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SYNTHESIS OF NAPHTHOQUINONE ANTIBIOTICS BY INTRAMOLECULAR ALKYNE CYCLOADDITION TO CARBENE–CHROMIUM COMPLEXES

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Abstract—The reaction of carbene–chromium complexes with alkynes provides a direct route to naphthoquinone derivatives and is the key step in a new approach to the isochromanone antibiotics exemplified by deoxyfrenolicin (1) and nanaomycin A (2). While the regioselectivity of intermolecular addition of the appropriate unsymmetrical disubstituted alkyne is unfavourable, two successful approaches have been developed. Allylacetylene reacts with methoxy-(*o*-methoxyphenyl)methylidene-$Cr(CO)_5$ with high regioselectivity. Bromination, lithiation, and reaction with acetaldehyde produced the desired precursor. Alkoxypalladation led to pyran ring formation and introduction of the acetate side chain. Following earlier procedures, nanaomycin A (2) was produced. A more convergent alternative involved intramolecular cycloaddition of an alkyne with the alkylidene-chromium unit. A series of model cyclizations established the feasibility and an alkyne with an ethylene glycol side chain was prepared. The ethylene glycol unit serves as the tether to hold the alkyne in place for cyclization and allows easy removal at a later stage. Deoxyfrenolicin (1) was produced in a highly convergent and efficient process.

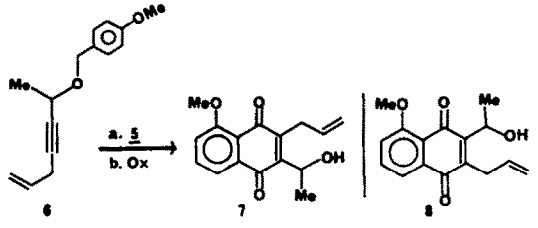
Deoxyfrenolicin (1)[1] and nanaomycin A (2)[2] are closely related structures and members of a fairly large set of molecules which bear the naphthoquinone nucleus, a fused pyran ring, and the 9-alkyl, 11-carboxymethyl substitution pattern. The significant antibiotic activity[3] and potential antitumour activity[4] of members of this set have prompted numerous successful synthesis efforts.[5] As part of a general study in naphthoquinone synthesis and especially to test the quinone synthesis method based on cycloaddition of an alkyne with a carbene–chromium complex,[6] we developed a general strategy (Scheme 1)[7] that relies on two key steps. In a retro-synthetic analysis, we see the pyran ring being formed by palladium-prompted alkoxy-carbonylation of the appropriate hydroxyalkene, 3 (Scheme 1). This reaction has strong general precedent beginning with the Wacker process,[8c] including intermolecular examples with mono-substituted alkenes[8,9] and, most recently, in a case[10] closely related to that proposed here. It was interesting to consider how the functionality in 3 might be compatible with the alkoxy-carbonylation conditions or how suitable protecting group sequences might be arranged.

The second key step is the cycloaddition/CO insertion of alkyne 4 with the arylmethylidene–chromium complex 5. The desired product is 3 and important questions of regioselectivity and functional group compatibility are obvious. Formation of 3 requires that the alkylidene carbon of 5 couples with the alkyne carbon of 4 which bears the larger substituent; little electronic directing effect is expected in the regioselectivity for a dialkylacetylene. A number of disubstituted alkynes have been studied in reaction with simple arylmethylidene complexes related to 5 and a rule is suggested that the steric effect of the alkyne substituents is the primary directing influence, and that the *less* crowded end of the alkyne tends to couple with the alkylidene carbon.[6,11] This trend obviously bodes ill for the desired regioselectivity.

RESULTS AND DISCUSSION

Nanaomycin A (2) via intermolecular alkyne–carbene cyclizations

Following the more basic rule that trends and models should be taken lightly, we tested the direct reaction of an example of 4 with 5. The sequential treatment of the tetrahydropyranyl ether of 1-butyne-3-ol with *n*-butyllithium, cuprous iodide, and allyl bromide gave the desired alkynol 4 (R = Me, P = H; after cleavage of the THP ether). Protection of the alcohol with a *p*-methoxylbenzyl group gave 6. Complex 5 was obtained according to the literature procedure[12] as red crystals. It is moderately air stable and can be purified by conventional column chromatography on silica gel. Reaction of 6 with 5 at 55° in THF produces a mixture which is oxidized directly with ceric ammonium nitrate to remove the chromium carbonyl residues, to oxidize the naphthols to naphthoquinones and to oxidatively remove the *p*-methoxybenzyl group.[13] A single naphthoquinone was detected and isolated by chromatography; it was identified as 7 (40% yield) through spectral data and confirmed in comparison with the opposite (and desired) regioisomer 8. Clearly,



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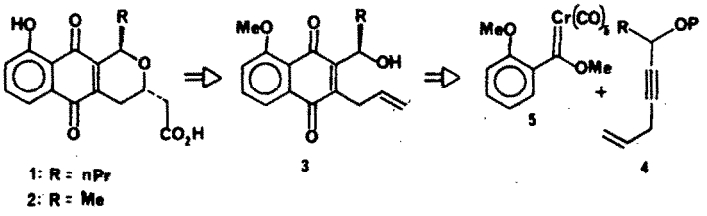
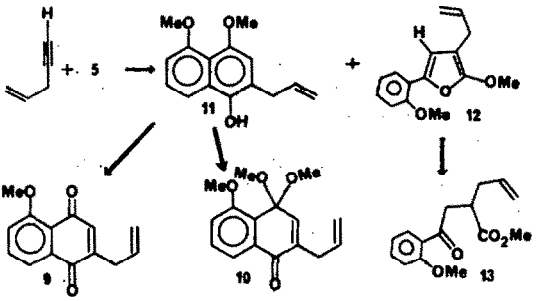


Scheme 1.

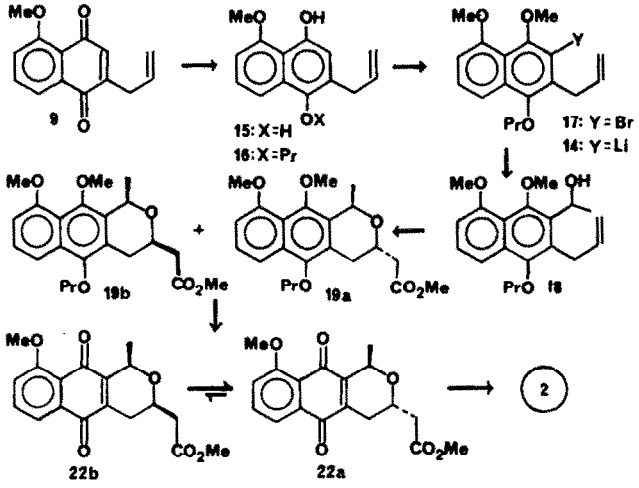


Scheme 2.

the direct approach was not feasible. Two alternatives appeared: (1) a simpler, mono-substituted alkyne might give high and useful regioselectivity and one side chain on the quinone ring of **8** could be added later or (2) the alkyne–carbene cycloaddition could be made intramolecular, restricting the possible orientations so as to favour the desired regioselectivity.

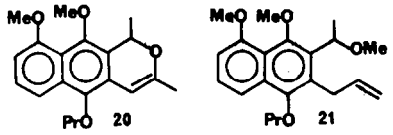
For the first alternative, a simple candidate is allylacetylene (Scheme 2). It reacted with **5** (45°, THF, 35 hr, 50% molar excess of the alkyne; aqueous ceric ammonium nitrate treatment of the crude product) to give 2-allyl-5-methoxy-1,4-naphthoquinone[14] (**9**) in a yield of 52% after chromatographic purification. Alternatively, oxidation of the crude product with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in methyl alcohol led directly to monoketal **10** (54% yield). The initially formed naphthol **11** could be isolated in 46% yield by chromatography before oxidation and then directly oxidized to **10** in 54% yield again using DDQ in methyl alcohol. A minor product (20% yield) in the alkyne–carbene reaction has been tentatively identified as the furan, **12**, through chemical manipulation and spectral data. Acid hydrolysis gives a ketoester, **13**. The formation of furans as minor products has been noted in earlier studies.[6]

Among the strategies for adding a 1-hydroxyalkyl side chain to **9**, **10** or **11** (to give **8**), we considered conjugate addition of carbon nucleophiles. However, only simple nucleophiles were successful (cyanide anion, nitromethane anion) and the products could not be manipulated into **8**.[15] We also studied reversing the polarity, activating the naphthalene unit as an aryl lithium species (e.g. **14** in Scheme 3). For this purpose, the naphthoquinone **9** was reduced to naphthohydroquinone **15** with sodium hydrosulphite in a two-phase THF–water mixture and selectively monoalkylated with *n*-propyl iodide in acetone to give **16** in 76% yield. The *n*-propyl group was chosen for its moderate steric effect, which appears to be highly effective in this case; neither dialkylation product nor unreacted hydroquinone was detected. Then bromination (*N*-bromosuccinimide, slow addition) and direct methylation of the remaining free phenolic hydroxyl group gave the bromonaphthalene **17** (70% from **16**). In the usual way, bromine–lithium exchange with *n*-butyllithium at low temperature was expected to give **14**; immediate trapping with acetaldehyde produced the key intermediate **18** as a colourless oil in 90% yield after chromatography.



Scheme 3. Conversion to nanaomycin A (**2**).

The Pd(II)-promoted cyclization–carbonylation of **18** proceeded at 23° in methyl alcohol with 1.1 atm of carbon monoxide using 0.10 mol equivalents of Pd chloride and excess cupric chloride as re-oxidant to recycle the Pd. Chromatography produced four pure compounds: the epimeric pyranoesters **19a** (45%) and **19b** (31%), the product from β-hydride elimination, **20** (9%), and the solvolysis product, **21** (4%). The *trans* configuration of the side chains on the pyran ring is



assigned to **19a** based on analysis of the ^{1}H-NMR data for the corresponding quinones (**22**, see below). The oxidations of **19a** and **19b** were carried out separately to give pyranoquinones **22a** (79%) and **22b** (75%). Both are known compounds[5b,e] and both have been converted to nanaomycin A (**2**) in two steps. The *cis* isomer can be equilibrated favourably to the *trans* in sulphuric acid.[5e] The overall process for this formal synthesis of nanaomycin A (**2**) is outlined in Scheme 3.

Models for intramolecular carbene–alkyne cyclizations

With the only modest success of the intermediates from direct, intermolecular cycloaddition of an alkyne to a carbene–chromium complex, a modified strategy was developed using an intramolecular process to control regioselectivity. This strategy has been applied in traditional cycloaddition reactions such as the Diels–Alder reaction[17] and requires that the reactants conveniently be tethered and later detached. The (methoxymethylidene)chromium complexes such as **5** offer a simple opportunity for tethering an alkyne reactant through nucleophile exchange with a hydroxy-alkyne as outlined formally in Scheme 3. No example of the intramolecular alkyne–carbene cyclization had been reported, so a series of models was investigated.

An important simplification is the anhydride-like reactivity of acetoxymethylidenechromium complexes which allows replacement of the acetoxy unit by alkoxy, amino and thioalkoxy nucleophiles, an analogue of acyl transfer.[18] A simple sequence involves two stages and one isolated intermediate (Scheme 4). Reaction of phenyllithium with chromium hexacarbonyl produces the lithium salt **23a** which is converted to the water insoluble tetra-(*n*-butyl)ammonium salt (**23b**)[19] as a means of purification and convenient storage. The salt **23b** can be prepared in large quantity and stored indefinitely at 25°. It is activated for exchange by acetylation at −20° in dichloromethane to produce the delicate, deep red acetate, **24**. The solution of freshly prepared **24** was mixed with an alkynol (**25**) at 25° to produce a red oil which was characterized by ^{1}H-NMR and IR spectral data as structure **26**, but it reacted slowly at 25°. After 20–30 hr at 35°, complete conversion of **26** to a new complex (**27**) was observed. This product was particularly sensitive to donor solvents such as acetone, in which the $Cr(CO)_3$ group moves to the less substituted ring and then is detached completely. For ease of isolation, the $Cr(CO)_3$ unit was rapidly detached from **27** with triphenylphosphine, in the presence of triethylamine and acetic anhydride, to give the acetyl derivatives, **28**.

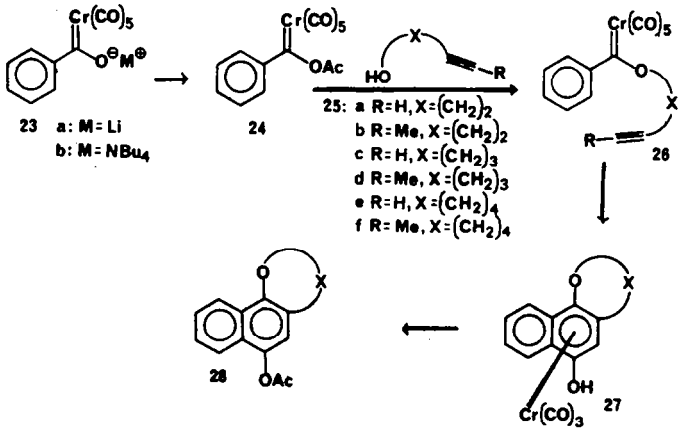
Table 1 presents the results from combination of **24** with six alkynols (**25a–25f**) which were chosen to define ring size preferences and the influence of alkyne substituents. From the reaction conditions required for complete conversion, it is clear that these intramolecular examples proceed considerably faster than related intermolecular cases (60°/10–20 hr). All three ring sizes (5–7) can form efficiently, but terminal alkynes

Table 1. Intramolecular alkyne–carbene reaction

Alkyne	Reaction conditions*	Naphthol acetate (**28**)	Isolated yield (%)†
25a	26 hr/25°	**7a**	16
25b	20 hr/35°	**7b**	81
25c	44 hr/25°	**7c**	18
25d	44 hr/35°	**7d**	62
25e	20 hr/35°	**7e**	38
25f	46 hr/35°	**7f**	62

*In Et_2O solution with complexes **26** used without purification.

†The yield is calculated overall from **23b** as starting material and is based on chromatographically pure material.

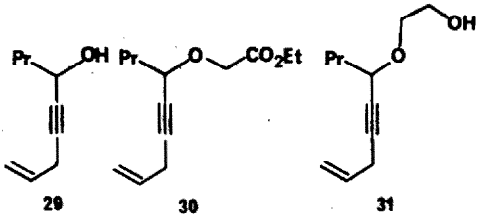


Scheme 4. Models for intramolecular carbene–alkyne reaction.

are distinctly less effective than the disubstituted alkynes. Reaction rates are approximately the same for all substrates; we suspect that terminal alkynes are more prone to metal-promoted oligomerization but the by-products have not been investigated.

Synthesis of deoxyfrenolicin (1) *via intramolecular carbene–alkyne cycloaddition*

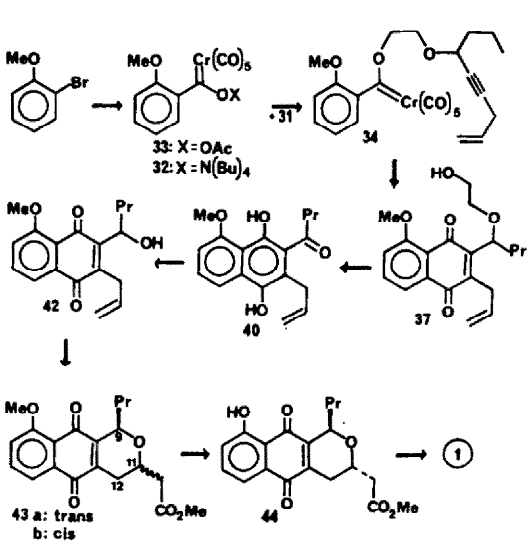
Using the intramolecular reaction to control regioselectivity through a convenient ethylene glycol tether, a direct synthesis of deoxyfrenolicin (1) was developed, as outlined in Scheme 5. For this purpose, the alcohol **29** was treated with ethyl bromoacetate to give **30** and reduction with lithium aluminum hydride



29 **30** **31**

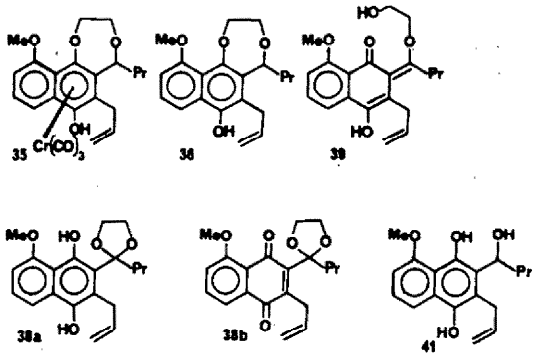
produced the ethylene glycol derivative, **31**. The ammonium salt **32** was prepared as before[19] from *o*-lithioanisole and activated with acetyl chloride as the acetate **33** (not isolated). Exchange of acetate with **31** gave a yellow solution from which a carbene complex (expected to be **34**) was isolated by concentration, trituration with *n*-pentane and removal of pentane from the filtrate. Spectral analysis indicated the presence of **34** in 90–95% purity. When heated at 33–37° in ether, complex **34** began to cyclize; after 64 hr, the volatile material was removed to leave a residue (expected to be **35**) from which the naphthol **36** could be isolated after treatment with excess triphenylphosphine in acetone at 25° (48% yield). More efficiently, the residue was treated directly with DDQ in aqueous acetonitrile to produce the oxidative-dealkylation product, **37** (51% yield after chromatography, Scheme 5).

Removal of the hydroxyethyl side chain might be accomplished in a number of ways and we had been



Scheme 5. Synthesis of deoxyfrenolicin, 1.

successful with a four-step procedure on a closely related compound (T. Sato, unpublished). Conversion of the primary hydroxyl to the iodide via the *p*-toluenesulphonate ester followed by reduction with Zn metal gave a hydroquinone and then re-oxidation afforded the desired quinone alcohol. However, the overall yield was not satisfactory and the several operations were inconvenient. It was welcome then, when **37** was noted to rearrange to the quinone ketal **38b** simply on standing in air at 25° for 3 weeks. Presumably, enolization of **37** to give the *o*-quinomethide **39** opens the opportunity for conjugate addition of the primary hydroxyl to form a ketal; the initially formed hydroquinone ketal **38a** would be air oxidized to quinone **38b**. By simple treatment with aqueous acid, **37** is converted directly to keto-hydroquinone **40** in 95% yield (Scheme 5). The overall process of *o*-quinomethide formation/nucleophile addition has parallels in the idea of 'bioreductive-alkylation', where the *o*-quinomethide is suggested to form by reductive cleavage of a benzylic heteroatom rather than by enolization.[4] Reduction of **40** with sodium borohydride followed by oxidation with ($KHCO_3$, methyl alcohol, 0°) gave **42** in 78% yield.



The final stage is Pd-promoted intramolecular alkoxycarbonylation, based on a closely related conversion in our first synthesis of deoxyfrenolicin.[10] Treatment of **42** with bis(acetonitrile)dichloroPd(II) (10 mol equivalents) in methyl alcohol under 1.1 atm of carbon monoxide [cupric chloride to recycle Pd(II)] at 25° produced the pyran ester, **43**, in 70% yield after chromatographic purification (Scheme 5). Analytical HPLC indicated a mixture of isomers in the ratio 75:25. Crystallization produced the major isomer in high purity as light orange needles, m.p. 134–136°, which was identified as the *trans* structure, **43a**. From the mother liquor was isolated the pure minor isomer (**43b**), m.p. 144.0–148.5°. The stereochemistry of each isomer was determined by analogy with the eleutherin–isoeleutherin system.[16] The pseudochair arrangement with the C-11 alkyl group equatorial is preferred. In the ^{1}H-NMR spectra, the homoallylic coupling between H-12 and H-9 is greater when the C-9 is pseudoaxial (eleutherin, C-9 shows J = 3.5 and 2.9 Hz for coupling to the H'_a and H'_e at C-12). Treatment of the mixture **43** with boron tribromide causes demethylation to the phenol and complete isomerization of the *cis* arrangement into the natural *trans* series, **44** (84% yield).[10] Saponification of the methyl ester with dilute potassium hydroxide (methyl alcohol) gave racemic deoxyfrenolicin (**1**) as a yellow–orange powder of m.p. 214–214.5° (97%). It was shown to be identical in

chromatographic and spectral properties with a sample of natural (−)-deoxyfrenolicin.†

Summary

The intramolecular cycloaddition of an alkyne with a carbene–chromium complex allows perfect control over the regioselectivity of the reaction. The anhydride-like properties of the acetoxymethylidene-chromium group can be used for easy connection of an alkynol and the product naphthohydroquinone monoalkyl ether can be readily oxidized to cleave the alkyl ether. The overall process is applied in a short synthesis of deoxyfrenolicin (1) comprised of five or six isolated intermediates.

EXPERIMENTAL

Spectra. ^{1}H-NMR spectra were recorded with a Perkin–Elmer R24B spectrometer operating at 60 MHz, or a JEOL FX-90Q Fourier transform spectrometer operating at 90 MHz. Peak positions are reported in ppm relative to TMS internal standard. ^{13}C-NMR spectra were recorded with a JEOL FX-90Q Fourier transform spectrometer operating at 22.5 MHz. Peak positions are reported in ppm relative to $CDCl_3$ (δ 77.00). Spectra which were recorded with off-resonance decoupling have peaks reported as singlets (s), doublets (d), triplets (t) or quartets (q). IR spectra were recorded on a Perkin–Elmer model 299 spectrometer. Peak intensities were recorded as strong (s), medium (m), or weak (w). The 1602 cm^{-1} signal of polystyrene was used for calibration. Mass spectra were recorded on an AEI MS-902 instrument or a Hewlett–Packard 5487 GC–MS with electron impact ionization.

Chromatography. Medium-pressure liquid chromatography (MPLC) was done by using Lobar prepacked silica gel columns at pressures up to 50 psi applied by a Fluid Metering Inc. model RP lab pump. UV-active fractions were detected with an ISCO Model UA-5 absorbance monitor. Column chromatography was done with E. Merck silica gel 60 (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was done with E. Merck Reagents silica gel 60 F-254 aluminium-backed plates with a 0.2 mm thickness. Developed plates were visualized under UV light and by charring with 25% aq H_2SO_4. Analytical high-performance liquid chromatography (HPLC) was performed with a Waters Associates system equipped with Radial-PAK B silica gel cartridges in a Model RCM-100 module, model 6000A solvent delivery system, model U6K universal liquid chromatograph injector, model 4400 UV absorbance detector, model R401 differential refractometer and a dual pen data module.

Reagents and solvents. Et_2O, THF and *p*-dioxane were distilled under Ar from benzophenone ketyl immediately before use. C_6H_6, chlorotrimethylsilane, dimethylformamide, propionitrile, hexamethylphosphoramide (HMPA), diisopropylamine, diethylamine and 2,2,6,6-tetramethylpiperidine were distilled from CaH_2 (under reduced pressure as necessary) and stored under Ar. *t*-BuOH was distilled from CaO under Ar. CH_2Cl_2 was distilled from P_2O_5, under Ar. MeOH was distilled from Mg under Ar. CuI was further purified according to the lit.[20] Anhydrous $CuCl_2$ was heated at 100° under vacuum (0.01 mm) for 15 hr and then stored under Ar. Et_3N was filtered through a short plug of alumina immediately before use. *n*-BuLi and MeLi were used as solns in hexane and their concentrations were determined as in the lit.[21]

General information. The term 'concentrated' refers to removal of solvent by rotary evaporation at aspirator pressure. The term 'under Ar' implies that the apparatus was evacuated to 0.01 mm and then filled with Ar three times. M.ps and b.ps were uncorrected. Elemental analyses were carried out by Scandinavian Microanalytical Labs, Herlev, Denmark. Lithium diisopropylamide prepared by treating a soln of the amine (1.1 mol equivalents) in THF or Et_2O at −78°, under Ar, with *n*-BuLi (1.0 mol equivalent). The soln was then warmed to 0° for 15 min followed by cooling to −78°.

Reaction of the O-(p-methoxybenzyl) derivative (6) of 6-hydroxyhex-1-en-4-yne[22] *with carbene complex* **5**. To a sample of **5** (red crystals,[14] m.p. 71–74°; 325 mg, 0.95 mmol) in a 100 ml round bottom flask under Ar was added a soln of **6** (665 mg, 2.9 mmol) in 60 ml of THF and the homogeneous soln was stirred at 55° for 14 hr. The mixture was cooled to 25° and poured into a soln 0.5 M in ceric ammonium nitrate and 0.1 M in HNO_3 (20 ml). After being stirred for 1 hr, the mixture was partitioned between H_2O and Et_2O, and from the Et_2O layer was obtained a yellow oil. Preparative TLC (silica gel, hexane–Et_2O–CH_2Cl_2, 5:1:1) produced the pure **7** (102 mg, 40% yield). ^{1}H-NMR ($CDCl_3$): δ 1.66 (d, J = 6.8 Hz, 3H, —CHMe), 3.14 (m, 2H, —CH_2—CH=), 3.93 (br s, 1H, —OH), 3.94 (s, 3H, —OMe), 5.09 (m, 2H, C=CH_2), 5.69 (m, 1H, CH=C), 6.07 (q, J = 6.8 Hz, CHMe), 6.8–7.5 (m, 3H, aryl-H). ^{13}C-NMR ($CDCl_3$): δ 23.0, 31.8, 58.0, 75.7, 110.0, 110.7, 110.9, 112.7, 128.7, 130.4, 132.0, 133.7, 136.6, 149.3, 176.0, 177.6. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600–3200 (m, —OH), 1680 (s), 1630 (s), 1595 (s), 1585 (s), 1465 (s), 1270 (s), 2245 (s), 845 (s). Mass spectrum *m/z* (rel. int.): 272 [M]$^+$ (63), 243 (68), 227 (49), 199 (89), 135 (100). Only one regioisomer was observed. The structural assignment is based on similarities and distinct differences compared to isomer **8** whose structure was confirmed by conversion to nanaomycin A (**2**) (see below).

Reaction of pent-4-en-1-yne with carbene complex **5**. To a soln of 4.00 g (11.7 mmol) of **5** in 100 ml of THF under Ar at 25° was added 1.5 ml (ρ = 0.777, 17.6 mmol) of pent-4-en-1-yne (allylacetylene)[23] and the mixture was stirred at 45° for 36 hr (water condenser). After being cooled, the mixture was concentrated by rotary evaporation and the residue (A) was dissolved in a mixture of acetonitrile (50 ml) and H_2O (10 ml). To this soln at 0° was added 32 g (58.4 mmol) of ceric ammonium nitrate in 50 ml of H_2O. The mixture was warmed to 25°, stirred for 0.5 hr and concentrated by rotary evaporation to remove most of the acetonitrile. The residue was washed with Et_2O five times, dried, and concentrated to leave a brown residue. Flash chromatography gave yellow crystals of **9** (1.40 g, 52% yield). Recrystallization from hexane–Et_2O gave fine yellow needles, m.p. 96.5–98°. Lit.[14] m.p. 96–97°.

Isolation of 4,5-dimethoxy-2-allyl-1-naphthol (**11**). Following the procedure immediately above, the residue A was chromatographed on silica gel, eluting with hexane–CH_2Cl_2 mixtures. First eluted was a colourless oil assigned structure **12** (20% yield). ^{1}H-NMR ($CDCl_3$): δ 3.07 (br d, 2H, J = 6.0 Hz), 3.90 (s, 3H), 3.96 (s, 3H), 4.8–5.2 (m, 2.0H), 5.5–6.1 (m, 1.0H), 6.61 (s, 1.0H), 6.7–7.2 (m, 3.0H), 7.57 (dd, 1.0H, J = 7.2, 0.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 27.8, 55.2, 59.6, 98.7, 110.9, 113.5, 114.8, 120.0, 120.6, 124.7, 126.7, 136.9, 140.3, 155.0, 155.5. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3070 (w), 2940 (m), 2835 (m), 1645 (s), 1495 (s), 1385 (s), 1283 (s). Mass spectrum *m/z* (rel. int.): 244 [M]$^+$ (67), 229 (76), 135 (100), 115 (10), 92 (15), 77 (31). Mass spectral MW: 244.1098. Calc for $C_{15}H_{16}O_3$: 244.1099. Confirmatory evidence for the structure **12** was obtained by acid hydrolysis to **13**. A soln of 312 mg (1.28 mmol) of **12** in 10 ml of MeOH and 2 ml of 10% aq HCl was stirred at 25° for 30 min. Et_2O and H_2O were added and the Et_2O layer was washed sequentially with H_2O and sat aq NaCl before drying over K_2CO_3. Concentration by rotary evaporation followed by chromatography of the residue on silica gel with mixtures of Et_2O, CH_2Cl_2 and hexane as eluent gave 180 mg (54%) of **13**. ^{1}H-NMR ($CDCl_3$): δ 2.2–2.5 (m, 2H), 2.9–3.5 (m, 3H), 3.68 (s, 3H), 3.90 (s, 3H), 4.9–6.0 (m, 3H), 6.8–7.8 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 36.1, 40.4, 45.0, 51.6, 55.4, 111.6, 117.1, 120.7, 127.8, 130.4, 133.6, 135.1, 158.7, 175.4, 199.8. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1731 (s), 1672 (s), 1601 (s), 1487 (s), 1440 (s), 1290 (s), 1245 (s), 2265 (s). Mass spectrum *m/z* (rel. int.): 262 [M]$^+$ (3), 231 (3), 203 (7), 150 (22), 135 (100), 92 (12), 77 (27).

† We are grateful to Dr. D. B. Borders, Lederle Division of the American Cyanamid Co. for a generous sample of natural (−)-frenolicin.

Next eluted was **11** as a low m.p. light pink solid (46% yield). ^{1}H-NMR ($CDCl_3$): δ 3.50 (br d, 2H), 3.87 (s, 3H), 3.92 (s, 3H), 4.9–5.4 (m, 2H), 5.7–6.2 (m, 1H), 6.55 (s, 1H), 6.75 (d, 1H, J = 8.0 Hz), 7.27 (t, 1H, J = 8.0 Hz), 7.60 (d, 1H, J = 8.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 35.4, 56.4, 57.6, 106.3, 110.2, 114.2, 116.6, 117.5, 119.1, 125.9, 125.5, 135.9, 143.3, 150.8, 156.4. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520 (w), 2930 (w), 1623 (w), 1598 (s), 1582 (s), 1380 (s), 1275 (s), 1060 (s). Mass spectrum *m/z* (rel. int.): 244 [M]$^+$ (100), 229 (12), 188 (9), 187 (8), 135 (9), 128 (9), 115 (11).

Oxidation of **11** *to give 2-allyl-4-oxo-1,1,5-trimethoxy-1,4-dihydronaphthalene* (**10**). To a soln of **11** (306 mg, 1.25 mmol) in 15 ml of MeOH under Ar was added 2,3-dichloro-5,6-dicyanoquinone (286 mg, 1.26 mmol) and $KHCO_3$ (131 mg, 1.31 mmol). The deep red mixture was stirred at 25° for 20 min, then diluted with 10 ml of CH_2Cl_2, and loaded on an alumina chromatography column (Woelm I neutral). Elution with CH_2Cl_2 gave **10** as a pale yellow solid, m.p. 71.5–73.5° (recrystallized from hexane), 254 mg, 74% yield. ^{1}H-NMR ($CDCl_3$): δ 3.15 (s, 6H), 3.20 (m, 2H), 3.95 (s, 3H), 5.0–6.2 (m, 3H), 6.56 (t, 1H, J = 1.3 Hz), 7.18 (dd, 1H, J = 7.7, 1.4 Hz), 7.47 (t, 1H, J = 7.7 Hz), 7.80 (dd, 1H, J = 7.7, 1.4 Hz). ^{13}C-NMR ($CDCl_3$): δ 33.1, 51.5, 56.5, 97.0, 116.4, 117.4, 119.3, 130.4, 134.0, 134.6, 140.6, 142.3, 158.0, 183.8 (only peaks observed). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1667 (s), 1648 (s), 1583 (s), 1470 (s), 1282 (s), 1068 (s). Mass spectral MW: 274.

Direct oxidation of residue **A** *(above) to* **10**. Exactly as above, residue **A** was obtained from allylacetylene and complex **5**. Treatment of residue **A** with a soln of 2,3-dichloro-5,6-dicyanoquinone in MeOH at 0° for 2 hr gave a mixture from which the usual extraction procedures afforded **10** as a pale yellow solid, m.p. 72–74°, 54% yield.

Preparation of the naphthohydroquinone monopropyl ether **16**. To a soln of 200 mg (0.876 mmol) of **9** at 23° in 15 ml of THF was added dropwise with vigorous stirring sodium hydrosulphite (1.5 g, 8.76 mmol) in 10 ml of H_2O. After 0.5 hr the yellow soln became colourless and no starting material was detected by TLC (*n*-hexane–Et_2O, 1:1). The resulting soln was extracted five times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated to give **15** as a pale yellow crystalline compound. It was dissolved in degassed Me_2CO (15 ml) and *n*-propyl iodide (0.427 ml, 4.38 mmol) and K_2CO_3 (1.2 g, 8.76 mmol) were added. After the mixture was heated under reflux for 1.5 hr, an additional 0.427 ml (4.38 mmol) of *n*-propyl iodide was added and the mixture was heated under reflux for an additional 8 hr. A final portion of *n*-propyl iodide (0.427 ml) and further reflux (1.5 hr) gave complete conversion. Et_2O (10 ml) and H_2SO_4 (15 ml of 1 M) were added. The mixture was washed five times with Et_2O and the combined organic extracts were washed sequentially with sat aq Na_2SO_4, H_2O and brine. After being dried ($MgSO_4$), the Et_2O soln was concentrated to leave a yellow–brown residue. Chromatography (silica gel) gave **16** as colourless crystals (181 mg, 76%, m.p. 43–44°). ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.0 Hz), 1.90 (sextet, 2H, J = 7.0 Hz), 3.52 (dt, 2H, J = 6.5, 2.7 Hz), 3.82 (t, 2H, J = 7.0 Hz), 4.00 (s, 3H), 4.96–5.24 (m, 2H), 5.94 (m, 1H), 6.73 (s, 1H), 6.70 (br d, 1H), 7.13 (t, 1H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 10.6, 23.5, 33.9, 55.9, 76.0, 103.8, 111.5, 114.5, 115.8, 116.0, 125.5, 133.5, 130.9, 136.9, 144.7, 150.3, 156.3. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3445, 2970, 1612, 1400, 1373, 1069. Mass spectrum *m/z* (rel. int.): 272 [M]$^+$ (79), 230 (36), 229 (100), 214 (7.7). Anal. C, H.

Bromination and methylation of **16** *to give* **17**. To a soln of **16** (480 mg, 1.76 mmol) in 30 ml of dry acetonitrile at −30° was added dropwise over 5 hr (syringe pump) a soln of *N*-bromosuccinimide (376 mg, 2.12 mmol) in 30 ml of dry acetonitrile. After addition was complete, sat aq Na_2SO_3 was added at −30° and the mixture was allowed to warm to 25°. It was diluted with H_2O (15 ml) and extracted five times with Et_2O. The combined extracts were washed with aq Na_2SO_3 and brine, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in MeOH, and NaOH (350 mg, 8.8 mmol) was added. After the mixture was stirred for 40 min, Me_2SO_4 (17 ml, 17.6 mmol) was added slowly over 5 min. The mixture was stirred for 2 hr at 25° and additional portions of NaOH (350 mg) and Me_2SO_4 (1.7 ml) were added. The additions were repeated twice more, after 4 and 6 hr. The mixture was then concentrated to *ca* 5 ml at aspirator pressure and extracted five times with Et_2O. The combined extracts were washed with aq $NaHCO_3$, H_2O and brine, and dried ($MgSO_4$). Concentration gave a brown oil (590 mg) which was chromatographed (silica gel; eluting with *n*-hexane–Et_2O, 20:1) to produce **17** as a yellow oil (450 mg, 70%). ^{1}H-NMR ($CDCl_3$): δ 1.13 (t, 3H, J = 7.0 Hz), 1.92 (sextet, 2H, J = 7.0 Hz), 3.76 (dt, 2H, J = 6.5, 2.7 Hz), 5.12 (m, 1H), 6.03 (m, 1H), 6.87 (dd, 1H, J = 7.6, 1.8 Hz), 7.40 (dd, 1H, J = 9.0, 7.6 Hz), 7.65 (dd, 1H, J = 9.0, 1.8 Hz). ^{13}C-NMR ($CDCl_3$): δ 10.5, 23.5, 34.7, 56.4, 61.5, 76.5, 106.7, 155.2, 155.7, 118.9, 126.5, 129.8, 130.6, 135.7, 149.6, 149.9, 154.6, 155.8. IR ν_{max}^{neat} cm^{-1}: 2940, 1575, 1342, 1263, 1070. Mass spectral MW: 364/366 (Br isotopes). Anal. C, H.

Preparation of hydroxyalkene **18**. To a soln of **17** (370 mg, 1.01 mmol) in 20 ml of Et_2O was added slowly (5 min) at −78° a soln of *n*-BuLi in hexane (0.830 ml, 1.21 mmol of a 1.46 M soln). After being stirred for 20 min, the mixture was cooled to −100° and acetaldehyde (0.565 ml, 10.1 mmol) in 10 ml of Et_2O was added over 10 min. After the mixture was stirred at −100° for 0.5 hr, 5 ml of sat aq NH_4Cl was added and the mixture was allowed to warm to 25°. It was extracted three times with Et_2O and the combined extracts were washed once with brine, dried ($MgSO_4$) and concentrated to leave a yellow oil. Chromatography (silica gel; mixtures of hexane–Et_2O) produced pure **18** (301 mg, 90%) as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 1.11 (t, 3H, J = 7.0 Hz), 1.62 (d, 3H, J = 7.0 Hz), 1.40 (sextet, 2H, J = 7.0 Hz), 3.64 (m, 2H), 3.84 (t, 2H, J = 7.0 Hz), 3.92 (s, 3H), 4.02 (s, 3H), 3.80–5.30 (m, 3H), 5.84–6.26 (m, 1H), 7.87 (dd, 1H, J = 7.2, 1.1 Hz), 7.38 (t, 1H, J = 7.2 Hz), 7.66 (dd, 1H, J = 7.2, 1.1 Hz). ^{13}C-NMR ($CDCl_3$): δ 10.5, 23.5, 25.3, 30.4, 56.0, 63.3, 67.3, 76.0, 106.1, 115.2, 115.5, 119.5, 125.9, 127.1, 130.7, 134.1, 137.1, 149.3, 151.0, 155.6. IR ν_{max}^{neat} cm^{-1}: 3450, 3090, 2970, 2935, 1613, 1570, 1355, 1263, 1070. Mass spectral MW: 330.1847. Found 330.1831. Anal. C, H.

Pd-*promoted cyclization–carbonylation of* **18** *to give* **19**. A soln of **18** (110 mg, 0.333 mmol) in 5 ml of MeOH was added over 2 hr (syringe pump) to a mixture of Pd chloride (6.0 mg, 0.033 mmol), $CuCl_2$ (134 mg, 1.00 mmol) and MeOH (5 ml) under 1.1 atm of CO (balloon reservoir of CO). After addition, the mixture was stirred for 2 hr at 25°, then concentrated, diluted with H_2O and extracted five times with Et_2O. The combined extracts were washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue showed four components by TLC (*n*-hexane–ether, 1:1) of R_f 0.7, 0.6, 0.45, 0.40. Each component was obtained in high purity by multidevelopment preparative TLC. The least polar component (R_f 0.7) was identified as **19b** (39 mg, 31%) from spectral data. ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.0 Hz), 1.62 (d, 3H, J = 6.8 Hz), 1.90 (sextet, 2H, J = 7.0 Hz), 2.66 (dd, 1H, J = 16.8, 10.8), 2.68 (d, 2H, J = 6.4 Hz), 3.08 (dd, 1H, J = 10.8, 3.6 Hz), 3.74 (s, 3H), 3.78 (s, 3H), 3.99 (s, 3H), 3.83 (t, 2H, J = 7.0 Hz), 4.44 (dtd, 1H, J = 10.8, 6.4, 3.6 Hz), 5.32 (q, 1H, J = 6.8 Hz), 6.81 (dd, 1H, J = 7.6, 1.1 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.64 (dd, 1H, J = 7.6, 1.1 Hz). ^{13}C-NMR ($CDCl_3$): δ 10.6, 20.6, 23.6, 28.7, 41.3, 51.6, 56.0, 61.8, 63.6, 69.0, 74.9, 105.6, 114.8, 119.3, 123.4, 125.5, 129.7, 130.2, 147.9, 148.3, 156.0, 171.4. IR ν_{max}^{neat} cm^{-1}: 2930, 1733, 1568, 1335, 1060. Mass spectral MW: 388.1887. Found: 388.1886.

The next component (R_f 0.6) was assigned structure **19a** (58 mg, 45%). ^{1}H-NMR ($CDCl_3$): δ 1.10 (t, 3H, J = 7.0 Hz), 1.62 (t, 3H, J = 6.1 Hz), 1.89 (sextet, 2H, J = 7.0 Hz), 2.60 (br dd, 1H, J = 15.6, 10.8 Hz), 2.62 (dd, 1H, J = 15.6, 6.1 Hz), 2.73 (dd, 1H, J = 15.6, 7.2 Hz), 3.80 (ddd, 1H, J = 15.6, 2.3, 0.7 Hz), 3.72 (s, 3H), 3.74 (s, 3H), 3.98 (s, 3H), 3.84 (m, 2H), 5.14 (q, 1H, J = 6.1 Hz), 6.79 (dd, 1H, J = 7.6, 1.1 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.65 (dd, 1H, J = 7.6, 1.1 Hz). ^{13}C-NMR ($CDCl_3$): δ 10.6, 23.1, 23.6, 30.1, 41.1, 51.6, 56.1, 61.5, 70.0, 71.5, 75.4, 105.7, 114.8, 120.5, 125.2, 125.7, 130.0, 130.2, 147.9, 149.0, 156.1, 171.5. Mass spectral MW: 388.1898. Found: 388.1886.

The next component (R_f 0.45) was identified as **20** (10 mg, 9%). ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.2 Hz), 1.46 (d, 3H, J = 7.0 Hz), 1.92 (br sextet, 2H, J = 7.2 Hz), 1.99 (d, 3H, J = 1.0 Hz), 2.86 (s, 3H), 2.98 (s, 3H), 3.96 (t, 2H, J = 7.0 Hz), 5.76 (q, 1H, J = 7.0 Hz), 5.92 (d, 1H, J = 1.0 Hz), 6.78 (dd, 1H, J = 7.7, 1.4

Hz), 7.32 (dd, 1H, J = 8.8, 7.7 Hz), 7.64 (dd, 1H, J = 8.8, 1.4 Hz). Mass spectrum (70 eV, EI) *m/z* (rel. int.): 328 $[M]^+$ (88), 285 (100), 167 (23), 255 (21), 212 (21). Mass spectral MW: 328.1669. Calc: 328.1675.

The next component (R_f 0.50) was identified as **21** (5 mg, 4%). ^{1}H-NMR ($CDCl_3$): δ 1.12 (t, 3H, J = 7.0 Hz), 1.62 (d, 3H, J = 7.0 Hz), 1.92 (sextet, 2H), 3.23 (s, 3H), 3.80 (s, 3H), 4.00 (s, 3H), 3.87 (t, 2H, J = 7.0 Hz), 3.76–3.90 (m, 2H), 4.80–5.08 (m, 2H), 5.12 (q, 1H, J = 7.0 Hz), 5.8–6.3 (m, 1H), 6.84 (dd, 1H, J = 7.4, 1.1 Hz), 7.34 (t, 1H, J = 7.4 Hz), 7.66 (dd, 1H, J = 7.4, 1.1 Hz). IR ν_{max}^{neat} cm^{-1}: 2930, 1610, 565, 1257, 1060, 910, 735. Mass spectrum (70 eV, EI) *m/z* (rel. int.): 344 $[M]^+$ (100), 269 (67), 254 (31), 239 (11). Mass spectral MW: 344.1978. Calc: 344.1988.

Oxidation of **19a** *to give* **22a**. To a soln of **19a** (40 mg, 0.103 mmol) in 4 ml of acetonitrile at 25° was added dropwise over 5 min a soln of ceric ammonium nitrate (169 mg) in H_2O (1.5 ml). After being stirred for 5 min, the mixture was diluted with H_2O (5 ml) and extracted three times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give an orange oil. Chromatography (1.5 g silica gel, hexane–Et_2O, 1 : 1) gave 27 mg (79%) of **22a** as yellow crystals (hexane–Et_2O), m.p. 144.5–145°. Spectral data match the published data (no m.p. given).[5b] Anal. C, H.

Oxidation of **19b** *to give* **22b**. By the same procedure as that for the *trans*-**19a**, the *cis* isomer **19b** (61 mg) was converted into **22b** (39 mg, 75%). Spectral data match the published data.[5b]

Preparation of alkynols **25b**, **25d** *and* **25f**. These key substrates for cyclization (Table 1) were prepared from commercially available alcohols (**25a**, **25c**, **25d**) by conversion to the tetrahydropyranyl ethers using conventional procedures and methylation of the alkynyl lithium derivative.

General procedure for methylation of THP ethers of **25a**, **25c** *and* **25d**. The reaction was performed under Ar. The THP ether was dissolved in degassed THF (~1.5 ml/mmol THP ether) and was cooled to −78°. *n*-BuLi (1.1 equivalents) was added and the reaction was stirred for 30 min at −78°. The soln was removed from the cold bath for 5–15 min to ensure complete metallation and then returned to −78°. The alkylating agent (MeI, 1.1 equivalents) was added all at once using a syringe and the reaction allowed to warm to 25°. Upon consumption of starting material (as indicated by GLPC) the solvent was removed on a rotary evaporator and the residue was partitioned between Et_2O and H_2O. From the organic layer was obtained a yellow oil which was purified by distillation. Simple distillation provides a product of sufficient purity for the next stage.

General procedure for cleavage of the THP ether of **25b**, **25d** *and* **25f**. The THP ether was dissolved in MeOH. Enough 1 M hydrochloric acid was added to make a 2 : 1 (v/v) soln of MeOH–HCl. If necessary, a further small amount of MeOH was added to keep the THP ether in soln. The soln was stirred at 25° until starting material was consumed (generally 1–2 hr; monitored by GLPC). The MeOH was removed on a rotary evaporator and the aq residue was extracted with Et_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator. The residue was purified by fractional distillation.

Preparation of 3*-pentyn-*1*-ol* (**25b**). Following the general procedure, the THP ether of 3-pentyn-1-ol (1.54 g, 9.2 mmol) and 1 M HCl (13 ml) were combined with 20 ml of MeOH and stirred for 48 hr. The usual isolation procedure gave 401 mg (52%) of **25b** as a light yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 1.80 (t, 3H, J = 3 Hz, —Me), 2.20–2.70 (m, 3H, —$CH_2C\equiv$ and OH), 3.67 (t, 2H, J = 7 Hz, C$\underline{H}_2$OH).

Preparation of 4*-hexyn-*1*-ol* (**25d**). Following the general procedure, the THP ether of 4-hexyn-1-ol (3.73 g, 21 mmol) and 3 M HCl (25 ml) were combined in MeOH (50 ml). After 17 hr, the usual isolation procedure and fractional distillation gave 926 mg (48%) of **25d** as a clear, colourless oil. ^{1}H-NMR ($CDCl_3$): δ 1.55–1.93 (t and m, 5H, —Me and —$CH_2C\underline{H}_2CH_2$—), 2.07 (s, 1H, OH), 2.25 (m, 2H, —$CH_2C\equiv$), 3.70 (t, 2H, J = 5 Hz, —C$\underline{H}_2$OH). IR ν_{max}^{neat} cm^{-1}: 3350 (vs, —OH), 2930 (vs), 1440 (s), 1060 (s).

Preparation of 5*-heptyn-*1*-ol* (**25f**). Following the general procedure, the THP ether of 5-heptyn-1-ol (350 mg, 1.79 mmol) and 1 M HCl (2.5 ml) were combined in MeOH (7 ml). After 1.25 hr, the usual isolation procedure gave 135 mg (67%) of 5-heptyn-1-ol (**25f**) as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 1.50–1.95 (m, 7H, —Me and —CH_2CH_2—), 2.15 (m, 2H, —$CH_2C\equiv$), 3.65 (m, 2H, —C$\underline{H}_2$OH). IR ν_{max}^{neat} cm^{-1}: 3350 (vs, —OH), 2940 (vs), 1440 (s), 1060 (s).

General procedure for intramolecular cyclization. Preparation of the carbene complexes, **26**. The salt **23b** (1.0 mol equivalent) was dissolved in CH_2Cl_2 (20 ml/mmol of **23b**) under Ar. The flask was covered with aluminium foil, cooled to −20° and from an addition funnel was added a soln of acetyl chloride (1.1 mol equivalent) in CH_2Cl_2 (7 ml/mmol of **23b**) dropwise over 5 min to give a deep red soln. After addition, the mixture was warmed to −10° and stirred for 45 min. The alkynol (**25**, 1.0 mol equivalent) was added as a soln in CH_2Cl_2 (1 ml/mmol) and the soln was stirred at 23° until the alkynol was consumed (1–6 hr; monitored by analytical TLC). The mixture was concentrated at aspirator pressure and the residue was washed with several small portions of pentane to dissolve carbene complex **26** (all operations under Ar). The collected pentane solns were concentrated to leave the carbene complex (**26**) as a red oil or solid. This material was used directly in the next operation. It was generally of high purity; representative spectral data are given below.

Complex **26b**. Complex **23b** (414 mg, 1.12 mmol), acetyl chloride (97 mg, 1.23 mmol) and 3-pentyn-1-ol (94 mg, 1.12 mmol) were combined following the general procedure. Complex **26b** was obtained as a deep red oil (293 mg, 72%). ^{1}H-NMR (d_6-C_6H_6): δ 1.43 (t, 3H, J = 3 Hz, $\equiv$C—Me), 2.1–2.4 (m, 2H, —$CH_2C\equiv$), 4.22 (t, 2H, J = 7 Hz, —OCH_2—), 6.90 (m, 5H, aryl-H). IR $\nu_{max}^{d_6\text{-}C_6H_6}$ cm^{-1}: 2050 (s, —C$\equiv$O), 1930 (vs, —C$\equiv$O), 1225 (m), 755 (m), 650 (s).

Complex **26d**. Complex **23b** (410 mg, 1.11 mmol), acetyl chloride (96 mg, 1.22 mmol) and 4-hexyn-1-ol (109 mg, 1.11 mmol) were combined following the general procedure. Complex **26d** was obtained as a deep red oil (339 mg, 81%). ^{1}H-NMR (d_6-Me_2CO): δ 1.68 (t, 3H, J = 3 Hz, $\equiv$C$\underline{Me}$), 2.15–2.55 (m, 4H, —CH_2CH_2—), 4.85 (t, 2H, J = 6 Hz, —OCH_2), 7.10–7.55 (m, 5H, aryl-H). IR $\nu_{max}^{d_6\text{-}Me_2CO}$ cm^{-1}: 2060 (s, —C$\equiv$O), 1940 (vs, —C$\equiv$O), 1440 (m), 1155 (m), 660 (s).

Complex **23b** (408 mg, 1.1 mmol), acetyl chloride (96 mg, 1.21 mmol) and 5-heptyn-1-ol (123 mg, 1.1 mmol), were combined following the general procedure. Complex **26f** was obtained as a deep red oil (327 mg, 76%). ^{1}H-NMR (d_6-Me_2CO): δ 1.7 (t, 3H, J = 2 Hz, $\equiv$C$\underline{Me}$), 205 (m, 6H, —$CH_2CH_2CH_2$—), 4.80 (t, 2H, J = 6 Hz, —$OC\underline{H}_2$—), 7.05–7.65 (m, 5H, aryl-H). Note: integration at δ 2.05 is complicated by d_6-Me_2CO absorption. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2070 (s, —C$\equiv$O), 1985 (s, —C$\equiv$O), 1940 (vs, —C$\equiv$O), 1215 (m), 660 (s).

Cyclization of model compounds **26**. The carbene complex was dissolved in Et_2O (~30 ml/mmol of **26**) under Ar. The soln was heated at 35° until the starting complex **26** was consumed (monitored by analytical TLC). The solvent was removed on an aspirator. The resulting chromium–arene complex **27** can be isolated as a bright orange powder by dissolving the residue in hexane–Et_2O (1 : 1) and filtering the soln through a short 1.5 × 1.0 in) silica gel column (under Ar), eluting with hexane–Et_2O (1 : 1). The products are sensitive to air and donor ligands (Me_2CO solvent), and were not obtained in analytical purity.

Ligand removal: isolation of the naphthol acetates, **28**. Crude **27** was dissolved in degassed Me_2CO (20 ml). Triphenylphosphine (2 mol equivalent), Ac_2O (1 ml/mmol carbene complex **27**) and Et_3N (0.5 ml/mmol carbene complex **27**) were added and the soln was stirred at 25° until starting material was consumed (12–24 hr). The solvent was removed on an aspirator and the residue was purified by medium pressure liquid chromatography to give **28** as a colourless solid. Analytically pure samples were obtained by dissolving the acetate in a minimum amount of Et_2O, adding a large excess of pentane and cooling to −15° until crystallization was complete.

Preparation of **28a**. Acylate salt **23b** (407 mg, 1.1 mmol), acetyl chloride (95 mg, 0.12 mmol, 0.86 ml) and 3-butyn-1-ol (77 mg, 1.1 mmol, 0.083 ml, ρ = 0.929) were combined as usual

in CH_2Cl_2 (20 ml). Carbene complex **26a** was obtained as an orange–red powder. The powder was immediately dissolved in Et_2O (30 ml) and stirred for 26 hr at 35°. The crude material was dissolved in Me_2CO (10 ml) and treated as described with triphenylphosphine (700 mg, 2.7 mmol), Ac_2O (1 ml), and Et_3N (0.5 ml), for 16 hr followed by medium pressure liquid chromatography (hexane to elute excess triphenylphosphine, then hexane–Et_2O, 10:1) gave 31 mg (16%) of **28a** as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 2.43 (s, 3H, —COMe), 3.37 (t, 2H, J = 7 Hz, $ArCH_2$—), 4.76 (t, 2H, J = 7 Hz, —OCH_2O—), 7.12 (s, 1H), 7.46 (m, 2H), 7.75 (m, 1H), 7.88 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 20.9, 30.7, 71.9, 115.4, 119.1, 120.7, 121.4, 121.8, 125.8, 126.1, 126.4, 138.0, 153.4, 170.0. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3065 (w), 1760 (s, C=O), 1365 (s), 1205 (s), 1060 (s), 905 (m). Mass spectral MW: 228. Anal: C, H.

Preparation of **28c**. Acylate salt **23b** (413 mg, 1.11 mmol), acetyl chloride (97 mg, 1.22 mmol, 0.088 ml) and 4-pentyn-1-ol (93 mg, 1.11 mmol, 0.098 ml, ρ = 0.940) were combined. Carbene complex **26c** was obtained as a deep red oil (337 mg, 83%) and was dissolved in Et_2O (30 ml). The reaction was complete after 44 hr at 35°. The crude product was dissolved in Me_2O (10 ml) and treated with triphenylphosphine (700 mg, 2.7 mmol), Ac_2O (1 ml) and Et_3N (0.5 ml). After 8 hr, medium pressure liquid chromatography (hexane to elute excess triphenylphosphine, then hexane–Et_2O, 10:1) gave 44 mg (18%) of **28c** as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 2.08 (m, 2H, $CH_2\underline{CH_2}CH_2$), 2.38 (s, 3H, COMe), 2.81 (t, 2H, J = 7 Hz, $ArCH_2$), 4.22 (m, 2H, —OCH_2—), 6.78 (s, 1H), 7.01–7.69 (m, 3H), 8.02 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 20.9, 22.3, 24.9, 66.7, 115.1, 119.6, 120.8, 121.8, 125.6, 126.1, 139.2, 143.0, 169.9. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3080 (w), 1765 (s, C=O), 1365 (s), 1200 (s), 910 (s). Mass spectral MW: 242. Anal: C, H.

Preparation of **28e**. Acylate salt **23b** (406 mg, 1.09 mmol), acetyl chloride (95 mg, 1.2 mmol, 0.086 ml) and 5-hexyn-1-ol (107 mg, 1.09 mmol, 0.113 ml) were combined as usual in CH_2Cl_2 (20 ml). Carbene complex **26e** was obtained as a deep red oil (342 mg, 83%). The carbene complex was heated in Et_2O at 35° for 20 hr. The crude product was dissolved in Me_2CO (10 ml) and treated with triphenylphosphine (700 mg, 2.7 mmol), Ac_2O (1 ml) and Et_3N (0.5 ml). The acetate **28e** was isolated by medium pressure liquid chromatography (hexane to elute excess triphenylphosphine, then hexane–Et_2O, 10:1) as a white solid (99 mg, 38%, m.p. 89.0–90.5°). ^{1}H-NMR ($CDCl_3$): δ 1.90 (m, 4H, —CH_2CH_2—), 2.35 (s, 3H, COMe), 2.86 (m, 2H, $ArCH_2$), 4.06 (m, 2H, —OCH_2—), 6.90 (s, 1H), 7.26–7.75 (m, 3H), 8.10 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 20.9, 25.6, 32.3, 34.3, 73.3, 120.8, 122.5, 125.9, 126.9, 126.1, 128.6, 129.7, 141.4, 153.3, 170.0. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3065 (w), 1770 (s, C=O), 1370 (s), 1200 (s), 1055 (s), 915 (s). Mass spectral MW: 256. Anal: C, H.

Preparation of **28b**. Acylate salt **23b** (409 mg, 1.1 mmol), acetyl chloride (96 mg, 1.21 mmol, 0.087 ml) and 3-pentyn-1-ol (92 mg, 1.1 mmol) were combined as described in CH_2Cl_2 (20 ml). Carbene complex **26b** was obtained as a deep red oil (343 mg, 85%). The crude product was dissolved in Me_2CO (10 ml) and treated with triphenylphosphine (750 mg, 2.9 mmol), Ac_2O (1.5 ml) and Et_3N (0.5 ml). Acetate **28b** was isolated by medium pressure liquid chromatography (hexane to elute excess triphenylphosphine, then hexane–Et_2O, 10:1) as a colourless solid (184 mg, 81%, m.p. 117.5–118.5°). ^{1}H-NMR ($CDCl_3$): δ 2.10 (s, 3H, ArMe), 2.34 (s, 3H, —COMe), 3.08 (t, 2H, J = 9 Hz, $ArCH_2$—), 4.50 (t, 2H, J = 9 Hz, —OCH_2—), 7.01–7.89 (m, 4H). ^{13}C-NMR ($CDCl_3$): δ 13.6, 20.3, 29.7, 71.6, 119.0, 120.0, 120.9, 121.5, 123.9, 124.6, 126.0, 126.6, 137.5, 152.6, 169.4. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3070 (w), 1760 (s, C=O), 1400 (s), 1210 (s), 1175 (s). Mass spectral MW: 242. Anal: C, H.

Preparation of **28d**. Acylate salt **23b** (413 mg, 1.11 mmol), acetyl chloride (97 mg, 1.22 mmol, 0.088 ml) and 4-hexyn-1-ol (109 mg, 1.11 mmol) were combined as described in CH_2Cl_2 (20 ml). Carbene complex **26d** was obtained as a red oil (368 mg, 87%). It was heated in Et_2O (30 ml) for 44 hr at 35°. The crude product was dissolved in Me_2CO (10 ml) and treated with triphenylphosphine (750 mg, 2.9 mmol), Ac_2O (1 ml) and Et_3N (0.5 ml). The acetate (**26d**) was isolated by medium pressure liquid chromatography (hexane to elute excess triphenylphosphine, then hexane–Et_2O, 10:1) as a colourless solid (153 mg, 62%, m.p. 117.5–119.5°). ^{1}H-NMR ($CDCl_3$): δ 2.02 (m, 2H, —$CH_2\underline{CH_2}$—), 2.10 (s, 3H, ArMe), 2.40 (m, 3H, —COMe), 2.64 (t, 2H, J = 6 Hz, $ArCH_2$), 4.18 (dd, 2H, —OCH_2—), 7.17–7.65 (m, 3H), 8.02 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 14.1, 22.0, 23.8, 29.3, 72.2, 105.3, 114.2, 118.9, 120.2, 122.8, 123.1, 123.3, 135.3, 145.9, 166.6. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3070 (w), 1760 (s, C=O), 1360 (s), 1210 (s), 1180 (s). Mass spectral MW: 256.1076. Calc: 256.1099.

Preparation of **28f**. Acylate salt **23b** (1.650 g, 4.45 mmol), acetyl chloride (385 mg, 4.9 mmol, 0.35 ml) and 5-hexyn-1-ol (498 mg, 4.45 mmol, 0.500 ml) were combined as usual in CH_2Cl_2 (100 ml). Carbene complex **26f** was obtained as a deep red oil (1.53 g, 83%). It was heated in Et_2O (125 ml) at 35° for 46 hr. The solvent was removed on an aspirator and the residue was washed once with hexane. Removal of residual solvent on a vacuum line gave 1.04 g (73%) of crude arene complex **27f** as an orange–yellow powder. A sample of **27f** (235 mg, 0.65 mmol) was dissolved in Me_2CO (5 ml) and treated for 4.5 hr at 25° with triphenylphosphine (500 mg, 1.94 mmol), Ac_2O (1 ml) and Et_3N (0.3 ml). Acetate **28f** was isolated by medium pressure liquid chromatography as a colourless solid (148 mg, 62% overall, m.p. 109.5–110.5°). ^{1}H-NMR ($CDCl_3$): δ 1.83 (m, 4H, —CH_2CH_2—), 2.20 (s, 3H, ArMe), 2.39 (m, 3H, —COMe), 2.91 (m, 2H, $ArCH_2$—), 4.04 (dd, 2H, —OCH_2—), 7.19–7.66 (m, 3H), 7.99 (m, 1H). ^{13}C-NMR ($CDCl_3$): δ 13.6, 20.5, 24.5, 28.2, 32.0, 73.0, 120.6, 122.1, 125.3, 126.1, 126.8, 130.5, 140.2, 153.7, 169.2. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3075 (w), 1765 (s, C=O), 1360 (s), 1200 (s), 1175 (s), 1060 (s). Mass spectral MW: 270. Anal: C, H.

Preparation of 1-*nonen*-4-*yn*-5-*ol* (**29**). The tetrahydropyranyl ether of 1-hexyn-3-ol was prepared by the general procedure (see above). A sample (364 mg, 2 mmol) was dissolved in THF (10 ml) and cooled to −78°. *n*-BuLi (1.0 ml of a 2.3 M soln in hexane) was added over 5 min. The soln was stirred at −78° for 10 min, removed from the cold bath for 10 min and then returned to −78°. Solid anhyd CuI_2 (Alfa, 382 mg, 2 mmol) was added all at once. The flask was removed from the cold bath and stirred at 23° for 30 min. Allyl bromide (266 mg, 2.2 mmol, 0.190 ml, ρ = 1.398) was added all at once and the mixture was stirred for 14 hr at 23°. Saturated aq NH_4Cl (5 ml) was added to quench the reaction. The THF was removed on a rotary evaporator and the aq residue was extracted with Et_2O. The organic phase was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator to give 484 mg of the tetrahydropyranyl ether of 1-nonen-4-yn-5-ol as a light yellow oil which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 1.92 (m, 3H, —Me), 1.62 (m, 10H), 2.95 (m, 2H, —$CH_2C{\equiv}C$), 3.36–3.95 (m, 2H, —OCH_2—), 4.37 (m, 1H, —OCHC≡), 4.81–5.93 (m, ABC pattern, 4H, allyl and —OCHO—). IR ν_{max}^{neat} cm^{-1}: 2950 (vs), 1645 (m, —C≡C—), 1200 (m), 1110 (s), 1020 (vs), 870 (m), 820 (m). Following the general procedure for hydrolysing tetrahydropyranyl ethers, the THP ether of 1-nonen-4-yn-5-ol (904 mg, 4.13 mmol) and 1 M HCl (6 ml) were combined in MeOH (12 ml). After 1 hr, the usual isolation procedures gave 549 mg (96%) of 1-nonen-4-yn-5-ol (**29**) as a colourless liquid. NMR ($CDCl_3$): δ 0.96 (m, 3H, —Me), 1.2–1.8 (m, 4H, —CH_2CH_2—), 1.95 (s, 1H, —OH), 3.0 (m, 2H, —$CH_2C{\equiv}C$), 4.36 (m, 1H, —CHC≡), 4.9–6.1 (m, ABC pattern, 3H, allyl). IR ν_{max}^{neat} cm^{-1}: 3350 (s, —OH), 2960 (s), 2140 (w, —C≡C—), 1640 (m, olefin), 1415 (m), 1020 (s), 920 (s).

Preparation of 6-(*ethoxycarbonylmethoxy*)*dec*-1-*en*-4-*yne* (**30**). NaI (4.68 g, 0.031 mol) was dissolved in Me_2CO (25 ml). Ethyl bromoacetate (4.17 g, 0.025 mol, 2.77 ml, ρ = 1.506) was added all at once and the mixture was heated under reflux for 1 hr. The Me_2CO was removed on a rotary evaporator. The crude reaction mixture was washed with Et_2O several times and filtered to separate the ethyl iodoacetate from NaBr. The Et_2O was removed on a rotary evaporator and the residue was dissolved in THF (35 ml). Non-1-en-4-yn-5-ol (**29**) (2.87 g, 0.021 mol) was added in one portion; the system was evacuated and filled with Ar. NaH (1.5 g of a 50% dispersion in mineral oil, 0.031 mmol) was added under a slow flow of Ar in small portions. After the suspension had been stirred for 48 hr at 23°, the solvent was removed on a rotary evaporator. The

residue was dissolved in Et_2O and washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator. Column chromatography (silica gel, 1 × 18 in column, hexane–Et_2O, 5:1) gave 2.29 g (49%) of **30** as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 0.95 (br t, 3H, —Me), 1.25 (t, 3H, J = 7 Hz, —$COOCH_2Me$), 1.66 (m, 4H, —CH_2CH_2—), 2.96 (m, 2H, —$CH_2C{\equiv}C$), 4.12 (q and s, 4H, —$COOCH_2Me$ and —OCH_2—), 4.85–6.05 (m, 4H, ABC pattern, allyl and —$OCHC{\equiv}$). IR ν_{max}^{neat} cm^{-1}: 2960 (vs), 2240 (w, —C≡C—), 1740 (vs), 1640 (m, —C=C—), 1260 (vs), 1200 (vs), 1120 (vs), 920 (s). Mass spectral MW: 196.

Preparation of 6-(2-*hydroxyethoxy*)*dec*-1-*en*-4-*yne* (**31**). Lithium aluminum hydride (777 mg, 20.45 mmol) was placed in a three-necked round bottomed flask equipped with a stopcock, dropping funnel and stirring bar. Et_2O (50 ml) was added and the system was placed under Ar. Compound **30** was dissolved in Et_2O (10 ml) and the soln was transferred via syringe to the dropping funnel and then added dropwise to the reaction mixture over 20 min. The mixture was stirred for 2 hr and then carefully quenched by addition of EtOAc (15 ml) and then H_2O (15 ml). The resulting white emulsion was thoroughly washed with Et_2O. The organic phase was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator to give 1.56 g (84%) of alcohol **31** as a colourless oil. NMR ($CDCl_3$): δ 0.95 (br t, 3H, —Me), 1.62 (m, 4H, —CH_2CH_2—), 2.35 (br s, 1H, —OH), 3.0 (m, 2H, —$CH_2C{\equiv}C$—), 3.40–4.20 (m, 5H, —OCH_2CH_2O— and —$OCHC{\equiv}$), 4.89–6.12 (m, 3H, ABC pattern, allyl). IR ν_{max}^{neat} cm^{-1}: 3400 (vs, —OH), 2940 (vs), 2220 (w, —C≡C—), 1640 (m, —C=C—), 1330 (s), 1105 (vs), 1050 (vs), 920 (vs), 740 (s). Mass spectral MW: 182.

Formation and cyclization of carbene complex **34**. *Preparation of* **37**. Exactly as above for **26**, the salt **32** (1.000 g, 2.49 mmol), acetyl chloride (216 mg, 2.74 mmol) and alcohol **31** (563 mg, 2.49 mmol) were combined in CH_2Cl_2 (30 ml). The standard isolation procedure gave 806 mg (66%) of carbene **34** as a red oil. The crude carbene complex was dissolved in Et_2O (50 ml) and the mixture was heated under reflux for 64 hr. The solvent was removed on an aspirator and the crude product was dissolved in 20 ml degassed acetonitrile–H_2O (10:1). DDQ (335 mg, 1.5 mmol) was added as a solid to the reaction mixture in small portions under a slow flow of Ar. The reaction is 'self-indicating' as excess DDQ is evidenced by the appearance of an intense brick red colour in the mixture. After addition was complete, the acetonitrile was removed on an aspirator and the residue was taken up in Et_2O and washed with sat aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and the solvent removed on the rotary evaporator. Medium pressure liquid chromatography (gradient elution with hexane and Et_2O) gave 273 mg (50%) of **37** as a yellow oil. ^{1}H-NMR ($CDCl_3$): δ 0.85 (br t, 3H, —Me), 1.49 (m, 4H, —CH_2CH_2—), 3.35–3.80 (m, 6H, —$CH_2C{\equiv}C$— and —OCH_2CH_2O—), 3.90 (s, 3H, —OMe), 4.82–5.09 (m, 3H, allyl and ArCHO—), 5.6–6.0 (m, 1H, allyl), 7.13–7.65 (m, 3H, aromatic). ^{13}C-NMR ($CDCl_3$): δ 13.5 (q), 19.4 (t), 29.7 (t), 37.3 (t), 56.0 (q), 61.3 (t), 71.2 (t), 75.9 (d), 116.2, 117.3, 118.6, 133.9, 134.3, 134.9, 143.7 (s), 147.2 (s), 159.0 (s), 184.1 (s), 184.8 (s). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3510 (s, —OH), 2970 (vs), 1650 (vs), 1630 (s, —C=C—), 1590 (vs), 1270 (vs), 1110 (vs), 1060 (vs), 920 (s). Mass spectral MW: 344.1620. Calc for $C_{20}H_{23}O_5$: 344.1623.

Preparation of ketohydronaphthoquinone (**40**). Quinone **37** (273 mg, 0.79 mmol) was dissolved in MeOH (10 ml) under Ar. Aqueous H_2SO_4 (10 ml of 1.25 M) was added and the reaction was stirred at 23° for 6 days. The solvent was removed on a rotary evaporator. The aq residue was extracted with Et_2O, the organic soln was dried ($MgSO_4$), filtered and the solvent removed on a rotary evaporator. The residue was purified by filtration through a 50:50 mixture of Celite and silica gel under Ar, eluting with hexane–Et_2O, to give **40** as an air-sensitive red–brown oil. ^{1}H-NMR ($CDCl_3$): δ 0.99 (t, 3H, J = 6 Hz, —Me), 1.48–1.81 (m, 2H, —CH_2CH_2Me), 2.82 (t, 2H, J = 6 Hz), 2.33 (dt, 2H, J = 5.0, 1.0 Hz, —$CH_2C{=}C$—), 3.96 (s, 3H, —OMe), 4.95–5.25 (m, 2H, allyl C=CH_2), 5.72–6.15 (m, 1H, allyl), 6.72 (dd, J = 6.0, 1.0 Hz, aromatic), 7.30 (t, 1H, J = 7 Hz, aromatic), 7.70 (dd, 1H, J = 6.0, 1.0 Hz, aromatic). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (m, —OH), 2960 (m), 2930 (m), 1690 (m), 1450 (m), 1400 (s), 1260 (s), 1060 (s). Mass spectral MW: 300.1365. Calc for $C_{18}H_{20}O_4$: 300.1361.

Preparation of 2,4 - *dihydroxy* - 3 - (1 - *hydroxybutyl*) - 5 - *methoxy*-2-(*pro*-2-*en*-1-*yl*)*naphthalene* (**41**). To a soln of **40** (376 mg, 1.25 mmol) in THF (10 ml) under Ar was added solid $NaBH_4$ (110 mg, 2.9 mmol) at 23°. The mixture was allowed to stir for 15 hr, then diluted with 1.0 ml of H_2O and carefully sat with K_2CO_3. The mixture was partitioned between 10 ml of degassed brine and 30 ml of degassed Et_2O–CH_2Cl_2 (2:1). The aq layer was further extracted with one 10 ml portion of Et_2O–CH_2Cl_2 (2:1). The combined organic solns were washed with degassed brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude triol **41** was obtained as an amber oil (369 mg, 98%). ^{1}H-NMR ($CDCl_3$): δ 9.5 (s, 2H), 7.7 (br d, 1H, J = 8.0 Hz), 7.25 (br t, 1H, J = 8.0 Hz), 6.73 (br d, 1H, J = 8.0 Hz), 6.2–5.7 (br m, 1H), 5.3–4.8 (m, 3H), 4.03 (s, 3H), 4.2–3.8 (m, 2H), 3.54 (br d, 1H, J = 7.0 Hz), 2.30–0.8 (m, 7H). IR ν_{max}^{neat} cm^{-1}: 3350 (br s), 3080 (w), 2970 (s), 2870 (m), 1630 (w), 1610 (m), 1580 (m), 1450 (s), 1380 (vs), 1250 (vs).

Preparation of 3-(-1-*hydroxybutyl*)-2-(*prop*-2-*enyl*)-5-*methoxy*-1,4-*naphthoquinone* (**42**). The crude **41** (312 mg, 1.03 mmol) was stirred in a mixture of DDQ (224 mg, 0.99 mmol), $KHCO_3$ (117 mg, 1.17 mmol) in 10 ml of MeOH under Ar at 0° for 1.0 hr. Dilution with CH_2Cl_2 and filtration through alumina gave crude **42** as an orange oil (242 mg). Flash chromatography on silica gel (15 g; elution with Et_2O–pet. ether, 4:1) gave pure **42** as an orange oil (134 mg, 45%) from **40**. ^{1}H-NMR ($CDCl_3$): δ 7.8–7.5 (m, 2H), 7.25 (dd, 1H, J = 8.0, 2.5 Hz), 6.1–5.6 (m, 1H), 5.3–5.0 (m, 2H), 4.9–4.6 (m, 1H), 4.00 (s, 3H), 3.72 (d, 1H, J = 11 Hz), 3.38 (br d, 2H, J = 3.5 Hz), 2.2–1.3 (m, 4H), 0.95 (t, 3H, J = 6.0 Hz). IR ν_{max}^{neat} cm^{-1}: 3500 (br s), 3800 (w), 2960 (s), 2880 (m), 2840 (m), 1650 (d vs), 1620 (s), 1590 (vs), 1470 (vs), 1450 (vs), 1280 (vs). Mass spectrum *m/z* (rel. int.): 300 $[M]^+$ (58), 282 (30), 271 (28), 257 (100), 239 (33), 229 (19), 214 (12).

Preparation of pyrano ester **45**. The hydroxynaphthoquinone **42** (174 mg, 0.58 mmol) was stirred with a mixture of bis(acetonitrile)Pd dichloride (14 mg, 0.058 mmol), anhyd $CuCl_2$ (171 mg, 1.27 mmol) and MeOH (3 ml) under CO (1.0 atm) for 3.3 hr and gave essentially one component by analytical TLC (Et_2O on silica gel, R_f 0.35). The mixture was concentrated at oil pump pressure, triturated with C_6H_6 (5 ml) and purified by flash chromatography on silica gel (5 g). Elution with Et_2O–pet. ether (7:2) gave as the main component an orange viscous oil (144 mg, 70%). Analysis by HPLC (Poracil column, hexane–EtOAc, 8:1, 5 ml/min; R_v *trans* 8.85 ml, R_v *cis* 10.3 ml), indicated a mixture of isomers in the ratio 75:25 later identified as a *trans–cis* mixture **43a** and **43b**. The chromatographed material was crystallized from 3 ml of warm hexane–EtOAc (3:1) to provide pure **43a** as dark orange needles, m.p. 128–133°. Recrystallization gave the analytical sample, m.p. 134–136°. ^{1}H-NMR ($CDCl_3$): δ 7.7–7.4 (m, 2H), 7.13 (dd, 1H, J = 7.5, 2.5 Hz), 4.80 (br t, 1H, J = 5.0 Hz), 4.4–4.1 (m, 1H), 3.97 (s, 3H), 3.70 (s, 3H), 2.85–2.58 (m, 3H), 2.22 (ddd, 1H, J = 17.0, 10.0, 1.0 Hz), 1.9–1.2 (m, 4H), 0.95 (t, 3H, J = 6.5 Hz). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3030 (m), 2960 (m), 2880 (m), 2840 (m), 1735 (s), 1660 (vs), 1590 (s), 1470 (m), 1440 (s), 1280 (vs). Anal: C, H. The *cis* isomer **43b** has been characterized previously.[11]

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