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Total Synthesis and Structural Confirmation of Malayamycin A: A Novel Bicyclic *C*-Nucleoside from *Streptomyces malaysiensis*

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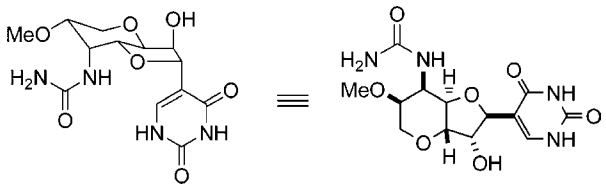
ABSTRACT



The stereocontrolled synthesis of malayamycin A, a novel naturally occurring bicyclic *C*-nucleoside of the perhydrofuropyran type, is described.

Nucleosides have a rich legacy in the realm of carbohydrate-based natural products, particularly as potent antitumor, antiviral, and antibiotic agents.[1] Their structures transcend the traditional *N*-glycosyl-linked purines and pyrimidines which are the cornerstones of the chemistry and biology of DNA and RNA. Nature has also provided *C*-nucleosides as anomerically stable variants with impressive biological properties.[2] Among this class are a small group of bicyclic *C*-nucleosides in which the glycosyl portion can be related to a perhydrofuropyran motif.[3] Ezomycin B_2[4] (Figure 1) is a representative example of such natural products with reported antifungal activity. This group also comprises bicyclic *N*-nucleosides such as ezomycin A_1 and A_2,[5] and the octosyl acids.[6,7] Quantamycin,[8] one of the earliest "rationally designed" ribosomal inhibitors also harbors a bicyclic sugar mimic.

We now wish to report on the total synthesis, structural identity, and stereochemical confirmation of malayamycin A **1**, a novel member of the antifungal family of bicyclic *C*-nucleosides (Figure 1).

Malayamycin was isolated from the soil organism *Streptomyces malaysiensis* by a group at the Syngenta Crop Protection laboratories in Jealott's Hill, U.K.[9] Its structure was determined by detailed NMR studies and by degradative work. Natural malayamycin A was found to be unstable

(1) For pertinent recent 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*, 269. (d) Isono, K.; *J. Antibiotics* **1988**, *41*, 1711 and earlier references therein.

(2) For pertinent examples, see: Chaudhuri, N. C.; Reu, R. X.-F.; Kool, E. T. *Synlett* **1997**, 341.

(3) (a) Hanessian, S.; Liak, T. J.; Dixit, D. M. *Carbohydr. Res.* **1981**, *88*, C14−C19. (b) Hanessian, S.; Dixit, D. M.; Liak, T. J. *Pure Appl. Chem.* **1981**, *53*, 129.

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

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

(6) Isono, K.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 943.

(7) For the total synthesis of octosyl acid A, 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.

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

(9) Benner, J. P.; Boehlendorf, B. G. H.; Kipps, 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.

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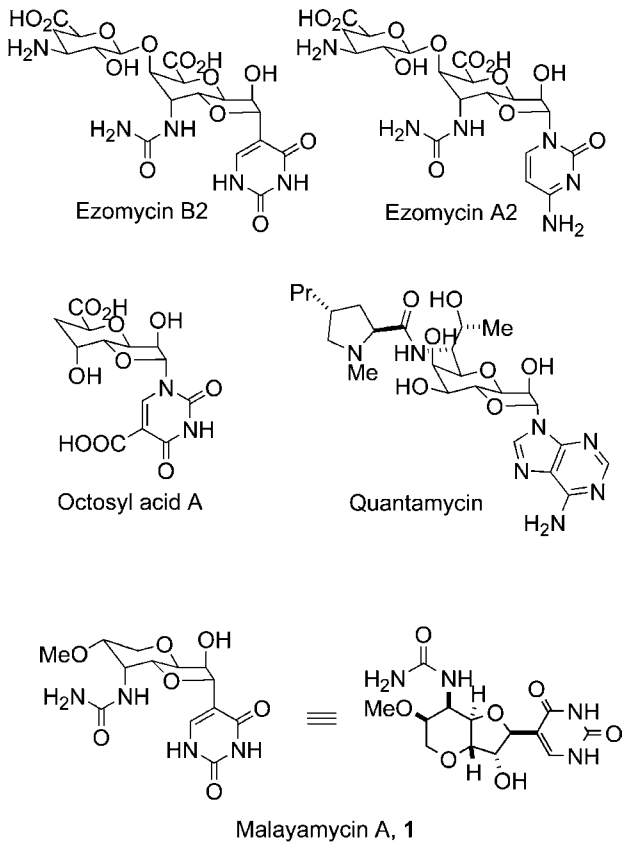


Figure 1.

under strongly acidic (pH <1) or basic conditions (pH >12), but could otherwise be easily handled at neutral pH.

The perhydrofuropyran motif in malayamycin A distinguishes itself from the structurally related ezomycins and octosyl acids by the absence of a carboxyl group, and the presence of a *cis*-vicinal amino alcohol in the "D-*ribo*-perhydropyran" portion. Clearly, the main challenges in planning the synthesis of malayamycin A consist of the 5-pyrimidinyl β-*C*-glycosidic bond, the *trans*-fused bicyclic perhydrofuropyran motif, and securing the relative as well as absolute configuration of stereogenic centers. Although the commercially available β-pseudouridine could be utilized as a starting material, its high cost[10] compelled us to seek an alternative synthesis that was amenable to scale-up.[11] Previously, our construction of the trans-fused perhydrofuropyran motif in quantamycin[8] and octosyl acid A[6,7] relied on an intramolecular oxycyclization of a thionium intermediate[3b,12] and oxymercuration[13] of an olefin, respectively.

The felicitous inclusion of the Grubbs olefin metathesis reaction[14] in our present-day repertoire of versatile methods for carbocyclization compelled us to adopt it in our plan for the synthesis of malayamycin A. Thus, the main challenge became one of peripheral manipulation of a diol in β-pseudouridine, installation of the vinyl and allyl ether appendages, and testing the Grubbs metathesis reaction to produce the strained trans-fused bicyclic motif. The judicious choice of reagents and timing of reactions from the unsaturated bicyclic motif would eventually lead to the intended target.

D-Ribonolactone **2** was converted to the corresponding 2,3-*O*-isopropylidene-5-(2-methoxy-2-methyl) ether **3** in excellent yield (Scheme 1). Treatment with 2,4-dimethoxy-5-lithiopyrimidine led to a mixture of anomeric hemiacetals, which was reduced with L-Selectride in the presence of $ZnCl_2$ to afford diol **5** with high stereoselectivity.[11] Under the conditions of the Mitsunobu reaction,[15] diol **5** underwent a site-selective oxycyclization to give the protected β-pseudouridine derivative **6** in 91% yield. Cleavage of the acetals, and selective etherification at C_3'/C_5' as the disiloxane derivative followed by treatment with *p*-methoxybenzyl bromide led to **7** in excellent yield. Mild selective cleavage of the disiloxane exposed the free primary alcohol, which was oxidized to the aldehyde and further converted to the olefin **9**. Allylation under standard conditions afforded **10**, which was subjected to a Grubbs metathesis reaction[14] to give the bicyclic tetrahydrofuropyran derivative **11** in 89% yield.[16] Treatment of **11** with NBS in aq THF[17] gave the bromohydrin **12**, which when treated with aqueous NaOH gave the epoxide **13** in good overall yield. Regioselective opening of the epoxide ring with NaN_3 led to the trans azido alcohol **14** as the major product (5:1) as ascertained by detailed NMR studies.

Oxidation of the alcohol to give **15** and NMR analysis confirmed the position of the azide group. Treatment of the

(10) (a) Grohar, P. J.; Chow, C. S. *Tetrahedron Lett.* **1999**, *40*, 2049. (b) Brown, D. M.; Ogden, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 723 and references therein. For the synthesis of unnatural *C*-linked nucleosides, see: (c) Matulic-Adamic, J. M.; Beigelman, L.; Portmann, S.; Egli, M.; Usman, N. *J. Org. Chem.* **1996**, *61*, 3909. (d) Matulic-Adamic, J. M.; Beigelman, L. *Tetrahedron Lett.* **1997**, *38*, 1669. (e) Schweitzer, B. A.; Kool, E. T. *J. Org. Chem.* **1994**, *59*, 7238. (f) Hildebrand, S.; Leumann, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1968. (g) Parsch, J.; Engels, J. W. *Helv. Chim. Acta* **2000**, *83*, 1791.

(11) Hanessian, S.; Machaalani, R. *Tetrahedron Lett.* In press.

(12) A related method was used in the synthesis of the octosyl nucleoside portion of ezomycin A_1: Knapp, S.; Shih, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, J. R. *J. Org. Chem.* **1994**, *59*, 948.

(13) Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 820.

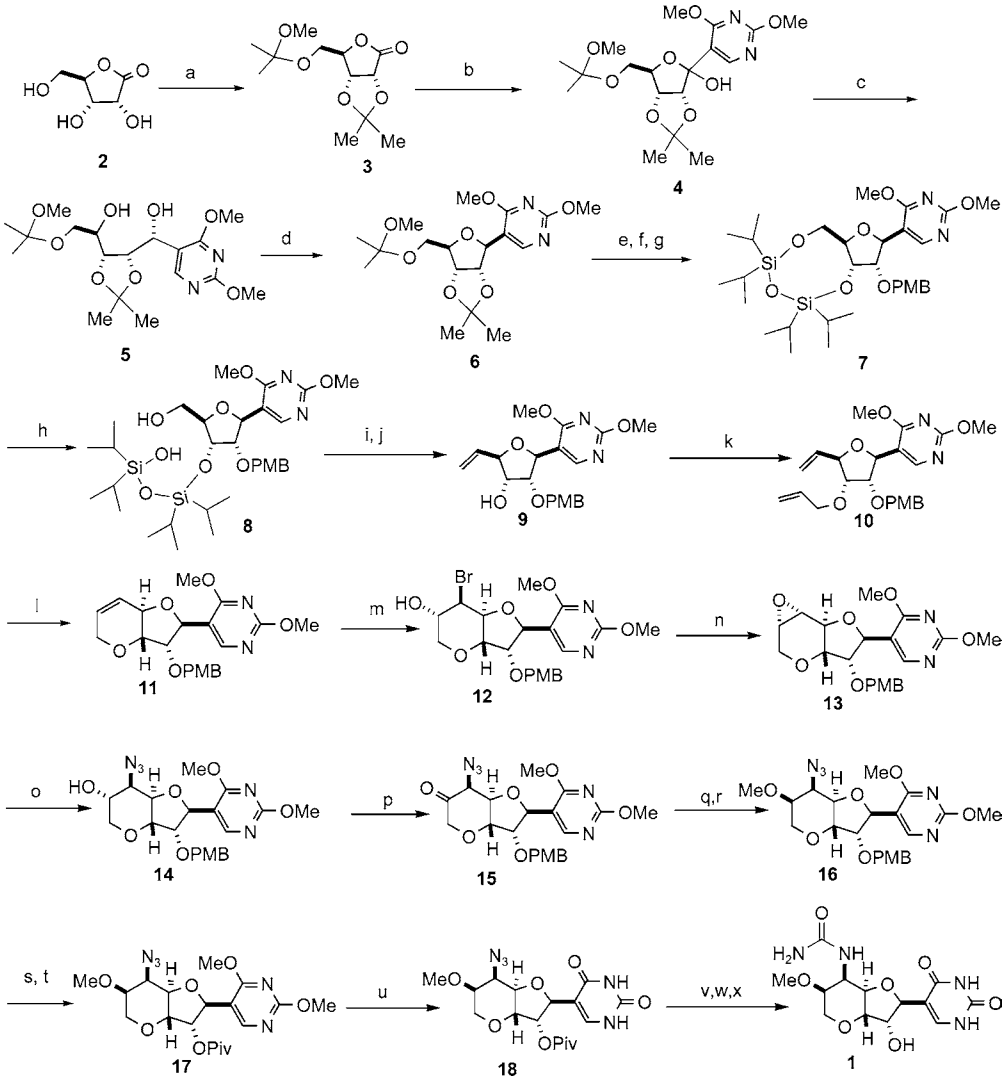
(14) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. For pertinent reviews, see: (b) Grubbs, R.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans.* **1998**, 371. Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, H. H. *Chem. Commun.* **1998**, 1315. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

(15) (a) Guianvarc'h, D.; Fourrey, J.-L.; Tran Huu Dau, M.-E.; Guérineau, V.; Benhida, R. *J. Org. Chem.* **2002**, *67*, 3724. For reviews, see: (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Hughes, D. C. *Org. React.* **1992**, *42*, 335.

(16) 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) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. *Synlett* **1997**, 1263. (e) Nicolaou, K. C.; Postema, H. D.; Claiborne, C. I. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (f) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (g) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (h) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 6299. (i) Peris, E.; Cavé, A.; Estornell, E.; Zafra,-Polo, M. C.; Frigadère, B.; Cortes, D.; Bermejó, A. *Tetrahedron* **2002**, *58*, 1335.

(17) (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.

Scheme 1[a]



[a] Reagents and conditions: (a) 2,2-dimethoxypropane, Na_2SO_4, PPTS, 94%; (b) 2,4-dimethoxy-5-iodopyrimidine, *t*-BuLi, 75%; (c) L-Selectride, $ZnCl_2$, DCM, 86%; (d) DIAD, Ph_3P, THF, 91%; (e) 70% AcOH, 85%; (f) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine, 89%; (g) NaH, PMBBr, DMF/THF, 84%; (h) 1 N HCl, Dioxane, 88%; (i) DMSO, $(COCl)_2$, *i*-Pr_2NEt, DCM; (j) Ph_3PCH_3Br, NaHMDS, THF (36%, 2 steps); (k) allyl bromide, NaH, DMF, 93%; (l) $Cl_2RuCHPh(PCy_3)_2$, DCM, reflux (89%); (m) NBS, H_2O, THF; (n) NaOH, THF; (o) NaN_3, methoxyethanol (5:1, 41%, 3 steps for 14); (p) Dess-Martin periodinane, DCM; (q) $NaBH_4$, MeOH; (r) NaH, MeI, DMF (93%, 3 steps); (s) DDQ, H_2O, DCM (84%); (t) PivCl, DMAP, NEt_3, pyridine; (u) TMSCl, NaI, acetonitrile (42%, 2 steps); (v) PMe_3, H_2O, THF; (w) trichloroacetylisocyanate, DCM; (x) $MeNH_2$, MeOH, H_2O (60%, 3 steps).

ketone with $NaBH_4$ and *O*-methylation gave **16** in excellent overall yield. Unfortunately, the PMB group was not compatible with the conditions of removal of the methoxy groups in the pyrimidine (NaI/TMSCl).[18] Thus, treatment of **16** with DDQ[19] followed by pivaloylation afforded the protected alcohol **17**. The methoxy groups were smoothly cleaved with NaI/TMSCl to the corresponding pyrimidinedione derivative **18**. Reduction of the azide group under Staudinger conditions,[20] followed by treatment of the resulting amine with trichloroacetyl isocyanate[12,21] gave the corresponding trichloroacetyl urea derivative. Finally, treatment with aqueous methylamine, followed by silica gel chromatography gave pure malayamycin A (**1**), which was found to be identical with the natural product in all respects (^1H, ^{13}C NMR, $[\alpha]_D$, HPLC, and plant fungicidal activity).

The regioselective formation of **14** is worthy of comment. When the tetrahydrofuropyran intermediate **11** was treated with *m*-CPBA and the resulting epoxide **19** opened with NaN_3, the main product was the wrong regioisomeric azido

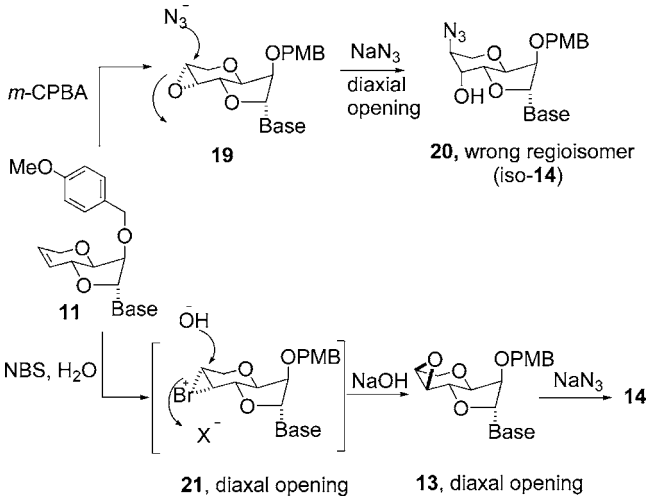
(18) (a) Kundu, N. G.; Das, B.; Spears, C. P.; Majundar, A.; Kang, S. *J. Med. Chem.* **1990**, *33*, 1975. (b) Silverman, R. B.; Radat, R. E.; Hacker, N. P. *J. Org. Chem.* **1979**, *44*, 4920.

(19) Horitai, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *42*, 3021.

(20) (a) Vaultier, M.; Knouz, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 263. (b) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(21) Hecker, S.; Minich, M. L.; Lackey, K. *J. Org. Chem.* **1990**, *55*, 4904.

Scheme 2



alcohol **20** (Scheme 2). This stereochemical result could arise from epoxidation of **11** from the least-hindered *endo*-face of the bicyclic motif, followed by a trans-diaxial ring opening with azide ion. On the other hand, solvolytic opening of the α-epibromonium ion **21** gives the trans-diaxial bromohydrin, which upon treatment with base leads to the *β*-epoxide **13**. A second trans-diaxial opening with azide ion affords the desired azido alcohol **14** as the major product.

The total synthesis of malayamycin A by a highly stereocontrolled route confirms the structure and absolute configuration proposed by NMR studies.[9] Further studies on the design and synthesis of analogues, congeners, and especially the *N*-nucleoside analogue of malayamycin A will be reported in due course.

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Supporting Information Available: Selected experimental procedures, ^{1}H and ^{13}C NMR spectra, compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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