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6-*Endo*- and 5-*Exo*-digonal Cyclizations of *o*-Hydroxyphenyl Ethynyl Ketones: A Key Step for Highly Selective Benzopyranone Formation

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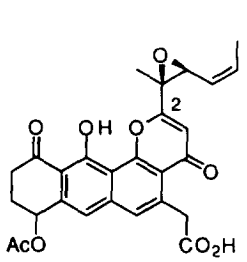
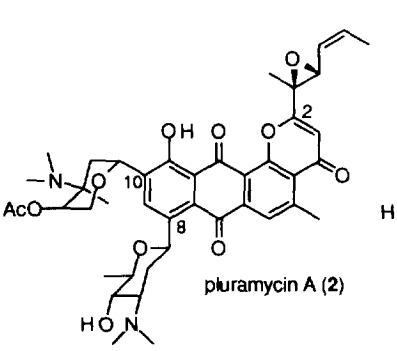
Abstract: The cyclization of *o*-hydroxyphenyl ethynyl ketones was examined from theoretical and experimental standpoints in order to develop efficient synthetic methods for the construction of 2-substituted pyranones possessing significant biological activities. *Ab initio* studies at HF/6-31G* level on the cyclization indicated that both 6-*endo-digonal* and 5-*exo-digonal* cyclizations giving benzopyranones and benzofuranones, respectively, were endothermic and reversible in aprotic media, and the irreversible protonation of the resulting anions would be critical for the products formation. We generated phenoxide ion under aprotic conditions *in situ* by desilylation of *o*-silyloxyphenyl ethynyl ketones with spray dried potassium fluoride and 18-crown-6 in anhydrous DMF. Under these conditions the cyclization of variety *o*-hydroxyphenyl ethynyl ketones proceeded smoothly to produce benzopyranone derivatives with exceedingly high selectivity. Theoretical and experimental results strongly suggested that the presence of a small amount of proton donor effecting the protonation of the resulting benzopyranone anion was essential for the high 6-*endo-digonal* selectivity.

INTRODUCTION

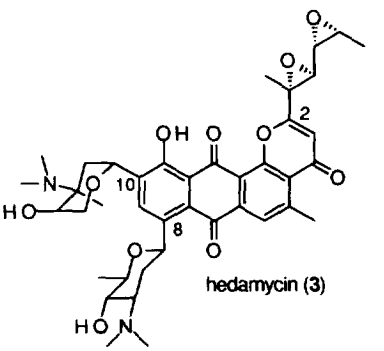
Kapurimycin A_3 (**1**) is an antitumor antibiotic possessing a novel anthra-γ-pyrone ring system with a vinyl epoxide side chain at the C2 position.[1] The structure of **1** is closely resembled to those of pluramycin family antibiotics,[2] which have a common 4*H*-anthra[1,2-*b*]pyrane ring system and characteristic functionalities attached to the C2 position as well as deoxyamino sugars at C8 and C10 positions. Pluramycin A (**2**),[3] hedamycin (**3**)[4] and **1** all having epoxide functionalities on the side chain attached to the C2 position are known to covalently bound to DNA by a nucleophilic ring opening of the epoxide with guanine N7 in DNA.[5-8]



Kapurimycin A_3 (**1**)

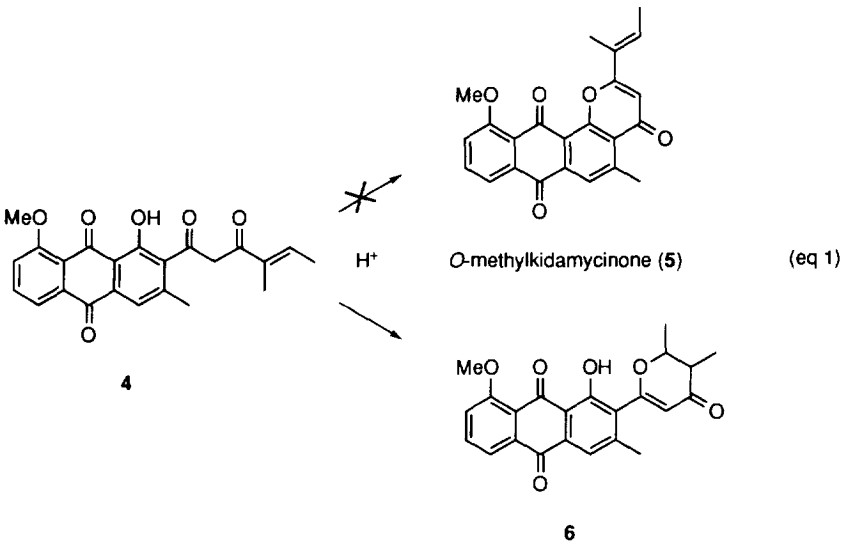


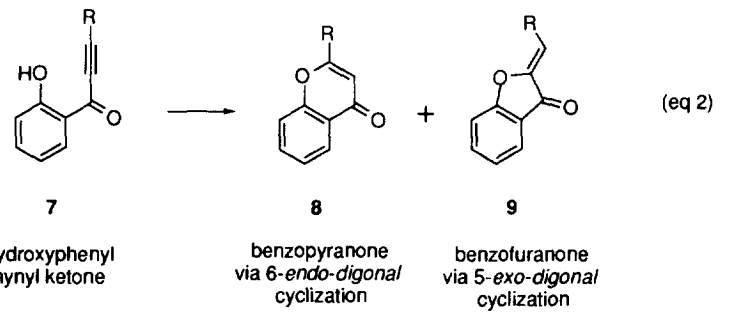
pluramycin A (**2**)



hedamycin (**3**)

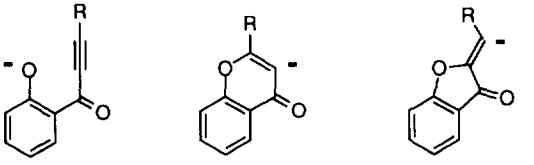
In spite of the significant biological features and unique reactivity toward DNA, the structure–activity relationships on these antibiotics was not examined primarily due to the difficulty in the synthesis of 2-substituted benzopyranone ring system.[9,10] For example, this problem has been addressed by the synthesis of *O*-methylkidamycinone (**5**) (eq 1),[9] showing that conventional synthetic scheme for benzopyranone systems using acid-catalyzed cyclization of 1-(*o*-hydroxyphenyl)-1,3-diketones[11,12] (*e.g.*, **4**) is not applicable to the synthesis of these antibiotics because of the competitive formation of undesired dihydropyranone (*e.g.*, **6**).





To investigate structure–activity relationship of these antibiotics we focused our attention on developing efficient synthetic methods for 2-substituted benzopyranone ring systems from readily available precursors. As a candidate for such a process, the 6-*endo-digonal* cyclization of *o*-hydroxyphenyl ethynyl ketones was first examined (eq 2), because the starting phenyl ethynyl ketones could be readily synthesized from salicylic aldehyde and acetylenic compounds. According to the Baldwin's rule[13] the 6-*endo-digonal* cyclization is a favorable process, although the cyclization of *o*-hydroxyphenyl ethynyl ketones **7** under basic conditions are reported to produce not only benzopyranone **8** via the 6-*endo-digonal* cyclization but also benzofuranone **9** by a simultaneous 5-*exo-digonal* cyclization, with the product ratio being highly dependent on the reaction

conditions.[14–16] To get insight into the factors governing the 6-*endo-digonal* and the 5-*exo-digonal* cyclization of *o*-hydroxyphenyl ethynyl ketones, we have investigated this reaction from theoretical and experimental viewpoints. We herein describe experimental results in combination with theoretical calculations indicating that both 6-*endo-digonal* and 5-*exo-digonal* cyclizations of *o*-hydroxyphenyl ethynyl ketones are reversible in aprotic media, and that the irreversible protonation of the resulting vinyl anion gives rise to the benzopyranone formation with exceedingly high selectivity.[17]



10 **11** **12**

(For calculation studies R denotes Me)

RESULTS AND DISCUSSION

Theoretical Calculations for 6-Endo-digonal and 5-Exo-digonal Cyclizations.

To discuss the cyclization of *o*-hydroxyphenyl ethynyl ketone in detail, *ab initio* molecular orbital calculations of phenoxide ion **10**, vinyl anions **11** and **12** (where R denotes Me), and two transition states ***TS–6*** and ***TS–5*** for the 6-*endo-digonal* and 5-*exo-digonal* cyclizations, respectively, were carried out.[18,19] While in our preliminary communication[17] we reported the theoretical calculations at the HF/3-21G(*) level, more accurate calculations at higher HF/6-31G* level were performed at this time for precise discussions. For these calculations the initial structures for **10**, **11**, and **12** were surveyed at the semiempirical PM3 level. Two stable *s-trans* and *s-cis* conformers were found for **10**, with the former being more stable than the latter by 1.80 kcal/mol. Therefore, the *s-trans* conformer of **10** shown in Figure 1 was used for further calculations.[20] While the reaction of nucleophiles to the carbon–carbon triple bond may proceed via either *syn* or *anti* addition,[19d,21] the *E*–configuration for the exocyclic alkene in **12** supported by previous theoretical studies[19b,c] was used for the calculation. We could not develop a reasonable transition state model for the *syn* addition of the phenoxide ion in **10** to the carbon–carbon triple bond via the 5-*exo-digonal* cyclization. These structures obtained by the PM3 calculations were optimized at the HF/3-21G(*) and then at the HF/6-31G* level. Two transition states ***TS–6*** and ***TS–5*** were initially generated empirically using the transition structure module incorporated in Spartan[18] and finally calculated at the HF/6-31G* level. Frequency analyses for ***TS–6*** and ***TS–5*** showed the only one imaginary vibrational frequency at 524.62*i* and 525.25*i* cm^{-1}, respectively (Figure 1) (For selected structural parameters, see experimental section).[22] In both structures the approaching angle of the phenoxide ion to the carbon–carbon triple bond was 115.4° and 118.9°, respectively. The potential energy diagram for the reaction of **10** to **11** and **12** was shown in Figure 2. The potential energies of two transition states ***TS–6*** and ***TS–5*** were very close in each other, therefore there was no obvious difference in the activation energies for the two cyclization processes (23.60 kcal/mol for $\Delta G^{\ddagger}_{10\rightarrow 11}$ and 24.22 kcal/mol for $\Delta G^{\ddagger}_{10\rightarrow 12}$). On the other hand, the produced vinyl anion **11** was more stable than anion **12** by 7.26 kcal/mol. As a result the activation energy for the ring-opening reaction of **12** to **10** (6.38 kcal/mol) was substantially smaller than that for the

conversion of **11** to **10** (13.02 kcal/mol). Since both cyclization reactions were shown to be endothermic processes, the irreversible protonation of the resulting anions **11** and **12** would be critical for the product formation. These theoretical results led to the following speculations for the cyclization of **10**: 1) under kinetically controlled conditions the selectivity for the 6-*endo-digonal* cyclization would not be so high, and 2) under thermodynamic conditions the product formation is favorable for the 6-*endo-digonal* process, if all three anions were equilibrated and the selective protonation of **11** proceeded irreversibly.

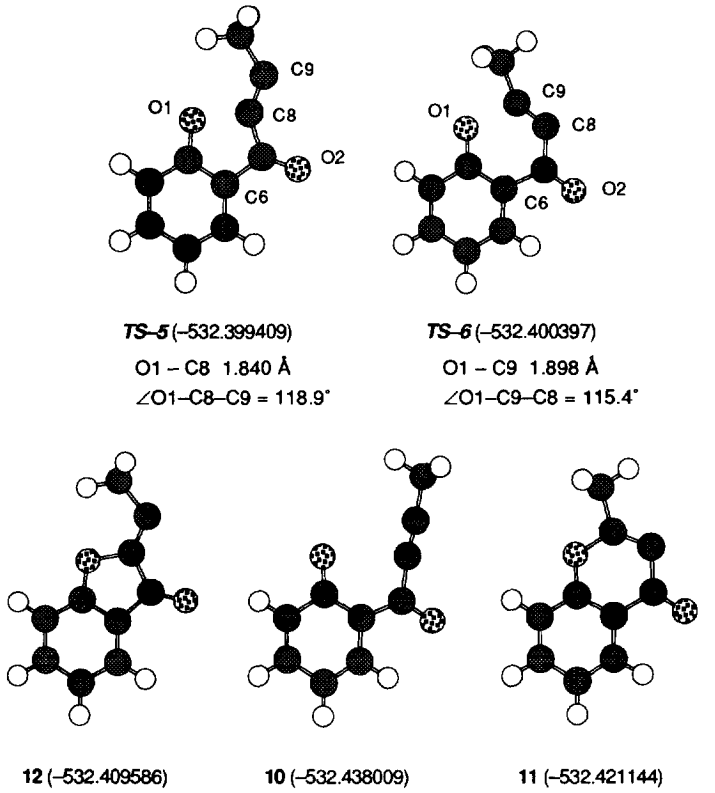


Figure 1. Optimized structures for **10**, **11**, **12**, ***TS–6***, and ***TS–5*** at the HF/6-31G* level. Numbers in parenthesis indicated the total energy in hartree.

Synthesis of o-Silyloxyphenyl Ethynyl Ketones.

To achieve thermodynamically controlled reaction conditions for the selective 6-*endo-digonal* cyclization, we examined *in situ* generation of the phenoxide in an aprotic medium by desilylation of *o*-silyloxyphenyl ethynyl ketone with fluoride. The *o*-silyloxyphenyl ethynyl ketone **16** used for the cyclization studies was synthesized from the silyl-protected salicylic aldehyde **13** and readily available **14** (Scheme 1). Addition of bromomagnesium salt **14** to **13** gave benzyl alcohol **15**. Oxidation of **15** with manganese dioxide (MnO_2) cleanly produced ethynyl ketone **16**. Desilylation of **15** followed by oxidation with MnO_2 produced phenol **18**.

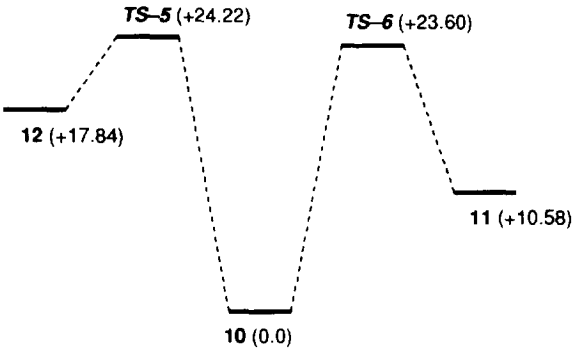
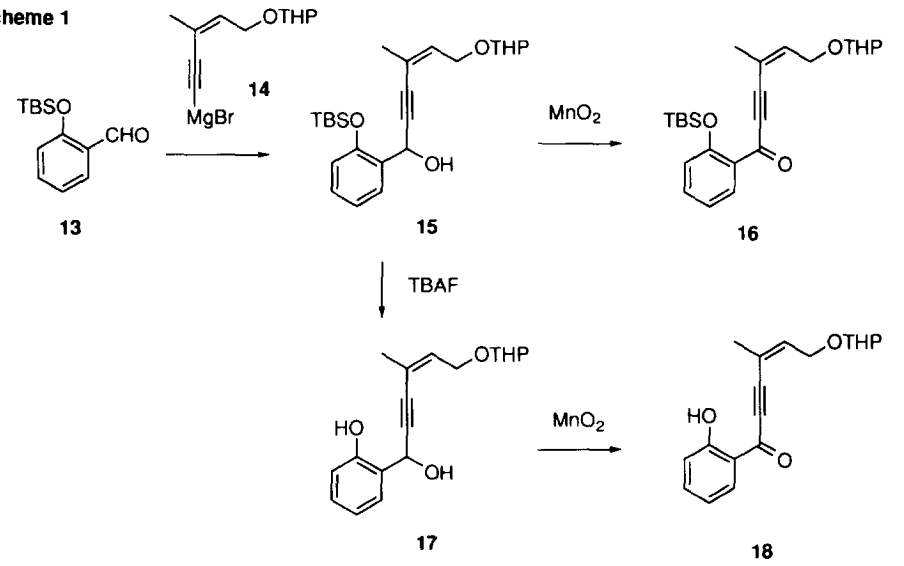


Figure 2. Potential energy diagram for the reaction of **10** to **11** and **12**. Numbers in parenthesis indicated the relative potential energy from **10** in kcal/mol.

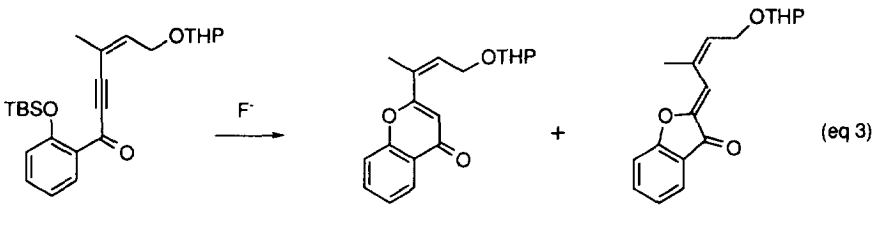
Scheme 1



Effects of Reaction Conditions for The 6-Endo-digonal Cyclization.

Various reaction conditions for the 6-*endo-digonal* cyclization were tested by using **16**. Considering that the protonation of the vinyl anion is essential for the product formation, we first examined the commercially available THF solution of tetra-n-butylammonium fluoride (TBAF) containing approximately 5% (v/v) of water as a fluoride ion source. The reaction of **16** with TBAF in THF at 0 °C for 1.5 h produced both **19** and **20** in 90% yield with very low selectivity (**19**:**20** = 47:53) (eq 3). In the early stage of the reaction the phenol **18** was detected on TLC indicating the existence of phenoxide ion under the conditions, which slowly underwent cyclization to **19** and **20**. The structure of **19** was unambiguously confirmed by the HMBC spectrum indicating

the hydrogen–carbon connectivities as shown in Figure 3. The stereochemistry of the exocyclic alkene in **20** was not confirmed by spectroscopic methods, but transition state for the 5-*exo-digonal* cyclization (***TS–5***) may suggest the preferential formation of Z-isomer. To reduce the concentration of proton donor (*e.g.*, water) in the reaction system, spray-dried potassium fluoride (KF) in the presence of 18-crown-6 was used for the fluoride source. The reaction of **16** with spray dried KF–18-crown-6 in *anhydrous* DMF proceeded smoothly giving **19** as a sole product in a quantitative yield (97%). The formation of **20** was not detected by ^{1}H NMR analysis of the crude mixture.



16 **19** **20**

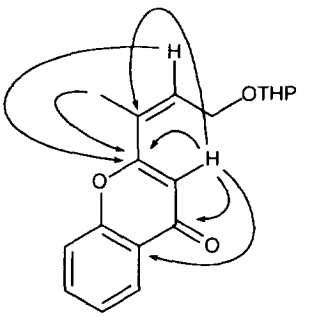
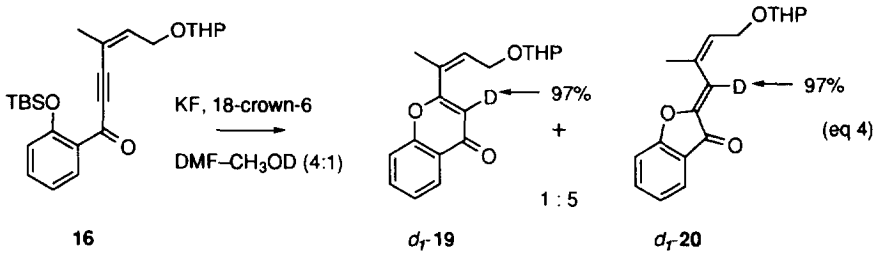


Figure 3. The selected hydrogen–carbon conectivities observed in the HMBC spectram of **19**.

To confirm the speculation that irreversible protonation of the vinyl anion is essential for the product formation, the reaction of **16** under KF–18-crown-6–DMF conditions was quenched with deuterated acetic acid (CH_3CO_2D) after the standard reaction period (2 h) at ambient temperature. As expected there was no sign of the incorporation of the deuterium into **19**, presumably due to *in situ* quenching of the resulting anion by moisture already contaminated in the reaction system. The observation that the cyclization of **16** became exceedingly slow when the reaction was carried out in the presence of the activated molecular sieves 4A, may support *in situ* protonation of the resulting anion. On the other hand, the addition of large excess of methanol (20% v/v) to the reaction mixture dramatically changed the reaction course giving **20** in 66% yield accompanied by the minor formation of **19** (13%). The formation of the substantial amount of **20** (9%) along with **19** (83%) by the cyclization of phenol **18** under KF–18-crown-6–DMF conditions revealed that even the phenolic hydrogen could be effective as a proton donor in the cyclization to result in a decrease of the selectivity for the formation of **19**. These results indicated that the presence of only a small amount of proton

donor like moisture in the reaction system plays a critical role not only in governing the selectivity but also in the smooth product formation. Evidence for the vinyl anion formation in the cyclization of **16** was obtained when the cyclization was carried out in DMF–CH_3OD (99 atom % D) (4:1) solution (eq 4). Both d_1-**19** and d_1-**20** formed in a ratio of 1:5 contained deuterium at the exocyclic olefinic position with the deuterium incorporation efficiency being more than 97% in both cases.



16 d_1-**19** d_1-**20**

The time-course of the cyclization of **16** was monitored by ^1H NMR spectroscopy. The reaction mixtures of **16** under KF–18-crown-6–DMF conditions at –20 °C were subjected to aqueous work-up at an indicated time interval and the ^1H NMR of each of the crude mixture was recorded (Figure 4). The starting material **16** was no more detected after 10 min reaction, with phenol **18**, benzopyranone **19**, and benzofuranone **20** being observed in a ratio of 29:52:19 (line b). While after 30 min the ratio of three compounds reached to 9:54:37 (line c), upon prolonged reaction (1 h) phenol **18** was completely consumed, with the ratio of **19** and **20** being 81:19 (line d). Warming the reaction mixture to 0 °C followed by aqueous work-up resulted in an almost exclusive formation of **19** (line e). The fact that the amount of the initially formed benzofuranone **20** decreased on a prolonged reaction with increase of benzopyranone **19** suggested that there was an equilibrium among either **18**, **19**, and **20** or their anions.

To identify the stage for the equilibration, we examined the interconversion between **19** and **20** under KF–18-crown-6–DMF conditions and found that both compounds were absolutely inert at ambient temperature under the conditions.[23] It was also confirmed that pentacoordinate silicate having strong Lewis acidity formed *in situ* in the reaction did not induce the ring opening of **20**. Thus, the reaction of a mixture of **16** and **20** (approximately 1:1) under KF–18-crown-6–DMF conditions afforded **19** with a complete recovery of **20** (eq 5). These experiments clearly indicated that protonation of benzopyranone and benzofuranone anions (e.g., **11** and **12**, respectively) was an irreversible process under the conditions, and the equilibration should, therefore, exist at anion states. When the reaction of **16** under the KF–18-crown-6–DMF conditions was quenched with D_2O before the equilibration is completed (e.g., after 15 min at –20 °C), it was confirmed that deuterium is efficiently incorporated into the exocyclic alkenic position of benzofuranone, while it was not the case for the benzopyranone (Figure 5). Thus, under these conditions protonation of the benzofuranone anion by a small amount of proton donor existing in the reaction system was much less efficient than that of benzopyranone anion.

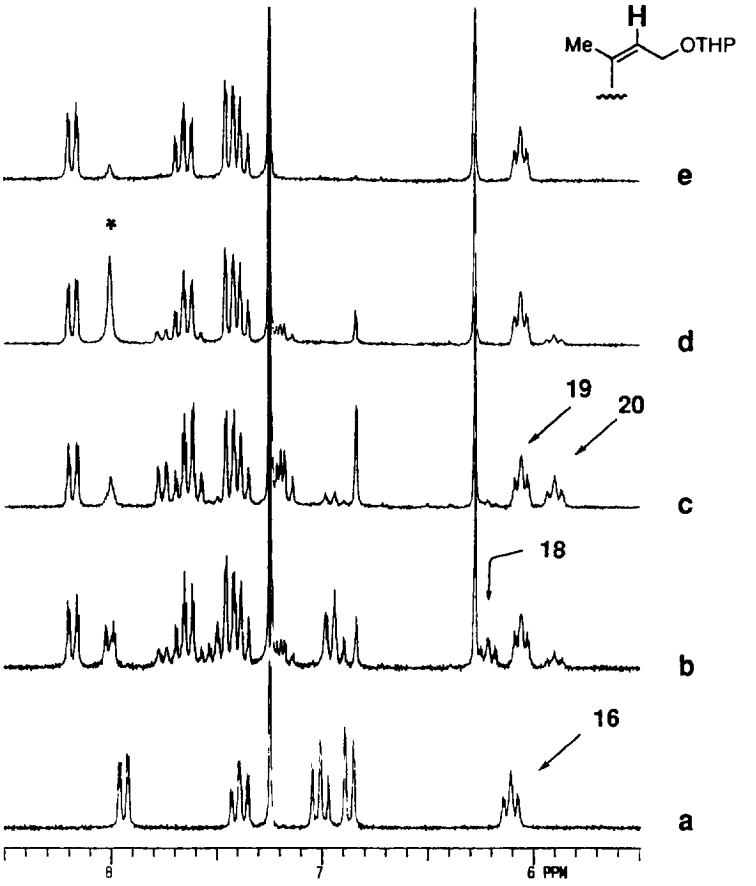
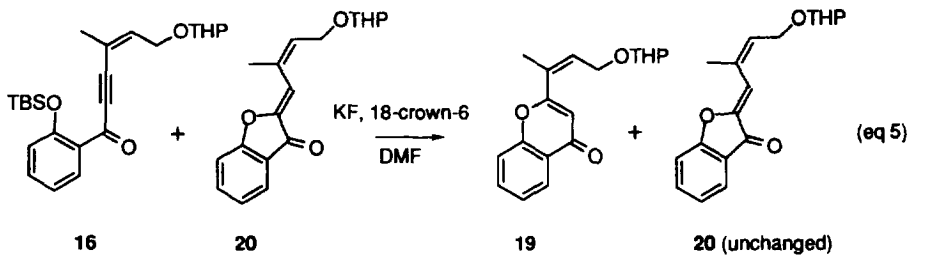


Figure 4. Selected ^{1}H NMR spectra (5.5 – 8.5 ppm) of the crude mixture for the reaction of **16** under the KF–18-crown-6–DMF conditions after aqueous work-up (aq. NH_4Cl) at the indicated reaction time. The compounds were identified by the triplet-like signals of the olefinic hydrogen observed at 6.11 ppm for **16**, 6.21 ppm for **18**, 6.06 ppm for **19**, and 5.90 ppm for **20**. line a; 0 min, **16**, line b; 10 min at –20 °C, line c; 30 min at –20 °C, line d; 1 h at –20 °C, line e; warming up to 0 °C after 1 h at –20 °C. * DMF



16 20 19 20 (unchanged)

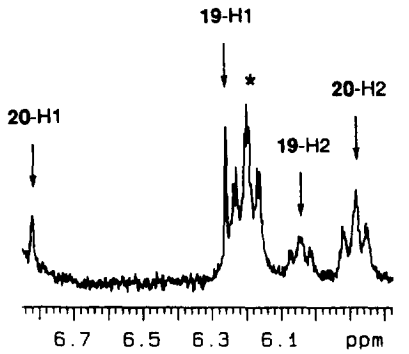
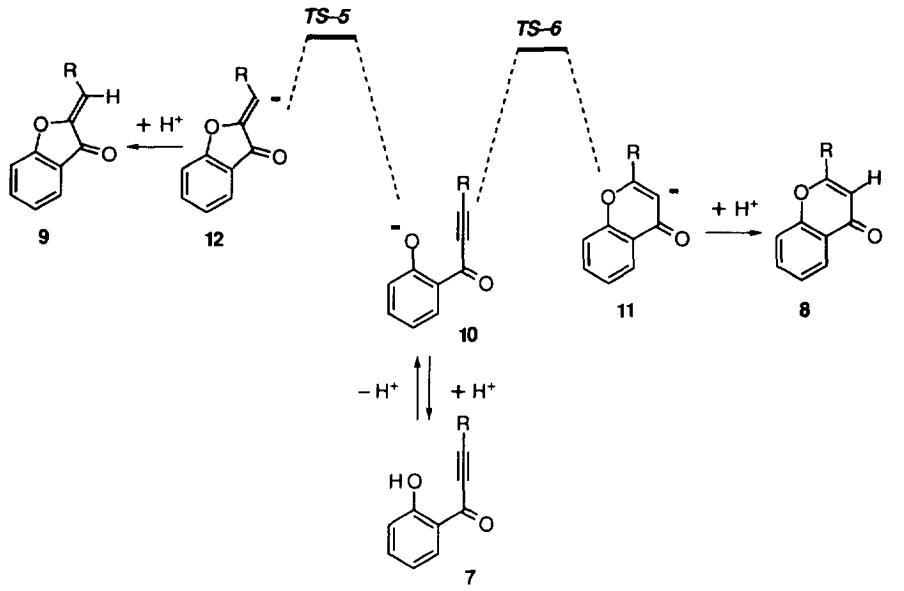


Figure 5. Selected ^{1}H NMR spectrum (5.8 – 6.9 ppm) of the crude mixture obtained by quenching the reaction of **16** under the KF–18-crown-6–DMF conditions with D_2O–ND_4Cl after 15 min at –20 °C. The newly formed olefinic hydrogens for **19** and **20** were indicated as **19**-H1 and **20**-H1, respectively. Hydrogens attached to the trisubstituted alkene were labeled as **19**-H2 and **20**-H2. A small singal for **20**-H1 in comparison with that for **20**-H2 clearly indicated the incorporation of deuterium at this position. The signal marked with asterisk was the olefinic hydrogen of **18**.

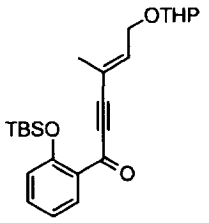
Scheme 2



Considering theoretical calculations and the experimental results obtained above, we can rationalize the cyclization reaction of *o*-hydroxyphenyl ethynyl ketones under basic conditions as illustrated in Scheme 2. Under the conditions where there is a sufficient amount of proton donor, the reaction produces varying amounts of both benzopyranone and benzofuranone anions **11** and **12**, which are protonated to give **8** and **9**, respectively. On the other hand, under the conditions where only a limited amount of the proton donor was available, all three anions **10**, **11**, and **12** are equilibrated. The most stable phenoxide anion **10** would be expected to be preferentially protonated to give phenol **7**. However, under the basic reaction conditions, **7**, if formed, would be equilibrated with **10** immediately. While the protonation of the benzofuranone anion **12** was relatively slow under the conditions, the benzopyranone anion **11** was immediately and irreversibly protonated. As a result of the equilibrium among these three anions and of the irreversible protonation of **11**, highly selective formation of benzopyranone **8** was attained. However, at this moment we do not know the reason why the protonation of **12** is relatively slow compared with that for **11**.

Synthesis of Various 2-Substituted Benzopyranones.

With an efficient synthetic method for the selective formation of benzopyranones in hand, we examined the reaction of phenyl ethynyl ketones **21**, **22**, **23**, and **24** under KF–18-crown-6–DMF conditions. The epoxy-substituted ketones **22** and **23** were synthesized using epoxy alkynes prepared from commercially available (*Z*)- and (*E*)-3-methyl-2-penten-4-yn-1-ol, respectively, as detailed in experimental section. As expected benzopyranones **25**, **26**, **27**, and **28** were selectively obtained in good to excellent yields as indicated in the parenthesis. The hydrolysis of THP group of **28** to the known 2-hydroxymethyl-4*H*-chromen-4-one gave further evidence for the structure.[24] Under these conditions the stereochemical integrity for the carbon–carbon double bond and the epoxide moiety was completely retained.



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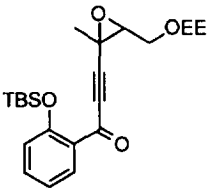

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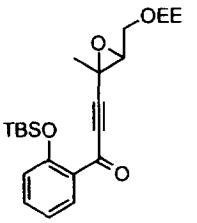

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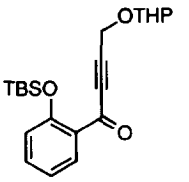

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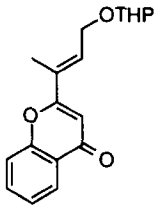
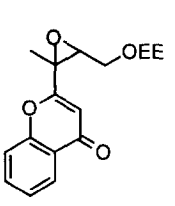
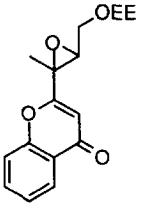


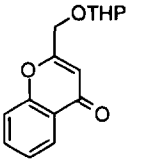
25 (83%)



26 (73%)



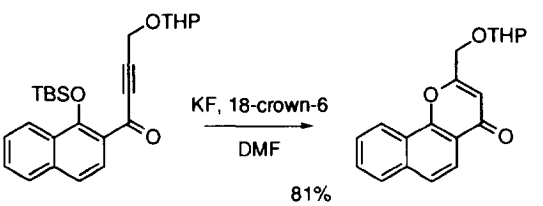
27 (72%)



28 (73%)

To examine the feasibility of this synthetic method for kapurimycin A_3 synthesis, we investigated the construction of tricyclic ring system as a simple kapurimycin model. Ethynyl ketone **29** was prepared from 1-silyloxy-2-naphthaldehyde according to the procedure described for the synthesis of **16**. The cyclization of **29** under KF–18-crown-6–DMF conditions at ambient temperature proceeded smoothly giving the tricyclic compound **30** in 81% yield (Scheme 3). These results clearly indicated that our method has a high potential for the synthesis of **1** and its congeners to study the structure–reactivity relationship of kapurimycin A_3. These studies are now actively in progress in these laboratories and will be reported in due course.

Scheme 3



29 **30**

EXPERIMENTAL SECTION

General Procedures. Theoretical calculations were performed on SGI INDY (R4000SC personal workstation) with Spartan molecular modeling software (*version* 3.1) and Gaussian 92 program. ^{1}H NMR spectra were measured with Varian GEMINI 200 (200 MHz), JEOL JNM α-400 (400 MHz) and JEOL JNM α-500 (500 MHz) spectrometers. Coupling constants (J values) are reported in Hz. ^{13}C NMR spectra were measured with Varian GEMINI 200 (50 MHz), JEOL JNM α-400 (100 MHz) and JEOL JNM α-500 (125 MHz) spectrometers. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using residual chloroform (δ = 7.24 in ^{1}H NMR, δ = 77.0 in ^{13}C NMR) and dimethylsulfoxide (δ = 2.49 in ^{1}H NMR, δ = 39.5 in ^{13}C NMR) as an internal standard. The following abbreviations were used for the description of the signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. IR spectra were recorded on a JASCO FT/IR-5M spectrophotometer. Melting points were obtained on a Yanagimoto Seisakusho micro melting point apparatus and are uncorrected. Electron impact mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on JEOL JMS-DX 300 or JEOL JMS-SX 102A. Pre-coated TLC plates Merck silica gel 60 F_{254} was used for monitoring the reactions and also for preparative TLC. Wako gel (C-200, particle size 75-150 μm, Wako) was used for silica gel flash chromatography. Anhydrous reactions were performed under N_2 atmosphere. Ether and tetrahydrofuran (THF) were distilled under N_2 from sodium/benzophenone ketyl prior to use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

Selected structural parameters for TS-6 and TS-5 (Figure 1).

bond length (Å)	TS-5	TS-6	bond angle (°)	TS-5	TS-6
O1–C8	1.840	———	C1–O1–C8	104.3	———
O1-C9	———	1.898	O1–C8–C7	97.6	———
O1–C1	1.276	1.276	O1–C8–C9	118.9	———
C6–C7	1.463	1.485	C1–O1–C9	———	113.4
C7–C8	1.466	1.475	O1–C9–C8	———	119.4
C7–O2	1.209	1.210	O1–C9–C10	———	95.5
C8–C9	1.271	1.249	C6–C7–C8	110.9	117.5
C9–C10	1.492	1.475	C6–C7–O2	125.2	120.6
			C8–C9–C10	128.1	———
			C7–C8–C9	———	125.4

2-(*t*-Butyldimethylsilyloxy)benzaldehyde (13). To a solution of salicylaldehyde (1.21 g, 10.8 mmol) and 2,6-lutidine (1.75 mL, 15.0 mmol) in dichloromethane (30 mL) was added *t*-butyldimethylsilyl trifuluoromethanesulfonate (3.50 mL, 15.2 mmol) at –78 °C, and the mixture was stirred at –78 °C for 2 h. After diluted with sat. $NaHCO_3$ the reaction mixture was warmed to ambient temperature and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 2% ethyl acetate/hexane) to give **13** (2.26 g, 89%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (d, 1H, J = 1.0 Hz), 7.79 (dd, 1H, J = 1.9, 7.7 Hz), 7.44 (ddd, 1H, J = 2.0, 7.3, 8.4 Hz), 7.02 (m, 1H), 6.87 (dd, 1H, J = 1.0, 8.3 Hz), 1.00 (s, 9H), 0.26 (s, 6H); IR ($CHCl_3$) 3016, 2957, 2932, 2860, 1684, 1600, 1478, 1256, 1217 cm^{-1}; MS m/z (%) 179 [(M–^{t}Bu)$^+$] (56), 57 (100); HRMS calcd for $C_9H_{11}O_2Si$ [(M–^{t}Bu)$^+$], 179.0528; found, 179.0506.

(Z)-1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4-methyl-6-(2-tetrahydropyranyloxy)-4-hexen-2-yn-1-ol (15). To a solution of (Z)-3-methyl-2-penten-4-yn-1-ol (5.30 g, 55.1 mmol) and 3,4-dihydro-2*H*-pyran (15.0 mL, 164 mmol) in dichloromethane (60 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at 0 °C, and the mixture was stirred for 3 h. The reaction mixture was diluted with sat. $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 10% ethyl acetate/hexane) to give (Z)-3-methyl-1-(2-tetrahydropyranyloxy)-2-penten-4-yne (9.78 g, 98%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1H), 4.63 (dd, 1H, J = 3.1, 4.1 Hz), 4.38 (ddq, 1H, J = 1.4, 6.2, 12.6 Hz), 4.22 (ddq, 1H, J = 1.0, 7.2, 12.5 Hz), 3.87 (m, 1H), 3.50 (m, 1H), 3.13 (s, 1H), 1.88 (q, 3H, J = 1.3 Hz), 1.81 (m, 1H), 1.70 (m, 1H), 1.60–1.49 (4H); IR ($CHCl_3$) 3305, 3010, 2948, 2855, 1442, 1202, 1118, 1023 cm^{-1}; MS m/z (%) 180 (M^+) (0.8), 149 (4), 85 (100), 79 (57); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.02; H, 8.95. To a solution of ethylmagnesium bromide (0.47 mL, 3 M in ethyl ether, 1.41 mmol) in THF (5 mL) was added a solution of the above acetylene compound (0.25 g, 1.40 mmol) in THF (2 mL) at 0 °C and the mixture was stirred at 50 °C for 1.5 h to give bromomagnesium salt **14**. A solution of **13** (0.34 g, 1.44 mmol) in THF (2 mL) was added to the solution of **14** at ambient temperature and the whole mixture was stirred for 1 h. The reaction mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **15** (0.37 g, 64 %) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (ddd, 1H, J = 2.0, 2.6, 7.6 Hz), 7.18 (m, 1H), 6.96 (dt, 1H, J = 1.1, 7.5 Hz), 6.80 (d, 1H, J = 8.0 Hz), 5.84 (m, 2H), 4.65, 4.63 (t×2, total 1H, J = 3.6 Hz), 4.35–4.22 (2H), 3.84 (m, 1H), 3.47 (m, 1H), 3.03, 2.97 (d×2, total 1H, J = 5.3 Hz), 1.88 (d, 3H, J = 0.8 Hz), 1.80 (m, 1H), 1.69 (m, 1H), 1.59–1.46 (4H), 1.02 (s, 9H), 0.26 (m, 6H); IR ($CHCl_3$) 3430, 3011, 2953, 2860, 1480, 1454, 1258, 1021, 916, 840, 762 cm^{-1}; MS m/z (%) 415 [$(M-H)^+$] (2), 398 [$(M-H_2O)^+$] (3), 314 (46), 257 (98), 85 (66), 75 (100); Anal. Calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 69.05; H, 8.64.

(Z)-1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4-methyl-6-(2-tetrahydropyranyloxy)-4-hexen-2-yn-1-one (16). To a solution of **15** (0.92 g, 2.20 mmol) in dichloromethane (30 mL) was added manganese (IV) oxide (2.0 g) and the mixture was stirred for 3 h at ambient temperature. The reaction mixture was diluted with ethyl ether, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **11** (0.89 g, 97%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, 1H, J = 1.7, 7.8 Hz), 7.38 (ddd, 1H, J = 1.8, 7.3, 8.3 Hz), 7.00 (m, 1H), 6.87 (dd, 1H, J = 0.8, 8.3 Hz), 6.11 (m, 1H), 4.62 (dd, 1H, J = 3.1, 4.2 Hz), 4.43 (ddq, 1H, J = 1.3, 6.2, 12.9 Hz), 4.28 (ddd, 1H, J = 1.0, 7.3, 12.8 Hz), 3.83 (m, 1H), 3.46 (m, 1H), 1.97 (d, 3H, J = 1.2 Hz), 1.79 (m, 1H), 1.69 (m, 1H), 1.57–1.50 (4H), 0.99 (s, 9H), 0.21 (s, 6H); IR ($CHCl_3$) 3012, 2952, 2860, 2189, 1643, 1478, 1447, 1257, 1233, 1022, 914, 841, 772, 759, 748 cm^{-1}; MS m/z (%) 357 [$(M-{}^tBu)^+$] (26), 273 (100), 235 (98), 85 (74).

(Z)-1-(2-Hydroxyphenyl)-4-methyl-6-(2-tetrahydropyranyloxy)-4-hexen-2-yn-1-ol (17). To a solution of **15** (33.5 mg, 80.4 μmol) in THF (1 mL) was added TBAF (80 mL, 1.0 M in THF, 80.0 μmol) at 0 °C and the mixture was stirred at ambient temperature for 20 min. The reaction mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **16** (23.0 mg, 95%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 1H), 7.21 (m, 1H), 6.90–6.85 (2H), 5.89 (m, 1H), 5.75 (d, 1H, J = 8.0 Hz), 4.72 (t×2, total 1H, J = 3.2 Hz),

4.35–4.21 (2H), 3.86 (m, 1H), 3.51 (m, 1H), 1.90 (s, 3H), 1.84–1.46 (8H); IR ($CHCl_3$) 3356, 3015, 2949, 2927, 1487, 1234, 1021 cm^{-1}; MS m/z (%) 284 [$(M-H_2O)^+$] (7), 200 (97), 171 (38), 84 (91), 55 (100).

(*Z*)-1-(2-Hydroxyphenyl)-4-methyl-6-(2-tetrahydropyranyloxy)-4-hexen-2-yn-1-one (18). To a solution of **17** (11.9 mg, 39.4 μmol) in dichloromethane (1 mL) was added manganese (IV) oxide (50.0 mg) and the mixture was stirred for 4 h at ambient temperature. The reaction mixture was diluted with ethyl ether, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 25% ethyl acetate/hexane) to give **18** (10.2 mg, 86%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 11.67 (s, 1H), 8.00 (dd, 1H, J = 1.7, 8.0 Hz), 7.49 (ddd, 1H, J = 1.7, 7.1, 8.5 Hz), 6.97 (m, 1H), 6.93 (ddd, 1H, J = 1.1, 7.3, 8.0 Hz), 6.21 (m, 1H), 4.66 (dd, 1H, J = 3.1, 4.2 Hz), 4.48 (ddq, 1H, J = 1.3, 6.4, 13.0 Hz), 4.33 (ddd, 1H, J = 1.1, 7.3, 13.0 Hz), 3.87 (ddd, 1H, J = 3.1, 8.3, 11.4 Hz), 3.51 (m, 1H), 2.03 (q, 3H, J = 1.3 Hz), 1.81 (m, 1H), 1.72 (m, 1H), 1.62–1.49 (4H); IR ($CHCl_3$) 2949, 2191, 1624, 1597, 1243, 1022 cm^{-1}; MS m/z (%) 300 (M^+) (0.2), 273 (3), 216 (13), 173 (31), 121 (44), 85 (100).

(*Z*)-2-[1-(2-Tetrahydropyranyloxy)buten-3-yl]-4*H*-chromen-4-one (19). To a solution of **16** (20.3 mg, 49.0 μmol) and 18-crown-6 (26.2 mg, 99.1 μmol) in *N*,*N*-dimethylformamide (1 mL) was added spray dried potassium fluoride (5.7 mg, 98.1 μmol) at 0 °C and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **19** (14.2 mg, 97 %) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (ddd, 1H, J = 0.5, 1.7, 7.9 Hz), 7.65 (ddd, 1H, J = 1.7, 7.2, 8.4 Hz), 7.43 (ddd, 1H, J = 0.5, 1.1, 8.4 Hz), 7.38 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 6.28 (s, 1H), 6.06 (m, 1H), 4.65 (m, 1H), 4.62 (ddq, 1H, J = 1.7, 5.7, 14.5 Hz), 4.41 (ddq, 1H, J = 1.4, 6.2, 14.3 Hz), 3.85 (m, 1H), 3.49 (m, 1H), 2.09 (q, 3H, J = 1.5 Hz), 1.81 (m, 1H), 1.72 (m, 1H), 1.60–1.51 (4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.7, 164.1, 156.3, 135.4, 133.9, 129.2, 125.8, 125.3, 123.9, 118.1, 110.7, 98.7, 65.0, 62.4, 30.5, 25.2, 21.0, 19.3; IR ($CHCl_3$) 3013, 2949, 2873, 2855, 1649, 1642, 1567, 1444, 1383, 1212, 1132, 1024 cm^{-1}; MS m/z (%) 300 (M^+) (1), 216 (100) [$(M-THP+H)^+$], 200 (77), 199 (75), 187 (63), 121 (83), 85 (79); HRMS calcd for $C_{13}H_{12}O_3$ [$(M-THP+H)^+$], 216.0787; found, 216.0806.

2-[2-Methyl-4-(2-tetrahydropyranyloxy)-2-butenylidenyl]benzofuran-3-one (20). To a solution of **16** (14.4 mg, 34.7 μmol) in THF (1 mL) was added a THF solution of TBAF (35 μL, 1 M in THF, 35 μmol) at 0 °C and the mixture was stirred for 90 min at that temperature. The reaction mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 25% ethyl acetate/hexane) to give **20** (5.0 mg, 48%) as a colorless oil accompanied with **19** (4.4 mg, 42%). **20**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (ddd, 1H, J = 0.6, 1.4, 7.7 Hz), 7.61 (ddd, 1H, J = 1.4, 7.3, 8.5 Hz), 7.21 (dt, 1H, J = 0.7, 8.3 Hz), 7.17 (dt, 1H, J = 0.7, 8.4 Hz), 6.83 (d, 1H, J = 0.9 Hz), 5.90 (m, 1H), 4.66 (dd, 1H, J = 3.1, 4.3 Hz), 4.46 (ddq, 1H, J = 1.4, 6.4, 13.3 Hz), 4.26 (ddq, 1H, J = 1.1, 7.3, 13.3 Hz), 3.89 (m, 1H), 3.54 (m, 1H), 2.24 (q, 3H, J = 1.3 Hz), 1.82 (m, 1H), 1.72 (m, 1H), 1.64–1.48 (4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.14, 166.28, 147.29, 136.99, 135.70, 132.46, 124.71, 123.36, 121.66, 112.96, 109.62, 98.38, 63.44, 62.31, 30.42, 25.23, 22.51, 19.29; IR ($CHCl_3$) 3020, 2947, 1717, 1606, 1462, 1300, 1129, 1031 cm^{-1}; MS m/z (%) 216 [$(M-THP+H)^+$] (23), 185 (37), 134 (100).

Internal quenching with DMF–CH_3OD. The reaction of **16** (33.3 mg, 0.08 mmol) with KF (9.3 mg, 0.15 mmol), 18-crown-6 (44.6 mg, 0.17 mmol) in DMF (2 mL) and CH_3OD (0.5 mL, 99 atm % D) was carried

out for 10 min at ambient temperature and worked-up as usual. Integration of the signal at 6.83 ppm for **20** in ^{1}H NMR showed the deuterium content of the produced **20** was 97%. More than 97% deuterium content for **19** was determined by the disappearance of the olefinc hydrogen in ^{1}H NMR. Chromatographic separation afforded *d*$_1$-**19** (2.7 mg, 11%) and *d*$_1$-**20** (11.6 mg, 48%). *d*$_1$-**19**: MS m/z (%) 301 (1) (M^+), 217 (100) [(M–THP+H)$^+$], 202 (79), 201 (80), 188 (56); HRMS calcd for $C_{13}H_{11}O_3D_1$ [(M–THP+H)$^+$], 217.0849; found, 217.0769. *d*$_1$-**20**: MS m/z (%) 301 (1) (M^+), 217 (28) [(M–THP+H)$^+$], 186 (41); HRMS calcd for $C_{13}H_{11}O_3D_1$ [(M–THP+H)$^+$], 217.0849; found, 217.0779.

Time-course of the cyclization of 16 (Figure 4). Four reactions of **16** under the standard KF–18-crown-6–DMF condirions (see the procedure for preparation of **19**) were carried out at –20 °C, and three of four reactions were quenched by adding aq. NH_4Cl after 10, 30, and 60 min at that temperature. The reamining reaction was warmed up to 0 °C after 60 min at –20 °C and quenched as previous. Each reaction mixture was extracted as for the preparation of **19** to give a crude mixture, which was analyzed by ^{1}H NMR in $CDCl_3$.

Cyclization of 16 in the presence of 21. In a NMR tube a solution of DMF-d_7 (1 mL) containing **16** (5.0 mg, 0.012 mmol), **21** (3.6 mg, 0.012 mmol), and 18-crown-6 (12.8 mg, 0.048 mmol) was prepared and ^{1}H NMR of the starting mixture was recorded. To the solution was added KF (2.8 mg, 0.048 mmol) at room temperature and the mixture was sonicated for 10 min. ^{1}H NMR spectrum of the resulting dark brown solution was then recorded.

D_2O quenching before the equilibration is completed (Figure 5). The reaction of **16** described for the time-course experiment was quenched by adding D_2O–ND_4Cl solution after 15 min at –20 °C. The resulting mixture was worked-up as usual and ^{1}H NMR spectrum of the crude product was recorded in $CDCl_3$.

(*E*)-1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4-methyl-6-(2-tetrahydropyranyloxy)-4-hexen-2-yn-1-one (21). According to the method described in the synthesis of **15** the reaction of (*E*)-3-methyl-2-penten-4-yn-1-ol (5.29 g, 55.0 mmol) gave (*E*)-3-methyl-1-(2-tetrahydropyranyloxy)-4-pentyn-2-ene (7.87 g, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (m, 1H), 4.61 (m, 1H), 4.26 (dd, 1H, J = 6.2, 13.2 Hz), 4.09 (dd, 1H, J = 7.2, 13.2 Hz), 3.84 (m, 1H), 3.50 (m, 1H), 2.80 (s, 1H), 1.82 (s, 3H), 1.80–1.48 (m, 6H); IR ($CHCl_3$) 3306, 3012, 2948, 2855, 1442, 1200, 1119, 1024 cm^{-1}; MS m/z (%) 180 (M^+), (4), 149 (11), 85 (100); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.45; H, 9.01. This compound (1.24 g, 6.87 mmol) was treated with EtMgBr as described in the synthesis of **15** to give the corresponding bromomagnesium salt, which was reacted with **13** (1.36 g, 5.74 mmol) to afford (*E*)-1-[2-(*t*-butyldimethylsiloxy)phenyl]-4-methyl-6-(2-tetrahydropyranyloxy)-2-hexyn-4-en-1-ol (1.34 g, 55% based on **13**) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, 1H, J = 1.8, 7.7 Hz), 7.18 (ddd, 1H, J = 1.8, 7.4, 8.0 Hz), 6.96 (dt, 1H, J = 1.1, 7.5 Hz), 6.81 (dd, 1H, J = 1.1, 8.1 Hz), 5.98 (m, 1H), 5.80 (d, 1H, J = 5.5 Hz), 4.60 (m, 1H), 4.24 (dd, 1H, J = 6.2, 12.5 Hz), 4.10 (dd, 1H, J = 7.1, 13.2 Hz), 3.84 (m, 1H), 3.50 (m, 1H), 2.71 (d, 1H, J = 5.6 Hz), 1.83 (d, 3H, J = 1.5 Hz), 1.81–1.49 (m, 6H), 1.02 (s, 9H), 0.29 and 0.26 (s×2, total 6H); IR ($CHCl_3$) 3592, 3015, 2954, 2860, 1488, 1454, 1258, 1023, 912, 840, 745 cm^{-1}; MS m/z (%) 359 [(M–^{t}Bu)$^+$], (3), 315 (12), 275 (19), 257 (35), 179 (100). Oxidation of this alcohol (1.16 g, 2.79 mmol) with MnO_2 (ca. 2 g) produced **21** (1.05 g, 91%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 1.9, 7.8 Hz), 7.38 (ddd, 1H, J = 1.8, 7.2, 8.1 Hz), 7.00 (ddd, 1H, J = 1.1, 7.3, 7.8 Hz), 6.86 (dd, 1H, J = 1.1, 8.2 Hz), 6.29 (m, 1H), 4.62 (t, 1H, J = 3.4 Hz), 4.32 (ddq, 1H, J = 1.1, 6.1, 14.0 Hz), 4.15 (ddd, 1H, J = 0.9, 7.0, 13.9 Hz), 3.84 (ddd, 1H, J = 3.2, 8.3, 11.6 Hz), 3.51 (m, 1H), 1.90 (d, 3H, J = 1.2 Hz), 1.80 (m, 1H), 1.70 (m, 1H), 1.62-1.49 (4H), 0.99 (s, 9H), 0.21 (s, 6H);

IR ($CHCl_3$) 3016, 2953, 2860, 2190, 1642, 1478, 1448, 1256, 910, 840, 761 cm^{-1}; MS m/z (%) 357 [(M–$^tBu)^+$] (12), 273 (8), 245 (46), 203 (24), 179 (17), 149 (18), 85 (100).

(4*R, 5*R**)-1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4,5-epoxy-6-(1-ethoxyethyloxy)-4-methyl-2-hexyn-1-one (22).** To a solution of (*Z*)-3-methyl-2-penten-4-yn-1-ol (2.51 g, 26.2 mmol) and Na_2HPO_4 (9.06 g, 63.8 mmol) in dichloromethane (100 mL) was added m-CPBA (9.08 g, 52.6 mmol) at 0 °C and the mixture was stirred at ambient temperature for 20 h. The mixture was diluted with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 30% ethyl acetate/hexane) to give (2*S**, 3*R**)-2,3-epoxy-3-methyl-4-pentyn-1-ol (2.45 g, 84%) as a colorless needle: ^1H NMR (500 MHz, $CDCl_3$) δ 3.91 (dd, 1H, J = 4.6, 12.3 Hz), 3.82 (dd, 1H, J = 6.2, 12.4 Hz), 3.08 (dd, 1H, J= 4.7, 6.1 Hz), 2.38 (s, 1H), 1.76 (br, 1H), 1.57 (s, 3H); IR ($CHCl_3$) 3427, 3305, 3015, 1440, 1377, 1090 cm^{-1}; Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found C, 64.15; H, 7.10. To a solution of this epoxide (0.45 g, 4.00 mmol) and ethyl vinyl ether (0.77 mL, 8.05 mmol) in dichloromethane (4 mL) was added a catalytic amount of PPTS at 0 °C and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was diluted with sat. $NaHCO_3$ and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give (2*R**, 3*R**)-2,3-epoxy-1-(1-ethoxyethoxy)-3-methyl-4-pentyne (0.65 g, 88%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (q, 1H, J = 5.4 Hz), 3.85–3.62 (m, 3H), 3.48 (m, 1H), 3.06 (t, 1H, J = 5.4 Hz), 2.35 and 2.36 (s×2, total 1H), 1.55(s, 3H), 1.32 (dd, 3H, J = 1.0, 5.4 Hz), 1.19 (t, 3H, J = 7.1 Hz); IR ($CHCl_3$) 3272, 3260, 2980, 2934, 2878, 1134, 1060 cm^{-1}; MS m/z (%) 169 [(M–Me)$^+$], (5), 95 (13), 73 (100); Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found C, 65.02; H, 8.92. To a solution of this compound (0.92 g, 5.01 mmol) in THF (5 mL) was added n-BuLi (3.10 mL, 1.62 M in hexane, 5.02 mmol) at –78 °C and the mixture was stirred at –78 °C for 15 min. After addition of a solution of **13** (1.18 g, 5.01 mmol) in THF (5 mL) was added at –78 °C the mixture was stirred for 2 h. The mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15–50% ethyl acetate/hexane) to give (4*R**, 5*R**)-1-[2-(*t*-butyldimethylsiloxy)phenyl]-4,5-epoxy-6-(1-ethoxyethoxy)-4-methyl-2-hexyn-1-ol (77% as a mixture of four diastereomeric isomers) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 6.80 (m, 1H), 5.72 (m, 1H), 4.73 (m, 1H), 3.85–3.58 (3H), 3.45(m, 1H), 3.08 (m, 1H), 2.86–2.66 (1H), 1.56 (m, 3H), 1.28 (m, 3H), 1.16 (m, 3H), 1.01 (s, 9H), 0.27 (m, 6H); IR ($CHCl_3$) 2955, 1488, 1259 cm^{-1}; MS m/z (%) 374 (2), 331 (9), 307 (25), 273 (100), 243 (88), 179 (100); Anal. Calcd for $C_{23}H_{36}O_5Si$: C, 65.68; H, 8.63. Found C, 65.77; H, 8.73. Oxidation of this alcohol (41.0 mg, 97.5 μmol) with MnO_2 gave **22** (30.7 mg, 75%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 1.8, 7.9 Hz), 7.40 (ddd, 1H, J = 1.8, 7.3, 8.3 Hz), 7.00 (m, 1H), 6.87 (ddd, 1H, J = 0.4, 1.1, 8.3 Hz), 4.74 (q, 1H, J = 5.3 Hz), 3.88–3.59 (3H), 3.46 (m, 1H), 3.19 (m, 1H), 1.64 (s, 3H), 1.30 (d, 3H, J = 5.3 Hz), 1.15 and 1.14 (t×2, total 3H, J = 7.1 Hz), 1.00 (s, 9H), 0.22 (s, 6H); IR ($CHCl_3$) 2933, 1650, 1478, 1256 cm^{-1}; MS m/z (%) 418 (M$^+$) (0.3), 289 (41), 235 (48), 152 (72), 143 (87), 121 (100).

(4*S, 5*R**)-1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4,5-epoxy-6-(1-ethoxyethoxy)-4-methyl-2-hexyn-1-one (23).** According to the method described in the synthesis of **22** the reaction of (*E*)-3-methyl-2-penten-4-yn-1-ol (2.51 g, 26.1 mmol) gave (2*R**, 3*R**)-2,3-epoxy-3-methyl-4-pentyn-1-ol (2.16 g, 74%) as a colorless

oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (dd, 1H, J = 4.4, 12.4 Hz), 3.69 (dd, 1H, J = 6.2, 12.4 Hz), 3.36 (dd, 1H, J = 4.5, 6.2 Hz), 2.31 (s, 1H), 1.78 (br, 1H), 1.54 (s, 3H); IR ($CHCl_3$) 3605, 3452, 3306, 3017, 1219, 1027, 733 cm^{-1}; Anal. Calcd for $C_6H_8O_2$: C, 63.98; H, 7.19. Found C, 64.27; H, 7.17. The alcohol (1.70 g, 15.1 mmol) was protected with ethoxyethyl group to give (2*S**, 3*R**)-2,3-epoxy-1-(1-ethoxyethoxy)-3-methyl-4-pentyne (2.46 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (q, 1H, J = 5.4 Hz), 3.68–3.44 (4H), 3.34 (t, 1H, J = 5.4 Hz), 2.29 (s, 1H), 1.51 (s, 3H), 1.312 and 1.309 (d×2, total 3H, J = 5.4 Hz), 1.19 (t, 3H, J = 7.1 Hz); IR ($CHCl_3$) 3306, 3015, 1384, 1229, 1133, 1083 cm^{-1}; Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found C, 64.94; H, 8.66. Lithiation of this acetylenic compound (0.89 g, 4.85 mmol) followed by the reaction with **13** (1.14 g, 4.83 mmol) produced (4*S**, 5*R**)-1-[2-(*t*-butyldimethylsiloxy)phenyl]-4,5-epoxy-6-(1-ethoxyethoxy)-4-methyl-2-hexyn-1-ol (1.41 g, 69% as a mixture of four diastereomeric isomers) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 6.80 (m, 1H), 5.70 (m, 1H), 4.74 (m, 1H), 3.70–3.45 (5H), 3.34 (m, 1H), 2.79 (m, 1H), 1.52 (m, 3H), 1.31 (m, 3H), 1.18 (m, 3H), 1.01 (s, 9H), 0.27 (m, 6H); IR ($CHCl_3$) 3020, 2933, 1488. 1258, 919 cm^{-1}; MS m/z (%) 405 [(M–Me)$^+$] (0.3), 375 (2), 363 (5), 331 (9), 317 (14), 273 (85), 243 (100), 179 (100). This alcohol (0.97 g, 2.31 mmol) was oxidized to give **23** (0.73 g, 76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H, J = 1.8, 7.8 Hz), 7.39 (ddd, 1H, J = 1.8, 7.3, 8.2 Hz), 7.00 (m, 1H), 6.86 (dd, 1H, J = 0.9, 8.3 Hz), 4.75 and 4.74 (q×2, total 1H, J = 5.3 Hz), 3.71–3.57 (3H), 3.48 (m, 1H), 3.45 (t, 1H, J = 5.4 Hz), 1.60 (s, 3H), 1.31 (d×2, total 3H, J = 5.4 Hz), 1.19 (t, 3H, J = 7.0 Hz), 0.99 (s, 9H), 0.21 (s, 6 H); IR ($CHCl_3$) 2933, 2210, 1649, 1479, 1254, 751 cm^{-1}; MS m/z (%) 403 [(M–Me)$^+$] (2), 361 (67), 289 (31), 259 (25), 201 (100), 179 (54).

1-[2-(*t*-Butyldimethylsilyloxy)phenyl]-4-(2-tetrahydropyranyloxy)-2-butyn-1-one (24). To a solution of 1-(2-tetrahydropyranyloxy)-2-propyne (0.33 g, 2.35 mmol) in THF (15 mL) was added n-BuLi (1.5 mL, 1.62 M in hexane, 2.43 mmol) at –78 °C and the mixture was stirred at –78 °C for 15 min. To the resulting alkynyllithium solution, THF (4 mL) solution of **13** (0.55 g, 2.35 mmol) was added at –78 °C and the mixture was stirred for 2 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15–50% ethyl acetate/hexane) to give 1-[2-(*t*-butyldimethylsiloxy)phenyl]-4-(2-tetrahydropyranyloxy)-2-butyn-1-ol (0.60 g, 68%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, 1H, J = 1.6, 7.5 Hz), 7.18 (dt, 1H, J = 1.8, 7.8 Hz), 6.96 (dt, 1H, J = 1.1, 7.5 Hz), 6.81 (m, 1H), 5.73 (m, 1H), 4.79 (t, 1H, J = 3.3 Hz), 4.38–4.25 (2H), 3.81 (m, 1H), 3.49 (m, 1H), 2.73 (d, 1H, J = 5.8 Hz), 1.85–1.46 (m, 6H), 1.01 (s, 9H), 0.28 and 0.26 (s×2, total 3H); IR ($CHCl_3$) 3010, 2951, 2933, 2860, 1480, 1258, 1221, 1025, 919, 840, 753 cm^{-1}; MS m/z (%) 275 (2), 236 (9), 217 (13), 179 (39), 85 (100); Anal. Calcd. for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found C, 66.71; H, 8.71. Oxidation of this alcohol (0.42 g, 1.12 mmol) with MnO_2 produced **24** (0.29 g, 69%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, 1H, J = 1.9, 7.9 Hz), 7.38 (ddd, 1H, J = 1.9, 7.3, 9.1 Hz), 7.00 (m, 1H), 6.86 (dd, 1H, J = 1.0, 8.4 Hz), 4.83 (t, 1H, J = 3.2 Hz), 4.45, 4.47 (d×2, each 1H, J = 17 Hz), 3.83 (m, 1H), 3.53 (m, 1H), 1.85–1.48 (6H), 0.99 (s, 9H), 0.22 (s, 6H); IR ($CHCl_3$) 3011, 2952, 2932, 2859, 1649, 1479, 1234, 1028, 755 cm^{-1}; MS m/z (%) 317 [(M-^{t}Bu)$^+$] (55), 233 (32), 217 (100), 189 (100), 85 (83); Anal. Calcd. for $C_{21}H_{30}O_4Si$: C, 67.34; H, 8.07. Found: C, 67.10; H, 7.96.

(*E*)-2-[1-(2-Tetrahydropyranyloxy)buten-3-yl]-4*H*-chromen-4-one (25). The same procedure described for the synthesis of **19** was applied for **21** (25.5 mg, 61.5 μmol) to afford **25** (15.3 mg, 83%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, 1H, J = 1.5, 7.9 Hz), 7.65 (ddd, 1H, J = 1.7, 7.2, 8.6 Hz),

7.47 (dd, 1H, J = 0.7, 8.5 Hz), 7.36 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 6.82 (m, 1H), 6.39 (s, 1H), 4.69 (m, 1H), 4.53 (m, 1H), 4.29 (m, 1H), 3.89 (m, 1H), 3.56 (m, 1H), 1.98 (d, 3H, J = 1.1 Hz), 1.90–1.51(6H); IR ($CHCl_3$) 3011, 2948, 2873, 2857, 1640, 1467, 1377, 1212, 1124, 1026, 775 cm^{-1}; MS m/z (%) 216 [(M–THP+H)$^+$] (79), 199 (58), 187 (88), 121 (66), 85 (100); Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.66; HRMS calcd for $C_{13}H_{12}O_3$ [(M–THP+H)$^+$], 216.0787; found, 216.0804.

2-[(2*R, 3*R**)-2,3-Epoxy-1-(1-ethoxyethyloxy)butan-3-yl]-4*H*-chromen-4-one (26).** The same procedure described for the synthesis of **19** was applied for **22** (11.7 mg, 28.0 μmol) to afford **26** (6.2 mg, 73%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, 1H, J = 1.6, 8.0 Hz), 7.66 (dddd, 1H, J = 0.3, 1.7, 7.2, 8.9 Hz), 7.45 (m, 1H), 7.40 (ddd, 1H, J = 1.0, 7.2, 8.0 Hz), 6.380 and 6.379 (s×2, total 1H), 4.63 and 4.60 (q×2, total 2H, J = 5.3 Hz), 3.63–3.24 (5H), 1.73 (s, 3H), 1.21, 1.19 (d×2, total 3H, J = 5.4 Hz), 1.02, 1.01 (t×2, total 3H, J = 7.1 Hz); IR ($CHCl_3$) 3025, 1650, 1466, 1388, 1129 cm^{-1}; MS m/z (%) 259 [(M–OEt)$^+$] (13), 232 (28), 162 (97), 73 (100).

2-[(2*S, 3*R**)-2,3-epoxy-1-(1-ethoxyethyloxy)butane-3-yl]-4*H*-chromen-4-one (27).** The same procedure described for the synthesis of **19** was applied for **23** (53.5 mg, 0.13 mmol) to afford **27** (28.0 mg, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, 1H, J = 1.6, 8.0 Hz), 7.65 (ddd, 1H, J = 1.7, 7.2, 8.7 Hz), 7.43 (m, 1H), 7.38 (m, 1H), 6.41 (s, 1H), 4.79, 4.78 (q×2, total 1H, J = 5.4 Hz), 3.97–3.62 (3H), 3.50 (m, 1H), 3.37 (dd, 1H, J = 5.1, 5.5 Hz), 1.71 and 1.68 (s×2, total 3H), 1.34 (d, 3H, J = 5.4 Hz), 1.19 (t, 3H, J = 7.1 Hz); IR ($CHCl_3$) 3011, 2990, 1609, 1466, 1383, 1131 cm^{-1}; MS m/z (%) 259 [(M–OEt)$^+$] (5), 232 (16), 214 (100), 189 (54), 171 (50).

2-[(2-tetrahydropyranyloxy)methyl]-4*H*-chromen-4-one (28).
The same procedure described for the synthesis of **19** was applied for **24** (40.7 mg, 0.11 mmol) to afford **28** (20.6 mg, 73%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, 1H, J = 1.7, 7.9 Hz), 7.65 (ddd, 1H, J = 1.7, 7.2, 8.7 Hz), 7.42 (dd, 1H, J = 0.6, 8.5 Hz), 7.38 (ddd, 1H, J = 0.8, 7.1, 8.1 Hz), 6.46 (t, 1H, J = 0.9 Hz), 4.78 (t, 1H, J = 3.3 Hz), 4.62 (dd, 1H, J = 1.0, 15.0 Hz), 4.44 (dd, 1H, J = 0.8, 14.9 Hz), 3.85 (m, 1H), 3.55 (m, 1H), 1.90–1.51 (6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.5, 165.9, 156.5, 133.8, 125.9, 125.2, 124.2, 118.1, 109.4, 98.3, 64.6, 62.0, 30.0, 25.1, 18.6; IR ($CHCl_3$) 3020, 3008, 2949, 2885, 1651, 1467, 1215, 1122, 1036, 745 cm^{-1}; MS m/z (%) 205 (6), 176 [(M–THP+H)$^+$] (37), 160 (100), 85 (79); Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.09; H, 6.19; HRMS calcd for $C_{10}H_8O_3$ [(M–THP+H)$^+$], 176.0474; found, 176.0485. Hydrolysis of **28** (10.5 mg, 40.3 μmol) in refluxing acetone (0.6 mL) and water (0.2 mL) containing a catalytic amount of PPTS gave 2-hydroxymethyl-4*H*-chromen-4-one (6.0 mg, 84%) as a white powder: ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.02 (dd, 1H, J = 1.8, 8.2 Hz), 7.79 (ddd, 1H, J = 1.7, 7.0, 8.5 Hz), 7.60 (dd, 1H, J = 1.0, 8.5 Hz), 7.47 (ddd, 1H, J = 1.1, 7.1, 8.1 Hz), 6.33 (s, 1H), 5.79 (br, 1H), 4.44 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 177.14, 170.09, 155.97, 134.40, 125.54, 125.13, 123.62, 118.38, 107.44, 59.81. These data were identical with those reported.[24]

1-[2-(1-*t*-Butyldimethylsiloxy)naphthyl]-4-(2-tetrahydropyranyloxy)-2-butyn-1-one (29). To a solution of ethylmagnesium bromide (3 M in ethyl ether, 0.26 ml, 0.78 mmol) in THF (4 mL) was added a solution of 1-(2-tetrahydropyranyloxy)-2-propyne (98.8 mg, 0.70 mmol) in THF (1 mL) at 0 °C and the mixture was stirred at 50 °C for 1 h. After the reaction mixture was cooled to ambient temperature, a solution of 2-(1-*t*-butyldimethylsilyloxy)naphthaldehyde (0.22 g, 0.77 mmol) in THF (1 mL) was added and the whole mixture was stirred at ambient temperature for 20 min. The mixture was diluted with sat. NH_4Cl and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give 1-[2-(1-*t*-butyldimethylsiloxy)naphthyl]-4-(2-tetrahydropyranyloxy)-2-butyn-1-ol (162 mg, 54%) as a mixture of diastereoisomer as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H), 7.77 (1H), 7.73 (d, 1H, J = 8.6 Hz), 7.54 (d, 1H, J = 8.6 Hz), 7.47–7.41 (2H), 6.00 (t, 1H, J = 1.7 Hz), 4.80 (t, 1H, J = 3.4 Hz), 4.38–4.28 (2H), 3.81 and 3.72 (m×2, total 1H), 3.50 (m, 1H), 2.20 (br, 1H), 1.85–1.47 (6H), 1.13 and 0.90 (s×2, total 9H), 0.19 and 0.08 (s×2, total 6H); IR ($CHCl_3$) 3020, 2953, 2860, 1374, 1260, 1213, 1088, 1024, 899, 841, 829, 785 cm^{-1}; MS m/z (%) 426 (M^+) (23), 285 (44), 267 (96), 193 (83), 85 (74), 69 (100); HRMS calcd for $C_{25}H_{34}O_4Si$ (M^+) 426.2226; found, 426.2207. To a solution of this alcohol (63.6 mg, 0.15 mmol) in dichloromethane was added manganese (IV) oxide (100.0 mg) and the mixture was stirred for 36 h at ambient temperature. The reaction mixture was diluted with ethyl ether, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **29** (46.8 mg, 73%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (m, 1H), 7.90 (d, 1H, J = 8.8 Hz), 7.78 (m, 1H), 7.56 (ddd, 1H, J = 1.3, 6.9, 8.1 Hz), 7.49 (dd, 1H, J = 1.5, 8.4 Hz), 7.48 (m, 1H), 4.85 (t, 1H, J = 3.2 Hz), 4.50 (s, 2H), 3.84 (ddd, 1H, J = 3.2, 9.3, 12.1 Hz), 3.53 (m, 1H), 1.84–1.50 (m, 6H), 1.12 (s, 9H), 0.10 (s×2, 6H, J = 0.7 Hz); IR ($CHCl_3$) 3021, 2952, 2932, 1649, 1619, 1395, 1231, 1122, 1027, 903, 827, 725 cm^{-1}; MS m/z (%) 409 [(M–Me)$^+$] (7), 367 (99), 283 (97), 267 (99), 239 (100); HRMS calcd for $C_{24}H_{29}O_4Si$ [(M–Me)$^+$] 409.1835; found, 409.1826.

2-[(2-tetrahydropyranyloxy)methyl]-4*H*-naphtho[1,2-*b*]pyran (30). To a solution of **29** (89.5 mg, 0.21 mmol) and 18-crown-6 (137 mg, 0.52 mmol) in *N*,*N*-dimethylformamide (3 mL) was added a potassium fluoride (24.6 mg, 0.42 mmol) at 0 °C and the mixture was stirred at ambient temperature for 4 h. The reaction mixture was diluted with sat. NH_4Cl, and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, 15% ethyl acetate/hexane) to give **30** (53.3 mg, 81%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (m, 1H), 8.13 (d, 1H, J = 8.6 Hz), 7.92 (m, 1H), 7.76 (d, 1H, J = 8.6 Hz), 7.69 (m, 1H), 7.65 (m, 1H), 6.62 (s, 1H), 4.85 (t, 1H, J = 3.2 Hz), 4.78 (dd, 1H, J = 0.8, 14.7 Hz), 4.61 (d, 1H, J = 14.7 Hz), 3.90 (ddd, 1H, J = 3.1, 9.3, 12.4 Hz), 3.59 (m, 1H), 1.91–1.53 (6H); IR ($CHCl_3$) 3021, 2358, 1652, 1212, 774 cm^{-1}; MS m/z (%) 310 (M^+) (100), 254 (38), 226 (61), 210 (98), 181 (85); HRMS calcd for $C_{19}H_{18}O_4$ (M^+) 310.1203; found, 310.1183.

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