon atmosphere, and the mixture was stirred for 2.5 h. After starting material disappeared, 20 mL of saturated $NaHCO_3$ solution and 20 mL of saturated $Na_2S_2O_3$ solution were added. The mixture was stirred for 10 min, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude ketone **15**.

To a solution of ketone **15** in 20 mL of MeOH was added 230 mg of $NaBH_4$ at 0 °C. The resulting mixture was stirred for 1 h and concentrated, and the residue was extracted with EtOAc (40 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford **16** as a crude oil.

To a solution of the above oil **16** in 20 mL of dry DMF was added NaH (60% suspension in oil) (60 mg, 1.50 mmol). After

stirring for 30 min at 0 °C under argon atmosphere, 100 mg of MeI was added, and the mixture was stirred for 3 h. The reaction was quenched by adding 10 mL of H_2O, and the mixture was extracted with EtOAc (40 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 10:1) to afford **17** (253 mg. 81%) as a colorless oil: $[\alpha]_D$ −11.6° (*c* 2.4, $CHCl_3$); IR (thin film) ν 2989, 2101, 1125, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.39 (s, 3H, −OMe), 3.45 (s, 3H, −OMe), 3.51 (ddd, 1H, *J* = 10.4, 2.7, 1.1 Hz), 3.73 (t, 1H, *J* = 10.4 Hz, H-5), 3.9−4.0 (m, 3H, H-3, H-5 and H-3a), 4.08 (dd, 1H, *J* = 9.8, 2.6 Hz, H-7a), 4.58 (t, 1H, *J* = 2.8 Hz, H-7), 4.62 (d, 1H, *J* = 12.0, $PhCH_2$−), 4.76 (d, 1H, *J* = 12.0 Hz, $PhCH_2$-), 4.92 (s, 1H, H-2), 7.2-7.4 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.6, 57.3, 59.2, 66.0, 72.1, 74.2, 75.9, 78.9, 108.6, 127.6, 127.7, 128.3, 137.5; HRMS (FAB) calcd for $C_{16}H_{21}N_3O_5$ [M^+] 335.1481, found 335.1481.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-3-benzoyloxy-2,6-dimethoxy-hexahydrofuro[3,2-*b*]pyran (18). To a solution of **17** (200 mg, 0.6 mmol) in 8 mL of $CH_3CN/CCl_4/H_2O$ (1:1:1.5) were added $RuCl_3{\cdot}3H_2O$ (28.4 mg, 0.12 mmol) and $NaIO_4$ (153 mg, 0.71 mmol) at 16 °C under argon atmosphere. The mixture was stirred for 24 h at this temperature, and 392 mg of $NaIO_4$ was added in portions during 24 h. After starting material disappeared, excess isopropyl alcohol (5 mL) and H_2O (20 mL) were added, and the mixture was extracted with CH_2Cl_2 (30 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash silica chromatography (hexanes/ethyl acetate, 10:1) afforded **18** (165 mg, 79%) as white solid: mp 85−87 °C; $[\alpha]_D$ +2.36° (*c* 0.57, $CHCl_3$); IR (thin film) ν 2929, 2108, 1726, 1583, 1439, 1268, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.44 (s, 3H, −OMe), 3.48 (s, 3H, −OMe), 3.50 (m, 1H, H-6), 3.60 (dd, 1H, *J* = 11.1, 10.5 Hz, H-5), 3.94 (dd, 1H, *J* = 11.1, 5.0 Hz, H-5), 4.05 (dd, 1H, *J* = 10.0, 2.7 Hz, H-7a), 4.17 (dd, 1H, *J* = 10.0, 4.3 Hz, H-3a), 4.61 (t, 1H, *J* = 2.7 Hz, H-7), 5.08 (s, 1H, H-2), 5.37 (d, 1H, *J* = 4.3 Hz, H-3), 7.42−8.05 (m, 5H, −Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 55.9, 57.4, 59.1, 66.1, 72.4, 73.9, 75.5, 76.2, 108.3, 128.3, 129.1, 129.7, 133.3, 165.1; FAB-MS *m/z* (relative intensity) 350 (M^+ + H, 32), 318 (M^+ − OMe, 30); HRMS (FAB) calcd for $C_{16}H_{20}N_3O_6$ [M + H^+] 350.1352, found 350.1358.

(1′*R*,2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(1′-benzoyloxy-2′,2′-bisphenylsulfanylethyl)-5-methoxy-tetrahydropyran-3-ol (19). To a solution of **18** (165 mg, 0.47 mmol) in 10 mL of dry CH_2Cl_2 were added PhSH (0.15 mL, 1.42 mmol) and $BF_3{\cdot}Et_2O$ (0.1 mL, 0.79 mmol) at −78 °C under argon atmosphere. After stirring for 3.5 h at this temperature, the mixture was quenched by adding saturated $NaHCO_3$ (10 mL), warmed to room temperature and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 5:1) to afford dithiane **19** (245 mg, 97%) as a colorless oil: $[\alpha]_D$ +20.6° (*c* 0.33, $CHCl_3$); IR (thin film) ν 2926, 2104, 1728, 1602, 1452, 1272, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.56 (d, 1H, *J* = 8.6 Hz, −OH), 3.47 (s, 3H, −OMe), 3.50 (m, 1H, H-5), 3.53 (dd, 1H, *J* = 11.2, 9.5 Hz, H-6), 3.60 (m, 1H, H-2), 3.75 (m, 1H, H-6), 4.08 (m, 2H, H-3 and H-4), 4.96 (d, 1H, *J* = 3.4 Hz, H-2′), 5.63 (dd, 1H, *J* = 3.4, 2.5 Hz, H-1′), 7.30−8.10 (m, 15H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 57.1, 60.3, 61.1, 62.2, 63.1, 68.8, 74.5, 76.6, 127.7, 128.1, 128.3, 128.9, 129.0, 129.4, 129.9, 132.3, 133.2, 133.4, 133.5, 134.4, 165.9; FAB-MS *m/z* (relative intensity) 537 (M^+, 2), 428 (M^+ − PhS, 15).

(1′*R*,2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(1′-hydroxy-2′,2′-phenylsulfanylethyl)-5-methoxy-tetrahydropyran-3-ol (22). To a solution of **19** (245 mg, 0.46 mmol) in 20 mL of methanol was added K_2CO_3 (10 mg) at room temperature. After stirring for 30 min, the mixture was evaporated under reduced pressure, and the residue was purified by flash silica gel chromatography (hexanes/ethyl acetate, 2:1) to afford **22** (184 mg, 93%) as a colorless oil: $[\alpha]_D$ +28.3° (*c* 0.79, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.22 (t, 1H, *J* = 10.6 Hz, H-6), 3.35 (ddd, 1H, *J* = 10.6, 4.8, 3.0 Hz, H-5), 3.40 (s, 3H, −OMe), 3.63 (ddd, 1H, *J* = 10.6, 4.8, 1.1 Hz, H-6), 3.69 (dd, 1H, *J* = 9.1, 3.2 Hz, H-3), 3.76 (t, 1H, *J* = 9.1 Hz, H-2), 3.90 (dd, 1H, *J* = 8.2, 2.2 Hz, H-1′), 4.26 (t, 1H, *J* = 3.2 Hz, H-4), 4.87 (d, 1H, *J* = 2.2 Hz, H-2′), 7.26−7.50 (m, 10H, −Ph);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.9, 62.4, 63.2, 71.9, 72.7, 75.6, 76.0, 127.9, 128.0, 128.9, 129.1, 132.3; FAB-MS *m/z* (relative intensity) 433 (M^+, 25), 324 (M^+ − PhS, 80); HRMS (FAB) calcd for $C_{20}H_{23}N_3O_4S_2$ [M^+] 433.1130, found 433.1132.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-6-methoxy-2-phenylsulfanyl-hexahydrofuro[3,2-*b*]pyran-3-ol (23). To a solution of diol **22** (185 mg, 0.43 mmol) in 20 mL of dry CH_2Cl_2 was added NBS (80 mg, 0.45 mmol) in an ice bath under argon atmosphere. After stirring for 20 min, the mixture was quenched by adding saturated $Na_2S_2O_3$ and then stirred for 10 min. The mixture was extracted with CH_2Cl_2 (30 mL × 4), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 3:1) afforded **23** (105 mg, 76%) as a colorless oil: $[\alpha]_D$ +87.5° (*c* 0.76, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.50 (d, 1H, *J* = 2.2 Hz, −OH), 3.48 (s, 3H, −OMe), 3.58 (ddd, 1H, *J* = 10.4, 5.1, 3.0 Hz, H-6), 3.69 (dd, 1H, *J* = 11.0, 10.6 Hz, H-5), 3.80 (dd, 1H, *J* = 9.8, 4.8 Hz, H-3a), 4.0 (dd, 1H, *J* = 11.0, 5.1 Hz, H-5), 4.06 (dd, 1H, *J* = 9.8, 2.8 Hz, H-7a), 4.55 (dd, 1H, *J* = 5.1, 4.1 Hz, H-3), 4.64 (dd, 1H, *J* = 3.0, 2.8 Hz, H-7), 5.80 (d, 1H, *J* = 4.1 Hz, H-2), 7.26−7.53 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 57.4, 58.8, 65.6, 69.5, 73.9, 74.1, 76.2, 93.8, 127.1, 128.9, 130.9, 134.4; FAB-MS *m/z* (relative intensity) 323 (M^+, 20); HRMS (FAB) calcd for $C_{14}H_{18}N_3O_4S$ [M + H]$^+$ 324.1018, found 324.1008.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-6-methoxy-2-phenylsulfanyl-3-pivaloyloxy- hexahydrofuro[3,2-*b*]pyran (24). To a solution of **23** (105 mg, 0.32 mmol) in 5 mL of dry pyridine were added DMAP (200 mg) and then PivCl (0.15 mL) at room temperature under argon atmosphere. The mixture was stirred overnight, pyridine was removed under reduced pressure, and the residue was dissolved with 50 mL of dichloromethane, washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 5:1) afforded **24** (130 mg, 100%) as a colorless oil: $[\alpha]_D$ +187.3° (*c* 0.41, $CHCl_3$); IR (thin film) ν 2977, 2107, 1741, 1480, 1279, 1146, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm)1.30 (s, 9H, PivO-); 3.47 (s, 3H, −OMe), 3.51 (m, 1H, H-6), 3.61 (dd, 1H, *J* = 11.6, 10.0, H-5), 3.84 (dd, 1H, *J* = 10.0, 3.4 Hz, H-3a), 3.92 (dd, 1H, *J* = 11.6, 4.4 Hz, H-5), 3.97 (dd, 1H, *J* = 10.0, 3.4 Hz, H-7a), 4.62 (t, 1H, *J* = 3.2 Hz, H-7), 5.68 (t, 1H, *J* = 3.4 Hz, H-3), 5.90 (d, 1H, *J* = 3.4 Hz, H-2), 7.27−7.51 (m, 5H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.6, 39.8, 57.9, 59.2, 66.0, 70.4, 73.9, 75.3, 76.8, 92.3, 127.8, 129.5, 131.6, 134.8, 177.1; FAB-MS *m/z* (relative intensity) 408 (M + H^+, 60), 407 (M^+, 15), 298 (M^+ − PhS, 100); HRMS (FAB) calcd for $C_{19}H_{26}N_3O_5S$ [M + H]$^+$ 408.1601, found 408.1586.

General Procedure for *N*-Glycosidation. To a solution of phenylthio glycoside **24** (0.1 mmol) in 2 mL of dry CH_2Cl_2 were added silylated base (0.2 mmol), NIS (0.2 mmol), and then triflic acid (0.1 mmol) at room temperature under argon atmosphere. After stirring for 2−5 h, the reaction was quenched by adding saturated $Na_2S_2O_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (30 mL × 3), and the combined organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash silica chromatography (CH_2Cl_2/MeOH, 40:1) afforded the *N*-nucleoside.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-3-benzyloxy-6-methoxy-2-phenylsulfanyl-hexahydrofuro[3,2-*b*]pyran (25). To a solution of **17** (112 mg, 0.33 mmol) in 10 mL of dry CH_2Cl_2 were added PhSH (0.1 mL, 0.95 mmol) and $BF_3{\cdot}Et_2O$ (0.1 mL, 0.79 mmol) at −78 °C under argon atmosphere. After stirring

for 3.5 h at this temperature, the mixture was quenched by adding saturated $NaHCO_3$ (10 mL), warmed to room temperature and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexane/ethyl acetate, 5:1) to afford the dithioacetal (160 mg, 91%) as a colorless oil.

To a solution of the above compound (160 mg, 0.3 mmol) in 10 mL of dry CH_2Cl_2 was added NBS (70 mg, 0.38 mmol) at 0 °C under argon atmosphere. After stirring for 20 min, the mixture was quenched by adding a saturated solution of Na_2SO_4 and stirred for 10 min. The mixture was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 5:1) afforded **25** (100 mg, 80%) as a colorless oil: $[\alpha]_D$ +25.0° (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 3.46 (s, 3H, − OCH3), 3.59 (m, 2H), 3.78 (dd, 1H, J = 10.0, 4.5 Hz), 3.98 (dd, 1H, J = 9.6, 3.2 Hz), 4.15 (dd, 1H, J = 10.0, 3.0 Hz), 4.27 (t, 1H, J = 4.3 Hz), 4.62 (m, 1H), 4.75 (d, 1H, J = 12.1 Hz), 4.91 (d, 1H, J = 12.1 Hz), 5.83 (d, 1H, J = 4.4 Hz), 7.22−7.52 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 56.8, 61.1, 61.9, 63.4, 71.0, 73.4, 75.1, 75.5, 83.9, 127.3, 127.5. 128.2. 128.4, 128.5, 128.9, 134.2, 135.0; MS (FAB) 414.2 ($M + H^+$).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-2-(2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (26) and (2*R*,3*R*,3a*R*,6*S*,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 (27). The combined yield was 85%. For **26**: $[\alpha]_D$ +85.5° (*c* 0.6, $CHCl_3$); IR (thin film) ν 2932, 2109, 1693, 1459, 1277, 1149, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (s, 9H, −OPiv), 3.49 (s, 3H, −OMe), 3.58 (m, 1H, H-6), 3.66 (dd, 1H, J = 11.0, 10.7 Hz, H-5), 3.79 (dd, 1H, J = 10.1, 2.7 Hz, H-7a), 3.84 (dd, 1H, J = 10.1, 5.0 Hz, H-3a), 3.99 (dd, 1H, J = 11.0, 5.1 Hz, H-5), 4.68 (brs, 1H, H-7), 5.28 (d, 1H, J = 5.0 Hz, H-3), 5.81 (d, 1H, J = 8.1 Hz, H-5′), 5.91 (s, 1H, H-2), 7.58 (d, 1H, J = 8.1 Hz, H-6′), 8.42 (brs, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.5, 39.3, 58.1, 59.3, 66.4, 72.4, 73.0, 76.2, 77.1, 91.2, 103.4, 139.7, 149.9, 163.0, 177.0; FAB-MS *m/z* (relative intensity) 410 ($M + H^+$, 20), 298 (M^+ − PhS, 35). For **27**: $[\alpha]_D$ +76.6° (*c* 0.95, $CHCl_3$); IR (thin film) ν 2977, 2110, 1693, 1609, 1439, 1275, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (s, 9H, −OPiv), 3.50 (s, 3H, −OMe), 3.59 (ddd, 1H, J = 10.7, 5.0, 3.0 Hz, H-6), 3.68 (dd, 1H, J = 11.1, 10.7, H-5), 3.86 (m, 2H, H-3a and H-7a), 3.99 (dd, 1H, J = 11.1, 5.0 Hz, H-5), 4.72 (brs, 1H, H-7), 5.32 (d, 1H, J = 4.1 Hz, H-3), 5.86 (s, 1H, H-2), 8.24 (s, 1H, H-6′), 8.76 (brs, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.5, 39.3, 58.1, 59.4, 60.8, 66.5, 68.7, 72.2, 72.9, 76.6, 91.2, 144.7, 149.6, 159.9, 176.8; FAB-MS *m/z* (relative intensity) 536 ($M + H^+$, 5), 298 (M^+ − PhS − I, 15); HRMS (FAB) calcd for $C_{17}H_{23}N_5O_{7I}$ [M^+] 536.0642, found 536.0664.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-2-(5′-methyl-2′,4′-dioxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (30). Colorless oil: yield 86%; $[\alpha]_D$ +80.8° (*c* 0.7, $CHCl_3$); IR (thin film) ν 2930, 2109, 1711, 1463, 1278, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$,) δ (ppm) 1.23 (s, (H, PivO-), 1.95 (s, 3H, -Me), 3.49 (s, 3H, −OMe), 3.56 (m, 1H, H-6), 3.66 (dd, 1H, J = 10.1, 2.4 Hz, H-7a), 3.77 (dd, 1H, J = 10.1, 2.6 Hz, H-3a), 3.92 (m, 1H, H-5), 3.96 (m, 1H, H-5), 4.68 (d, 1H, J = 2.4 Hz, H-7), 5.28 (d, 1H, J = 2.6 Hz, H-3), 5.92 (s, 1H, H-2), 7.37 (s, 1H, H-6′), 8.8 (s, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.1, 27.5, 39.3, 58.1, 59.4, 66.2, 72.5, 73.0, 76.2, 76.9, 93.0, 111.9, 135.5, 150.0, 163.8, 177.9; FAB-MS *m/z* (relative intensity) 424 ($M + H^+$, 18), 408 (M^+ − Me, 10), 298 (M^+ − thymine, 35).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-2-(4′-acetylamino-2′-oxo-3′,4′-dihydro-2*H*-pyrimidin-1′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (31). Colorless oil: yield 71%; $[\alpha]_D$ +98.8° (*c* 0.8, $CHCl_3$); IR (thin film) ν 2934, 2110, 1712, 1666, 1562, 1493, 1385, 1277, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (s, 9H, PivO-), 2.25 (s, 3H, CH_3-CO-), 3.46 (s, 3H, −OMe), 3.56 (m, 1H, H-6), 3.58 (t, 1H, J = 10.6 Hz, H-5), 3.77 (dd, 1H, J = 10.0, 4.5 Hz, H-3a), 3.87 (dd, 1H, J = 10.0, 2.8 Hz, H-7a), 3.95 (dd, 1H, J = 10.6, 4.3 Hz, H-5), 4.70 (s, 1H, H-7), 5.32 (d, 1H, J = 4.5 Hz, H-3), 5.99 (s, 1H, H-2), 7.48 (d, 1H, J = 7.5 Hz, H-5′), 8.15 (d, 1H, J = 7.5 Hz, H-6′), 10.1 (brs, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.9, 29.4, 38.7, 57.6, 58.8, 65.8, 71.6, 72.3, 75.9, 76.6, 91.1, 96.8, 143.8, 154.3, 162.9, 170.9, 178.2; LC-MS *m/z* (relative intensity) 350 (M^+, 100).

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-2-(6′-oxo-1′,6′-dihydropurin-9′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (32). Colorless oil: yield 75% based on recovered starting material; $[\alpha]_D$ +80.0° (*c* 0.6, $CHCl_3$); IR (thin film) ν 2932, 2111, 1709, 1590, 1480, 1348, 1180, 1149, 1093, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, 9H, PivO-), 3.50 (s, 3H, −OMe), 3.63 (m, 2H, H-5 and H-6), 4.0 (m, 3H, H-5, H-3a and H-7a), 4.76 (m, 1H, H-7), 5.58 (d, 1H, J = 3.9 Hz, H-3), 6.47 (s, 1H, H-2), 8.22 (s, 1H, H-2′), 8.51 (s, 1H, H-8′), 11.8 (brs, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 27.5, 39.4, 58.2, 59.5, 66.5, 71.8, 73.9, 76.9, 77.1, 92.2, 114.6, 141.6, 145.2, 156.3, 159.3, 176.9; FAB-MS *m/z* (relative intensity) 434 ($M + H^+$, 6), 298 (M^+ − hypoxanthine, 30); HRMS (FAB) calcd for $C_{18}H_{24}N_7O_6$ [$M + H]^+$ 434.1788, found 434.1774.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-2-(6′-benzoylamino-purin-9′-yl)-6-methoxy-3-pivaloyloxy-hexahydrofuro[3,2-*b*]-pyran (33). Colorless oil: yield 22%; $[\alpha]_D$ +55.3° (*c* 0.7, $CHCl_3$); IR (thin film) ν 2933, 2108, 1741, 1704, 1610, 1582, 1480, 1455, 1280, 1146 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (s, (H, PivO-); 3.50 (s, 3H, −OMe), 3.61 (m, 1H, H-6), 3.73 (t, 1H, J = 11.0 Hz, H-5), 3.93 (dd, 1H, J = 10.2, 3.2 Hz, H-7a), 4.02 (dd, 1H, J = 11.0, 5.4 Hz, H-5), 4.52 (dd, 1H, J = 10.2, 4.5 Hz, H-3a), 4.69 (m, 1H, H-7), 5.58 (d, 1H, J = 4.5 Hz, H-3), 6.21 (s, 1H, H-2), 7.52 (t, 2H, J = 7.8 Hz, −Ph), 8.37 (s, 1H, H-2′), 8.83 (s, 1H, H-8′), 8.96 (brs, 1H, −NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.9, 38.8, 57.5, 58.7, 65.9, 71.9, 72.7, 76.2, 76.3, 89.3, 123.1, 127.7, 128.7, 130.9, 132.7, 133.4, 140.9, 149.5, 151.0, 152.9, 164.3, 176.6; FAB-MS *m/z* (relative intensity) 537 ($M + H^+$, 5), 298 (M^+ − N^6-benzoyladenine, 10); HRMS (FAB) calcd for $C_{25}H_{29}N_8O_6$ [$M + H]^+$ 537.2210, found 537.2200.

General Procedure for the Formation of Urea. To a solution of azide (0.02 mmol) in 2 mL of anhydrous THF was added 1 M Me_3P in toluene (50 μL, 0.05 mmol) at room temperature under argon atmosphere. After stirring for 30 min, 3 μL of H_2O was added, and the resulting mixture was refluxed for 40 min and then evaporated. The residue was dried under reduced pressure (1 mmHg) for 1.5 h and dissolved in 2 mL of dry CH_2Cl_2. To this solution was added trichloroacetyl isocyanate (10 μL) at room temperature under argon atmosphere. After stirring for 60 min, CH_2Cl_2 was removed and the residue was dissolved with MeOH (2 mL) and 40% $MeNH_2$ in H_2O (2 mL), and stirred over 3 days. The mixture was evaporated and purified by flash silica gel chromatography (CH_2Cl_2/MeOH, 9:1) to afford product.

(2*R*,3*R*,3a*S*,6*S*,7*R*,7a*R*)-3-Hydroxyl-2-(2′,4′-dioxo-3′,4′-dihyro-2*H*-pyrimidin-1′-yl)-6-methoxy-hexahydrofuro-[3,2-*b*]pyran-7-yl]-urea (*N*-Malayamycin) (6). White solid: yield 50%; $[\alpha]_D$ +27.5° (*c* 0.08, MeOH); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 3.37 (s, 3H, −OMe), 3.46 (dd, 1H, J = 11.9, 11.0 Hz, H-5), 3.54 (m, 1H, H-6), 3.67 (dd, 1H, J = 11.0, 5.4 Hz, H-5), 3.97 (dd, 1H, J = 11.4, 5.4 Hz, H-3a), 4.01 (dd, 1H, J = 11.4, 5.4 Hz, H-7a), 4.25 (d, 1H, J = 5.4 Hz, H-3), 4.95 (m, 1H, H-7), 5.66 (d, 1H, J = 8.3 Hz, H-5′), 5.68 (s, 1H, H-2), 7.67 (d, 1H, J = 8.3 Hz, H-6′); ^{13}C NMR (100 MHz, CD_3-OD) δ (ppm) 48.3, 55.2, 66.0, 72.3, 73.8, 74.2, 77.6, 94.1, 101.2, 10.8, 150.9, 161.3, 164.8; HRMS (FAB) calcd for $C_{13}H_{18}N_4O_7$-Na [$M + Na]^+$ 365.1073, found 365.1064.

(2*R*,3*R*,3a*S*,6*S*,7*R*,7a*R*)-3-Hydroxy-6-methoxy-[2-(5′-methyl-2′,4′-dioxo-3′,4′-dihyro-2*H*-pyrimidin-1-yl)-hexahydrofuro[3,2-*b*]pyran-7-yl]-urea (34). White solid: yield 76%; $[\alpha]_D$ +72.0° (*c* 0.125, MeOH); ^1H NMR (400 MHz, CD_3OD) δ

(ppm) 1.90 (s, 3H, -Me), 3.37 (s, 3H, −OMe), 3.50 (m, 2H, H-5 and H-6), 3.69 (m, 1H, H-5), 3.95 (dd, 1H, J = 10.5, 5.4 Hz, H-3a), 4.02 (dd, 1H, J = 10.5, 3.4 Hz, H-7a), 4.21 (d, 1H, J = 5.4 Hz, H-3), 4.96 (m, 1H, H-7), 5.68 (s, 1H, H-2), 7.52 (s, 1H, H-6′); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 11.7, 48.6, 55.8, 66.6, 72.6, 73.7, 74.0, 76.9, 93.9, 106.0, 139.0, 151.2, 161.0, 163.0; FAB-MS *m/z* (relative intensity) 379 (M + Na^+, 40), 357 (M + H^+, 100); HRMS (FAB) calcd for $C_{14}H_{21}N_4O_7$ [M + H]$^+$ 357.1410, found 357.1418.

(2*R*,3*R*,3a*S*,6*S*,7*R*,7a*R*)-[2-(4′-Amino-2′-oxo-2*H*-pyrimidin-1′-yl)-3-hydroxy-6-methoxy-hexahydrofuro[3,2-*b*]pyran-7-yl]-urea (35). White solid: yield 50%; $[\alpha]_D$ +91.7 (*c* 0.06, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.35 (m, 1H, H-6), 3.37 (s, 3H, −OMe), 3.50 (m, 2H, H-5 and H-6), 3.66 (dd, 1H, J = 10.6, 5.3 Hz, H-3a), 3.96 (dd, 1H, J = 11.6, 5.4 Hz, H-5), 4.05 (dd, 1H, J = 10.6, 2.3 Hz, H-7a), 4.19 (d, 1H, J = 4.3 Hz, H-3), 4.97 (m, 1H, H-7), 5.67 (s, 1H, H-2), 5.87 (d, 1H, J = 7.5 Hz, H-5′), 7.73 (d, 1H, J = 7.5 Hz, H-6′); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 48.8, 55.8, 66.6, 72.6, 73.5, 74.1, 76.9, 94.7, 94.8, 140.7, 156.9, 161.3, 166.7; FAB-MS *m/z* (relative intensity) 364 (M + Na^+, 35), 342 (M + H^+, 18), 325 (M^+ − NH_2, 8).

(2*R*,3*R*,3a*S*,6*S*,7*R*,7a*R*)-3-Hydroxy-[2-(6′-oxo-1′,6′-dihydro-purin-9′-yl)-6-methoxy-hexahydrofuro[3,2-*b*]pyran-7-yl]-urea (36). White solid: yield 42%; $[\alpha]_D$ +95.0° (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.37 (s, 3H, −OMe), 3.51 (dd, 1H, J = 11.6, 10.8 Hz, H-5), 3.70 (m, 2H, H-6 and H-7a), 3.98 (dd, 1H, J = 11.6, 5.6 Hz, H-5), 4.16 (dd, 1H, J = 10.7, 4.2 Hz, H-3a), 4.42 (d, 1H, J = 4.2 Hz, H-3), 5.02 (brs, 1H, H-7), 6.30 (s, 1H, H-2), 8.03 (s, 1H, H-2′), 8.26 (s, 1H, H-8′); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 48.0, 55.3, 66.1, 72.7, 73.2, 73.6, 76.8, 94.2, 115.2, 140.4, 144.9, 154.3, 156.5, 162.2; FAB-MS *m/z* (relative intensity) 366 (M^+, 8).

(2*R*,3*R*,3a*S*,6*S*,7*R*,7a*R*)-[2-(6′-Amino-purin-9′-yl)-3-hydroxy-6-methoxy-hexahydrofuro[3,2-*b*]pyran-7-yl]-urea (37). White solid: yield 30%; $[\alpha]_D$ +44.0° (*c* 0.15, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 3.29 (m, 1H, H-6), 3.39 (s, 3H, −OMe), 3.56 (t, 1H, J = 11.0 Hz, H-5), 3.69 (dd, 1H, J = 10.0, 4.7 Hz, H-7a), 4.00 (dd, 1H, J = 11.0, 5.1 Hz, H-5), 4.11 (dd, 1H, J = 10.0, 3.2 Hz, H-3a), 4.51 (d, 1H, J = 4.5 Hz, H-3), 4.96 (brs, 1H, H-7), 6.03 (s, 1H, H-2), 8.12 (s, 1H, H-2′), 8.23 (s, 1H, H-8′); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 48.8, 55.9, 66.6, 72.6, 73.8, 74.3, 76.8, 93.1, 112.3, 139.5, 148.6, 152.8, 156.8, 161.8; LC-MS *m/z* (relative intensity) 366 (M + H^+, 100).

3-Azido-1,2,4-Tri-*O*-benzoyl-3-deoxy-D-xylopyranose (39). Compound **38**[32] (1.075 g, 5.0 mmol) was dissolved in water (125 mL) and acetic acid (125 mL). After refluxing for 3 h, the mixture was concentrated, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 1:4) to give the desired triol (757 mg, 86%) as an oil, which was very difficult to dry. An 85:15 mixture of pyranose and furanose was obtained, both being a mixture of α and β isomers.

To a mixture of the above triol (757 mg, 4.3 mmol), anhydrous Et_3N (3.62 mL, 26.0 mmol) and DMAP (32 mg, 2.6 mmol), dissolved in dry CH_2Cl_2 (15 mL) and cooled to 0 °C, was added dropwise a solution of BzCl (3.0 mL, 26.0 mmol) in anhydrous CH_2Cl_2 (15 mL) under argon atmosphere. After stirring for 1 h at room temperature, the mixture was diluted with EtOAc (210 mL), and the organic phase was washed successively with saturated $NaHCO_3$ (210 mL × 2) and brine (210 mL × 2), then dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 2:1) gave the expected triester (2.0 g, 97%), as a pyranose (major) and furanose (minor) mixture. IR (thin film) ν 3073, 3011, 2887, 2678, 2564, 2112, 1727, 1690, 1602, 1585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.22 (m, 2H), 4.49 (t, 1H, J = 3.49 Hz), 5.68−5.55 (m, 2H), 6.48 (d, 1H, J = 5.10 Hz), 7.29−7.24 (m, 1H), 7.57−7.39 (m, 9H), 7.69−7.59 (m, 4H), 8.00−7.97 (m, 1H), 8.09−8.01 (m, 1H), 8.23−8.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 58.4, 58.5, 59.9, 63.2, 66.6, 68.3, 68.6, 69.3, 89.1, 91.6, 95.1, 99.3, 128.8, 128.9, 129.0, 129.0, 129.0, 129.1, 129.1, 129.2, 130.4, 130.5, 130.6, 130.6, 134.1, 134.2, 134.2, 134.4, 164.8, 4 × $3CO_2$ esters, 165.0, 165.4, 165.5, 165.7, 165.9, 166.2, 166.6; FAB-MS *m/z* (relative intensity) 488.1 (M + H^+, 7), 366.2 (M^+ − $PhCO_2$, 100).

(3*R*,4*S*,5*S*)-4-Azido-3,5-bis-*O*-benzoyl-tetrahydropyran-2-carbonitrile (40). Method A. To a mixture of **39** (487 mg, 1.0 mmol) and TMSCN (400 μL, 3.0 mmol) in 10 mL of dry $MeNO_2$ at 0 °C was added 181 μL (1.0 mmol) of TMSOTf. After stirring for 18 h, the solution was diluted with EtOAc (40 mL × 2), and quenched with saturated $NaHCO_3$ (40 mL). The aqueous phase was extracted with EtOAc (40 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexanes/ethyl acetate, 3:1) gave **40** (287 mg, 73%) as a 4:1 β and α mixture, in favor of the β anomer (determined by NMR): IR (thin film) ν 3065, 2960, 2885, 2114, 1728, 1602, 1585, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer δ (ppm) 3.95 (t, 1H, J = 10.11 Hz,), 4.13 (dd, 1H, J = 11.46, 3.97 Hz), 4.62 (m, 1H), 8.16−8.07 (m, 4H), 4.83 (d, 1H, J = 8.22 Hz), 5.459−5.42 (m, 2H), 7.51−7.46 (m, 4H), 7.64−7.59 (m, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 59.6, 60.8, 63.1. 64.5, 64.7, 67.7, 69.3, 70.2, 76.5, 80.8, 115.5, 116.2, 128.4, 128.6, 129.0, 129.1, 129.1, 129.2, 129.6, 130.3, 130.4, 130.5, 130.6, 134.0, 134.3, 134.6, 134.7, 165.3, 165.6; HRMS (EI): calcd for $C_{20}H_{16}N_4O_5$ [M$^+$] 392.1120, found 392.1123.

Method B. To a mixture of **39** (974 mg, 2.0 mmol) and TMSCN (800 μL, 6.0 mmol) in 10 mL of dry $MeNO_2$ was added 253 μL (2.0 mmol) of $BF_3{\cdot}OEt_2$. After stirring for 17 h at room temperature, the solution was diluted with EtOAc (48 mL), and quenched by a $NaHCO_3$ saturated solution (48 mL). The aqueous phase was extracted with EtOAc (48 mL × 2), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexanes/ethyl acetate 3/1) afforded **40** (426 mg, 54%) as a 14:1 β and α mixture, in favor of the β anomer (determined by NMR). ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer δ (ppm) 3.95 (t, 1H, J = 10.11 Hz,), 4.13 (dd, 1H, J = 11.46, 3.97 Hz), 4.62 (m, 1H), 4.83 (d, 1H, J = 8.22 Hz), 5.459−5.42 (m, 2H), 7.51−7.46 (m, 4H), 7.64−7.59 (m, 2H), 8.16−8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 59.6, 60.8, 64.5, 64.7, 67.7, 69.3, 70.2, 76.5, 80.9, 115.4, 128.6, 129.0, 129.1, 129.2, 130.3, 130.4, 130.5, 130.6, 133.9, 134.3, 134.5, 134.6, 165.3, 165.6.

(2*R*,3*R*,4*S*,5*S*)-4-Azido-3,5-bis(*tert*-butyldimethylsilanyloxy)-tetrahydropyran-2-carboxylic Acid Methoxy-methylamide (41). To a solution of cyanide **40** (6.66 g, 17 mmol) in 100 mL of distilled MeOH was added 3.4 mL (1.7 mmol) of a NaOMe solution (0.5 M in MeOH). After stirring for 1 h at room temperature the solvent was evaporated under vacuum. The crude product was hydrolyzed upon heating in a mixture of 50 mL of a 5 M aqueous NaOH solution and 50 mL of MeOH at 45 °C for 3 h. The pH was then brought to 1 by addition of a 1 M HCl solution, and the solvent was removed under reduced pressure. The mixture was resolved in MeOH, and the NaCl formed was filtered under vacuum. The solvent was evaporated again, and the crude acid dissolved in 100 mL of distilled MeOH was treated with TMSCl (6.5 mL, 51 mmol) for 13 h at room temperature. After evaporation the residue was purified by flash chromatography (ethyl acetate/hexanes, 4:1), affording the expected methyl ester (2.72 g, 75%) as an α,β-mixture.

A mixture of the above diol (2.72 g, 12.5 mmol), TBDMSCl (7.55 g, 50 mmol), and imidazole (3.41 g, 50 mmol), in anhydrous CH_2Cl_2 (60 mL) under argon atmosphere, was stirred for 15 h at room temperature. The reaction was quenched by addition of water (120 mL), and the aqueous phase was extracted with EtOAc (120 mL × 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 9:1) gave the expected product (5.3 g, 95%), isolated as a sticky oil of α,β-anomers.

To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (2.51 g, 25.7 mmol, 2.2 equiv) in CH_2Cl_2 (140 mL) under argon

atmosphere at 0 °C was slowly added 12.85 mL of a 2 M in toluene $AlMe_3$ solution (25.7 mmol, 2.2 equiv). After stirring for 40 min at 0 °C, a solution of protected methyl ester (5.20 g, 11.68 mmol) in 25 mL of CH_2Cl_2 under argon atmosphere was added dropwise. The mixture was stirred for 22 h letting the temperature slowly rise with the ice bath to room temperature, then it was cooled to 0 °C again, and the reaction was quenched by careful addition of a 0.5M HCl solution (65 mL) (**Caution**: can be quite violent). The aqueous phase was extracted with CH_2Cl_2 (140 mL × 2), the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. Flash silica gel chromatography (hexanes/ethyl acetate, 4:1) afforded **41** (3.70 g, 68%) as a sticky oil, along with 1 g of α-anomer (19%): $[\alpha]_D$ −25.0° (*c* 1.0, CH_2Cl_2); IR (thin film) ν 2957, 2931, 2898, 2859, 2106, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.06 (s, 3H, $-CH_3$), 0.10 (s, 3H, $-CH_3$), 0.14 (s, 6H, 2 × $-CH_3$), 0.90 (s, 9H, 3 × $-CH_3$), 0.94 (s, 9H, 3 × $-CH_3$), 3.23 (s, 3H, −NMe), 3.58 (t, 1H, J = 10.59 Hz, H-5), 3.68 (dd, 1H, J = 10.91, 5.05 Hz, H-5), 3.77 (s, 3H), 3.93 (m, 1H, −OMe), 4.00 (ddd, 1H, J = 10.14, 5.18, 3.20 Hz, H-4), 4.06 (dd, 1H, J = 9.14, 3.14 Hz, H-2), 4.49 (d, 1H, J = 9.16 Hz, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.6, −4.4, −4.2, −4.1, 18.4, 18.4, 26.0, 26.1, 32.5, 62.5, 66.8, 68.5, 68.6, 69.8, 70.7, 169.9.

(2*R*,3*R*,4*S*,5*S*)-4-Azido-3,5-bis(*tert*-butyldimethylsilanyloxy)-tetrahydropyran-2-carbaldehyde (42). A solution of **41** (237 mg, 0.5 mmol) in anhydrous toluene (5 mL) under argon atmosphere was cooled to −78 °C and treated with 750 μL (0.75 mmol) of a 1 M in DIBAL-H in hexanes. After stirring for 2 h at −78 °C, the mixture was quenched by addition of a 1 M HCl solution (1 mL), warmed to room temperature, then diluted with EtOAc (50 mL). Rochelle's salt (50 mL) was added, and the mixture was stirred at room temperature until the two phases became clear. The aqueous phase was extracted with EtOAc (50 mL × 2), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was dissolved in 50 mL of CH_2Cl_2, and Dess−Martin periodinane reagent (318 mg, 0.75 mmol) and solid $NaHCO_3$ (109 mg, 1.3 mmol) were added to the solution. After stirring for 2 h at room temperature, the reaction was quenched by addition of a $NaHCO_3$ saturated solution (50 mL) and saturated $Na_2S_2O_3$ (50 mL). The mixture was stirred for 30 min, and the aqueous phase was extracted with CH_2Cl_2 (100 mL × 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The aldehyde, isolated as a white crystalline solid, was used directly in the next step without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.16 (s, 12H, 4 × $-CH_3$), 0.94 (s, 18H, 6 × $-CH_3$), 3.54 (t, 1H, J = 10.39 Hz, H-6), 3.74−3.69 (m, 1H, H-6), 3.81 (dd, 1H, J = 9.62, 2.90 Hz, H-2), 3.90−3.86 (m, 2H, H-4 + H-5), 4.08 (d, 1H, J = 9.63 Hz, H-2), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) −4.6, −4.5, −4.3, −3.7, 18.4, 18.4, 26.0, 26.0, 66.3, 68.2, 68.4, 69.6, 79.1, 199.2.

(1*R*,2′*R*,3′*R*,4′*S*,5′*S*)-1-[4′-Azido-3′,5′-bis(*tert*-butyldimethylsilanyloxy)-tetrahydropyran-2′-yl]-2,2-bis-phenylsulfanyl-ethanol (43). To a solution of $(PhS)_2CH_2$ (279 mg, 1.2 mmol) in anhydrous THF (12 mL) under argon atmosphere, cooled to −10 °C, was added dropwise 0.85 mL (1.15 mmol) of a 1.35 M BuLi solution in hexanes (titrated). After stirring for 25 min at −10 °C, the mixture was cooled to −78 °C, and a solution of the crude aldehyde (0.5 mmol) dissolved in anhydrous THF (5 mL) under argon atmosphere and cooled to −78 °C, was slowly added to the flask. The reaction was stirred for 30 min at −78 °C and quenched by adding 2 mL of a 1 M HCl solution. After warming to room temperature, the mixture was diluted with EtOAc (50 mL) and water (50 mL), and the aqueous phase was extracted with EtOAc (100 mL × 2). The combined organic phases were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 95:5) gave the desired product **43** (161 mg, 50%) as a white crystalline solid, along with the *S* diastereoisomer (82 mg, 25%). For **43**: $[\alpha]_D$ +69.6° (*c* 0.5, CH_2Cl_2); IR (thin film): ν 2856, 2931, 2859, 2107, 1473 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.17 (s, 12H, 4 × $-CH_3$), 0.96 (s, 18H), 3.39 (t, 1H, J = 10.59 Hz, H-6′), 3.49 (dd, 1H, J = 10.64, 5.10 Hz, H-6′), 3.62 (s, 1H, H-2), 3.90−3.73 (m, 5H, H-2′, H-3′, H-4′, H-5′ and −OH), 4.79 (s, 1H, H-1), 7.28 (m, 6H), 7.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −4.4, −4.3, −4.3, 3.5, 18.4, 18.5, 26.1, 26.2, 63.2, 66.8, 68.1, 69.2, 73.2, 73.8, 75.6, 128.0, 128.2, 129.3, 129.3, 133.1, 133.7, 134.9, 135.0. For *epi*-**43**: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.13 (s, 12H, 4 × $-CH_3$), 0.93 (s, 18H), 2.97 (d, 1H, J = 5.21 Hz, −OH), 3.32 (t, 1H, J = 10.39 Hz, H-6′), 3.55 (dd, 1H, J = 10.52 Hz, 4.67, H-6′), 3.76 (dd, 1H, J = 8.52, 5.32 Hz, H-1), 3.92−3.84 (m, 3H, H-3′, H-4′ and H-5′), 4.01 (d, 1H, J = 9.62 Hz, H-2′), 4.62 (d, 1H, J = 9.21 Hz, H-1), 7.37−7.24 (m, 6H), 7.52−7.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) −4.6, −4.4, −4.2, −3.8, 18.4, 18.5, 26.1, 26.1, 63.8, 66.7, 68.3, 68.7, 69.0, 69.7, 73.7, 128.3, 128.9, 129.3, 129.4, 129.5, 132.4, 133.2, 134.4, 134.5.

(4*R*,5*R*,7*S*,8*S*,9*R*)-(8-Azido-4-(bis-phenylsulfanylmethyl)-2,2-dimethyl-hexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (44). To a mixture of **43** (450 mg, 0.70 mmol) and 4 Å MS suspended in anhydrous THF (7 mL) under argon atmosphere was added dropwise TBAF solution (1 M in THF) (1.53 mL, 1.53 mmol). After stirring for 16 h at room temperature, the reaction was quenched by addition of silica gel, filtered under vacuum and concentrated. The crude product was directly purified by flash silica gel chromatography (ethyl acetate/hexanes 3:1) to afford triol (264 mg, 91%): $[\alpha]_D$ +175.4° (*c* 0.5, CH_2Cl_2); IR (thin film): ν 3401, 3059, 2926, 2110, 1582, 1480, 1439 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.06 (t, 1H, J = 10.70 Hz), 3.44 (d, 1H, J = 2.74 Hz), 3.58 (dd, 1H, J = 10.75, 5.14 Hz), 3.68 (m, 1H), 3.81 (m, 2H), 3.92 (m, 1H), 4.17 (m, 2H), 4.90 (s, 1H), 7.42−7.28 (m, 8H), 7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 63.0, 65.6, 66.2, 72.9, 73.6, 76.4, 128.4, 128.7, 129.6, 129.8, 132.8, 132.8, 133.6.

Method A. To a mixture of above the triol (25 mg, 0.06 mmol), PTSA (6 mg, 0.03 mmol), and solid Na_2SO_4 (85 mg, 0.6 mmol, dried in the oven for 24 h prior to use) in anhydrous CH_2Cl_2 (1.8 mL) under argon atmosphere was added slowly 2-methoxypropene (29 μl, 0.3 mmol). After stirring for 4 h at room temperature, the reaction mixture was poured into 10 mL of saturated $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded **44** (22 mg, 81%) as a white crystalline solid, along with 3 mg (12%) of recovered starting material.

Method B. To a mixture of the above triol (25 mg, 0.06 mmol), PTSA (6 mg, 0.03 mmol), and solid Na_2SO_4 (85 mg, 0.6 mmol, dried in the oven for 24 h prior to use) in anhydrous CH_2Cl_2 (1.8 mL) under argon atmosphere was added slowly 2,2-dimethoxypropane (37 μl, 0.3 mmol). After stirring for 4 h at room temperature, the reaction mixture was poured into 10 mL of a $NaHCO_3$ saturated solution, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 2). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded **44** (23 mg, 84%) as a white crystalline solid: $[\alpha]_D$ +145.2° (*c* 1.95, CH_2Cl_2); IR (thin film) ν 3437, 2995, 2939, 2869, 2110, 1642, 1471, 1440, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.47 (s, 3H, CH_3), 1.52 (s, 3H, $-CH_3$), 2.09 (d, 1H, J = 10.53 Hz, OH-7), 3.16 (t, 1H, J = 10.71 Hz, H-6), 3.80−3.67 (m, 3H, H-6, H-7 and H-9), 4.12 (d, 1H, J = 9.43 Hz, H-4), 4.17 (s, 1H, H-8), 4.76 (s, 1H), 7.30−7.28 (m, 6H), 7.47−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 19.8, 29.2, 60.3, 63.2, 66.5, 67.5, 69.2, 71.8, 75.3, 101.2, 127.8, 128.3, 129.3, 129.4, 132.5, 133.4, 133.7, 134.7.

(1′*R*,2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(1′-hydroxy-2′,2′-bis-phenylsulfanylethyl)-5-methoxy-tetrahydropyran-3-ol (22). To a solution of **44** (39 mg, 0.08 mmol) dissolved in anhydrous DMF (2 mL) under argon atmosphere and cooled to 0 °C, was

added 2.5 mg (0.1 mmol) of a 95% NaH suspension. After 5 min, 11.5 μL (0.1 mmol) of MeI was added dropwise, and the mixture was stirred for 1 h at 0 °C. A spatula tip of additional NaH was added to consume the remaining starting material, and the reaction was quenched by addition of MeOH (2 mL). The mixture was diluted with water (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 3:1) gave the desired methylated product (37 mg, 93%).

To a solution of product (33 mg, 0.07 mmol) in distilled MeOH (6 mL) under argon atmosphere was added 13 mg (0.07 mmol) of PTSA. After stirring for 24 h at room temperature, the reaction was quenched by addition of saturated $NaHCO_3$ (3 mL), and the product was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash silica gel chromatography (hexanes/ethyl acetate, 1:1) gave **22** (30 mg, quant): $[\alpha]_D$ +28.0° (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.22 (t, 1H, J = 10.6 Hz, H-6), 3.35 (ddd, 1H, J = 10.6, 4.8, 3.0 Hz, H-5), 3.40 (s, 3H, −OMe), 3.63 (ddd, 1H, J = 10.6, 4.8, 1.1 Hz, H-6), 3.69 (dd, 1H, J = 9.1, 3.2 Hz, H-3), 3.76 (t, 1H, J = 9.1 Hz, H-2), 3.90 (dd, 1H, J = 8.2, 2.2 Hz, H-1′), 4.26 (t, 1H, J = 2.2 Hz, H-4), 4.87 (d, 1H, J = 2.2 Hz, H-2′), 7.26−7.50 (m, 10H, −Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 56.9, 62.4, 63.2, 71.9, 72.7, 75.6, 76.0, 127.9, 128.0, 128.9, 129.1, 132.3

(3a*R*,3b*R*,7a*R*,8a*R*)-2,2-Dimethyl-3a,5,7a,8a-tetrahydro-3b*H*-1,3,4,8-tetraoxa-cyclopenta[*a*]indene (46). To a solution of **45**[11c] (2 g, 7.8 mmol) in CH_2Cl_2 (860 mL) was added Grubbs catalyst (375 mg, 0.45 mmol) and the mixture was stirred at reflux (45 °C) for 3 h. The solvent was removed by evaporation and the crude product was purified by flash silica gel chromatography (hexanes/ethyl acetate, 4:1) to afford the product **46** as a white solid (1.42 g, 7.17 mmol, 92%): R_f = 0.16 (hexanes/ethyl acetate, 4:1); mp 64−65 °C; $[\alpha]_D$ +17.7° (*c* 3.3, $CHCl_3$); IR (thin film) ν 3142, 1620, 1384, 1215, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (s, 3H, $-CH_3$), 1.53 (s, 3H, $-CH_3$), 3.26 (dd, 1H, J = 8.14, 3.92 Hz), 4,38 (s, 1H), 4.40 (s, 2 H), 4.63 (t, 1H, J = 3.57 Hz), 5.64 (d, 1H, J = 2.06 Hz, H-7), 5.83 (d, 1H, J = 3.50 Hz, H-6), 6.18 (d, 1H, J = 8.14 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.8, 26.0, 68.6, 69.4, 76.1, 78.9, 105.6, 113.2, 126.3, 127.3; LRMS (ESI) 199.1 $[M + H]^+$.

(3a*R*,3b*R*,6*R*,7*R*,7a*R*,8a*R*)-7-Azido-2,2-dimethyl-hexahydro-1,3,4,8-tetraoxa-cyclopenta[*a*]inden-6-ol (47). To a mixture of **46** (1.41 g, 7.73 mmol), THF (133 mL) and water (133 mL) was added NBS (1.6 g, 9.2 mmol). The solution was stirred at room temperature (in the absence of light) for 2 h, and water (133 mL) was added followed by $Na_2S_2O_3 \cdot 5H_2O$ (0.1 g, 0.40 mmol). After stirring for 5 min, the solution was extracted with ether (250 mL × 3), and the combined organic phases were dried with Na_2SO_4 and concentrated.

The crude product was then dissolved in THF (255 mL), a solution of 1 M NaOH (67 mL) was added, and the mixture was stirred at reflux (110 °C) for 1 h. Once the mixture was cooled to room temperature, water (133 mL) was added and the organic phase was extracted with ether (300 mL × 3). The combined organic phases were then dried over Na_2SO_4 and concentrated to afford a white crude solid.

This was then dissolved in 2-methoxyethanol (400 mL), NaN_3 (7 g, 108.7 mmol) was added, and the mixture was stirred at reflux (126 °C) for 1 h. The solution was then cooled to room temperature, concentrated (45 °C, 1 mmHg), and diluted with ether (400 mL) and with brine (200 mL). The two phases were separated, the aqueous phase was extracted with ether (100 mL × 3), and the combined organic phase was dried with Na_2SO_4. After evaporation, the crude oil was purified by flash silica gel chromatography (ethyl acetate/hexanes, 1:1) to afford the product **47** as a white solid (1.14 g, 4.43 mmol, 57% 3 steps): R_f = 0.23 (ethyl acetate/hexanes, 1:1); mp 117−118 °C; $[\alpha]_D$ +42.5° (*c* 2, $CHCl_3$); IR (thin film) ν 3310, 2107, 1261, 1132, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.35 (s, 3H, $-CH_3$), 1.58 (s, 3H, $-CH_3$), 2.58 (s, 1H), 3.54 (dd, 1H, J = 9.79, 4.21 Hz), 3.72−3.90 (m, 3 H), 4.31 (dd, 1H, J = 9.78, 3.28 Hz), 4.34 (s, 1H), 4.66 (t, 1H, J = 3.56 Hz), 5.84 (d, 1H, J = 3.38 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.9, 26.1, 68.5, 68.6, 69.7, 72.0, 75.0, 76.3, 104.3, 113.8; LRMS (ESI): 258.1 $[M + H]^+$.

(3a*R*,3b*R*,6*S*,7*S*,7a*R*,8a*R*)-7-Azido-6-methoxy-2,2,6-trimethyl-hexahydro-1,3,4,8-tetraoxa-cyclopenta[*a*]indene (48). To a solution of **47** (600 mg, 2.33 mmol) in CH_2Cl_2 (70 mL) was added Dess−Martin periodinane reagent (2.36 g, 7.74 mmol) and the mixture was stirred at room temperature for 2.5 h. Saturated solutions of $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (30 mL) were added to the mixture and stirred at room temperature for 10 min. The two phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (50 mL) and dried with Na_2SO_4. After concentration, the crude product was dried in vacuo for 30 min, then dissolved in THF (30 mL) and cooled to −78 °C. MeMgBr (1 mL, 3.0 mmol, 3 M solution in ether) was added, and the mixture was stirred at −78 °C for 1 h and then at room temperature for 30 min. The mixture was quenched with a saturated solution of NH_4Cl (30 mL) and extracted with ether (50 mL × 3), and the combined organic phases were washed with brine (50 mL) and dried with Na_2SO_4. The crude oil was then purified by flash silica gel chromatography (ethyl acetate/hexanes, 1:1) to afford the product as a colorless gum (115 mg, 0.42 mmol, 18%, 2 steps): R_f = 0.41 (ethyl acetate/hexanes, 1:1); $[\alpha]_D$ +72.9° (*c* 3.8, $CHCl_3$); IR (thin film) ν 3469, 2988, 2936, 2872, 2111, 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.34 (s, 3H, $-CH_3$), 1.40 (s, 3H, $-CH_3$), 1.57 (s, 3H, $-CH_3$), 2.41 (s, 1H), 3.48 (q, 2H, J = 11.3 Hz), 3.60 (m, 1H), 4.09 (s, 1H), 4.11 (d, 1H, J = 3.04 Hz), 4.86 (t, 1H, J = 3.59 Hz), 5.86 (d, 1H, J = 3.37 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.2, 25.8, 26.1, 66.9, 69.3, 73.2, 73.5, 75.4, 75.7, 105.6, 113.8.

To a solution of the above alcohol (115 mg, 0.42 mmol) in DMF (14 mL) at 0 °C was added NaH (22 mg, 0.55 mmol, 60% dispersion in mineral oil) and the mixture was stirred at 0 °C for 10 min. Iodomethane (0.035 mL, 0.55 mmol) was then added, and the mixture was stirred at room temperature for 2 h. The mixture was quenched with a saturated solution of NH_4Cl (14 mL) and extracted with ethyl acetate (40 mL × 3) and the combined organic phases were washed with water (20 mL) and with brine (20 mL). The organic phase was dried with Na_2SO_4, concentrated and the residue was purified by flash silica gel chromatography (ethyl acetate/hexanes, 1:1) to afford the product **48** as a white solid (90 mg, 0.32 mmol, 75%): R_f = 0.54 (ethyl acetate/hexanes, 1:1); mp 117−120 °C; $[\alpha]_D$ +58.26° (*c* 2.25, $CHCl_3$); IR (thin film) ν 2987, 2937, 2108, 1460, 1376, 1057 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.34 (s, 3H), 1.41 (s, 3H), 1.57 (s, 3H), 3.29 (s, 3H), 3.71 (m, 3H), 3.97 (dd, 1 H, J = 3.07, 3.05 Hz), 4.25 (d, 1H, J = 2.3 Hz), 4.62 (t, 1H, J = 3.62 Hz), 5.84 (d, 1H, J = 3.41 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.6, 25.8, 26.1, 49.2, 62.5, 71.8, 72.2, 74.6, 75.6, 75.7, 105.6, 113.6; LRMS (ESI) 286.3 $[M + H]^+$.

(3a*R*,3b*R*,6*S*,7*S*,7a*R*,8a*R*)-7-Azido-6-fluoro-2,2-dimethyl-hexahydro-1,3,4,8-tetraoxa-cyclopenta[*a*]indene (49). Compound **47** (400 mg, 1.56 mmol) in CH_2Cl_2 (5 mL) was added to a solution of diethylamino sulfurtrifluoride (DAST) (0.8 mL, 6.23 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The mixture was stirred at room temperature for 18 h followed by the slow addition of water (4 mL). The two phases were separated, the aqueous phase was extracted with CH_2Cl_2 (4 mL × 3), the combined organic phases were washed with brine (10 mL) and dried with Na_2SO_4. After concentration, the crude product was purified by flash silica gel chromatography (hexanes/ethyl acetate, 3:1) to afford **49** as a colorless oil (120 mg, 0.46 mmol, 30%): R_f = 0.27 (hexanes/ethyl acetate, 3:1); $[\alpha]_D$ +52.3° (*c* 6, $CHCl_3$); IR (thin film) ν 2989, 2939, 2360, 2112, 1113, 1003;

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.33 (s, 3H, $-CH_3$), 1.57 (s, 3H, $-CH_3$), 3.57 (dd, 1H, J = 9.52, 4.15 Hz), 3.75 (dd, 1H, J = 42.6, 13.7 Hz), 4.22 (t, 1H, J = 3.37 Hz), 4.30 (m, 1H), 4.57 (m, 2H), 4.67 (t, 1H, J = 3.6 Hz), 5.82 (d, 1H, J = 3.31 Hz, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 25.8, 26.1, 58.2, 58.5, 67.1, 72.0, 74.4, 88.4, 104.5, 113.9; LRMS (ESI) 260.0 $[M + H]^+$.

General Procedure for Dithioacetals 50 and **51.** To a solution of **48** (90 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was added PhSH (0.33 mL, 3.2 mmol) followed by Amberlyst-15 (107 mg). The mixture was stirred at room temperature for 18 h, quenched with a saturated solution of $NaHCO_3$ (10 mL) and stirred for 5 min. After the separation of the two phases, the aqueous phase was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phases were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash silica gel chromatography (hexanes/ethyl acetate, 2:1) to afford the product as a white solid.

(1′*R*,2*R*,3*R*,4*S*,5*S*)-4-Azido-2-(1′-hydroxy-2′,2′-bis-phenylsulfanyl-ethyl)-5-methoxy-5-methyl-tetrahydro-pyran-3-ol (50). Yield: 80% from **48**; R_f = 0.54 (hexanes/ethyl acetate, 1:1); mp 137−140 °C; $[\alpha]_D$ +147.3 ° (*c* 2.8, $CHCl_3$); IR (thin film) ν 3436, 2109, 1582, 1086, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.25 (s, 3H, $-CH_3$), 3.21 (d, 2H, J = 10 Hz), 3.25 (s, 3H, $-OCH_3$), 3.50 (s, 2H), 3.80 (m, 2H), 3.96 (m, 2H), 4.89 (d, 1H, J = 2.0 Hz), 7.29 (m, 6H), 7.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.3, 49.1, 62.5, 65.7, 68.3, 70.5, 73.9, 74.1, 75.9, 127.8, 127.9, 128.9, 129.1, 132.4, 133.5, 133.9.

(1′*R*,2*R*,3*R*,4*S*,5*S*)-4-Azido-5-fluoro-2-(1′-hydroxy-2′,2′-bis-phenylsulfanyl-ethyl)-tetrahydro-pyran-3-ol (51). Yield: 85% from **49**; R_f = 0.21 (hexanes/ethyl acetate, 4:1); mp 127−129 °C; $[\alpha]_D$ +184.2° (*c* 4, $CHCl_3$); IR (thin film) ν 3369, 2114, 1439, 1272, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.33 (dd, 1H, J = 40.3, 13.7 Hz), 3.72 (t, 1H, J = 14 Hz), 3.87 (t, 1H, J = 8.89 Hz), 4.12 (m, 3H), 4.48 (d, 1H, J = 42.0 Hz), 4.92 (s, 1H), 7.31 (m, 6H), 7.44 (m, 2H), 7.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 59.6, 59.9, 62.3, 64.2, 64.4, 70.2, 72.8, 75.9, 86.3, 88.7, 127.9, 128.2, 129.0, 132.2, 132.5, 132.9, 133.9; LRMS (ESI) 422.2 $[M + H]^+$.

Thioglycoside Formation 52 and **53.** To a solution of **50** (96 mg, 0.22 mmol) in CH_2Cl_2 (11 mL) at 0 °C, NBS (61 mg, 0.34 mmol) was added and the mixture was stirred at 0 °C for 45 min. A saturated solution of $Na_2S_2O_3$ (18 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 (10 mL × 3). The combined organic phases were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated. Flash silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded the product as a white solid.

To a mixture of the above product (50 mg, 0.15 mmol), pyridine (3 mL) and DMAP (92 mg, 0.75 mmol) was added PivCl (0.055 mL, 0.45 mmol) and the mixture was stirred at room temperature for 18 h. The mixture was then concentrated and the crude product was purified by flash silica gel chromatography (hexanes/ethyl acetate, 4:1) to afford the product.

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*,8*R*,9*R*)-7-Azido-6-methoxy-6-methyl-2-phenylsulfanyl-3-pivaloyloxy-hexahydrofuro[3,2-*b*]-pyran (52). Colorless oil: yield 72% (2 steps) from **50**; R_f = 0.44 (hexanes/ethyl acetate, 4:1); $[\alpha]_D$ +183.9° (*c* 1.5, $CHCl_3$); IR (thin film) ν 2977, 2108, 1809, 1743, 1480, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.33 (s, 9H), 1.39 (s, 3H), 3.31 (s, 3H), 3.47 (d, 1H, J = 1.1 Hz), 3.51 (d, 1H, J = 1.1 Hz), 3.80 (dd, 1H, J = 5.35, 4.61 Hz), 4.13 (dd, 1H, J = 10.1, 3.10 Hz), 4.33 (d, 1H, J = 3.01 Hz), 5.69 (t, 1H, J = 3.93 Hz), 5.86 (d, 1H, J = 4.45 Hz), 7.33 (m, 3H), 7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.5, 26.4, 27.1, 39.3, 49.2, 62.5, 69.8, 71.3, 73.6, 74.5, 74.6, 91.5, 127.3, 128.9, 130.9, 134.3, 176.5; LRMS (ESI) 422.1 $[M + H]^+$.

(2*R*,3*R*,3a*R*,6*S*,7*R*,7a*R*)-7-Azido-6-fluoro-2-phenylsulfanyl-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (53). Colorless oil: yield 69% (2 steps) from **51**; R_f = 0.43 (hexanes/ethyl acetate, 4:1); $[\alpha]_D$ +141.0° (*c* 2, $CHCl_3$); IR (thin film) ν 2976, 2908, 2107, 1742, 1480, 1279 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 9H), 3.71 (m, 2H), 4.05 (t, 1H, J = 15.1 Hz), 4.55 (m, 3H), 5.73 (t, 1H, J = 4.35 Hz), 5.85 (d, 1H, J = 4.35 Hz), 7.29 (m, 3H), 7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 27.0, 39.3, 58.1, 58.4, 66.5, 66.8, 70.2, 73.2, 73.4, 85.9, 88.3, 90.2, 127.2, 128.9; LRMS (ESI) 396.1 $[M + H]^+$.

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-2-(4′-Acetylamino-2″-oxo-2*H*-pyrimidin-1′-yl)-7-azido-6-methoxy-6-methyl-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (54). To a mixture of **52** (55 mg, 0.13 mmol), N^4-acetyl bis-*O*-TMS cytosine (100 mg, 0.44 mmol) and NIS (100 mg, 0.44 mmol) in CH_2Cl_2 (1.7 mL) at room temperature was added TfOH (20 μL, 0.23 mmol) portionwise over a period of 20 min. Mixture was stirred at room temperature for 4 h, followed by the addition of a saturated solution of $Na_2S_2O_3$ (2 mL), and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL × 3), and the combined organic phases were washed with a saturated solution of $NaHCO_3$ (5 mL) and dried with Na_2SO_4. After concentration, the crude product was purified by flash silica gel chromatography (CH_2Cl_2/MeOH, 20:1) to afford the product as a colorless oil: yield 66%; R_f = 0.3 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ +188.5° (*c* 0.87, MeOH); IR (thin film) ν 2972, 2106, 1710, 1664, 1138, 1065 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 1.26 (s, 9H), 1.41 (s, 3H), 2.17 (s, 3H), 3.32 (s, 3H), 3.47 (d, 1H, J = 11.2 Hz), 3.68 (d, 1H, J = 11.2 Hz), 3.88 (m, 1H), 4.08 (m, 1H), 4.64 (s, 1H), 5.37 (d, 1H, J = 4.77 Hz), 5.87 (s, 1H), 7.48 (d, 1H, J = 7.51 Hz), 8.25 (d, 1H, J = 7.56 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 20.9, 24.6, 27.6, 30.6, 39.9, 64.1, 72.8, 73.8, 74.1, 76.5, 93.2, 98.2, 145.5, 157.3, 164.7, 173.0, 177.7; LRMS (ESI) 465.2 $[M + H]^+$.

(2*R*,3*R*,3a*R*,6*S*,7*S*,7a*R*)-2-(4′-Acetylamino-2″-oxo-2*H*-pyrimidin-1′-yl)-7-azido-6-fluoro-3-pivaloyloxy-hexahydrofuro[3,2-*b*]pyran (55). Same procedure as for compound **54**. Yield: 70% from **53**; R_f = 0.3 (CH_2Cl_2/MeOH, 20:1); $[\alpha]_D$ +165.1° (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 1.25 (s, 9H), 2.19 (s, 3H), 3.85 (dd, 1H, J = 42.8, 14.0 Hz), 4.09 (m, 2H), 4.21 (s, 1H), 4.80 (m, 2H), 5.50 (s, 1H), 5.89 (s, 1H), 7.49 (d, 1H, J = 6.98 Hz), 8.10 (d, 1H, J = 7.10 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 24.6, 27.5, 30.6, 39.9, 59.9, 60.4, 72.7, 74.2, 76.3, 87.5, 89.9, 93.2, 98.3, 146.1, 157.3, 164.8, 173.0, 178.2; LRMS (ESI) 439.1 $[M + H]^+$.

(2*R*,3*R*,3a*S*,6*S*,7*S*,7a*R*)-[2-(4′-Amino-2′-oxo-2*H*-pyrimidin-1′-yl)-3-hydroxy-6-methoxy-6-methyl-hexahydrofuro-[3,2-*b*]pyran-7-yl]urea (56). To a solution of **54** (35 mg, 0.075 mmol) in THF (8 mL) was added Me_3P (0.19 mL, 1 M in THF) and the mixture was stirred at room temperature for 30 min. Water (11 μL) was then added and the mixture was stirred at reflux (65 °C) for 60 min, cooled to room temperature, concentrated and dried under vacuo for 2 h.

The crude product was dissolved in CH_2Cl_2 (8 mL), trichloroacetyl isocyanate (35 μL) was added, and the mixture was stirred at room temperature for 2 h and concentrated. The product was then dissolved in MeOH (2 mL), $MeNH_2$ (2 mL, 40% in water) was added, the solution was stirred at room temperature for 3 days and concentrated, and the crude product was purified by flash silica gel chromatography (15% MeOH in CH_2Cl_2) to afford the final compound as a white solid: yield 9% (3 steps); R_f = 0.14 (30% MeOH in CH_2Cl_2); $[\alpha]_D$ +33.55° (*c* 0.1, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 1.48 (s, 3H), 3.30 (s, 3H), 3.43 (dd, 1H, J = 10.08, 4.71 Hz), 3.52 (s, 2H), 4.15 (m, 2H), 4.62 (d, 1H, J = 3.05 Hz), 5.65 (s, 1H), 5.83 (d, 1H, J = 7.52 Hz), 7.71 (d, 1H, J = 7.53 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 22.2, 48.1, 49.9, 73.5, 74.4, 75.7, 76.8, 95.6, 141.8, 167.7; LRMS (ESI) 356.1 $[M + H]^+$.

(2*R*,3*R*,3a*S*,6*S*,7*S*,7a*R*)-[2-(4′-Amino-2′-oxo-2*H*-pyrimidin-1′-yl)-6-fluoro-3-hydroxy-hexahydrofuro[3,2-*b*]pyran-7-yl]urea (57). Same procedure as for compound **56**. Yield: 30% (3 steps) from **55**; R_f = 0.16 (30% MeOH in CH_2Cl_2); $[\alpha]_D$ +20.1° (*c* 0.33, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 2.55 (s, 1H), 3.91 (m, 2H), 4.16 (d, 1H, J = 14 Hz), 4.24 (m,

1H), 4.35 (d, 1H, $J = 5.25$ Hz), 4.74 (m, 2H), 5.51 (s, 1H), 5.91 (d, 1H, $J = 7.52$ Hz), 7.67 (d, 1H, $J = 7.50$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 25.4, 51.1, 68.8, 73.5, 74.3, 88.7, 91.1, 96.2, 144.2, 158.0, 161.5, 167.9; HRMS (FAB) calcd for $C_{12}H_{16}N_5O_5F$ [M + H^+] 330.12082, found 330.12108.

Acknowledgment. We thank NSERC and Syngenta for generous financial support. We also thank Thomas Vifian (Syngenta, Basel, Switzerland) for skillful technical assistance and Dr. Patrick Crowley (Syngenta, U.K) for stimulating discussions.

Supporting Information Available: Spectral data (^{1}H NMR and ^{13}C NMR) for compounds **6**, **11**, **14**, **17**, **18**, **22**−**24**, **26**, **34**−**37**, **41**−**44**, and **46**−**57**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050727B