Regiospecific Total Synthesis of (±)-Nanaomycin A Using Phthaloylcobalt Complexes

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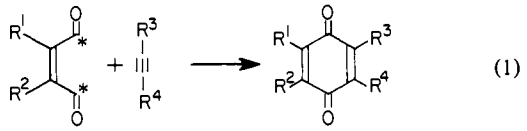
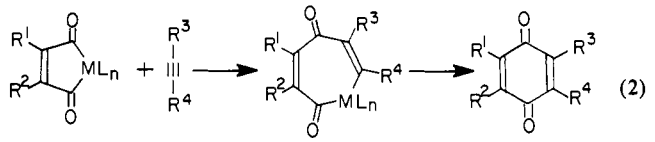
Abstract: Highly functionalized benzocyclobutenediones substituted with pendant alkynes are converted in high yield to phthaloylcobalt complexes which undergo regiospecific intramolecular reactions to give macrocyclic naphthoquinones. These macrocyclic naphthoquinones are easily converted to pyranonaphthoquinones by a reductive procedure (Zn, H^+) that presumably generates orthoquinone methide intermediates. By use of this approach the natural product (±)-nanaomycin A has been synthesized.

Quinones constitute an important class of compounds that show wide-ranging biological activities. For example, simple benzoquinones (i.e., methylbenzoquinone, ethylbenzoquinone) are used by arthropods as defensive agents against predators,[1] plastoquinones and ubiquinones are important in photosynthetic[2] and respiratory[3] electron transport, respectively, menaquinones are involved in the blood clotting process,[4] and many benzoquinone-, naphthoquinone-, and anthraquinone-derived natural products show significant antibiotic and/or antitumor properties.[5] Associated with this diversity of biological activity is a corresponding diversity of molecular structure. We have been interested in developing a general approach to quinones that would accommodate the synthesis of natural products of benzoquinone, naphthoquinone, and anthraquinone origin. To achieve such generality our approach has focused on construction of the quinone nucleus by the convergent joining of a four-carbon maleoyl species with an alkyne or equivalent functionality (eq 1). Our solution



(1)

to forming the desired carbon–carbon bonds, as required in eq 1, has come from the field of organotransition-metal chemistry. We realized that an alkyne could, in principle, react with a maleoylmetal complex **1** via an insertion–reductive elimination sequence to give a benzoquinone (eq 2).[6] A similar reaction with



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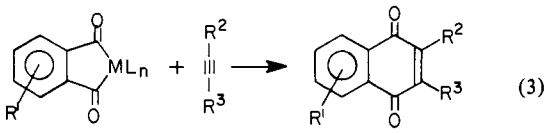
a phthaloylmetal complex **2** could provide access to naphthoquinones (eq 3). If these reactions were compatible with functionality on the alkyne as well as on the metal complexes, the synthesis of anthraquinone and heterocyclic quinones could be envisaged through standard manipulations of the primary benzoquinone and naphthoquinone products.



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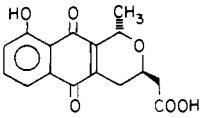
Our investigation of this organotransition-metal method for quinone synthesis commenced with a study of phthaloylmetal complexes **2** as precursors to naphthoquinones. We have found that many low-valent transition-metal complexes react with benzocyclobutenediones[7] to give high yields of phthaloylmetal complexes[8,9] and good to excellent yields of a wide variety of naphthoquinones have been obtained from a number of phthaloylmetal species when reacted with almost any simple or functionalized alkyne.[9,10] A short synthesis of menaquinones has been realized using this method.[11]

To further explore the potential of this naphthoquinone synthesis, we undertook the total synthesis of nanaomycin A (**3**) a



3, nanaomycin A

moderately functionalized antibiotic pyranonaphthoquinone that has received significant attention from synthetic organic chemists[12–26] because of the potential antitumor properties of pyrano-

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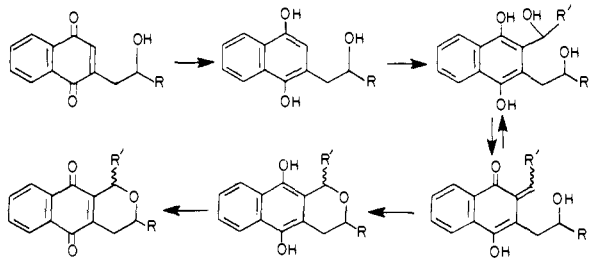
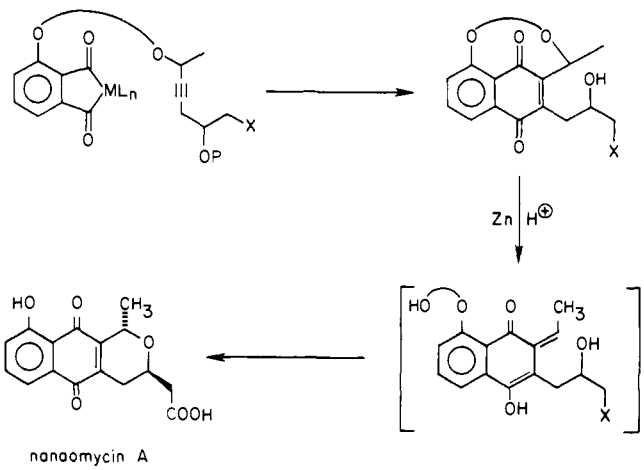
Scheme I. Pyranoquinone Formation via an Orthoquinone Methide



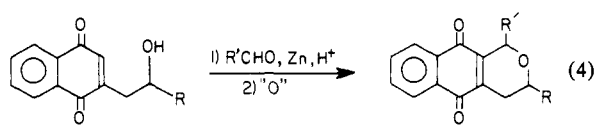
Scheme II. Pyranoquinones via Intramolecular Cyclization



nanaomycin A

quinones.[27]

Strategy. The pyran ring of a number of pyranonaphthoquinones has been generated by the condensation of (2-hydroxyalkyl)-substituted naphthoquinones with an aldehyde under acidic, reducing conditions (eq 4).[12,15,28] A reasonable mechanistic

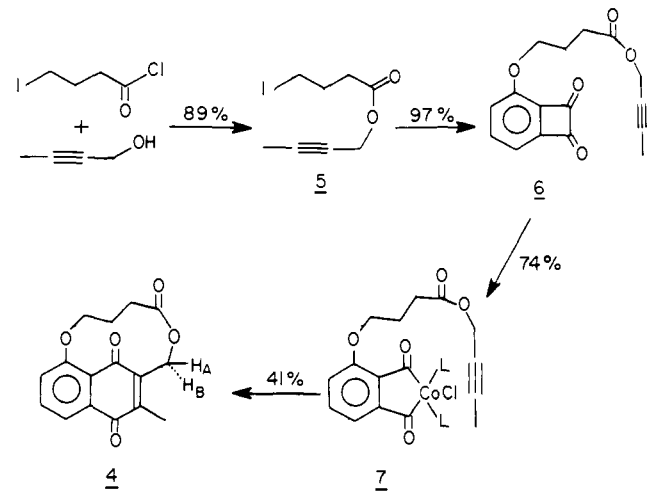


(4)

interpretation of this reaction is shown in Scheme I and proceeds by (a) rapid reduction of the quinone to the hydroquinone, (b) condensation of the aldehyde with the hydroquinone, (c) dehydration to an orthoquinone methide, and (d) formation of the pyran ring by an intramolecular 6-endo-trig ring closure.[29]

By using phthaloylmetal complexes and incorporating an orthoquinone methide approach to the pyran ring, we envisaged controlling the substituent regiochemistry as required in nanaomycin A through the use of an intramolecular version of the naphthoquinone synthesis as shown in Scheme II. All of the carbon atoms and the appropriate functionality required for nanaomycin A would be introduced via a fully elaborated alkyne that is connected through a linking group to the phenol functionality of the phthaloyl ring. The regiochemistry of the naphthoquinone-forming step would be rigorously controlled by the intramolecular nature of the process through the judicious choice of a linking group short enough to only allow formation of the desired regioisomer. Then, if the postulate of an orthoquinone methide precursor to the pyran ring is correct (see Scheme I), simple treatment of the resulting macrocyclic quinone with

Scheme III. Synthesis of a Model Macrocyclic Quinone



Zn/H_3O^+ should open the macrocycle and produce a pyranonaphthoquinone after oxidation of the hydroquinone to the quinone (the formation of a pyranoquinone by the intramolecular trapping of a reductively generated orthoquinone methide was originally suggested by Moore[27]). The linking group having served its purpose could be removed from the phenolic oxygen with $AlCl_3$ giving the desired natural product. Control of the relative stereochemistry of the pyran ring substituents is not a critical synthetic issue because trans stereochemistry is known to predominate when pyranonaphthoquinones are equilibrated by acid.[15,16,22-24,26]

Results and Discussion

Having settled on an intramolecular reaction to control regiochemistry, we first needed to prove that a highly functionalized phthaloylmetal complex could be prepared and would react intramolecularly with a pendant alkyne to give a macrocyclic naphthoquinone product as illustrated in Scheme II. To avoid synthetic complications we required a phthaloylmetal complex that would not react with its attached alkyne until required, so we chose to focus our studies on phthaloyl*cobalt* complexes, which do not react with alkynes until activated with $AgBF_4$.[9] Rather than attempting to carry a simple phthaloylcobalt complex through a variety of synthetic operations to obtain a naphthoquinone precursor, we decided to synthesize a fully elaborated benzocyclobutenedione and then introduce the cobalt to give the phthaloylcobalt complex. So that an acetylenic alcohol could be tethered to the benzocyclobutenedione for intramolecular reaction, a linking group was required that carried functionality at its termini that could be used to sequentially attach a propargyl alcohol at one end and 3-hydroxybenzocyclobutenedione at the other end. A study of molecular models indicated that a linking group containing from four to six contiguous atoms would allow the formation of only one naphthoquinone regioisomer. 4-Iodobutanoyl chloride and 6-iodohexanoyl chloride, easily prepared from butyrolactone and caprolactone, respectively, fulfilled the necessary linking group requirements.

The synthesis of a model macrocyclic quinone, **4**, using the shorter linking group, is shown in Scheme III. 4-(Dimethylamino)pyridine-mediated esterification of 1-hydroxy-2-butyne with 4-iodobutanoyl chloride gave a high yield of iodopropargylic ester **5** which was reacted with 3-hydroxybenzocyclobutenedione[7] using diazabicycloundecene as a base to give benzocyclobutenedione **6** (97% yield). Reaction of **6** with $ClCo(PPh_3)_3$ in benzene at 40 °C gave a good yield of phthaloylcobalt complex **7** (L = PPh_3, 74%) proving that the presence of a propargyl ester did not hinder insertion of the cobalt into the benzocyclobutenedione ring. As anticipated from our earlier studies of phthaloylcobalt complexes,[9] complex **7** was resistant to naphthoquinone formation until activated with $AgBF_4$. When a 0.02 M solution of phthaloylcobalt complex **7** in CH_3CN was treated with 5 equiv of $AgBF_4$ and heated at reflux for 6 h, a 41% yield of macrocyclic naphthoquinone **4**, mp 123–124 °C, was obtained after chromatography

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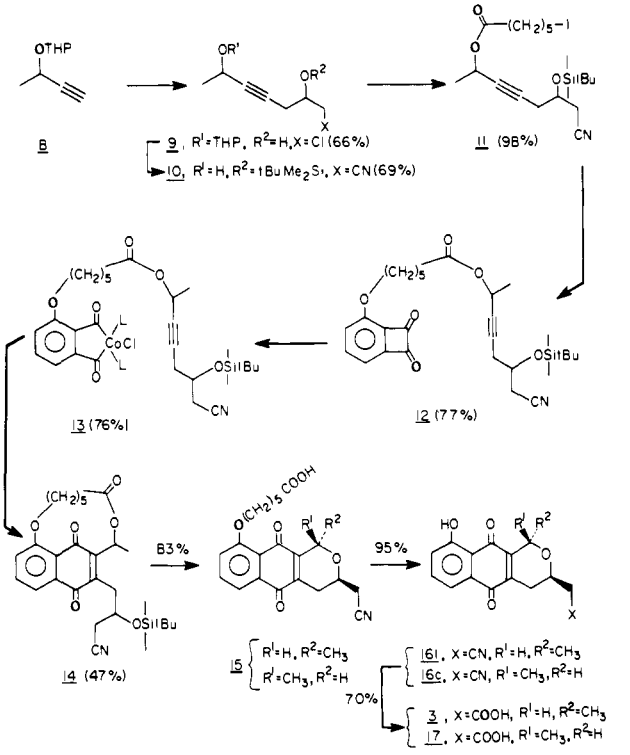
Scheme IV. Total Synthesis of Nanaomycin A



on silica gel. The methylene protons adjacent to the quinone ring in **4** (H_A and H_B) were diastereotopic as indicated by their significantly different chemical shifts (5.79 and 4.84 ppm) and no perceptible coalescence of these absorptions was apparent in spectra run between 27 and 67 °C. These data imply that the linking butanoyl group probably lies above or below the plane of the naphthoquinone ring and is conformationally restricted on the NMR time scale within the indicated temperature limits. The modest yield associated with the formation of naphthoquinone **4** is not caused by product loss through intermolecular reactions because similar yields were obtained from reactions run under more dilute conditions. The longer linking group also gave similar results (vida infra). In previous work we noticed that isolated yields from 40% to 60% were typical for (2-alkoxyalkyl)-substituted naphthoquinones that were synthesized from propargylic ethers and esters, while other functionalized alkynes usually gave product yields between 70% and 90%. We observed that prolonged reaction times led to destruction of quinone **4**, and we suspected that (2-alkoxyalkyl)-substituted naphthoquinones were sensitive to the strong Lewis acidic reaction conditions necessary to activate the phthaloylcobalt complexes. However, for the purposes of the present synthesis, we found that an excess of $AgBF_4$ and shorter reaction times reproducibly gave macrocyclic naphthoquinones in isolated yields approaching 50%.

Having convinced ourselves that highly functionalized phthaloylcobalt complexes could be prepared and that the naphthoquinone synthesis could be performed in an intramolecular fashion, we turned our attention to the synthesis of nanaomycin A by the route shown in Scheme IV. Because of the presence of multiple chiral centers and a possible chiral plane (**14**) in the intermediates shown in Scheme IV, mixtures of diastereomers were encountered throughout the synthetic sequence. However, no attempt was made to separate diastereomers until the final step because all of the stereochemical problems associated with diastereomeric mixtures are transient–at the pyranonaphthoquinone stage acid-catalyzed equilibration predominates the trans-disubstituted pyran ring.[15,16,22-24,26] Conversion of 1-butyne-3-ol tetrahydropyranyl ether **8** into the selectively protected cyanoacetylenic diol **10** was achieved by condensation of lithio-**8** with epichlorohydrin in the presence of excess $BF_3 \cdot Et_2O$ (THF, −78 °C)[30] to give acetylenic chlorohydrin **9** (66%), which was treated with NaCN (74%), then *tert*-butyldimethylsilyl chloride (97%, protection of the free alcohol), and finally pyridinium *p*-toluenesulfonate to provide **10** by selective removal of the tetrahydropyranyl ether (96%). The propargyl alcohol functionality of **10** was esterified with 6-iodohexanoyl chloride to give **11** in excellent yield. The longer linking group was arbitrarily chosen for use in this sequence in an attempt to eliminate the hindered rotation previously observed in the model macrocyclic quinone **4**. Conversion to the fully functionalized phthaloylcobalt complex **13** was achieved by reaction of **11** with 3-hydroxybenzocyclobutenedione (DBU in CH_3CN, 77%) to give **12** followed by insertion of $ClCo(PPh_3)_3$ without complication to provide **13** (L = PPh_3, 76%). Intramolecular reaction of the alkyne with the phthaloylcobalt ring was triggered with $AgBF_4$ in CH_3CN and gave macrocyclic naphthoquinone **14** as a mixture of at least two major diastereomers (47%).

The critical pyran ring formation proceeded as planned when macrocyclic naphthoquinone **14** was treated with zinc in the two-phase system 12 N HCl/ether and the crude product subjected to workup by treating the ether layer with Ag_2O. The very polar pyranonaphthoquinone diastereomers **15** were obtained in very good yield (83%) but assignment of the diastereomeric ratio at this stage by NMR was made difficult by the insolubility of **15** in $CDCl_3$. The hexanoyl linking group was removed in high yield (95%) with $AlCl_3$ and gave **16t** and **16c**, the cyano analogues of nanaomycin A and its epimer. A 3:1 ratio of **16t**/**16c** was assigned by comparison of the coupling constants of the pyran ring protons with the corresponding data for the related natural products isoeleutherin and eleutherin.[31] Finally, hydrolysis with 9 N H_2SO_4 gave in 70% yield a mixture of nanaomycin A (**3**) and its cis epimer (**17**) in a 3:1 ratio. Pure racemic nanaomycin A was obtained by crystallization of the crude product from CH_2Cl_2/hexane and had identical melting point[15] and spectral data[32] (IR, ^1H NMR, mass spectrum) with those reported.

Conclusions

We have demonstrated that phthaloylcobalt complexes can be used to synthesize a moderately complex naphthoquinone natural product. Of significance in the present report is the preparation of highly functionalized benzocyclobutenediones and their manipulation via phthaloylmetal complexes to functionalized naphthoquinones.

Experimental Section

General Methods. ^1H NMR spectra were obtained on a JEOL C60-HL or a Bruker HX-270 and absorptions are expressed in parts per million (δ) with Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer, and absorptions are reported in wavenumbers. Low-resolution electron-impact mass spectra were obtained on a Finnigan 4510 GC/MS system by a direct insertion probe. High-resolution electron-impact mass spectra were obtained on a A.E.I. MS-902 instrument also by a direct insertion probe. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, TN. Melting points are uncorrected. Preparative-scale separations were effected by preparative plate thin-layer chromatography using E. Merck silica gel 60F-254 glass-backed plates, with 2.0 and 0.5 mm thickness, and by gravity column chromatography using Baker silica gel 60–200 mesh. Analytical thin-layer chromatography was done with E. Merck silica gel 60F-254 glass-backed plates with 0.25 mm thickness and visualized with appropriate combinations of UV light, phosphomolybdic acid stain, $FeCl_3$ stain, and $KMnO_4$ stain. Gas–liquid chromatograms were obtained with a Varian 3700 instrument equipped with a 6 ft × 0.125 in. stainless-steel column packed with 3% OV-17 on 80/100 Chrom W-HP. Diethyl ether (ether) and tetrahydrofuran (THF) were purified by distillation from sodium–benzophenone under nitrogen. Acetonitrile and methylene chloride were purified by passage through E. Merck activity 1 alumina and stored under N_2 over 3-Å molecular sieves. Benzene was purified by distillation from calcium hydride and stored under N_2 over 3-Å molecular sieves. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under reduced pressure and stored under N_2.

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Synthesis of Macrocyclic Quinone 4. Preparation of 2-Butynyl 4-Iodobutyrate (5). To a 250-mL round-bottomed flask equipped with a magnetic stirring bar were added 1-hydroxy-2-butyne (5.0 g, 71.4 mmol), CH_2Cl_2 (143 mL), and 4-(dimethylamino)pyridine (DMAP) (13.0 g, 107.1 mmol). The reaction mixture was placed under a nitrogen atmosphere, cooled to 0 °C, and 4-iodobutanoyl chloride[33] (24.9 g, 107.1 mmol) was then added dropwise via syringe to the stirred solution. After the addition was complete the reaction mixture was allowed to warm to room temperature, stirred for 2 h, transferred to a separatory funnel, and washed with 1.2 N HCl (2 × 75 mL) and then saturated $NaHCO_3$ (2 × 75 mL). The organic layer was dried ($MgSO_4$) and filtered, and volatiles were removed on a rotary evaporator. The resulting crude oil was flash chromatographed (SiO_2, 3 cm × 0.5 m, 9/1 petroleum ether/ether) and gave **5** as a clear oil (16.9 g, 89%) after removal of solvents on a rotary evaporator and a vacuum pump: IR (neat, cm^{-1}) 2241, 1736; ^1H NMR (60 MHz, $CDCl_3$) δ 4.58 (q, 2 H, J = 2 Hz), 3.21 (t, 2 H, J = 6 Hz), 2.66–1.90 (m, 4 H), 1.84 (t, 3 H, J = 2 Hz); mass spectrum (70 eV), m/e (relative intensity) 266 (M^+, 1), 197 (18), 105 (32), 104 (15), 87 (77), 76 (20), 69 (54), 53 (100), 52 (32), 50 (28).

Preparation of Substituted Benzocyclobutenedione 6. To a 25-mL round-bottomed flask equipped with a magnetic stirring bar were added 3-hydroxybenzocyclobutenedione[7] (500 mg, 3.4 mmol), iodoalkyne **5** (1,078 mg, 4.1 mmol), CH_3CN (7 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (565 mg, 3.7 mmol). The flask was equipped with a reflux condenser and the reaction mixture was refluxed under N_2 for 2 h. After it was cooled to room temperature, the solution was transferred to a separatory funnel containing 75 mL of ether and wased with 1.2 N HCl (2 × 560 mL) and saturated $NaHCO_3$ (2 × 50 mL), and the organic layer was dried ($MgSO_4$). Filtration followed by removal of volatiles on a rotary evaporator left a crude yellow oil, which was chromatographed (SiO_2, 2 cm × 0.5 m, 3/2 ether/petroleum ether) to give **6** (937 mg, 97%) as a yellow solid: mp 80–81 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2, cm^{-1}) 2237, 1763, 1732; ^1H NMR (60 MHz, $CDCl_3$) δ 7.93–7.38 (m, 2 H), 7.03 (dd, 1 H, J = 7, 1.5 Hz), 4.58 (q, 2 H, J = 2 Hz), 4.46 (t, 2 H, J = 6 Hz), 2.73–1.93 (m, 4 H), 1.72 (t, 3 H, J = 2 Hz); mass spectrum (70 eV), m/e (relative intensity) 287 ($M^+ + 1$, 0.3; intensity varies directly with source concentration of sample), 286 (M^+, 0.1), 233 (28), 189 (29), 161 (19), 144 (29), 121 (25), 120 (45), 115 (16), 92 (45), 91 (24), 87 (80), 85 (26), 76 (20), 75 (29), 69 (90), 63 (27), 53 (100), 52 (26), 50 (28); mass spectral M_r calcd for $C_{16}H_{14}O_5$ 286.0841, found 286.0841.

Preparation of Phthaloylcobalt Complex 7. To a 25-mL round-bottomed flask equipped with a magnetic stirring were added benzocyclobutenedione **6** (856 mg, 3.0 mmol), $Co(PPh_3)_3Cl$[9] (5.27 g, 6.0 mmol), and benzene (15 mL). The flask was placed under a nitrogen atmosphere and stirred at 40 °C for 5 h. After this time the contents of the flask were added to 50 mL of ether and the excess $Co(PPh_3)_3Cl$ that precipitated was removed by filtration. Removal of the solvents on a rotary evaporator left the crude phthaloylcobalt complex **7**, which was purified by rapid chromatography (florisil, 2 cm × 6 cm, 1/1 CH_2Cl_2/EtOAc) followed by trituration of the resulting brown oil with petroleum ether (3 × 100 mL) to leave cobalt complex **7** as a viscous red-brown oil (2.0 g, 74%): IR (CH_2Cl_2, cm^{-1}) 1740, 1635; ^1H NMR (60 MHz, $CDCl_3$) δ 7.90–7.06 (7, 30 H), 7.00–6.23 (m, 4 H), 4.75 (q, 2 H, J = 2 Hz), 3.73 (br t, 2 H, J = 6 Hz), 2.66–1.66 (m, 4 H), 1.83 (t, 3 H, J = 2 Hz). The complex as a crude brown oil was sufficiently pure for further reactions and was used as such. However, after it was allowed to stand, crystallization occurred to give a red-brown solid: mp 210–212 °C (CH_2Cl_2/hexane). Anal. Calcd for $CoC_{52}H_{44}ClP_2O_5$: C, 68.99; H, 4.81. Found: C, 68.78; H, 4.97.

Preparation of Macrocyclic Quinone 4. To a 25-mL round-bottomed flask containing cobalt complex **7** (181 mg, 0.2 mmol) dissolved in CH_3CN (8.0 mL) under N_2 and equipped with a magnetic stirring bar was added a solution of $AgBF_4$ (195 mg, 1.0 mmol) in CH_3CN (2.0 mL) via syringe with stirring. The flask was then fitted with a reflux condenser and the mixture was refluxed under N_2 for 6 h. The solvent was removed on a rotary evaporator and the residue was rapidly filtered through a column of SiO_2 (2 cm × 6 cm, CH_2Cl_2 then ether). After removal of volatiles the crude quinone product was chromatographed (E. Merck SiO_2 plate, 20 cm × 20 cm × 0.5 mm, 2/1 hexane/ether) to give macrocyclic naphthoquinone **4** (23 mg, 41%) as a yellow solid: mp 123–124 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2, cm^{-1}) 1750, 1675; ^1H NMR (270 mHz, $CDCl_3$) δ 7.67 (dd, 1 H, J = 7.5, 1 Hz), 7.49 (dd, 1 H, J = 8.5, 7.5 Hz), 7.21 (dd, 1 H, J = 8.5, 1 Hz), 5.79 (dq, 1 H, J = 12.5, 1.5 Hz) 4.84 (d, 1 H, 12.5 Hz), 4.50 (ddd, 1 H, J = 12, 10, 5.5 Hz), 4.04 (ddd, 1 H, J = 12, 10, 5.5 Hz), 2.24 (dd, 2 H, J = 7, 5 Hz), 2.10 (d, 3 H, J = 1.5 Hz), 2.09–1.87 (m, 2 H); mass spectrum (70 eV), m/e (relative intensity) 286 (M^+, 5), 218 (28), 202 (60), 200 (16), 173 (17), 172 (32), 119 (17), 115 (25), 91 (18), 85 (100), 69 (52), 68 (22), 63 (17); mass spectral M_r calcd for $C_{16}H_{14}O_5$ 286.0840, found 286.0823.

Synthesis of Nanaomycin A. Preparation of Alkyne 9 (Mixture of Diastereomers).[30] To a flame-dried 250-mL round-bottomed flask equipped with a magnetic stirring bar were added 1-butyne-3-ol tetrahydropyranyl ether **8** (10.0 g, 64.9 mmol), and THF (45 mL). The reaction was brought under a N_2 atmosphere and cooled at 0 °C, and n-BuLi (1.6 M in hexane, 45 mL, 71.4 mmol) was added dropwise via syringe to the stirred reaction. After 15 min at 0 °C, the reaction mixture was cooled to −78 °C and BF_3·Et_2O (5.15 g, 36.0 mmol) was added dropwise. The solution was stirred for 15 min and epichlorohydrin (7.21 g, 78 mmol) was added dropwise via syringe. After the mixture was stirred at −78 °C for 4 h, H_2O (4 mL) was added and the solution was allowed to warm to room temperature, diluted with ether (200 mL), and washed in a separatory funnel with 1.2 N HCl (2 × 100 mL). The organic layer was dried ($MgSO_4$), filtered, and condensed on a rotary evaporator to leave a crude oil, which was chromatographed (SiO_2, 4 cm × 0.75 m, 1/1 ether/hexane) to give 10.6 g (66%) of alkyne **9** as a clear oil (mixture of diastereomers): IR (neat, cm^{-1}) 3450, 2280; ^1H NMR (60 MHz, $CDCl_3$) δ 5.08–4.66 (m, 1 H), 4.53 (br, q, 1 H, J = 6 Hz), 4.16–3.26 (m, 6 H), 2.55 (br d, 2 H, J = 6 Hz), 1.93–1.22 (m, 6 H), 1.43 (d, 3 H, J = 6 Hz).

Preparation of Alkyne 10 (Mixture of Diastereomers). To a 250-mL round-bottomed flask equipped with a magnetic stirring bar were added alkyne **9** (5.0 g, 20.3 mmol), CH_2Cl_2 (40 mL), H_2O (40 mL), NaCN (12 g, 250 mmol), and Aliquat 336[35] (808 mg, 2.0 mmol). The flask was fitted with a reflux condensor and refluxed under a N_2 atmosphere for 24 h. After it was cooled to room temperature, the reaction was diluted with CH_2Cl_2 (100 mL) and washed in a separatory funnel with saturated $NaHCO_3$ (3 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and condensed on a rotary evaporator, and the residue was chromatographed (SiO_2, 3 cm × 0.75 m, 3/1 ether/hexane) to give 3.6 g (74%) of the cyanide displacement product of **9** as a clear oil (mixture of diastereomers): IR (neat, cm^{-1}) 3411, 2245; ^1H NMR (60 mHz, $CDCl_3$) δ 4.96–4.70 (m, 1 H), 4.70–4.23 (m, 1 H), 4.00–3.20 (m, 3 H), 3.20–2.90 (m, 1 H), 2.83–2.30 (m, 4 H), 1.93–1.20 (m, 6 H), 1.42 (d, 3 H, J = 6 Hz).

The cyanoalkyne prepared above was silylated to give the tetrahydropyranyl ether of **10** in the following manner. To a 250-mL round-bottomed flask equipped with a magnetic stirring bar were added the cyano alkyne prepared above (4.8 g, 20.3 mmol), CH_2Cl_2 (100 mL), DMAP (3.7 g, 30.4 mmol), and *tert*-butyldimethylsilyl chloride (4.6 g, 30.4 mmol). The mixture was stirred under N_2 at room temperature for 24 h, diluted with ether (100 mL), and washed in a separatory funnel with 1.2 N HCl (3 × 50 mL) and saturated $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$) and filtered, and the solvents were removed on a rotary evaporator to leave a crude oil, which was chromatographed (SiO_2, 3 cm × 1 m, 9/1 hexane/ether) to give 6.9 g (97%) of the tetrahydropyranyl ether of alkyne **10** as a clear oil (mixture of diastereomers): IR (neat, cm^{-1}) 2278; ^1H NMR (60 MHz, $CDCl_3$) δ 5.08–4.92 (m, 1 H), 4.46 (br q, 1 H, J = 6 Hz), 3.98–2.88 (m, 3 H), 2.88–2.38 (m, 4 H), 1.78–1.32 (m, 6 H), 1.40 (d, 3 H, J = 6 Hz), 0.90 (s, 9 H), 0.66 (s, 6 H); mass spectrum (70 eV), m/e (rel intensity) 337 (M − 14, 0.12), 101 (15), 85 (100), 81 (27), 79 57), 77 (16), 75 (76), 69 (15), 67 (42), 66 (14), 65 (15).

Selective hydrolysis of the tetrahydropyranyl ether gave alkyne **10** by the following procedure. To a 25-mL round-bottomed flask equipped with a magnetic stirring bar were added the previously prepared compound (2.83 g, 8.02 mmol), MeOH (8 mL), and pyridinium *p*-toluenesulfonate (1.0 g, 4.0 mmol). The flask was sealed with a septum cap and the mixture was stirred at 40 °C for 2 h. After it was cooled to room temperature, the mixture was diluted with ether (150 mL) and washed with saturated $NaHCO_3$ (3 × 50 mL) in a separatory funnel. The organic layer was dried ($MgSO_4$) and filtered, and the solvents were removed on a rotary evaporator to leave a crude oil, which was chromatographed (SiO_2, 3 cm × 0.5 m, 3/1 ether/hexane) to give 1.84 g (96%) of alkyne **10** as a clear oil (mixture of diastereomers): IR (neat, cm^{-1}) 3450, 2280; ^1H NMR (60 MHz, $CDCl_3$) δ 4.52 (br q, 1 H, J = 6 Hz), 4.35–3.88 (m, 1 H), 3.32 (br s, 1 H), 2.66 (d, 2 H, J = 6 Hz), 2.48 (br d, 2 H, J = 6 Hz), 1.43 (d, 3 H, J = 6 Hz), 0.93 (s, 9 H), 0.13 (s, 6 H).

Preparation of Alkyne 11 (Mixture of Diastereomers). To a 50-mL round-bottomed flask equipped with a magnetic stirring bar were added alkyne **10** (2.31 g, 9.7 mmol), CH_2Cl_2 (18 mL), and DMAP (1.77 g, 14.5

(33) Oelschlaeger, H.; Schmersahl, P.; Toproski, W. *Arch. Pharm.* (*Weinheim, Ger.*) **1961**, *294*, 488–498; *Chem. Abstr.* **1961**, *56*, 3343*a*.

(34) Prepared from caprolactone using the procedure described in ref 33 for the conversion of butyrolactone to 3-iodobutanoyl chloride.

(35) Aliquat 336 is a phase-transfer catalyst available from Aldrich Chemical Co.

mmol). The reaction mixture was brought under a N_2 atmosphere, cooled to 0 °C, and stirred while 6-iodohexanoyl chloride[34] (3.77 g, 14.5 mmol) was added dropwise via syringe. After the addition was complete, the reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was subjected to the same workup and purification previously described for compound **5**. After chromatography, 4.4 g (98%) of alkyne **11** were obtained as a clear oil (mixture of diastereomers): IR (neat, cm^{-1}) 2275, 1744; ^1H NMR (60 MHz, $CDCl_3$) δ 5.35 (br q, 1 H, J = 6 Hz), 4.23–3.76 (m, 1 H), 3.15 (t, 2 H, J = 6 Hz), 2.48–2.12 (m, 6 H), 1.98–1.22 (m, 6 H), 1.4 (d, 3 H, J = 6 Hz), 0.90 (s, 9 H), 0.15 (s, 6 H).

Preparation of Benzocyclobutenedione 12 (Mixture of Diasteromers). To a 25-mL round-bottomed flask equipped with a magnetic stirring bar were added alkyne **11** (2.27 g, 4.62 mmol), 3-hydroxybenzocyclobutenedione (570 mg, 3.85 mmol), CH_3CN (8 mL), and DBU (645 mg, 4.24 mmol). The flask was fitted with a reflux condenser, brought under a N_2 atmosphere, and refluxed for 2 h. After a work up and purification procedure identical with that used for compound **6**, 1.52 g (77%) of benzocyclobutenedione **12** was obtained as a yellow oil (mixture of diastereomers): IR (CH_2Cl_2, cm^{-1}), 2270, 1775, 1738, 1603; ^1H NMR (60 MHz, $CDCl_3$) v 7.56–7.16 (m, 2 H), 6.88 (dd, 1 H, J = 7, 1 Hz), 5.33 (br q, 1 H, J = 6 Hz), 4.42 (t, 2 H, J = 6 Hz), 2.73–2.16 (m, 4 H), 2.10–1.20 (m, 6 H), 1.46 (d, 3 H, J = 6 Hz), 0.93 (s, 9 H), 0.15 (s, 6 H); mass spectrum (70 eV), m/e (relative intensity) 511 (M^+, 0.51), 320 (23), 319 (100), 245 (41), 184 (16), 118 (20), 75 (35), 73 (57), 69 (52), 55 (17); mass spectral M_r calcd for $C_{28}H_{37}O_6NSi$ 511.2387, found 511.2389.

Preparation of Phthaloylcobalt Complex 13 (Mixture of Diastereomers). To a 25-mL round-bottomed flask equipped with a magnetic stirring bar were added benzocyclobutenedione **12** (668 mg, 1.31 mmol), Co $(PPh_3)_3Cl$ (2.30 g, 2.61 mmol), and benzene (13 mL). After it was flushed with N_2, the flask was sealed with a septum cap and heated with stirring at 40 °C for 6 h. After a workup and purification procedure identical with that previously described for complex **7**, 1.12 g (76%) of phthaloylcobalt complex **13** was obtained as a red-brown oil (mixture of diastereomers): IR (CH_2Cl_2, cm^{-1}) 2275, 1738, 1633, 1605; ^1H NMR (60 MHz, $CDCl_3$) δ 7.48–6.75 (m, 30 H), 6.62–5.92 (m, 3 H), 5.26 (br q, 1 H, J = 6 Hz), 4.38–3.42 (m, 3 H), 2.53 (d, 2 H, J = 6 Hz), 2.65–2.05 (m, 4 H), 1.95–1.08 (m, 6 H), 1.43 (d, 3 H, J = 6 Hz), 0.90 (s, 9 H), 0.12 (s, 6 H).

Preparation of Macrocyclic Naphthoquinone 14 (Mixture of Diastereomers). To a flame-dried 15-mL round-bottomed flask equipped with a magnetic stirring bar were added phthaloylcobalt complex **13** (113 mg, 0.10 mmol) and CH_3CN (3 mL). The reaction mixture was placed under N_2 and stirred while a solution of $AgBF_4$ (97.3 mg, 0.50 mmol) in CH_3CN (2 mL) was added dropwise via syringe. A reflux condenser equipped with a N_2 inlet was attached to the flask and the mixture was refluxed under N_2 for 5 h. After this was cooled to room temperature, the volatiles were removed on a rotary evaporator and the crude reaction mixture was filtered through a short SiO_2 column (2 cm × 6 cm, CH_2Cl_2 then ether). After removal of solvents the crude product was chromatographed (E. Merck preparative SiO_2 plate, 0.5 mm, ether) to give 24 mg (47%) of macrocyclic quinone **14** as a yellow oil (mixture of diastereomers): IR (CH_2Cl_2, cm^{-1}) 2270, 1730, 1672, 1595; ^1H NMR (270 MHz, $CDCl_3$) δ 7.63–7.50 (m, 2 H), 7.29–7.22 (m, 1 H), 5.62, 5.59 (two overlapping q, 1 H total, J = 7 Hz each), 4.58–4.28 (m, 2 H), 4.07–3.87 (m, 1 H), 3.15–2.98 (m, 1 H), 2.72–2.11 (m, 5 H), 1.83, 1.82 (two d, 3 H total, J = 7 Hz) each), 1.74–1.07 (m, 6 H), 0.88, 0.87 (two s, 9 H total), 0.13, 0.12, 0.07, 0.02 (all s, 6 H total); mass spectrum (70 eV), m/e (relative intensity) 511 (M^+, 0.90), 455 (19), 454 (50), 436 (18), 341 (19), 340 (53), 299 (31), 115 (23), 97 (36), 75 (46), 73 (76), 69 (100), 55 (42); mass spectral M_r calcd for $C_{28}H_{37}O_6NSi$ 511.2387, found 511.2379.

Preparation of Pyranoquinones 15. To a 10-mL round-bottomed flask equipped with a magnetic stirring bar were added macrocyclic quinone **14** (51 mg, 0.1 mmol), ether (5 mL), 12 M HCl (0.4 mL), and Zn (131 mg, 2.0 mmol). After it was stirred under N_2 at room temperature for 1 h, the reaction mixture was transferred to a separatory funnel and partitioned between EtOAc and 1.2 N HCl. The organic layer was dried ($MgSO_4$), filtered, and condensed on a rotary evaporator, and the residue was oxidized to the quinone with Ag_2O (232 mg, 1.0 mmol) in ether (5 mL). After stirring 1 h at room temperature, the reaction was filtered, and the Ag_2O was washed with MeOH to remove any adhered product. Volatiles were removed on a rotary evaporator and the crude quinone was chromatographed (E. Merck preparative SiO_2 plate, 0.5 mm, 1/1 acetone/hexane) to give 33 mg (83%) of **15** as a yellow oil: IR (CH_3CN, cm^{-1}) 3550, 1710, 1662, 1590; ^1H NMR (270 MHz, CD_3OD) δ 7.70–7.59 (m, 2 H), 7.42 (br d, 1 H, J = 8 Hz) 4.98, 4.90–4.76 (br q and m, 1 H total, J = 6.5 Hz), 4.55–3.88, 3.85–3.70 (two m, 3 H total), 2.94–2.62 (m, 3 H), 2.37–2.15 (m, 3 H), 1.96–1.51 (m, 6 H), 1.51, 1.49 (two d, 3 H total, J = 6.5 Hz each); mass spectrum (70 eV), m/e (relative intensity) 397 (M^+, 0.94, 277 (20), 184 (16), 115 (27), 97 (19), 75 (100), 73 (98), 69 (60), 57 (20), 55 (29); mass spectral M_r calcd for $C_{22}H_{23}NO_6$ 397.1525, found 397.1519.

Preparation of Pyranoquinones 16t/16c. To a 10-mL round-bottomed flask equipped with a magnetic stirring bar were added the mixture of quinones **15** (40 mg, 0.1 mmol), CH_2Cl_2 (1 mL), and $AlCl_3$ (266 mg, 2.0 mmol). The reaction mixture was placed under a N_2 atmosphere and stirred at room temperature for 1 h. The solution was then transferred to a separatory funnel containing ether (75 mL) and washed with 1.2 N HCl (2 × 50 mL). The organic layer was dried ($MgSO_4$) and filtered, solvents were removed on a rotary evaporator, and the crude quinone was chromatographed (E. Merck preparative SiO_2 plate, 0.5 mm, 3/2 hexane/ether) to give 27 mg (95%) of cyanopyranoquinones **16t/16c** as an orange solid (3:1 ratio, respectively): IR (CH_2Cl_2, cm^{-1}) 3300, 1668, 1645, 1621; ^1H NMR (270 MHz, $CDCl_3$) δ 11.94, 11.92 (two s, 1 H total), 7.67–7.57 (m, 1 H), 7.29–7.22 (m, 1 H), 5.08, 4.98–4.95 (dq and m, 1 H total, J = 6.5, 2 Hz, the dq at 5.08 is due to the C-9 methine of the trans isomer **16t** and the m at 4.98–4.85 is due to the C-9 methine of the cis isomer **16c**, ratio 3:1, assignment is based on analogy with the isoeleutherin/eleutherin series),[31] 4.21–4.09, 3.84–3.73 (two m, 1 H total), 2.94, 2.90 (dt and dd, 1 H total, J = 18, 2 and 19.5, 3 Hz, respectively), 2.75–2.86 (m, 2 H), 2.42 (br dd, 1 H, J = 19.5, 10 Hz), 1.61, 1.60 (two d, 3 H total, J = 7, 6.5 Hz, respectively); mass spectrum (70 eV), m/e (relative intensity) 283 (M^+, 100), 268 (22), 243 (74), 229 (20), 228 (34), 225 (28), 213 (24), 200 (24), 139 (20), 128 (32), 127 (21), 121 (37), 120 (23), 115 (46), 92 (54), 77 (26), 65 (43), 64 (37), 63 (70), 55 (23), 53 (25), 51 (32); mass spectral M_r calcd for $C_{16}H_{13}NO_4$ 283.0845, found 283.0840.

Preparation of Nanaomycin A (3) and Its Epimer (17). To a 10-mL round-bottomed flask equipped with a magnetic stirring bar were added the cyanopyranoquinone mixture **16t/16c** (28 mg, 0.1 mmol) and 50% H_2SO_4 (5 mL). The reaction mixture was heated under a N_2 atmosphere at 90 °C for 5 h. After it was cooled to room temperature, the reaction mixture was transferred to a separatory funnel and partitioned between ether and H_2O (50 mL each). The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed on a rotary evaporator to leave a crude product, which was chromatographed (E. Merck preparative SiO_2 plate, 0.5 mm, ether) to give 21 mg (70%) of a mixture of nanaomycin A and its cis epimer as a yellow solid (3:1 ratio, respectively). Pure nanaomycin A was obtained by recrystallization from CH_2Cl_2/hexane: mp 171–172 °C (lit.[15] 171–174 °C); IR (CH_2Cl_2, cm^{-1}) 3100, 1715, 1662, 1645, 1620; ^1H NMR (270 MHz, $CDCl_3$) δ 11.97 (s, 1 H), 7.66–7.56 (m, 2 H), 7.28–7.21 (m, 1 H), 6.76 (br s, 1 H), 5.05 (br q, 1 H, J = 7 Hz), 4.40–4.26 (m, 1 H), 2.86 (br, d, 1 H, J = 9 Hz), 2.72 (d, 2 H, J = 6 Hz), 2.36 (dd, 1 H, J = 19.10 Hz), 1.59 (d, 3 H, J = Hz); mass spectrum (70 eV), m/e (relative intensity) 302 (M^+, 58), 287 (23), 284 (81), 262 (20), 243 (47), 242 (100), 241 (67), 239 (21), 229 (23), 227 (74), 225 (23), 215 (24), 214 (57), 213 (57), 199 (24), 197 (28), 185 (23), 183 (27), 171 (21), 157 (23), 139 (32), 128 (35), 127 (21), 121 (56), 120 (23), 115 (42), 92 (43), 91 (21), 77 (32), 71 (20), 69 (29), 65 (34), 64 (23), 63 (37), 57 (37), 55 (42), 51 (33); mass spectral M_r calcd for $C_{16}H_{14}O_6$ 302.0789, found 302.0781. From the mother liquor above the cis isomer of nanaomycin (**17**) was obtained and recrystallized: mp 168–170 °C (CH_2Cl_2/hexane); IR (CH_2Cl_2, cm^{-1}) 3100, 1715, 1662, 1645, 1620; ^1H NMR (270 MHz, $CDCl_3$) δ 11.95 (s, 1 H), 7.66–7.56 (m, 2 H), 7.29–7.21 (m, 1 H), 6.67 (br s, 1 H), 4.98–4.83 (m, 1 H), 3.98–3.86 (m, 1 H), 2.90 (dt, 1 H, J = 18.5, 2.5 Hz), 2.73 (d, 2 H, J = 6 Hz), 2.44–2.20 (m, 1 H), 1.59 (d, 3 H, J = 7 Hz); mass spectral M_r calcd for $C_{16}H_{14}O_6$ 302.0789, found 302.0778.

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