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CHIRAL SYNTHESIS OF THE DEF-RING SYSTEM OF NOGALAMYCIN[1]

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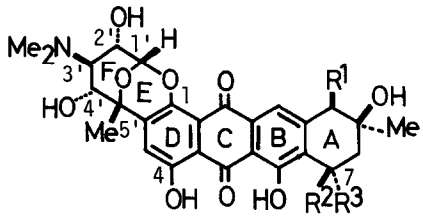
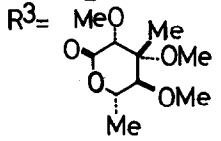
Abstract: The DEF-ring system of nogalamycin (1), a potent antitumor antibiotic of the anthracycline family, was stereoselectively synthesized in an optically active form starting from readily available D-arabinose.

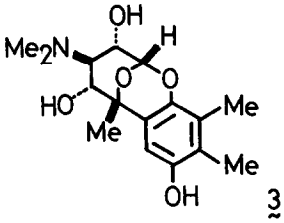
Nogalamycin (1) is a notable member of the anthracycline family because of its prominent antitumor activity and reduced cardiotoxicity compared with adriamycin and related compounds.[2,3] 7-Con-O-methylnogarol (2), the semisynthetic derivative of 1, has been reported to show superior antitumor activity to the parent compound.[2] These compounds (1 and 2) have the characteristic DEF-ring system, in which the aminosugar (F-ring) is fused to anthracycline D-ring to form new E-ring. Their promising antitumor activity and unique structures distinguish



1 : R^1 = CO_2Me, R^2 = H, R^3 =



2 : R^1 = R^3 = H, R^2 = OMe

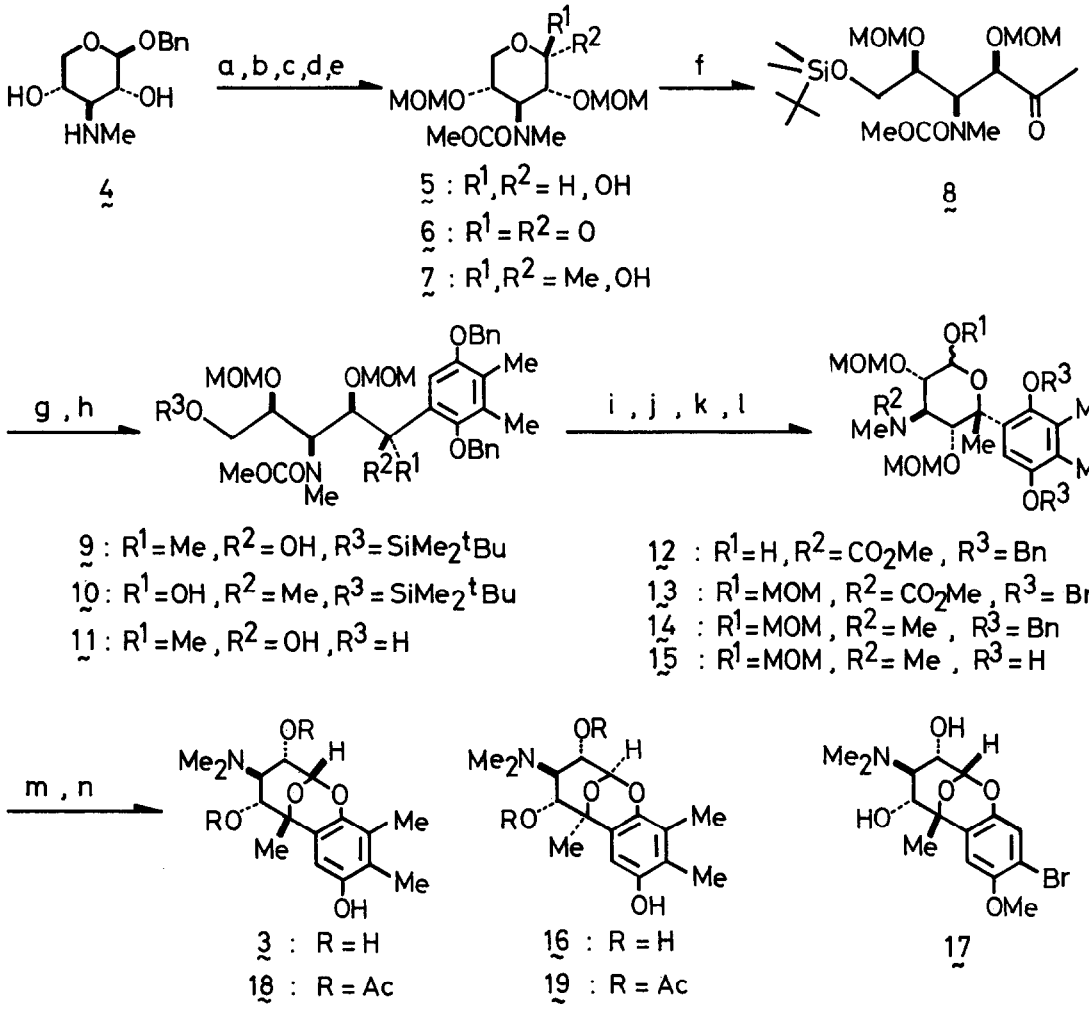


3

these compounds as unusually attractive targets for total synthesis.[4] Moreover, synthetic studies on these complex molecules (1 and 2) are anticipated to contribute to further elucidation of structure-activity relationships, leading to development of new analogues which may show more improved therapeutic properties.

For total synthesis of 1 and 2, it is indispensable to develop a new synthetic scheme for constructing the bicyclic DEF-ring system in an optically active form. We wish to report here a novel synthesis of the optically pure bicyclic acetal (3) corresponding to the DEF-ring system of 1 and 2 starting from D-arabinose.

Benzyl β-D-gentosaminide (4), m.p. 151-152°C, $[\alpha]_D^{20}$ -76.9° (c 0.45, EtOH), which has the desired stereochemistry at $C_{2'}$, $C_{3'}$, and $C_{4'}$-positions (nogalamycin numbering), was prepared in 8 steps from D-arabinose according to the method reported for the corresponding methyl glycoside.[5] Successive protection of the methylamino and two alcoholic groups of 4 followed by debenzylation afforded the protected hemiacetal (5), which was treated under the condition



(a) MeOCOCl, K_2CO_3, Me_2CO, reflux, 20 min, 85% (b) MOMCl, $(i\text{-}Pr)_2NEt$, THF, reflux, 30 min, 90% (c) H_2, Pd-C, EtOH, r.t., 15 h, 100% (d) $CrO_3 \cdot 2Py$, CH_2Cl_2, 40°C, 1 h, 92% (e) MeLi, THF, -78°C, 2 h, 94% (f) TBDMSCl, imidazol, DMF, r.t., 16 h, 88% (g) $Li[C_6HMe_2(OBn)_2]$, ether-THF (4:1), 0°C, 1 min, 74% (h) $(n\text{-}Bu)_4N^+F^-$, THF, r.t., 1 h, 94% (i) DMSO, $SO_3 \cdot Py$, Et_3N, THF, r.t., 2 h, 88% (j) MOMCl, $(i\text{-}Pr)_2NEt$, THF, reflux, 12 h, 91% (k) $LiAlH_4$, ether, reflux, 30 min, 94% (l) H_2, Pd-C, EtOH, r.t., 3 h (m) TMSBr, CH_2Cl_2, reflux, 15 min, 82% (2 steps) (n) Ac_2O, MeOH, 40°C, 30 min, 93%

of Collins oxidation, giving the lactone (6). Addition of methyllithium to 6 readily produced the hemiacetal (7) as a mixture of two epimers. Treatment of 7 under the usual silylation condition afforded the open chain methylketone (8), caramel, $[\alpha]_D^{20}$ -28.8° (c 1.10, $CHCl_3$).

For stereocontrolled formation of the C_5, asymmetric center which constitutes the key step of our synthetic scheme, nucleophilic addition of the aryllithium generated from 1,4-dibenzyloxy-5-bromo-2,3-dimethylbenzene[6] to 8 was examined. Interestingly, the stereo-

selectivity and chemical yields of the resulting two epimers at $C_{5'}$-position were found to highly depend on reaction solvent as described below. Thus, when THF was employed as a solvent at 0°C, the epimeric alcohols (9 and 10) were obtained in 7:1 ratio and 56% combined yield. Unreacted 8 was recovered in 32% yield. On the other hand, the reaction in ether at 0°C afforded 9 and 10 in 77% combined yield and a small amount of 8 was also recovered (7%). The ratio of 9 to 10 was found to be 2:1. After repeated experiments, the most satisfactory result was finally obtained in a mixture of ether-THF (4:1) at 0°C, giving 9 and 10 in 8:1 ratio and 74% combined yield along with a recovery of 8 (16%).[7] These two epimers (9 and 10) and 8 could be readily separated by silica gel chromatography. Although the stereochemistry at $C_{5'}$-position of 9 and 10 could not be determined at this stage, the major epimer (9) was assumed to have the desired configuration since it is well known that addition of an organolithium reagent to an α-alkoxyketone generally gives a chelation-controlled product as a major isomer.[8] This assignment was obviously confirmed by successful conversion of 9 into the objective compound (3) (vide infra).

After desilylation of the major alcohol (9), oxidation of the resulting primary alcohol (11) and protection of the formed lactol (12) afforded the acetal (13) as an epimeric mixture at $C_{1'}$-position. Reduction of 13 took place smoothly to afford the dimethylamine (14). Debenzylation of 14 afforded the unstable p-hydroquinone (15), which was immediately subjected to the next reaction without purification. Brief exposure of 15 to trimethylsilyl bromide effected simultaneous clean cleavage of the three methoxymethyl ethers and intramolecular acetal formation, furnishing the bicyclic acetal (3),[9] caramel, $[\alpha]_D^{20}$ -35.6° (c 0.50, MeOH). On the other hand, the minor alcohol (10) obtained from 8 was derived to the isomeric bicyclic acetal (16),[9] caramel, $[\alpha]_D^{20}$ -50.1° (c 1.40, MeOH), following exactly the same procedure as described for 9. Comparison of the chemical shifts and coupling constants of 3 and 16 with those of 1 and the model compound (17)[4] clearly disclosed the structure of 3 and 16 as shown in the figure. Acetylation of 3 and 16 readily produced the well-crystalline diacetates (18 and 19), 18: m.p. 216-218°C, $[\alpha]_D^{20}$ -57.6° (c 0.50, $CHCl_3$) and 19: m.p. 174-175°C, $[\alpha]_D^{20}$ -69.1° (c 0.54, $CHCl_3$).[9] X-ray crystallographic analyses of 18 and 19 unambiguously established the structure of 3 and 16 assigned above.[10]

The first chiral synthesis of the DEF-ring system of 1 was successfully accomplished in excellent overall yield starting from readily available D-arabinose. Based on the information accumulated in these synthetic studies, the total synthesis of 2 is pursued in this laboratory.

Acknowledgement: The authors are indebted to Prof. P.G. Sammes and Dr. G.T. Thomson for providing us with the spectral data of the bicyclic acetal (17). X-ray analyses of the diacetates (18 and 19) were performed by Drs. K. Shirahata and N. Hirayama, Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., to whom authors' thanks are due.

References and Notes

(1) This paper is dedicated to Prof. Shun-ichi Yamada on the occasion of his 70th birthday.
(2) P.F. Wiley, Lloydia, 42, 569 (1979); Idem., "Anthracycline Antibiotics," ed by H.S. El Khadem, Academic Press, New York (1982), pp97-117; P.F. Wiley, D.W. Elrod, D.J. Houser, and F.A. Richard, J. Med. Chem., 25, 560 (1982); P.F. Wiley, D.W. Elrod, D.J. Houser, J.L.

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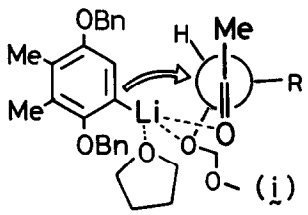
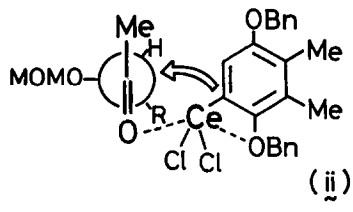
(4) The bicyclic acetal (17) (the DEF-ring system of 1) has already been synthesized in a racemic form: M.A. Bates and P.G. Sammes, J. Chem. Soc., Chem. Commun., 896 (1983).

(5) H. Maehr and C.P. Schaffner, J. Am. Chem. Soc., 89, 6787 (1967); D.J. Cooper, Pure Appl. Chem., 28, 455 (1969).

(6) This compound, mp 98-100°C, was prepared from 2,3-dimethylphenol by sequential oxidation [$ON(SO_3K)_2$, KH_2PO_4, H_2O], addition of hydrogen bromide (47% HBr in AcOH) and benzylation [BnBr, NaH, DMF, 43% (3 steps)].

(7) Interestingly, treatment of 8 (THF, -78°C) with $CeCl_2[C_6HMe_2(OBn)_2]$, generated by treating the aryllithium with cerium chloride [T. Imamoto et al., J. Org. Chem., 49, 3904 (1984)], selectively afforded the undesired epimer (10) in 15:1 ratio and 95% combined yield. These notable selectivity could be nicely explained by assuming that intramolecular interaction between a metal cation and an oxygen atom of the adjacent benzyl ether is stronger in $CeCl_2[C_6HMe_2(OBn)_2]$ than in $Li[C_6HMe_2(OBn)_2]$. Thus, in the reaction of $Li[C_6HMe_2(OBn)_2]$, the lithium cation interacts with the oxygen atom of the MOM group adjacent to the carbonyl group of 8 more preferentially than with the oxygen atom of benzyl ether involved in the aromatic ring. Especially in the presence of THF which can readily solvate a lithium cation, the intramolecular interaction should be much weaker. Therefore, the usual chelation model (i) seems to be well consistent with the transition state of addition reaction with aryllithium. On the other hand, the cerium cation chelates with the oxygen atom of the adjacent benzyl ether more strongly than the lithium cation. Accordingly, the addition reaction with $CeCl_2[C_6HMe_2(OBn)_2]$ seems to proceed through the transition state corresponding to Felkin-Anh model (ii).





(8) M.T. Reetz, Angew. Chem. Int. Ed. Engl., 23, 556 (1984).

(9) Representative ^{1}H-NMR spectra of 3, 16, 18, and 19 are as follows.

3 [$(CD_3)_2CO$]: δ 2.31 (1H, t, J=10.3Hz, 3'-H), 3.47 (1H, d, J=10.3Hz, 4'-H), 3.92 (1H, dd, J=3.4 and 10.3Hz, 2'-H), 5.41 (1H, d, J=3.4Hz, 1'-H).

16 [$(CD_3)_2CO$]: δ 2.56 (1H, dd, J=8.1 and 11.3Hz, 3'-H), 3.59 (1H, dd, J=3.1 and 11.3Hz, 2'-H), 3.91 (1H, d, J=8.1Hz, 4'-H), 5.33 (1H, d, J=3.1Hz, 1'-H).

18 ($CDCl_3$): δ 2.67 (1H, t, J=10.5Hz, 3'-H), 5.05 (1H, d, J=10.5Hz, 4'-H), 5.11 (1H, dd, J=4.2 and 10.5Hz, 2'-H), 5.67 (1H, d, J=4.2Hz, 1'-H).

19 ($CDCl_3$): δ 3.01 (1H, dd, J=7.7 and 11.7Hz, 3'-H), 5.05 (1H, dd, J=3.1 and 11.7Hz, 2'-H), 5.24 (1H, d, J=7.7Hz, 4'-H), 5.43 (1H, d, J=3.1Hz, 1'-H).

(10) K. Shirahata and N. Hirayama, to be published.

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