Total Synthesis of (±)-7-*con*-*O*-Methylnogarol

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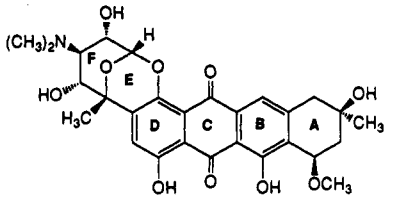
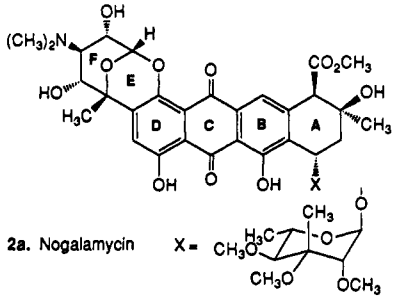
Summary: A convergent, regiospecific total synthesis of the semisynthetic anthracycline (±)-7-*con*-*O*-methylnogarol is described.

Their complexity, unusual structures and anticancer activity[1] have prompted interest in the preparation[2] of the anthracycline nogalamycin (**2a**) and its semisynthetic derivative 7-*con*-*O*-methylnogarol (**1**). Recently, Terashima et al.[3] reported a route to (+)-**1**, which utilized a Diels–Alder reaction as a key construction step. We have achieved a shorter and conceptually different total synthesis of (±)-7-*con*-*O*-methylnogarol (**1**) that is based on use of an isobenzofuranone annelation.[4,5]



1 7-Con-O-Methylnogarol

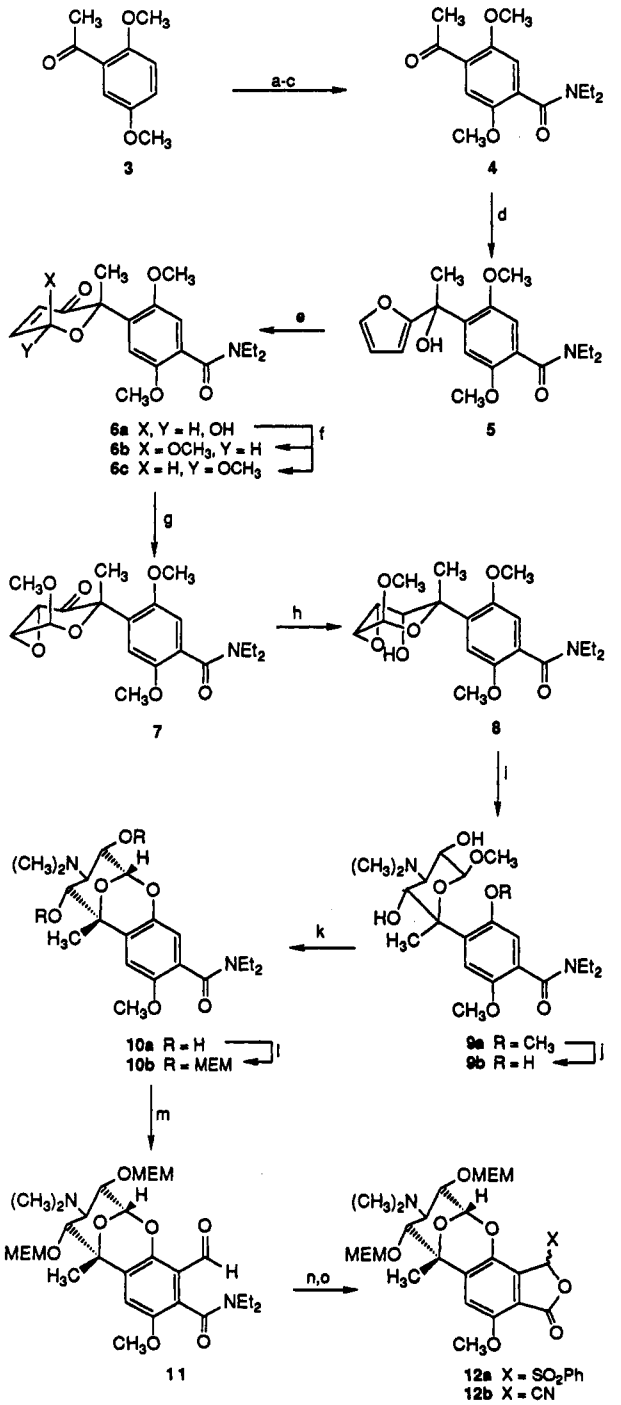


2a. Nogalamycin X =

2b. Nogalamycinone X = OH

The C-aryl sugar substituted isobenzofuranone **12**, a CDEF-synthon, was synthesized in a highly stereoselective manner as shown in Scheme I. This plan was based on earlier work that demonstrated efficient construction of the bicyclic epoxyoxocin portion of this intermediate from a (2-hydroxyphenyl)furylcarbinol.[2a,b] Commercially available 2,5-dimethoxyacetophenone (**3**) was regiospecifically converted to the diethylamide **4** in 63% overall yield[6] via sequential ketalization ($HOCH_2CH_2OH$, PhH, TsOH), metalation (*s*BuLi, TMEDA, THF), and then reaction with diethylcarbamoyl chloride.[7] Addition of fu-

Scheme I[a]



[a] (a) $(CH_2OH)_2$, PhH, TsOH; (b) *s*BuLi, TMEDA, THF, −78 °C then $ClCONEt_2$; (c) H_3O^+, 63% from **3**; (d) 2-furyllithium, THF, 75%; (e) MCPBA, $CHCl_3$; (f) HCO_2H, MeOH, 90% from **5**; (g) tBuOOH, triton B, CH_2Cl_2, 90%; (h) $NaBH_4$, 2-PrOH, 95%; (i) Me_2NH, sealed tube, 145 °C, 85%; (j) EtSLi, DMF, 100 °C; (k) HOAc, 3 N HCl, 75 °C, 75% from **9a**; (l) 2 equiv of *s*BuLi, THF, MEMCl, 85%; (m) 5 equiv of *s*BuLi, TMEDA, THF, −78 °C, DMF, 75%; (n) KCN, 18-crown-6, TMSCN, CH_2Cl_2, 88%; (o) HOAc.

(1) (a) Wiley, P. F. In *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press, New York: 1982; p 97–117 and references cited therein. (b) Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Krueger, W. C.; Moscowitz, A. *J. Org. Chem.* **1979**, *44*, 4030. Hacksell, U.; Daves, G. D. *Prog. Med. Chem.* **1985**, *22*, 1.

(2) Most of the synthetic work has focused on the preparation of the C-aryl sugar fragment, an epoxyaryloxocin. (a) Bates, M. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1983**, 896. (b) Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 1169. (c) Hauser, F. M.; Adams, T. C., Jr. *J. Org. Chem.* **1984**, *49*, 2296. (d) Joyce, R. P.; Parvez, M.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 4885. (e) Smith, T. H.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 3566. (f) Hauser, F. M.; Ellenberger, W. P. *J. Org. Chem.* **1988**, *53*, 1118. DeShong, P.; Li, W.; Kennington, J. W., Jr.; Ammon, H. L. *J. Org. Chem.* **1991**, *56*, 1364.

(3) Kawasaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 2693; *Ibid.* **1986**, *27*, 2145. *Idem. Tetrahedron* **1988**, *44*, 5727.

(4) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061. (b) Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. (c) Hauser, F. M.; Bagdanov, V. M. *Ibid.* **1984**, *40*, 4719 and references cited therein.

(5) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263.

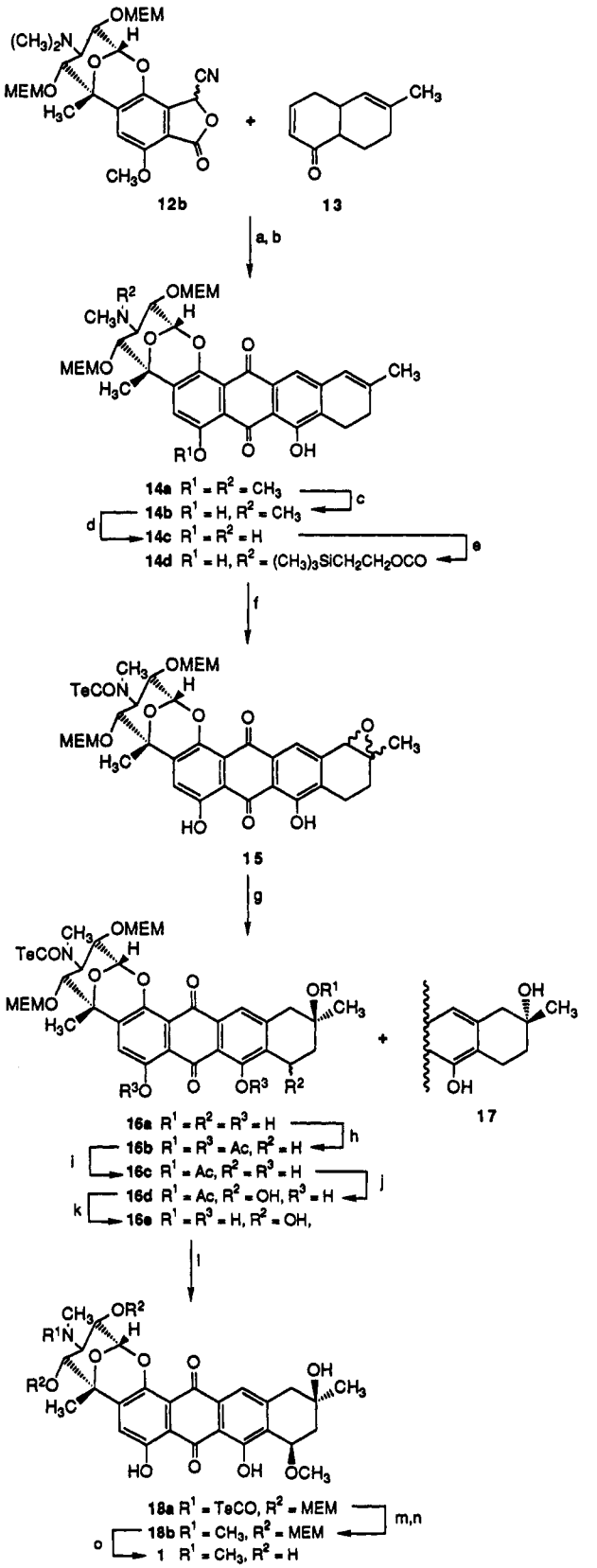
0022-3263/91/1956-5248$02.50/0

ryllithium to 4 (THF, −78 °C; 75%) followed by oxidation (MCPBA, $CHCl_3$) of the furyl carbinol intermediate 5 (mp 147–148 °C) gave the hexenulose **6a**,[8,9] which on methanolysis (HCO_2H, MeOH) afforded the methyl glycosides **6b** and **6c** in a 5:1 ratio (90% combined yield). Although the individual anomers **6b** and **6c** could be isolated at this stage, it was experimentally advantageous to carry out epoxidation (*t*BuOOH, CH_2Cl_2, triton B; 90%)[10] on the mixture since the epoxy ketone **7** was more readily separable from the minor anomer. Reduction ($NaBH_4$, 2-propanol) of the ketone **7** was stereospecific and furnished the alcohol **8** (95%). Opening of the oxirane in **8** with dimethylamine (sealed tube, 145 °C, 15 h) was both regio- and stereospecific and yielded the amino diol **9a** (95%), which exists solely in the conformation shown.[11] Regioselective demethylation (NaSEt, DMF, 100 °C)[12] of **9a** and cyclization (HOAc, 3N HCl) of the resultant phenol **9b** gave the epoxybenzoxocin **10a** (76% from **9a**).

Construction of the isobenzofuranone **12** through introduction of a formyl group ortho to the benzamide functionality in **10a** proved to be experimentally challenging. Ultimately, it was found that the bis-MEM ether derivative[13] **10b** (2 equiv. *s*BuLi, THF, MEMCl; 86%) underwent metalation with 5 equivalents[14] of *s*BuLi (TMEDA, THF, −78 °C) and yielded the aldehyde **11** (75%) upon quenching with DMF.[15] Preparation of the 3-(phenylsulfonyl)isobenzofuranone **12a**[4] was initially attempted, but when problems[16] were encountered with its preparation, synthesis of the cyano analogue **12b** was performed instead. Conversion of **11** to **12b** (88%) was straightforwardly accomplished using the protocol reported by Yoshii et al.[17] (TMSCN, 18-Crown-6, KCN).

Condensation of the anion of **12b** (LDA, THF, HMPA, −78 °C) with the naphthalenone **13**[18] (2 equiv) and oxi-

Scheme II[a]



[a] (a) LDA, HMPA, THF, 65%; (b) O_2, DMF, salcomine, 78%; (c) LiI, pinacolone, $PhCO_2H$ (2 equiv), 98%; (d) ACE-Cl, $ClCH_2CH_2Cl$, $NaHCO_3$ then MeOH, $NaHCO_3$, 81%; (e) $Me_3SiCH_2CH_2OCOCl$, $NaHCO_3$, CH_2Cl_2, 87%; (f) MCPBA, CH_2Cl_2, 92%; (g) Pd/C, EtOH–EtOAc, triethanolamine, 95%; (h) Ac_2O, Py, DMAP, 85%; (i) NaOH, DME, H_2O, 92%; (j) NBS, $(BzO)_2$, CCl_4, H_2O, 52%; (k) NaOH, DME, H_2O, 70%; (l) TFAA, CH_2Cl_2 then NaOMe, MeOH, 92%; (m) TBAF, THF, 90%; (n) xs CH_3I, 98%.

(6) Distillation of **4** (bp 173–176 °C (0.4 mm)) resulted in recovery of **3** in 37% yield.

(7) Metalation of the dimethylacetal of 2,4-dimethoxybenzaldehyde with subsequent carboxylation gives an identical regiochemical outcome. Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.

(8) Achmatowicz, O., Jr.; Bukowski, P.; Szecher, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 4711. Achmatowicz, O., Jr.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.

(9) Lefebvre, Y. *Tetrahedron Lett.* **1972**, 133.

(10) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

(11) The conformation of the pyranose ring in **9a** was established through ^1H NMR. The magnitude of the coupling constants was consistent with the protons on C-2, C-3, and C-4 being axial. Furthermore, the C-1 proton, originally at 5.09 ppm in **8**, is shifted upfield to 4.07 ppm in **9a**, since it lies in the shielding cone of the axially disposed phenyl group. The conformational inversion is not surprising since the attack of dimethylamine at C-3 initially forms an intermediate, which has axial substituents at C-2, C-3, and C-4.

(12) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

(13) Protection of the alcohols was dictated by the observation that on attempted metalation, **10a** furnished the *sec*-butyl ketone (87%) from attack of *s*-BuLi on the diethylamide moiety. This result was somewhat surprising since the combination of BuLi and alkoxide anions is known to promote the metalation of aromatic rings. Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741.

(14) Undoubtedly, complexation of BuLi with the oxygens of the MEM ethers and the dimethylamine group is occuring.

(15) Serendipity may have played a role in the successful metalation of **10b**; recently, we found that the SEM ether derivative does not undergo aromatic ring metalation. We suspect that treatment of **10b** with butyllithium initially organizes the MEM ethers and that the methoxyl on the MEM ether attached to the oxygen at C-2 then facilitates metalation of the aromatic ring.

(16) Hydrolysis of **11** to the phthaldehydic acid, followed by reaction with benzenethiol, gave the (3-phenylthio)isobenzofuranone in high overall yield. When oxidation (H_2O_2, HOAc or MCPBA, CH_2Cl_2) of the sulfide was attempted, only a modest yield (18%) of the sulfone **12a** was obtained. We suspected that oxidation of the dimethylamino group was the source of the problem; however, when the oxidation was attempted in the presence of added TFA to protonate the amine group, the yield was not significantly improved.

(17) Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402.

dation (O_2, Co-salcomine,[19] DMF, 50 °C) of the resultant hydroquinone intermediate (65%) yielded the hexacyclic compound **14a** (73%; mp 175–176 °C) regiospecifically (Scheme II). Subsequent demethylation (LiI, pinacolone, $PhCO_2H$)[20] of **14a** furnished the phenol **14b** (92%; mp 148–150 °C).

The next objective was introduction of the 9-hydroxyl group via epoxidation of the 9,10-olefinic moiety in **14b**.[4b] Under a variety of conditions, the best yield was only 15%. The source of the low yields was thought to be due to concurrent oxidation of the dimethylamino group, and this was shown to be correct (vide supra). In order to protect the nitrogen and provide for its subsequent conversion back to the dimethylamino group under mild conditions, **14b** was demethylated[21] ((i) ACE-Cl, $NaHCO_3$, DCE, 85 °C; (ii) MeOH, $NaHCO_3$) and the resultant secondary amine **14c** was converted to the silyl carbamate **14d** (TeCOCl, $NaHCO_3$, CH_2Cl_2; mp 108–110 °C; 82% overall).[22] Oxidation of **14d** (MCPBA, CH_2Cl_2) proceeded in excellent yield (98%) and reductive opening[23] of the epoxide **15** (10% Pd/C, H_2, EtOH–EtOAc, triethanolamine, 24 h) provided the readily separable tertiary alcohols **16a** and **17** in 55% and 36% yield, respectively. As expected,[24] the major alcohol was the desired diastereoisomer **16a** and this was proven by its conversion to **1**.

Earlier work by us had shown that introduction of a 7-hydroxyl group in 9-alkyl-9-hydroxyanthracyclinones, via bromination–solvolysis, is sensitive to the substitution pattern, i.e., highest yields are obtained when the 9-OH is protected as the acetate and there is a phenolic group at C-6.[4b] In order to achieve this substitution pattern, **16a** was first converted to the triacetate **16b** (Ac_2O, Py, DMAP; 88%). Chemoselective hydrolysis (2 equiv NaOH, DME–H_2O) of the phenolic acetates furnished **16c** (90%; mp 91–93 °C), which on bromination–solvolysis gave the 7-hydroxy compound **16d** (50%).[25] Saponification of **16d** afforded the diol **16e** (70%) as a 1:1 diastereomeric mixture, epimeric at the 7-position. The presence of a mixture at this point was inconsequential since treatment of either epimer of **16e** with trifluoroacetic anhydride followed by methoxide gave stereospecifically a single methoxy compound,[1b] **18a** (80%). Removal of the silylcarbamate[26] ($nBu_4N^+F^-$, THF; 100%) followed by methylation (CH_3I, $NaHCO_3$, CH_2Cl_2; 98%) of the secondary amine intermediate produced **18b**. Cleavage of the MEM ethers (2.5 N HCl–HOAc, 45 °C, 4 h) provided 7-*con*-*O*-methylnogarol (**1**) (70%).[27] For purposes of characterization, **1** was converted to the diacetate derivative, which was identical in all respects (IR, NMR, and TLC in different solvents) to an authentic sample.

We believe this route is general and can be modified to accomplish optically active syntheses. Currently, we are exploring conversion of the hexacyclic compound **14** to nogalamycinone (**2b**)[18] and these results will be reported in due course.

Acknowledgment. The authors express their gratitude to Dr. Donald Harper of the Upjohn Company for an authentic sample of 7-*con*-*O*-methylnogarol and to Dr. Shiro Terashima for a sample of 7,9-*epi*-7-*con*-*O*-methylnogarol. This work was generously supported by the National Cancer Institute of the National Institutes of Health under Grant No. CA-18141.

Supplementary Material Available: Full experimental and spectroscopic data (13 pages). Ordering information is given on any current masthead page.

(18) We have recently developed methodology for construction of the 10-carbomethoxy-7,9-dihydroxy-9-alkyl fragment present in nogalamycinone from a naphthacene intermediate with a 9,10-olefinic moiety, an analogue of **14**. Hauser, F. M.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1989**, *54*, 5110.

(19) Van Dort, H. M.; Geursen, H. S. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 520.

(20) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1969**, 616.

(21) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(22) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

(23) Rizzi, J. P.; Kende, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4247. Rizzi, J. P.; Kende, A. S. *Tetrahedron* **1984**, *40*, 4693.

(24) The oxocin fragment in **14** is perpendicular to the aromatic system and although somewhat remote from the 13,14-olefin, its presence nevertheless sterically biases the subsequent epoxidation.

(25) This yield is based on 33% reclaimed **16c**. In contrast to our experience here with **16c**, introduction of the hydroxyl group in the analogue devoid of the sugar moiety was straightforwardly accomplished in good yield (9:1 ratio of epimers; 67%).[4b]

(26) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104.

(27) Removal of the MEM ethers results in modest hydrolysis (5–10%) of the 7-methoxyl to a hydroxyl group. The problem is rectified by treating the initially received hydrolysis product with TFAA and then with methoxide.