NOVEL INTRAMOLECULAR RADICAL Ar-C GLYCOSYLATION-LACTONIZATION REACTION IN THE TRANSFORMATION OF CAPURAMYCIN[φ]

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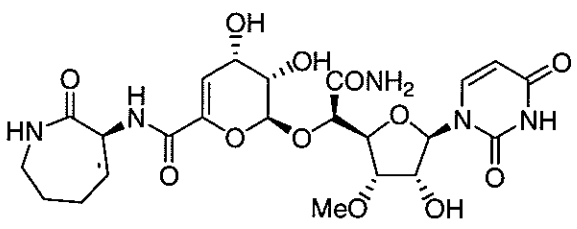
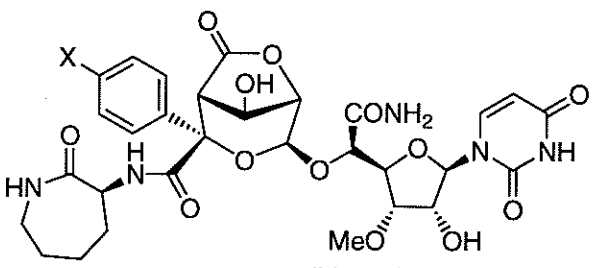
Abstract- Radical deoxygenation of capuramycin derivative (**2a,b**) gave the unexpected lactone (**3a,b**) in moderate yield *via* a novel intramolecular radical Ar-C glycosylation-lactonization reaction. R-115381 and R-116022, thus obtained, showed weak antimicrobial activity against several Gram-positive bacteria.

Capuramycin, a complex nucleoside antibiotic consisting of a nucleoside, sugar and lactam, was originally isolated from the culture broth of *Streptomyces griseus* 446-S3.[1] This compound exhibits antibacterial activity against *Streptococcus pneumoniae* and *Mycobacterium smegmatis* ATCC 607. In the course of screening for new antibiotics, we also isolated capuramycin from *Streptomyces griseus* SANK 60196. Chemical modifications of capuramycin were carried out to extend the antibacterial spectrum. R-115381 and R-116022 with antibacterial activity against Gram-positive bacteria were synthesized *via* a novel intramolecular radical Ar-C glycosylation-lactonization reaction as described hereinafter.



capuramycin

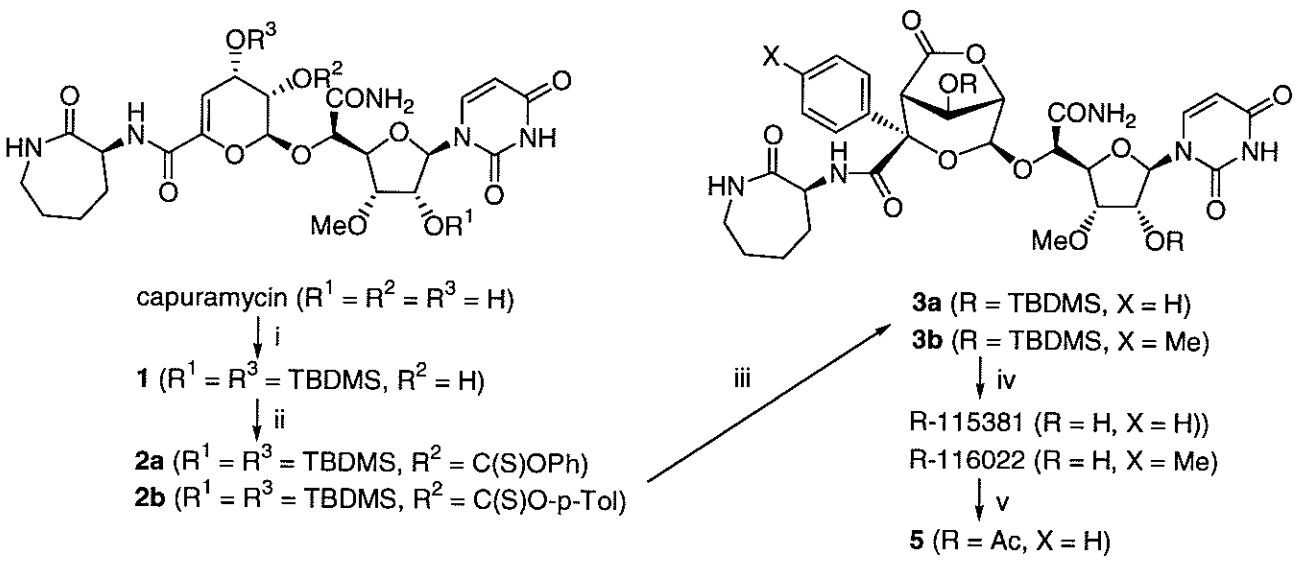


R-115381 (X = H)
R-116022 (X = Me)

[φ] This paper is dedicated to Dr. Teruaki Mukaiyama, Professor of Science University of Tokyo, in connection with the pre-celebration of his 73rd birthday.

At first, we planned the deoxygenation of one of the three hydroxyl groups of capuramycin according to the Robins' modification[2] of the Barton method.[3] It was found that the silylation of capuramycin with *tert*-butyldimethylsilyl chloride in pyridine gave the bis-silylated derivative (**1**) in 59% yield along with the 3"-TBDMS derivative ($R^1 = R^2 = H$, R^3 = TBDMS; 9%) and the 2'-TBDMS derivative (R^1 = TBDMS, $R^2 = R^3 = H$; 13%) (Scheme 1). Subsequent reaction of **1** with excess phenyl chlorothionoformate (4.5 equiv.) in the presence of DMAP formed the 2"-phenoxythiocarbonyl derivative (**2a**, 70%) along with the recovery of **1** (12%). Unexpectedly, the reaction of **2a** with tributyltin hydride and a catalytic amount of AIBN in toluene under reflux gave the lactone (**3a**) in 49% yield together with a trace amount of the desired 2"-deoxycapuramycin derivative (**4**). Deprotection of **3a** using TBAF gave R-115381 in 88% yield.[4]

Scheme 1

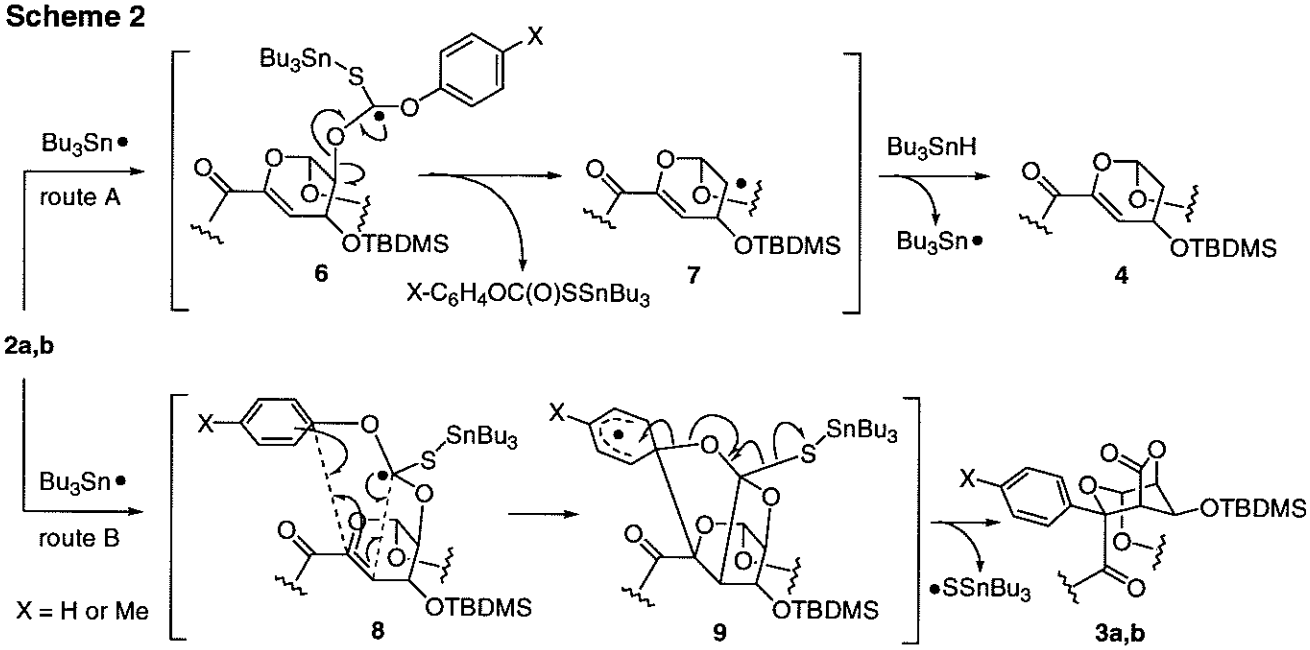


Reagents and conditions: (i) TBDMSCl, pyridine; (ii) X-$C_6H_4OC(S)Cl$, DMAP, CH_2Cl_2; (iii) Bu_3SnH, AIBN, PhMe, reflux; (iv) TBAF, THF; (v) Ac_2O, pyridine

The structure of R-115381 was determined in terms of data from HR-FABMS, UV, and $^1H/^{13}C$ NMR (DQFCOSY, PFG-HMQC, PFG-HMBC,[5] and NOESY), and also by the corresponding diacetate (**5**) to assign the position of the bridge junction. The 2"-tolyloxythiocarbonyl derivative (**2b**) was obtained in 73% yield in the same manner as described for **2a**. Radical deoxygenation of **2b** afforded the lactone (**3b**) in 63% yield along with the 2"-deoxycapuramycin derivative (**4**, 36%). After deprotection of **3b**, R-116022 was obtained in 69% yield.[6]

The novel intramolecular radical Ar-C glycosylation-lactonization reaction occurring in the transformation of capuramycin is thought to proceed as shown in Scheme 2. Homolytic C-O bond

Scheme 2



cleavage of the initial radical intermediate (**6**) affords **7**, which is then trapped by a hydrogen radical to generate the 2"-deoxycapuramycin derivative (**4**) (route A). On the other hand, when the carbon radical of the initial radical intermediate is in the vicinity of the double bond in the same molecule (**8**), both the lactonization and the Ar-C glycosylation according to the S_H2 (homolytic substitution) reaction at the phenyl group may take place to give **3a,b** (route B). However, preliminary molecular mechanics calculations for a model compound lacking the uridine moiety and the lactam moiety demonstrated instability in this intermediate. Therefore, in the case of complete capuramycin derivative, it can be suggested that it is both the pseudo-equatorial TBDMS group and the uridine moiety that are directing the carbon radical towards the double bond, as in the case of intermediate (**8**). Further studies on the mechanism as well as the scope and limitation of this novel reaction are currently underway.

The *in vitro* antimicrobial activity of capuramycin, R-115381 and R-116022 is shown in Table 1.

Table 1. *In vitro* antimicrobial activity of capuramycin, R-115381 and R-116022. MIC (μg/mL)

	capuramycin	R-115381	R-116022
M. smegmatis SANK 75075	12.5	50	100
S. aureus 209P	>200	25	50
S. aureus 56R	>200	25	50
S. aureus 535 (MRSA)	>200	25	50
B. subtilis ATCC 6633	>100	25	50
E. faecalis 681	>200	25	50

Capuramycin exhibited antimicrobial activity only against *M. smegmatis* SANK 75075. On the other hand, both R-115381 and R-116022 showed weak activity against *M. smegmatis* SANK 75075 as well as against several Gram-positive organisms involving MRSA.

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REFERENCES AND NOTES

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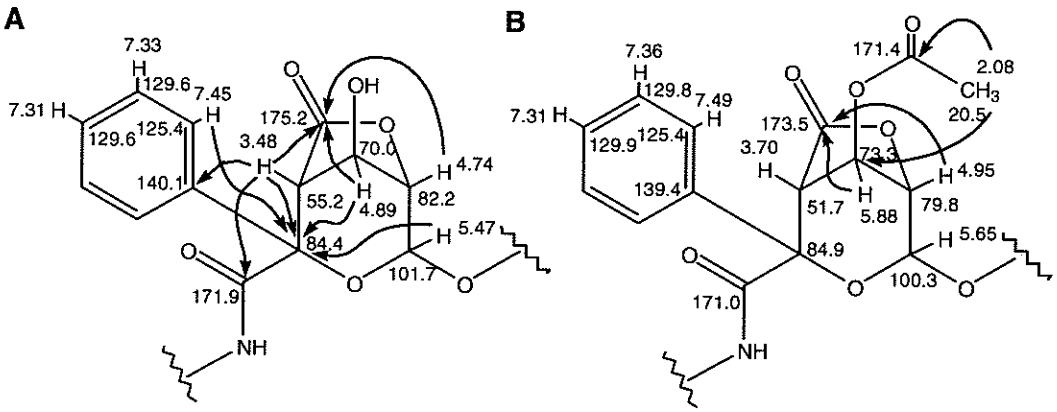
2. M. J. Robins, J. S. Wilson, and F. H. Hansske, *J. Am. Chem. Soc.*, 1983, **105**, 4059.
3. D. H. R. Barton and S. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.
4. Data for R-115381: ^{1}H NMR (CD_3OD) δ 7.76 (d, J = 8.1 Hz, 1H), 7.43 (m, 2H), 7.35 (m, 3H), 5.86 (d, J = 8.1 Hz, 1H), 5.81 (d, J = 8.1 Hz, 1H), 5.48 (d, J = 2.9 Hz, 1H), 4.87 (m, 1H), 4.74 (m, 1H), 4.66 (d, J = 5.9 Hz, 1H), 4.45 (d, J = 10.2 Hz, 1H), 4.28 (dd, J = 5.9 and 7.3 Hz, 1H), 4.15 (dd, J = 2.2 and 5.9 Hz, 1H), 3.94 (dd, J = 1.6 and 5.9 Hz, 1H), 3.49 (s, 1H), 3.45 (s, 3H), 3.25 (m, 2H), 1.95-1.10 (m, 6H); IR (KBr) ν 3350, 2933, 2856, 1806, 1686, 1481, 1384, 1335, 1273, 1199, 1161, 1117, 1073, 1001 cm^{-1}; HR-FABMS *m/z* 696.2103 $(M+Na)^+$ $\Delta_{ppm} = -3.7$.
5. Informative C-H long-range couplings for R-115381 (A) and **5** (B) are as follows:



6. Data for R-116022: ^{1}H NMR (DMSO-d_6) δ 11.41 (d, J = 2.0 Hz, 1H), 8.00 (t, J = 6.0 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 4.1 Hz, 1H), 7.56 (d, J = 6.3 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.17 (d, J = 2.7 Hz, 1H), 5.79 (m, 2H), 5.57 (d, J = 6.9 Hz, 1H), 5.41 (d, J = 2.7 Hz, 1H), 4.80 (m, 1H), 4.66 (m, 1H), 4.53 (d, J = 5.6 Hz, 1H), 4.28 (dd, J = 6.4 and 11.0 Hz, 1H), 4.16 (d, J = 5.3 Hz, 1H), 4.09 (m, 1H), 3.73 (d, J = 5.3 Hz, 1H), 3.16 (s, 3H), 3.05 (m, 2H), 2.27 (s, 3H), 1.80 (m, 1H), 1.67 (m, 2H), 1.56 (m, 2H), 1.30 (m, 1H), 1.10 (m, 2H); IR (KBr) ν 3376, 2934, 2806, 1686, 1502, 1480, 1461, 1437, 1409, 1384, 1335, 1273, 1198, 1161, 1117, 1071 cm^{-1}; HR-FABMS *m/z* 710.2265 $(M+Na)^+$ $\Delta_{ppm} = -2.9$.

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