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FIRST TOTAL SYNTHESES OF (+)-7-DEOXYNOGAROL AND (+)-7-CON-*O*-METHYLNOGAROL

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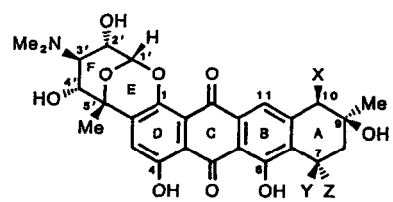
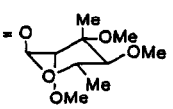
Abstract: The first total syntheses of (+)-7-deoxynogarol (**2**) and (+)-7-con-*O*-methylnogarol (**3**), the notable members of nogalamycin congeners, were achieved employing the Diels-Alder reaction of the highly functionalized dienes (**11** and **20**) with the (+)-naphthoquinone (**6**), the CDEF-ring system of nogalamycin congeners, as a key synthetic step.

Nogalamycin (**1**) and its congeners are notable members of the anthracycline family because of their prominent antitumor activity. Especially, (+)-7-con-*O*-methylnogarol (**3**), the most well-known semisynthetic derivative of **1**, has been selected for clinical trials due to its broad spectrum activity and lower cardiotoxicity than that observed for adriamycin. Furthermore, these compounds carry the characteristic C-glycoside moiety (DEF-ring system) in which the amino sugar (F-ring) is fused to anthracycline D-ring to form the new E-ring.[1] Their promising antitumor activity and unique structures definitely distingwish these compounds as unusually attractive targets for total synthesis.

From retrosynthetic perspective on **1** and its congeners, the construction of their 11-deoxyanthracyclinone frameworks by the regioselective Diels-Alder reaction employing the naphthoquinone (**6**), the CDEF-ring system of nogalamycin congeners, as a dienophile, was anticipated to hold promise as one of the most convenient and flexible synthetic routes. Based on this synthetic strategy, we have already completed the stereocontrolled synthesis of optically pure (+)-**6** and succeeded in the first total syntheses of (+)-nogarene (**4**), the simplest congener of **1**, and (+)-7,8-dihydronogarene (**5**), the hitherto unknown congener of **1**.[2]

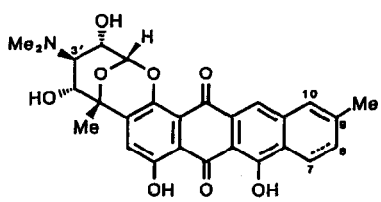
In this communication, we wish to report the first total syntheses of (+)-7-deoxynogarol (**2**) and (+)-7-con-*O*-methylnogarol (**3**) achieved featuring the same synthetic strategy. These syntheses consist of short-step preparation of the complex dienes (**11** and **20**), incorporating all the functionalities present in the A-rings of **2** and **3**, and highly efficient construction of **2** and **3** employing the regioselective Diels-Alder reactions of **11** and **20** with **6**.[3]



X = CO_2Me, Y = H, Z =  **1**

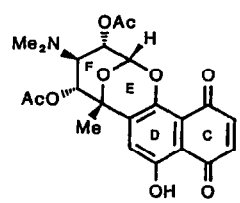
X = Y = Z = H **2**

X = H, Y = OMe, Z = H **3**

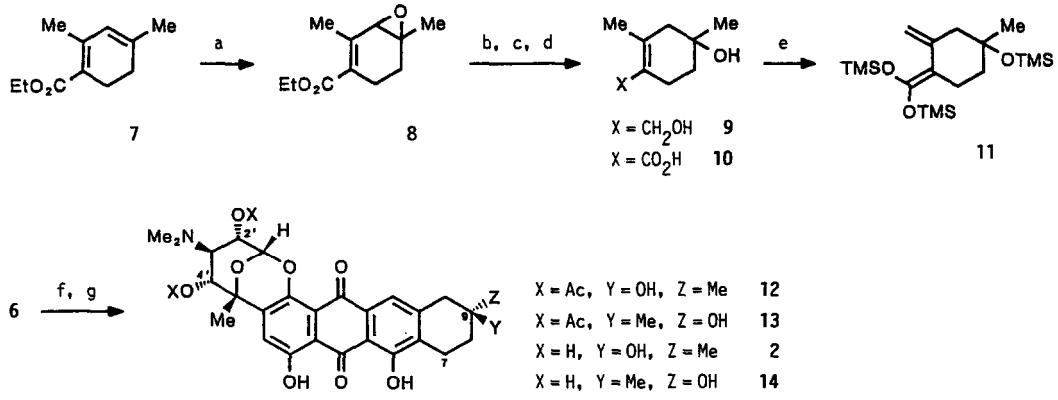


$C_{7,8}$ = CH=CH **4**

$C_{7,8}$ = CH_2-CH_2 **5**



6

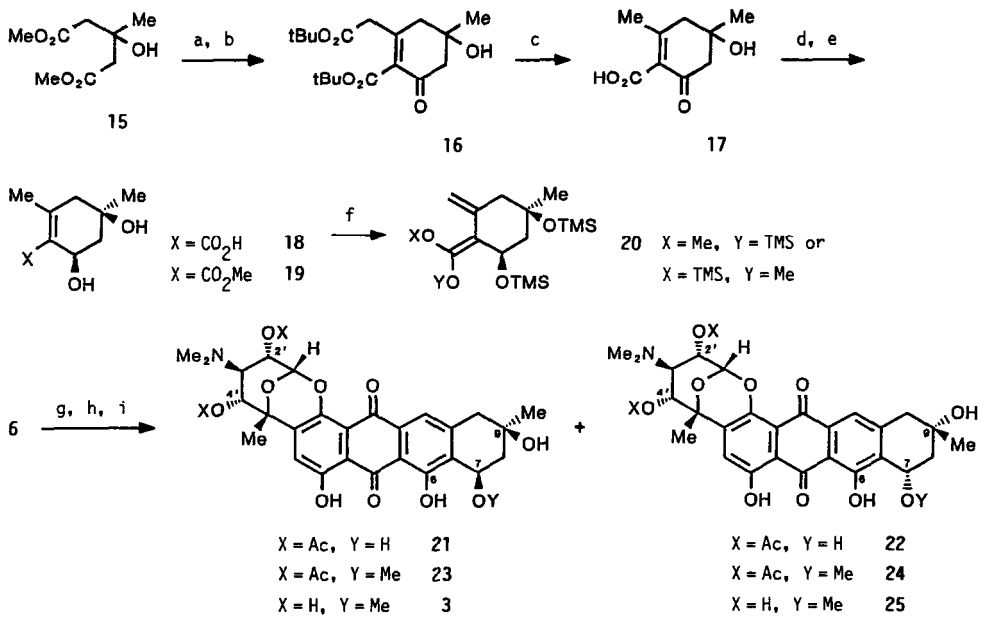


a) mCPBA, PhMe, 0 °C, 50% b) $LiEt_3BH$, THF, rt, 87% c) MnO_2, THF-Hex, rt, 88% d) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, ^tBuOH-H_2O, 0 °C, 75% e) LDA, TMSCl, THF, -78 °C → rt f) 1) **11**, THF, 60 °C 2) 3N-HCl, air, rt, 14% (**12**, from **6**), 50% (**13**, from **6**) g) K_2CO_3, MeOH, 50 °C, 75% (**2**), 64% (**14**).

Since preparation and Diels-Alder reaction of the highly functionalized dienes such as **11** and **20** had scarcely been studied in the field of anthracyclinone synthesis,[4] the synthesis of **2**, the simpler congener of **1** than **3**, was first examined according to the explored synthetic strategy. The requisite diene (**11**) was prepared in a racemic form in short steps as described below. Thus, the γ,δ-double bond of the diene ester (**7**)[2] was selectively oxidized to yield the epoxy ester (**8**). Reductive opening of the epoxide ring of **8** with superhydride was found to proceed regioselectively along with reduction of the ester group, affording the diol (**9**). Stepwise oxidations of **9** to the hydroxy carboxylic acid (**10**) followed by treating the trianion of **10** with trimethylsilyl chloride produced racemic **11**.

As expected, the regioselective Diels-Alder reaction of **11** with **6** followed by concomitant air oxidation of the addition products during mild acidic workup gave rise to the mixture of (+)-2',4'-di-*O*-acetyl-7-deoxynogarol (**12**) and (+)-2',4'-di-*O*-acetyl-9-*epi*-7-deoxynogarol (**13**) (**12**:**13** = 1:3.6).[5] These products (**12** and **13**) could be cleanly separated by TLC (SiO_2), **12**: mp 268-271 °C (decomp.); $[\alpha]_D^{20}$ +390° (c 0.155, $CHCl_3$), and **13**: mp 182-184 °C; $[\alpha]_D^{20}$ +327° (c 0.102, $CHCl_3$). Synthetic **12** was found to be identical with the sample independently prepared from authentic **2** by our hand in all respects (mp, mmp, $[\alpha]_D^{20}$, 400 MHz ^{1}H-NMR, IR, MS). Deacetylation of **12** and **13** readily produced natural (+)-7-deoxynogarol (**2**), mp 215-218 °C; $[\alpha]_D^{20}$ +1090° (c 0.100, $CHCl_3$), and unnatural (+)-9-*epi*-7-deoxynogarol (**14**), mp 215-217 °C; $[\alpha]_D^{20}$ +413° (c 0.135, $CHCl_3$), respectively. Synthetic **2** was identical with authentic **2** in all respects (mp, mmp, $[\alpha]_D^{20}$, 400 MHz ^{1}H-NMR, IR, MS).

Being encouraged by completion of the first total synthesis of **2**, the synthesis of **3** having more complex structure was next attempted. However, it was found to be very difficult to prepare the precursors of **20** such as the dihydroxy carboxylic acid (**18**) or the dihydroxy methyl ester (**19**) due to their increased tendency toward aromatization. After numerous experimentations to overcome these difficulties, the short-step synthesis of **19** could be finally realized employing the keto diester (**16**) as the starting material. The diester (**16**) was prepared from dimethyl 2-hydroxy-2-methylglutarate (**15**) modifying the procedure reported by Yamaguchi.[6] Cleavage of the two *t*-butyl ester groups of **16** with formic acid effected concurrent decarboxylation to give the keto carboxylic acid (**17**). The desired *cis*-methyl



a) $LiCH_2CO_2{}^tBu$, THF, rt b) $Ca(OAc)_2$, MeOH, rt, 50% (2 steps) c) HCO_2H, rt, 52% d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, H_2O, rt e) CH_2N_2, ether-H_2O, 0 °C, 31% (2 steps) f) LDA, TMSCl, THF, -78 °C → rt g) 1) **20**, PhMe, 100 °C 2) 3N-HCl, air, rt, 45% (from **6**) h) 1) CF_3CO_2H, 0 °C 2) NaOMe, MeOH, 0 °C, 12% (**23**), 35% (**24**) i) NaOMe, MeOH, 50 °C, 92% (**3**), 77% (**25**).

ester (**19**) was produced by sequential highly stereoselective reduction of **17** and esterification of the resulting carboxylic acid (**18**). Treatment of the trianion of **19** with trimethylsilyl chloride gave recemic **20**.

The Diels-Alder reaction of **20** with **6** occurred in a similar regioselective manner, affording the mixture of 2',4'-di-*O*-acetyl-con-nogarol (**21**) and 2',4'-di-*O*-acetyl-7,9-di-*epi*-con-nogarol (**22**) (**21**:**22** = 1:3.2)[5] after air oxidation of the adducts during mild acidic workup. In contrast to other examples of the similar Diels-Alder reactions, the corresponding C_6-methyl ethers could not be detected although the methoxysiloxydiene (**20**) was employed.[7] Without separation of **21** and **22**, stereoselective introduction of the C_7-methoxy group was attempted according to the reported procedure.[1] Thus, reaction of the mixture of **21** and **22** with trifluoroacetic acid followed by treatment with sodium methoxide yielded the mixture of (+)-2',4'-di-*O*-acetyl-7-con-*O*-methylnogarol (**23**) and (+)-2',4'-di-*O*-acetyl-7,9-di-*epi*-7-con-*O*-methylnogarol (**24**) (**23**:**24** = 1:2.9).[5] This could be readily separated by TLC (SiO_2), **23**: mp 180-183 °C; $[\alpha]_D^{20}$ +308° (c 0.120, $CHCl_3$), and **24**: mp 217-219 °C (decomp.); $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$). Synthetic **23** was shown to be identical with the sample independently prepared from authentic **3** by our hand in all respects (mp, mmp, $[\alpha]_D^{20}$, 400 MHz ^{1}H-NMR, IR, MS). Both acetates (**23** and **24**) were deprotected, affording natural (+)-7-con-*O*-methylnogarol (**3**), mp 250-254 °C (decomp.); $[\alpha]_D^{20}$ +867° (c 0.045, $CHCl_3$), and unnatural (+)-7,9-di-*epi*-7-con-*O*-methylnogarol (**25**), mp 213-216 °C (decomp.); $[\alpha]_D^{20}$ +447° (c 0.076, $CHCl_3$), respectively. Synthetic **3** was identical with an authentic sample in all respects (mp, mmp, $[\alpha]_D^{20}$, 400 MHz ^{1}H-NMR, IR, MS).

As mentioned above, the first total syntheses of **2** and **3** were accomplished by featuring

the regioselective Diels-Alder reaction as a key step. It is evident that the explored synthetic scheme is highly promising as one of the convenient and flexible synthetic methods of nogalamycin congeners. This method makes it possible to produce various types of the artificial nogalamycin congeners, opening new opportunity for exploring other novel analogues which may show superior antitumor activity than **3**.[8]

Acknowledgement: We are grateful to the late Dr. P.F. Wiley, The Upjohn Company, for providing us with the authentic samples and spectral data of **2** and **3**.

References and Notes

1) P.F. Wiley, "*Anthracycline Antibiotics*," Ed. by H.S. El Khadem, Academic Press, New York, p97 (1982); J.P. McGovren, K.G. Nelson, M. Lassus, J.C. Cradock, J. Plowman, and J.P. Christopher, *Investigational New Drugs*, **2**, 359 (1984).

2) M. Kawasaki, F. Matsuda, and S. Terashima, *Tetrahedron Lett.*, **27**, 2145 (1986).

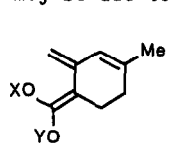
3) At the outset of this work, it was expected that the A-rings of **2** and **3** can be elaborated from the diacetates of **5** and **2**, respectively. However, oxidation of the C_9-C_{10} double bond of the diacetate of **5** and bromination of the benzylic C_7-position of the diacetate of **2** (**12**) were found to produce complex reaction products probably due to preferential oxidative removal of the $C_{3'}$-dimethylamino group.

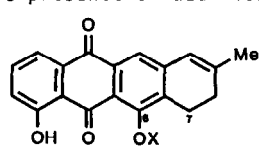
4) J.G. Bauman, R.C. Hawley, and H. Rapoport, *J. Org. Chem.*, **50**, 1569 (1985).

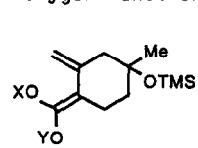
5) The observed diastereoselectivity of the Diels-Alder reaction can be nicely rationalized by assuming that the addition reaction follows the *endo*-rule and the dienes (**11** and **20**) approach the naphthoquinone surface of **6** from the direction opposite to the sterically congested F-ring. M. Kawasaki, F. Matsuda, and S. Terashima, to be published.

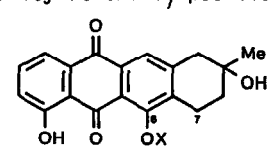
6) M. Yamaguchi, *Yuki Gosei Kagaku Kyokai Shi*, **45**, 969 (1987).

7) The regioselective Diels-Alder reaction of the alkoxysiloxydiene (**26**[2] or **29**) with juglone was found to give the mixture of the 7-deoxyanthracyclinone (**27** or **30**) and the C_6-alkyl ether (**28** or **31**), respectively. The specific formation of **21** and **22** by the reaction of **20** with **6** may be due to the presence of additional oxygen functionality at the C_7-position.









26 X = Et, Y = TMS or X = TMS, Y = Et

X = H **27**

X = Et **28**

29 X = Me, Y = TMS or X = TMS, Y = Me

X = H **30**

X = Me **31**

8) The nogalamycin congeners (**12**, **13**, **2**, **14**, **23**, **24**, **3**, and **25**) were subjected to P388 murine leukemia *in vitro* cytotoxicity assay. Following IC_{50} (μg/ml) values were recorded: **12**, 0.17; **13**, 0.30; **2**, 0.41; **14**, 0.31; **23**, 0.014; **24**, 0.53; **3**, 0.006; **25**, 0.40. It is of interest that marginal cytotoxity is only observed for **25** in contrast to **3** and its C_7-epimer, 7-dis-*O*-methylnogarol, showing significant antitumor activity against P388 murine leukemia *in vitro* and *in vivo*.[1] Accordingly, absolute stereochemistry of the C_9-position seems to play a key role for the antitumor activity of nogalamycin congeners. Further studies on the antitumor activity of artificial nogalamycin congeners are in progress and will be reported shortly. We are indebted to Dr. K. Sakai and Miss K. Yamada, Sagami Chemical Research Center, for performing *in vitro* cytotoxicity assay.

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