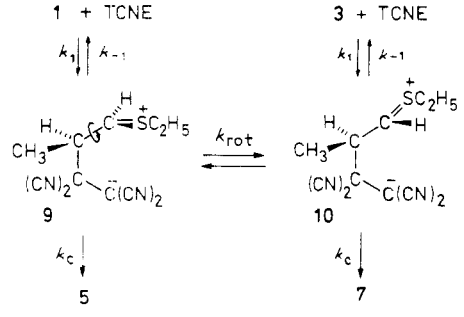
Table I. Nonstereospecific Portion (% in 100 % Adduct) in TCNE Cycloadditions to Thioenol Ethers at 25 °C

solvent	% thioenol ether adducts 7	8	% enol ether adducts 7[a]	8[a]
(a) Cis Ether 1 or 2				
benzene	11	12	5	2
ethyl acetate	10	17	6	10
dichloromethane	11	14	5	7
acetone	13	22	8	
acetonitrile	17	27	15	18
	% thioenol ether adducts 5	6	% enol ether adducts 5[a]	6[a]
(b) Trans Ether 3 or 4				
benzene	6	2.9	4	2
ethyl acetate	4	2.8	10	5
dichloromethane	5	4.0	6	3
acetone	6	3.9		
acetonitrile	6	3.6	23	16

[a] Corresponding cycloadducts with OC_2H_5 instead of SC_2H_5 from enol ethers.

latter, until the charge-transfer color disappeared; this required at 25 °C 1 min for **3** in acetonitrile, but 30 days for **2** in benzene due to the high dependence of the rate constant on solvent polarity.[1] The presence of 0.04–0.095 M *p*-benzoquinone suppressed a thermal cis,trans isomerization of the thioenol ethers. The cis,trans ratios of the quantitatively formed cycloadducts were determined by NMR analysis of the 1-H doublets. Reproducibility in duplicate runs was ±1%.

The nonstereospecificity observed is evidence that rotation in the zwitterionic intermediates **9** and **10** competes with their cyclization. The data are compared in Table I with those of TCNE cycloadditions to the corresponding enol ethers.[2] Starting with the *cis*-alkenyl sulfides **1** and **2**, the nonstereospecific portion of the cycloadduct, i.e., the trans adducts **7** and **8**, rose from 11 and 12% in benzene up to 17 and 27% in acetonitrile. The values of percent trans adduct from the cis enol ethers (**1** and **2**, O instead of S) are lower in the nonpolar benzene, but increase faster with rising polarity.[2]



S and O ethers differ more in the *trans*-1-alkenyl series. Whereas **3** and **4**, with O instead of S provide similar nonstereospecific portions (now cis adducts) as the cis enol ethers, the trans thioethers **3** and **4** afforded 4–6% **5** and 3–4% **6**, virtually independent of solvent polarity.

The cis,trans isomeric adducts **5**–**8** were configurationally stable even in the most polar solvent, acetonitrile,

(1) H. Graf and R. Huisgen, *J. Org. Chem.*, preceding paper in this issue.
(2) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5054 (1973); R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).

Table II. TCNE and *cis*-1-Propenyl Ethyl Sulfide (1) in Acetonitrile at 25 °C; Cis → Trans Isomerization of Unconsumed 1

[1], mM	[1]/[TCNE]	unconsumed sulfide mM calcd	mM found	1:3	(2 + 2) cyclo-adducts 5:7
719	1.05	33	19	80:20	84:16
608	1.11	60	63	84:16	88:12
723	1.20	118	142	97:3	87:13

at 25 °C. However, with 2 M $LiClO_4$ in diethyl ether[3] a cis,trans equilibrium of 7% **6** and 93% **8** was established with $k_{cis} + k_{trans} = 2.9 \times 10^{-4}$ s^{-1} at 25 °C. Thus, the larger free-energy difference, $\Delta G = 1.5$ kcal mol^{-1}, vs. $\Delta G = 0.9$ kcal mol^{-1} for the corresponding cycloadducts with C_2H_5O instead C_2H_5S might be responsible for the lower level of percent of **5** and **6** from **3** and **4**.

After reacting 0.608 M *cis*-1-propenyl sulfide **1** (99.6% pure) with 0.548 M TCNE (ratio 1.11:1) in acetonitrile in the presence of 0.06 M benzoquinone, VPC of the excess of thioenol ether indicated 16% **3** besides 84% **1** as a result of cis,trans isomerization. When we ascribe the isomerization to rotation **9** → **10** and subsequent dissociation, **10** → **3**, one must take into account that **3** combines faster than **1** with TCNE.[1]

The still unsatisfactory numerical results of Table II do not warrant the unwieldy calculation of k_c/k_{-1} for the trans zwitterion **10**. This rate ratio is larger here than for the zwitterions **9** and **10**, O instead of S, where it was found to be 1.1 and 0.9, respectively.[4] The premise of double conformational rotation being forbidden[4] leads to $k_c/k_{rot} = 2.7$ for **9** and 27 for **10** in acetonitrile.

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(3) Y. Pocker and D. L. Ellsworth, *J. Am. Chem. Soc.*, **99**, 2284 (1977), and previous papers.
(4) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5055 (1973).

Synthetic Studies on Anthracyclines

Summary: Brief, regiospecific syntheses of the functionalized tetracyclic hydronaphthacene analogues **5a**, **5b**, and **5c** of the anthracyclinones of daunomycin, adriamycin, and carminomycin have been accomplished.

Sir: The anthracycline antibiotics adriamycin,[1a] daunomycin,[1b] and carminomycin[2] have attracted much synthetic interest[3] because of their antineoplastic activity. Several

(1) (a) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbier, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964); (b) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.*, 1007 (1969).
(2) M. Wani, H. L. Taylor, M. E. Wall, A. T. McPhail, and K. D. Onan, *J. Am. Chem. Soc.*, **97**, 5955 (1975); G. R. Pettit, J. J. Einck, C. L. Herald, R. H. Ode, R. Von Dreele, P. Brown, M. G. Brazhnikova, and G. F. Gause, *ibid.*, **97**, 1387 (1975).
(3) Only the most recent papers are listed here. References 3a and 3b contain extensive current bibliographies. (a) J. R. Wiseman, N. I. French, R. K. Hallmark, and K. G. Chiong, *Tetrahedron Lett.*, 3765 (1978); (b) J. S. Swenton and P. W. Raynolds, *J. Am. Chem. Soc.*, **100**, 6188 (1978); (c) F. A. J. Kerdesky and M. P. Cava, *J. Am. Chem. Soc.*, **100**, 3635 (1978); (d) A. S. Kende, J. Rizzi, and J. Riemer, *Tetrahedron Lett.*, 1201 (1979); (e) K. A. Parker and J. L. Kallmerten, *ibid.*, 1197 (1979).

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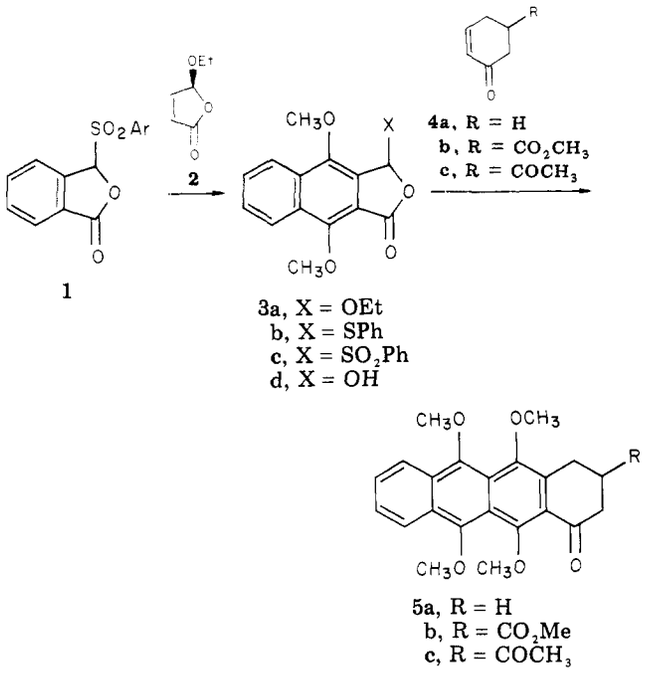
Scheme I

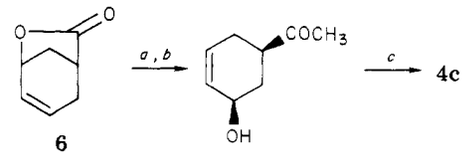


total syntheses of the antibiotics have been described,[4] but only recently have regiospecific syntheses been reported.[3b,3d,5]

We have demonstrated that the repetitive annelation strategy[6] and adjunct ring construction methodology[6-8] developed for the isomer-selective preparation of linear polynuclear aromatic systems[9] can be employed to synthesize naturally occurring naphthalenes[10] and anthraquinone[11] systems. We report here that direct extension of the developed methods[12] provides an excellent synthesis of the substituted hydroxylated hydronaphthacene framework of the anthracyclinones of the daunorubicin family of antibiotics.

For these syntheses, significant reduction in the number of steps required for construction of the tetracyclic system was achieved by use of 5-ethoxy-2(5*H*)-furanone[13] (**2**) and 5-substituted 2-cyclohexen-1-ones **4a–c** as Michael acceptors in the first and second ring construction cycles. 5-Ethoxy-2-furanone (**2**) was employed as a latently functionalized intermediate to facilitate reintroduction of the phenylsulfonyl residue[7] required for the next ring construction cycle.[6] The use of 5-substituted 2-cyclohexen-1-ones **4a–c** as Michael acceptors accomplishes

Scheme II



[a] $^-CH_2SON^-C_6H_4CH_3$/THF. [b] H_3O^+. [c] ClCOCOCl, Me_2SO.

direct introduction of the terminal alicyclic A ring concomitant with construction of the aromatic B ring (Scheme I).

The anion of 3-phenylsulfonyl-1(3*H*)-isobenzofuranone[7] (**1**) was generated [lithium diisopropylamide (LDA), tetrahydrofuran (THF), −78 °C] and condensed with 5-ethoxy-2(5*H*)-furanone[13] (**2**) to afford, after methylation (dimethyl sulfate, K_2CO_3, acetone), 3-ethoxy-4,9-dimethoxynaphtho[2,3-*c*]furan-1(3*H*)-one (**3a**) in 65% yield [mp 117–118 °C; ^{1}H NMR (acetone-d_6) δ 8.25–8.40 (m, 1 H), 8.05–8.20 (m, 1 H), 7.45–7.70 (m, 2 H), 6.44 (s, 1 H), 4.32 (s, 3 H), 4.08 (s, 3 H), 3.92 (q, J = 6 Hz, 2 H), 1.36 (t, J = 6 Hz, 3 H)]. The ethoxyl-substituted furanone fragment of **3a** is latently functionalized for reintroduction of a phenylsulfonyl group. Heating **3a**, benzenethiol, and toluenesulfonic acid in benzene with azeotropic removal of ethanol afforded sulfide **3b** (mp 120–122 °C) in 93% yield. Oxidation (*m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C) of sulfide **3b** gave sulfone **3c** (mp 175–176 °C) in 65% yield and naphthaldehydic acid **3d** (mp 200–202 °C) in 32% yield.[14,15]

The terminal saturated ring was introduced as a large single fragment by generating the anion of **3c** (LDA, THF, −78 °C) and condensing it with 2-cyclohexen-1-one (**4a**). The initially received product was unstable and was immediately methylated to give tetracyclic ketone **5a** in 68% yield [mp 205–208 °C; ^{1}H NMR (CCl_4) δ 8.25–8.40 (m, 2 H), 7.40–7.70 (m, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 3.94 (s, 3 H), 3.80 (s, 3 H), 3.12 (t, J = 6 Hz, 2 H), 2.66 (t, J = 6 Hz, 2 H), 2.12 (p, J = 6 Hz, 2 H)].

In order to provide a manipulative functionality at the 9[16] position and to initially test the feasibility of direct introduction of such a functionality, 5-carbomethoxy-2-cyclohexen-1-one (**4b**)[17] was prepared and incorporated into the scheme. Condensation of the anion of **3c** with substituted cyclohexenone **4b** afforded, following methylation, ketocarbomethoxy-substituted tetracyclic product **5b** in 87% yield [mp 138–141 °C; ^{1}H NMR ($CDCl_3$) δ 8.25–8.45 (m, 2 H), 7.40–7.70 (m, 2 H), 4.02 (s, 3 H), 3.98 (s, 6 H), 3.85 (s, 3 H), 3.72 (s, 3 H), 3.50–3.70 (m, 1 H), 2.90–3.33 (m, 4 H)].

Construction of 5-acetyl-2-cyclohexen-1-one (**4c**) was undertaken to determine if direct incorporation of the 9-acetyl group was possible (Scheme II). Condensation of bicyclic unsaturated lactone **6**[17] with the dilithium anion

(4) C. M. Wong, D. Popien, R. Schwenk, and J. TeRaa, *Can. J. Chem.*, **49**, 2712 (1971); C. M. Wong, R. Schwenk, D. Popien, and T. L. Ho, *ibid.*, **51**, 466 (1973); R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, *Tetrahedron Lett.*, 3385 (1976); A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976); A. S. Kende, D. P. Curran, Y. Tsay, and J. Mills, *Tetrahedron Lett.*, 3537 (1977).

(5) P. W. Raynolds, M. J. Manning, and J. S. Swenton, *Tetrahedron Lett.*, 2383 (1977); F. Suzuki, S. Trenbeath, R. D. Gleim, and C. J. Sih, *J. Am. Chem. Soc.*, **100**, 2272 (1978); T. R. Kelly, J. W. Gilliard, R. N. Goerner, and J. M. Lyding, *ibid.*, **99**, 5513 (1977).

(6) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **99**, 4533 (1977).

(7) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, **43**, 178 (1978).

(8) F. M. Hauser and S. Pogany, *J. Heterocycl. Chem.*, **15**, 1535 (1978).

(9) For a related ring annealation approach see: G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 2263 (1978).

(10) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, **42**, 4155 (1977).

(11) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **101**, 1628 (1979).

(12) We have previously shown[7] that the directed annelation methodology developed by us is completely regiospecific. Moreover, the 7-methoxy analogue of phthalide **1**, needed for the introduction of the 4-methoxyl group in the naphthacene nucleus, has been prepared by us and used in similar ring annelations.[7,11]

(13) F. Farina, M. Lora-Tamayo, and M. V. Martin, *An. R. Soc. Esp. Fis. Quim, Ser. B*, **60**, 715 (1964); *Chem. Abstr.*, **63**, 4213 (1965).

(14) Naphthaldehydic acid (**3d**) is readily recycled to sulfone **3c** by condensing **3d** with benzenethiol in benzene to give **3b**, which is again oxidized.

(15) Other methods for the oxidation of sulfide **3b** to sulfone **3c** such as vanadenyl acetylacetonate/*t*-BuOOH and HOAc/H_2O_2 gave lesser amounts of sulfone **3c** and larger amounts of **3d**.

(16) The numbering scheme for the anthracycline nucleus is used.

(17) Bicyclic lactone **6** was employed to construct both **4b** and **4c**. The preparation of **6** and its methanolysis to furnish 5-carbomethoxy-2-cyclohexen-1-ol was performed according to the procedure of Trost [B. M. Trost, J. M. Timko, and J. L. Stanton, *J. Chem. Soc., Chem. Commun.*, 436 (1978)]. Oxidation of the methanolysis product with sodium dichromate in acetic acid furnished **4b** as an oil: ^{1}H NMR (CCl_4) δ 6.80–7.00 (dt, 1 H, J = 10 and 4 Hz), 5.85–6.05 (dt, 1 H, J = 10 and 2 Hz), 3.68 (s, 3 H), 2.90–3.15 (m, 1 H), 2.40–2.70 (m, 4 H).

of methanesulfin-*p*-toluidide[18] produced a β-ketosulfinamide intermediate which was cleaved by acidification to give 5-acetyl-2-cyclohexen-1-ol (**7**) as an oil in 65% yield. Oxidation of **7** using the oxalyl chloride–Me_2SO reagent[19] furnished unsaturated ketone **4c** as an oil [^1H NMR ($CDCl_3$) δ 6.80–6.70 (dt, J = 10 Hz, J = 4 Hz, 1 H), 5.90–6.10 (dt, J = 10 Hz, J = 2 Hz, 1 H), 2.90–3.20 (m, 1 H), 2.40–2.65 (m, 4 H), 2.12 (s, 3 H)].

Condensation of **4c** with the anion of **3c** gave, following methylation, 9-acetyl tetracyclic ketone **5c** in 68% yield[20] [mp 108–110 °C; ^1H NMR δ 8.25–8.45 (m, 2 H), 7.40–7.60 (m, 2 H), 3.98 (s, 3 H), 3.95 (s, 6 H), 3.82 (s, 3 H), 3.50–3.75 (m, 1 H), 2.75–3.20 (m, 4 H), 2.24 (s, 3 H)].

The methodology presented here for construction of the naphthacene nucleus is extremely brief, regiospecific, and accomplished in high overall yield.

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Registry No. 1 (Ar = Ph), 65131-08-0; **2**, 2833-30-9; **3a**, 70550-13-9; **3b**, 70550-14-0; **3c**, 70562-37-7; **3d**, 70550-15-1; **4a**, 930-68-7; **4b**, 37051-55-1; **4c**, 70550-16-2; **5a**, 70550-17-3; **5b**, 70550-18-4; **5c**, 70550-19-5; **6**, 4720-83-6; **7**, 70550-20-8; methanesulfin-*p*-toluidide dilithium anion, 70550-21-9.

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(19) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2840 (1978).
(20) Using a different approach, the thioketal of **5c** has been prepared by Whitlock et al.: R. J. Boatman, B. J. Whitlock, and H. W. Whitlock Jr., *J. Am. Chem. Soc.*, **99**, 4822 (1977).
(21) Recipient of a Career Development Award, 1978–1983, from the National Cancer Institute (CA 00486).