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**Registry No.** **4**, 67116-20-5; **5**, 77224-28-3; **6**, 77224-29-4; **7**, 77224-30-7; **8**, 77224-31-8; **9**, 77224-32-9; **10**, 77224-33-0; dimethyl acetylenedicarboxylate, 762-42-5; methyl propiolate, 922-67-8; diphenylacetylene, 501-65-5; (trimethylsilyl)acetylene, 1066-54-2.

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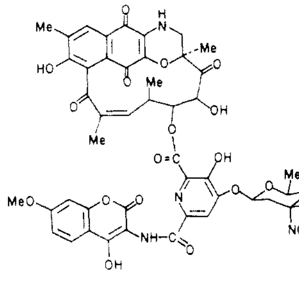
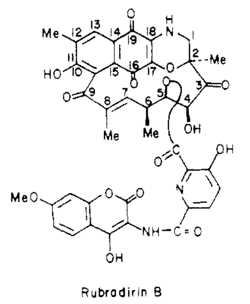
# Studies Directed toward the Total Synthesis of the Rubradirin Antibiotics. 2. Synthesis of the Unique Morpholinonaphthoquinone Chromophore: A Lesson in Diels-Alder Regiocontrol by Diene Substituent Selection

*Summary:* A Diels-Alder approach to the aromatic/heterocyclic portion of the rubradirins is detailed.

*Sir:* Rubradirin and rubradirin B represent a unique class of ansamycin-related products. The structures of these compounds have been elucidated by a combination of NMR and X-ray methods.[1] The antibiotic rubradirin interferes with ribosomal functions related to enzymatic peptide chain initiation. The aglycone of rubradirin retains moderate inhibitory activity toward ribosomal functions but also acts as an extremely potent inhibitor of RNAP. Rubradirin B, on the other hand, exclusively affects ribosomal functions, but to a smaller degree than rubradirin, and does not impair the function of RNAP at all.[2]



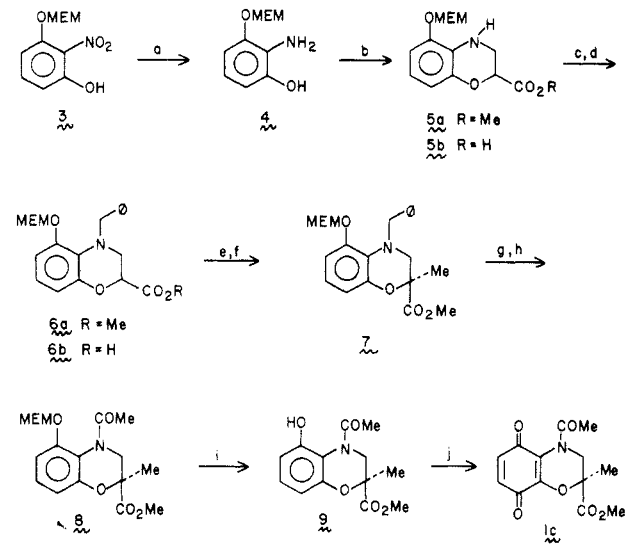
Rubradirin



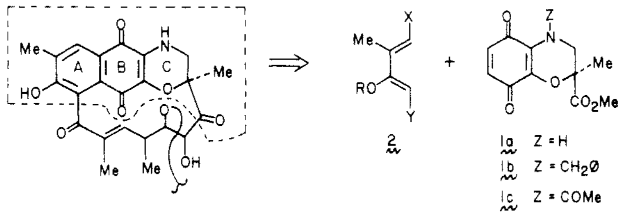
Rubradirin B
Absolute configuration 2S, 4S, 5R, 6S

The promising biological activity of the products in combination with the unique structures has led us to embark on a program to design a total synthesis route to these materials. In accomplishing this objective, we have initially focused our attention on the preparation of the morpholinoquinone chromophore. Since, to our knowledge, only one such related compound has ever been prepared, this exercise in aromatic/heterocyclic chemistry posed a considerable challenge.[3] After some preliminary studies,[4] we decided that the best way to achieve access to this substructure was to consider preparing first the B, C portion, the morpholinoquinone **1**, and then to anneal this unit to the ring A portion by a Diels-Alder reaction. An important regiochemical question would have to be addressed in this study, for the precise course of the cycloaddition reaction would depend on the nature of the substituents X and Y of the diene, and, most likely, on the type of Z group affixed to the dienophilic component.

Scheme I. Preparation of the Morpholinoquinone **1c**[a]



[a] (a) $H_2$, 10% Pd/C, $NaBH_4$, 2 N NaOH, 30 min, room temperature; (b) $BrCH_2CH(Br)CO_2Me$, $K_2CO_3$, acetone, Δ, 12 h; (c) $PhCH_2Cl$, NaI, $K_2CO_3$, acetone, 90 °C, 15 h (sealed tube); (d) 1:1:1 5% KOH-EtOH-THF, room temperature, 1 h; (e) (1) 4 equiv of LDA, THF, −50 °C, 2 h; (2) MeI, −50 °C to room temperature; (f) $CH_2N_2$, MeOH; (g) $H_2$, 10% Pd/C, HCl, PhH-EtOH, room temperature, 6 h; (h) $Ac_2O$, pyr, 110 °C, 5 h; (i) HCl gas, MeOH, 40 °C, 10 min; (j) Fremy's salt, $^1/_6$ M $KH_2PO_4$, room temperature, 2 h.



The synthesis of **1** commenced with the readily available starting material 2-nitroresorcinol (**3**,[5] Scheme I). One of the phenolic groups was protected as its MEM ether,[6] and the nitro group was converted in quantitative yield to amine by palladium-catalyzed sodium borohydride re-

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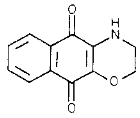
[1] (a) Hoeksema, H.; Lewis, C.; Mizsak, S. A.; Shiley, J. A.; Wait, D. R.; Whaley, H. A.; Zurenko, G. E. *J. Antibiot.* **1978**, *31*, 945. (b) Bhuyan, B. K.; Owen, S. P.; Dietz, A. *Antimicrob. Agents Chemother.* **1965**, 91. (c) Meyer, C. E. *Ibid.* **1965**, 97. (d) Hoeksema, H.; Chidester, C.; Mizsak, S. A.; Baczynskyj, L. *J. Antibiot.* **1978**, *31*, 1067. (e) Hoeksema, H.; Mizsak, S. A.; Baczynskyj, L. *Ibid.* **1979**, *32*, 773. (f) Mizsak, S. A.; Hoeksema, H.; Pschigoda, L. M. *Ibid.* **1979**, *32*, 771.

[2] Reusser, F. *J. Antibiot.* **1979**, *32*, 1186; *Biochemistry* **1973**, *12*, 1136.

[3] The parent system pictured below was made by treatment of 2-amino-3-aziridino-1,4-naphthoquinone with $OH^-$ followed by HI: Casini, G.; Claudi, F.; Felici, M.; Ferrapi, M.; Grifantini, M. *Farmaco, Ed. Sci.* **1969**, *24*, 732.

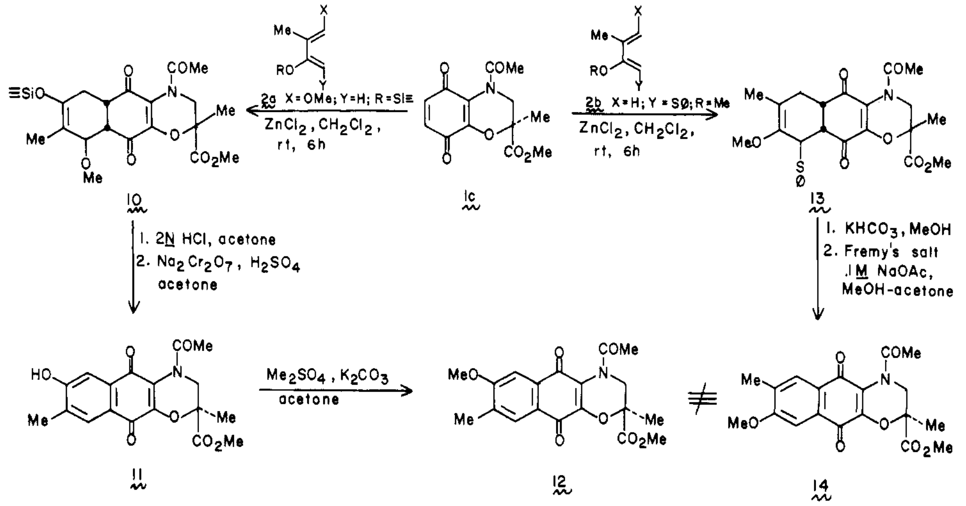


[4] Kozikowski, A. P.; Sugiyama, K. and Springer, J. P. *Tetrahedron Lett.* **1980**, 3257.

[5] This compound was purchased from the Eastman Kodak Co. and used without further purification.

[6] Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Scheme II. Diels-Alder Reactions of 1c



duction in alkaline solution.[7] Treatment of 4 under very carefully controlled conditions with methyl 2,3-dibromopropionate in the presence of potassium carbonate in acetone as solvent gave the benzoxazine 5a in 98% yield. Since we did need to have a methyl group positioned at C-2 (rubradirin numbering) of the benzoxazine, we tried reacting 4 with methyl 2,3-dibromo-2-methylpropionate under conditions identical with those used to produce 5a. Unfortunately, and not unexpectedly, only extensive polymerization of the dibromide was found to occur in this case.[8]

We thus sought to introduce this C-2 methyl group into 5a by an alkylation strategy. The ester 5a was benzylated in 96% yield and hydrolyzed to the corresponding acid 6b in quantitative yield.[9] Treatment of 6b in turn with *4 equiv* of lithium diisopropylamide followed by addition of methyl iodide[10] and esterification of the isolated crude carboxylic acid with diazomethane gave benzoxazine 7 in 94% overall yield from 6a.

At this stage, we were ready to remove the MEM group of 7 and oxidize the phenol to quinone. Deprotection was effected in a satisfactory manner by treatment of 7 with methanolic hydrogen chloride at 40 °C for 10 min (99%). The free phenol was now reacted with Fremy's salt. Unfortunately, *none* of the desired quinone was produced. We had noted previously, however, that oxidation of aminophenols to the corresponding quinones could generally be accomplished in high yield if the nitrogen is deactivated, for example, by N-acetylation.[11] Since the nitrogen and oxygen atoms in 7 are differentially protected, we were able to hydrogenolyze the *N*-benzyl group (100%), N-acetylate (94%), and then cleave the MEM group (as above, 99%) to give 9 selectively: 60-MHz $^1$H NMR (CDCl$_3$) $\delta$ 7.76 (br s, 1 H), 7.07 (m, 1 H), 6.59 (m, 2 H), 4.40 (d, 1 H, $J$ = 13 Hz), 3.75 (s, 3 H), 3.38 (d, 1 H, $J$ = 13 Hz), 2.40 (s, 3 H), 1.65 (s, 3 H). Oxidation of 9 with Fremy's salt in a buffered solution of potassium dihydrogenphosphate did indeed produce the long sought morpholinoquinone 1c in 84% yield: mp 175–176 °C; 60-MHz $^1$H NMR (CDCl$_3$) $\delta$ 6.67 (s, 2 H), 4.85 (d, 1 H, $J$ = 13 Hz), 3.69 (s, 3 H), 2.80 (d, 1 H, $J$ = 13 Hz), 2.07 (s, 3 H), 1.70 (s, 3 H).

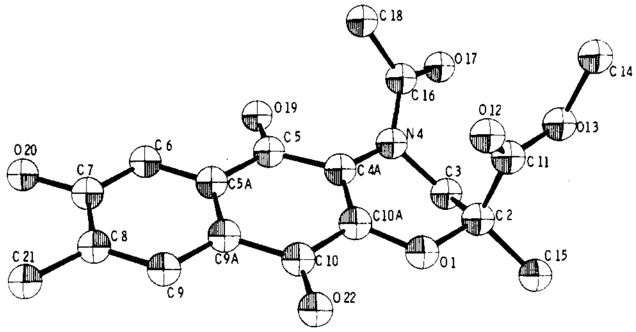


**Figure 1.** Perspective drawing of 11 with the hydrogens omitted for clarity.

At this point it is appropriate to mention that at the beginning of our studies we did hope to be able to generate quinone 1 with Z = H or alkyl, for we believed that such a compound would give the desired Diels–Alder regioisomer on reaction with 1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene (2a) as the diene component. We hypothesized that the nitrogen atom of 1a or 1b should deactivate the C-16 (rubradirin numbering) carbonyl group more than oxygen deactivates the C-19 carbonyl group, so C-15 is the more electron-deficient site. Attempts to deacetylate 1c, however, under both acidic and basic conditions were fruitless, for it underwent only extensive decomposition.

We thus opted to go ahead and run the Diels–Alder reaction between 1c and 2a (X = OMe, Y = H, R = Si(Me)$_3$). Here, however, one cannot comfortably make a prediction as to whether the nitrogen or the oxygen atom should control the Diels–Alder regiochemistry. We believed, in fact, that probably the wrong regioisomer would emerge from this reaction ($\sigma_p$ of CH$_3$CONH = −0.015; $\sigma_p$ of CH$_3$O = −0.268).[12] The [4 + 2] cycloaddition (Scheme II) was run at room temperature in benzene for 15 h (the

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[7] Neilson, T.; Wood, H. C. S.; Wylie, A. G. *J. Chem. Soc.* **1962**, 371.

[8] Predvoditeleva, G. S.; Shchukina, M. N. *Zh. Obshch. Khim.* **1963**, *33*, 145 (Engl. Ed., p 138). The mechanism of benzoxazine formation from alkyl dibromopropionates may well require initial elimination of hydrogen bromide from the dibromide to form a reactive Michael acceptor. This may account for the failure of methyl 2,3-dibromo-2-methylpropionate in the reaction described in the text.

[9] Attempted methylation of the anion derived from 6a failed, for ejection of methoxide occurred with production of a ketene, as evidenced by isolation of the acid 6b on aqueous workup. For related observations, see: Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.

[10] Adam, W.; Fick, H.-H. *J. Org. Chem.* **1978**, *43*, 772. Adam, W.; Encarnacion, L. A.; Fick, H.-H. *Synthesis* **1978**, *10*, 828.

[11] Wunderer, H. *Chem. Ber.* **1972**, *105*, 3479 and ref 4.

[12] Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191. To the extent that the conformation of the morpholine ring of 1c in solution resembles that of 11 in the solid state, resonance interaction between the nitrogen atom and the C-16 carbonyl group is frustrated due to the fact that the nitrogen lone pair is not perpendicular to the quinone ring.

use of zinc chloride as a catalyst in methylene chloride as solvent led to complete reaction within 6 h). Processing the initial cycloadduct **10** sequentially with 2 N hydrochloric acid and sodium dichromate–sulfuric acid gave in 92% overall yield a morpholinonaphthoquinone (dihydronaphthoxazinedione, **11**) which by 300-MHz $^1$H NMR analysis proved to be nearly a single regioisomer (isomer ratio for thermal reaction = 13:1, for $ZnCl_2$-catalyzed reaction = 39:1): mp 221–223 °C; 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 8.28 (br s, 1 H), 7.83 (s, 1 H), 7.37 (s, 1 H), 4.90 (br s, 1 H), 3.72 (s, 3 H), 3.00 (br s, 1 H), 2.31 (s, 3 H), 2.14 (s, 3 H), 1.76 (s, 3 H). Since the assignment of structure could not be made securely by NMR analysis, we resorted to an X-ray structural determination. The cycloadduct generated and pictured in Figure 1 was indeed the *incorrect isomer.*[13]

It thus became essential to modify the diene unit such that it would still carry the requisite methyl and alkoxy groups at C-2 and C-3 of **2** but would bear at the diene terminus C-4 an eliminatable functional group (Y) which could provide the proper sort of electronic releasing effect to steer the cycloaddition in the desired sense (Scheme II). Several possible candidates were envisioned. Of course, with the pioneering work of Cohen[14] and Trost[15] in the area of sulfur-substituted dienes, the most obvious choice for the new diene **2** was that with Y = SPh. The zinc chloride catalyzed reaction between dienophile **1c** and diene **2b**[16] was examined and found to be complete within 6 h at room temperature. Processing the crude cycloadduct **13** sequentially with potassium bicarbonate in methanol[17] and then with Fremy's salt gave a fully aromatic A-ring compound **14** which again proved to be almost a single regioisomer by 300-MHz $^1$H NMR (isomer ratio 48:1): mp 222–224 °C; 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.83 (s, 1 H), 7.49 (s, 1 H), 4.97 (br s, 1 H), 4.00 (s, 3 H), 3.90 (s, 3 H), 2.87 (br s, 1 H), 2.32 (s, 3 H), 2.08 (s, 3 H), 1.75 (s, 3 H).

For comparison purposes, the wrong isomer, **11**, was methylated, and the 300-MHz $^1$H NMR spectra of the two compounds **12** and **14** were compared; **12**: mp 242–244 °C; 300-MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.97 (s, 1 H), 7.44 (s, 1 H), 4.97 (br s, 1 H), 3.99 (s, 3 H), 3.70 (s, 3 H), 2.92 (br s, 1 H), 2.32 (s, 3 H), 2.10 (s, 3 H), 1.75 (s, 3 H). These compounds exhibited significant chemical shift differences for the aromatic A-ring protons, thus leading us to assign structure **14**, the desired isomer, to the new morpholinonaphthoquinone.

In summary, a high-yield route for the regiospecific construction of morpholinonaphthoquinone **14** has been developed (50% overall yield via a 13-step reaction sequence from the monoprotected resorcinol **3**!), and a dramatic example of regiochemical steering in the Diels–Alder reaction through diene substituent selection has been discovered. These efforts complete the construction of a goodly portion of the ansamycin unit of the rubradirins. Studies are now in progress to construct the bridging aliphatic chain in chiral form and to attach it to the quinone **14**.[18]

**Acknowledgment.** We are indebted to the Alfred P. Sloan Foundation and Merck Sharp & Dohme for financial support. The 300-MHz Bruker NMR instrument used in these studies was purchased through funds provided by the National Science Foundation (Grant No. CHE-79-05-185). We thank Edward Huie for experimental assistance and Professor Kendall Houk for informative discussions.

**Registry No. 1c**, 77270-56-5; **2a** (X = OMe; Y = H; R = $Si(Me)_3$), 77228-16-1; **2b** (X = H; Y = SPh; R = Me), 77270-57-6; **3**, 77270-58-7; **4**, 77270-59-8; **5a**, 77270-60-1; **6a**, 77270-61-2; **6b**, 77270-62-3; **7**, 77270-63-4; **8**, 77270-64-5; **9**, 77270-65-6; **10**, 77270-66-7; **11**, 77270-67-8; **12**, 77270-68-9; **13**, 77270-69-0; **14**, 77270-70-3; methyl 2,3-dibromopropionate, 1729-67-5.

**Supplementary Material Available:** Tables of the fractional coordinates and temperature parameters, bond distances, and bond angles for **11** (5 pages). Ordering information is given on any current masthead page.

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[13] Preliminary X-ray diffraction photographs indicated that the symmetry of the crystals of **11** was $P2_1/n$ with $a$ = 16.021 (2) Å, $b$ = 7.352 (1) Å, $c$ = 19.423 (1) Å and $\beta$ = 109.40 (1)°; 2346 unique reflections were observed ($I \geq 3\sigma I$) from the 2896 measured with $2\theta \leq 114°$. Standard direct-methods techniques provided initial coordinates which were refined by using full-matrix least-squares techniques. The function $\Sigma w(|F_o| - |F_c|)^2$ with $w = (1/\sigma F_o)^2$ was minimized to give an unweighted residual of 0.054. A molecule of ethyl acetate was found cocrystallized in the asymmetric unit. A strong hydrogen bond of 2.70 Å links the solvent's ester carbonyl to the phenolic oxygen of **11**. Figure 1 is a computer-generated perspective drawing of **11** from the X-ray coordinates. The following library of crystallographic programs was used: "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data"; University of York: England, 1978; "The X-Ray System, Version of June 1972"; Report TR-192; Computer Science Center, University of Maryland: College Park, MD, 1972; "ORTEP-II: A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustrations"; U.S. Atomic Energy Commission Report ORNL-3794 (2nd Rev, with Supplemental Instructions), Oak Ridge National Laboratory: Oak Ridge, TN, 1970.

[14] Cohen, T.; Mura, A. J.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218. Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R. *Org. Synth.* **1980**, *59*, 202.

[15] Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548, 3554.

[16] Cohen, T.; Kosarych, Z. *Tetrahedron Lett.* **1980**, 3955. We thank Professor Cohen for a generous sample of this diene. In carrying out the Diels–Alder reaction of **2b** + **1c**, the dienophile and zinc chloride were first stirred for 30 min at room temperature, and then the diene was added.

[17] Elimination of thiophenol occurs during the reaction with potassium bicarbonate. Formation of some of the quinone **14** by air oxidation during this step is also apparent.

[18] All new compounds reported had spectral properties and high-resolution mass spectra for the molecular ion fully compatible with the assigned structures.

[19] Fellow of the Alfred P. Sloan Foundation, 1978–1980.

[20] University of Pittsburgh Research Assistant Professor.

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## Concurrent Strong Acid and Base Catalysis. Synthesis of Cyclopentenones

*Summary:* 2-Alkyl-2-cyclopenten-1-ones were prepared in one operation from $\gamma$-keto aldehyde acetals by acid-catalyzed hydrolysis of the acetal and base-catalyzed aldol cyclization using mixed ion-exchange resins.

*Sir:* There are numerous reversible reactions which are not directly useable in preparative schemes owing to an unfavorable equilibrium constant. Other reactions are inefficient because polymerization is faster than the desired intramolecular processes. The two-step synthesis shown in Scheme I is burdened with both of these problems. When the steps are carried out separately, the acid-catalyzed hydrolysis of the dioxane ring is so unfavorable that a large excess of water gives only a small conversion.[1]