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Synthetic studies on nogalamycin congeners. Total syntheses of (+)-nogarene, (+)-7-con-*O*-methyl-nogarol, and their related compounds

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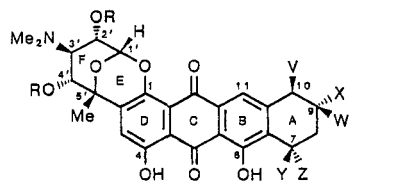
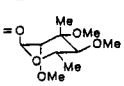
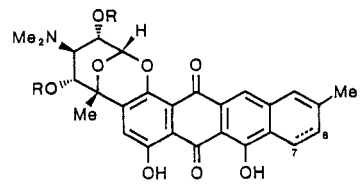
Abstract: The title total syntheses have been accomplished employing commercially available D-arabinose (**10**) as the starting material. The explored synthetic scheme involves the following novel features: (1) convergent synthesis of the methyl ketone (**13**) from **10**, (2) stereoselective addition of an aryllithium to **13**, (3) regioselective oxidation of the 1,4,5,8-tetramethoxynaphthalene (**20**), (4) efficient intramolecular acetalization, and (5) regiospecific Diels-Alder reaction of the naphthoquinone (**8**: R=Ac), the CDEF-ring system, with highly functionalized dienes. Cytotoxicity assay of the produced nogalamycin congeners and their related compounds disclosed novel aspects of the structure-activity relationships.

Nogalamycin (**1a**) and its congeners are notable members of the anthracycline family because of their prominent antitumor activity (ref. 1). Especially, (+)-7-con-*O*-methyl-nogarol (**2a**), the most well-known semisynthetic derivative of **1a**, has been selected for clinical trials due to its superior antitumor activity to the parent compound (**1a**) (ref. 1). Furthermore, these compounds (**1a** and **2a**) carry the characteristic DEF-ring system in which the aminosugar (F-ring) is fused to the D-ring of 11-deoxyanthracyclinone to form the new E-ring. Their promising antitumor activity and unique structures distinguish these compounds as unusually attractive targets for total synthesis (ref. 2).

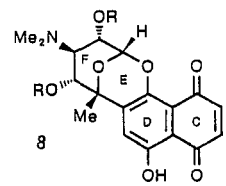


1: V = CO_2Me, W = OH, X = Me, Y = H, Z = 

2: V = H, W = OH, X = Me, Y = OMe, Z = H
3: V = H, W = Me, X = OH, Y = H, Z = OMe
4: V = H, W = OH, X = Me, Y = Z = H
5: V = H, W = Me, Y = OH, Y = Z = H



6: $C_{7,8}$ = CH=CH
7: $C_{7,8}$ = CH_2-CH_2



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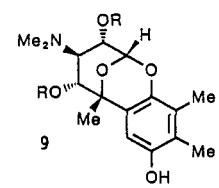


9

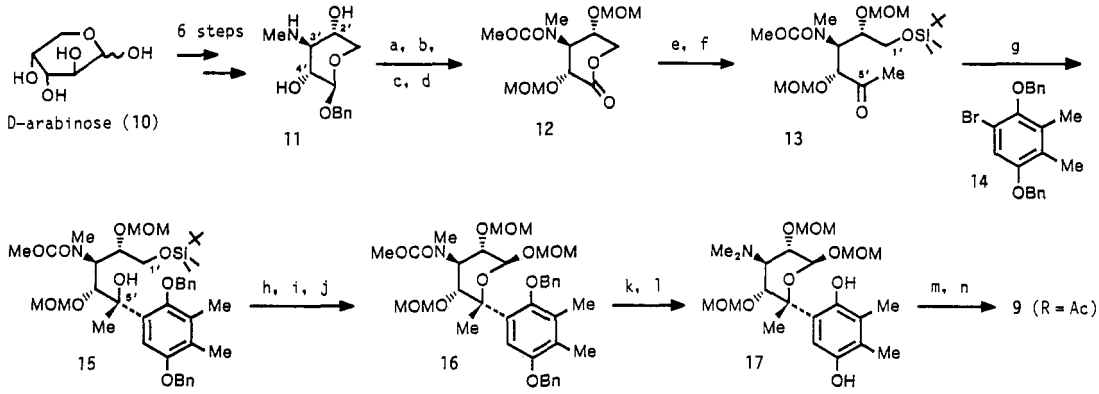
a: R = H b: R = Ac

This report concerns with the first total syntheses and cytotoxicity assay of the nogalamycin congeners, (+)-nogarene (**6a**), (+)-7-deoxynogarol (**4a**), **2a**, and their related compounds. The latter studies disclosed novel aspects of the structure-activity relationships of nogalamycin congeners (ref. 3).

From retrosynthetic perspective on **1** and its congeners, it was anticipated that their 11-deoxyanthracyclinone frameworks could be effectively constructed by the regioselective Diels-Alder reaction employing the naphthoquinone (**8**), the CDEF-ring system of **1**, as a dienophile in a similar manner to those established for the syntheses of usual 11-deoxyanthracyclinones (ref. 4). Prior to the synthesis of **8**, the preparation of the DEF-ring system (**9**) was first studied to explore an efficient and reliable synthetic scheme to produce the characteristic bicyclic acetal structure of **8** in an optically active form.

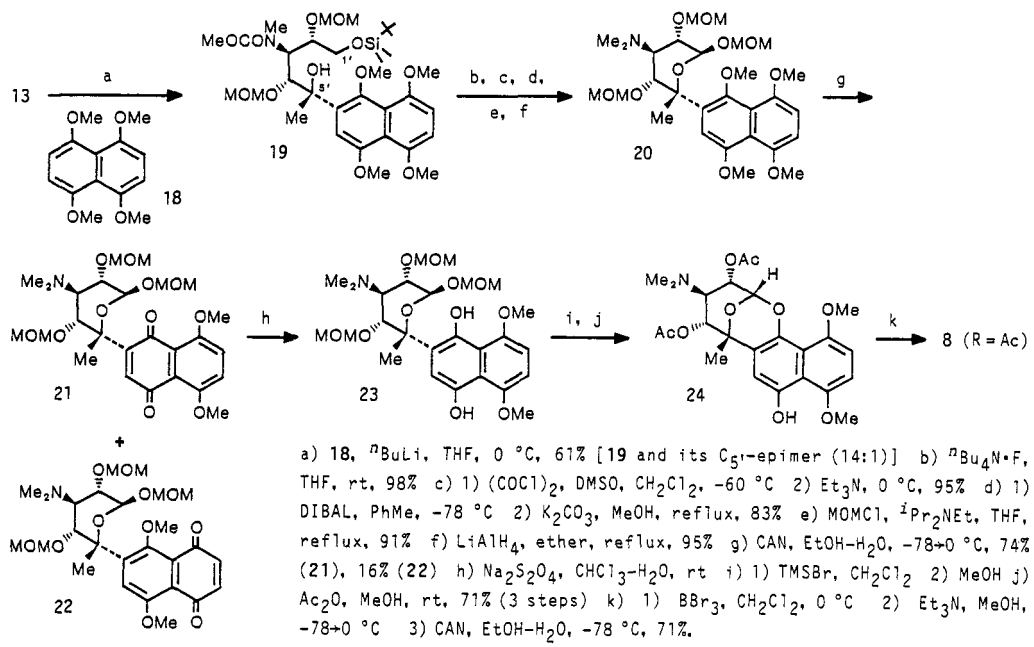
Syntheses of the DEF- and CDEF-Ring Systems (9 and 8): (ref. 3a,b) As shown in **Scheme 1**, we succeeded in obtaining the optically active DEF-ring system (**9**: R=Ac) from commercially available D-arabinose (**10**) by way of benzyl β-D-gentosaminide (**11**) (ref. 5). The benzyl glycoside (**11**) prepared in 8 steps from **10** according to the method reported for the corresponding methyl glycoside (ref. 6), involves the desired stereochemistries concerning the C-2', C-3', and C-4' positions (the nogalamycin numbering). Successive protection of the methylamino and the two hydroxy groups of **11** followed by debenzylation and oxidation afforded the lactone (**12**). This was readily converted to the methyl ketone (**13**) (ref. 5) by

Scheme 1



a) $ClCO_2Me$, K_2CO_3, Me_2CO, reflux, 85% b) MOMCl, $^iPr_2NEt$, THF, reflux, 97% c) H_2, 10% Pd-C, 12N-HCl, EtOH, 99% d) 1) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C 2) Et_3N, -20 °C, 88% e) MeLi, THF, -78 °C, 94% f) TBDMSCl, ImH, DMF, rt, 84% g) **14**, ^nBuLi, THF-ether, 0 °C, 74% [**15** and its $C_{5'}$-epimer (8:1)] h) $^nBu_4N{\cdot}F$, THF, rt, 94% i) $SO_3{\cdot}Py$, DMSO, Et_3N, THF, rt, 88% j) MOMCl, $^iPr_2NEt$, THF, reflux, 85% k) $LiAlH_4$, ether, reflux, 94% l) H_2, 10% Pd-C, EtOH, 99% m) TMSBr, CH_2Cl_2, reflux, 82% n) Ac_2O, MeOH, 40 °C, 93%.

Scheme 2

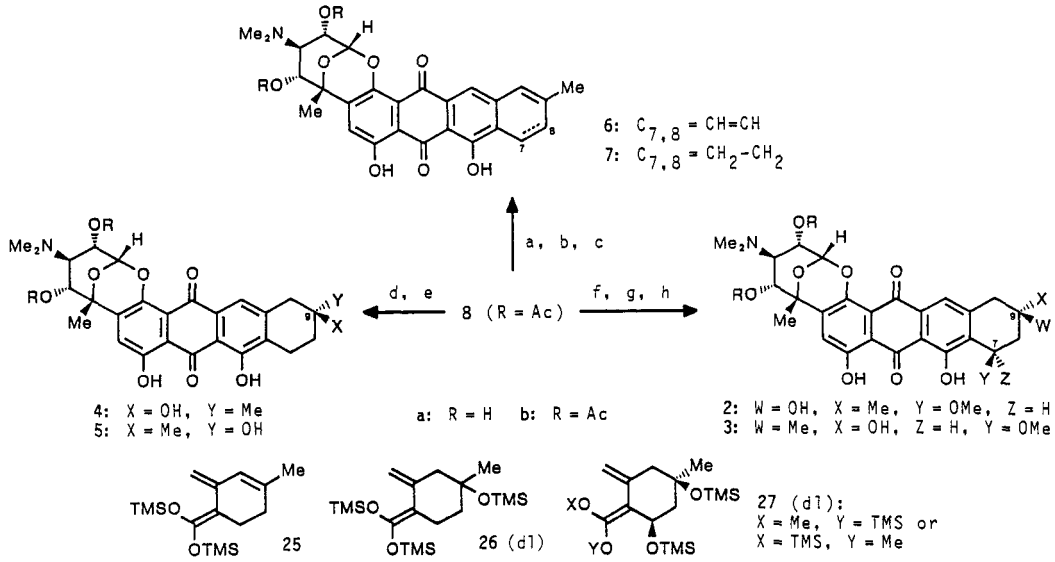


a) **18**, ^nBuLi, THF, 0 °C, 61% [**19** and its $C_{5'}$-epimer (14:1)] b) $^nBu_4N{\cdot}F$, THF, rt, 98% c) 1) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C 2) Et_3N, 0 °C, 95% d) 1) DIBAL, PhMe, -78 °C 2) K_2CO_3, MeOH, reflux, 83% e) MOMCl, $^iPr_2NEt$, THF, reflux, 91% f) $LiAlH_4$, ether, reflux, 95% g) CAN, EtOH-H_2O, -78→0 °C, 74% (**21**), 16% (**22**) h) $Na_2S_2O_4$, $CHCl_3$-H_2O, rt i) 1) TMSBr, CH_2Cl_2 2) MeOH j) Ac_2O, MeOH, rt, 71% (3 steps) k) 1) BBr_3, CH_2Cl_2, 0 °C 2) Et_3N, MeOH, -78→0 °C 3) CAN, EtOH-H_2O, -78 °C, 71%.

sequential addition of methyllithium and silylation. Reaction of **13** with aryllithium generated from **14** proceeded in a stereoselective manner to give a mixture of the alcohol (**15**) and its C-5' epimer (8:1). The selective formation of **15** can be reasonably explained by a chelation-controlled mechanism (ref. 3a). The alcohol (**15**) was derived to the acetal (**16**) in 3 steps. Reduction of **16** followed by debenzylation produced the unstable hydroquinone (**17**). Treatment of **17** with trimethylsilyl bromide cleanly effected simultaneous cleavage of the three methoxymethyl groups and intramolecular acetalization, giving the bicyclic acetal (**9**: R=H). This was acetylated to produce **9** (R=Ac) (ref. 5). X-ray crystallographic analysis of **9** (R=Ac) unambiguously established the assigned structure.

According to the the synthetic scheme similar to that explored for **9** (R=Ac), the preparation of **8** (R=Ac) was next attempted. As shown in **Scheme 2**, addition of the aryllithium generated from **18**, similarly took place in a highly stereoselective manner, yielding the alcohol (**19**) and its C-5' epimer (14:1). The major alcohol (**19**) was assumed to have the desired stereochemistry by taking into account the results obtained in the preparation of **9** (R=Ac). This was converted to the acetal (**20**) in 5 steps. Oxidation of **20** with ceric ammonium nitrate (CAN) was found to occur in a regioselective manner to give the desired naphthoquinone (**21**) along with its regioisomer (**22**) (5:1). This notable regioselectivity can

Scheme 3



a) 1) **25**, THF, rt 2) 3N-HCl, air, rt, 85% (**7b**) b) DDQ, CSA, PhH, reflux, 85% (**6b**) c) 1N-HCl, reflux, 87% (**6a**), 88% (**7a**) d) 1) **26**, THF, 60 °C 2) 3N-HCl, air, rt, 14% (**4b**), 50% (**5b**) e) K_2CO_3, MeOH, 50 °C, 75% (**4a**), 64% (**5a**) f) 1) **27**, PhMe, 100 °C 2) 3N-HCl, air, rt, 45% g) 1) CF_3CO_2H, 0 °C 2) NaOMe, MeOH, 0 °C, 12% (**2b**), 35% (**3b**) h) NaOMe, MeOH, 50 °C, 92% (**2a**), 77% (**3a**).

be rationalized by the electron density of naphthalene ring. After reduction of **21**, the formed unstable dihydronaphthoquinone (**23**) was transformed to the bicyclic acetal (**24**) in a similar manner to that described for the preparation of **9** (R=Ac). Cleavage of the two methyl ethers of **24** followed by quenching with triethylamine and oxidation of the formed triethylamine complex with CAN, produced **8** (R=Ac) (ref. 5).

Syntheses of the Nogalamycin Congeners (2–7): (ref. 3b,c) With **8** (R=Ac) in hand, the synthesis of **6a**, the simplest congener which had been derived from **1a**, was first examined. As shown in **Scheme 3**, the Diels-Alder reaction of **8** (R=Ac) with **25** (ref. 7) followed by air oxidation of the addition product and desilylation during mild acidic workup, gave rise to **7b**. The regioselectivity of this reaction can be explained well by the hypothesis proposed by Boeckman (ref. 8). Dehydrogenation of **7b** readily afforded **6b**. Acidic hydrolyses of **6b** and **7b** produced **6a** and (+)-7,8-dihydronogarene (**7a**), the hitherto unknown congener of **1a**, respectively (ref. 5). When the recemic diene (**26**) (ref. 7) was subjected to the Diels-Alder reaction with **8** (R=Ac) in place of **25** the mixture of **4b** and **5b** could be obtained in 1:4 ratio after mild acidic workup. This diastereoselectivity can be rationalized by assuming that 1) the addition reaction follows the endo-rule, 2) **26** approaches **8** (R=Ac) from the direction opposite to the sterically congested F-ring, and 3) the steric bulkiness of the trimethylsilyloxy group is larger than that of the methyl group. Deacetylation of **4b** and **5b** gave **4a** and unnatural (+)-9-*epi*-7-deoxynogarol (**5a**), respectively (ref. 5). With an aim to obtain **2a**, the highly functionalized recemic diene (**27**) (ref. 7) was allowed to react with **8** (R=Ac). Mild acidic workup of the Diels-Alder addition products, followed by stereoselective introduction of the C-7 methoxy group according to the reported procedure (ref. 1), gave a mixture of **2b** and **3b** (**2b**:**3b** ≈ 1:3). Both 2',4'-diacetates (**2b** and **3b**) were deacetylated to afford **2a** and unnatural (+)-7,9-di-*epi*-7-con-*O*-methylnogarol (**3a**), respectively (ref. 5). Synthetic **2a**, **4a**, and **6a** were identical with the corresponding authentic samples derived from **1a**, in all respects.

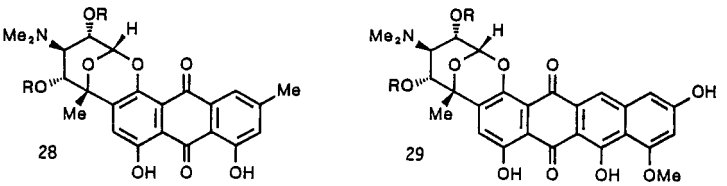
***In Vitro* Cytotoxicity of the Nogalamycin Congeners (2–7) and Their Related Compounds (8, 9, 28, and 29):** (ref. 3b-d) With completion of the total syntheses, **2a,b**-**7a,b** and their related compounds such as **8** (R=Ac), **9** (R=H or Ac), **28a,b**, and **29a,b** (ref. 9), were subjected to *in virto* cytotoxicity assay against P388 murine leukemia cells to disclose novel aspects of the structure-activity relationships of nogalamycin congeners. Based on the results of cytotoxicity assay (**Table 1**), it appeared evident that all the carbon framework (the ABCDEF-ring system) and the C-7 methoxy group are both indispensable for pronounced cytotoxicity. Furthermore, it was also revealed that, for the congeners carrying the C-7 methoxy group, the stereochemistry of the C-9 position may play an important role for inhibitory activity.

Conclusion: As mentioned above, the first total syntheses of nogalamycin congeners have been accomplished starting from commercially available **10**. The explored synthetic route

Table 1 ***In Vitro*** **Cytotoxicity of the Nogalamycin Congeners (2–7) and Their Related Compounds (8, 9, 28, and 29) against P388 Murine Leukemia Cells**

Compound	IC_{50} (μg/ml)[a]	Compound	IC_{50} (μg/ml)[a]	Compound	IC_{50} (μg/ml)[a]
2a (natural)	0.006	**5a**	0.31	**9** (R=H)	> 10
2a (synthetic)	0.003–0.012	**5b**	0.30	**9** (R=Ac)	> 10
2b	0.014	**6a**	0.11	**28a**	1.4
3a	0.40	**6b**	0.17	**28b**	1.5
3b	0.53	**7a**	0.13	**29a**	0.032
4a	0.41	**7b**	0.58	**29b**	0.016
4b	0.17	**8** (R=Ac)	0.10		

a) Cell growth inhibition (percent) after incubation for 48 h at 37 °C.



a: R = H b: R = Ac

involving numerous novel aspects is anticipated to hold promise as the most efficient and reliable method for synthesizing a wide range of nogalamycin congeners obtainable (**2a**, **4a**, and **6a**) or not obtainable (**3a**, **5a**, and **7a**) from **1a**. Studies on the cytotoxic activity also uncovered novel aspects of the structure-activity relationships of nogalamycin congeners.

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