Intramolecular Oxygen versus Carbon Alkylation of Naphthoate Esters. A Caveat on the Mechanistic Aspects of Neocarzinostatin Chemistry[1]

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Abstract: α-Hydroxy naphthoate esters are shown to be capable of undergoing intramolecular alkylation at carbon as well as at both oxygen centers. Basic reaction conditions favor intramolecular oxygen alkylation of the phenol moiety in addition to intramolecular carbon alkylation leading to spirolactones. Chemistry in neutral or acidic media appears to proceed via γ-oxo ketene acetal intermediates that are converted to products derived from addition of water followed by cleavage of the resultant orthoacid. γ-Oxo ketene acetal intermediates derived from naphthoate esters are at least 40 times more reactive than those derived from simple β-keto esters. These studies give credence to the proposal that the α-hydroxy naphthoate moiety in neocarzinostatin is capable of participation during the epoxide-opening reaction. Mechanistic consequences of such participation are discussed.

Introduction

Current Mechanistic Understanding of Neocarzinostatin. The enediyne class of antitumor antibiotics represents some of the most potent antitumor agents discovered. Their biological properties appear to be a consequence of their ability to interact with cellular DNA and initiate double-stranded cleavage. Neocarzinostatin[2] was the first member of this family to be discovered. The native drug consists of chromophore **1a** (NCS-chrom), noncovalently complexed with an apoprotein. Chromophore **1a** possesses the full cytotoxic and DNA damaging properties of the parent drug.

Mechanistic understanding of the chemistry of **1a** is rapidly evolving.[2-5] Building upon the seminal biochemical contributions of the Goldberg group at Harvard Medical School, Myers has shown that low-temperature addition of thiol to **1a** under acidic conditions affords cumulene **2a** which undergoes Bergman cyclization to diradical **3a** upon warming in an NMR probe.[3] More recently compound **4**, a simplified version of chromophore **1a**, devoid of both the sugar moiety and the naphthoate residue, has been shown to cyclize to adduct **5** under far more forcing conditions.[4] Myers has further demonstrated that *N*-nitroso derivative **1b** is unreactive up to 0 °C under the acetic acid/thiol conditions which convert **1a** to **2a**; higher temperatures result in decomposition. Based upon these experiments, Myers postulated a mechanism whereby the amino group of the sugar moiety serves to intramolecularly deliver thiolate to the β-face of **1a** at C-12 (Scheme I).

The presence of thiol-containing reagents increases the **efficiency** of DNA functionalization of **1** by a factor of 1000, yet it has been demonstrated that DNA cleavage occurs in the absence of added thiols.[5] Neocarzinostatin chromophore **1a** is also known to be more rapidly consumed with increasing pH, with maximum rate at about pH 8,[6] the approximate pK_a value of methyl thioglycolate,[3b] glutathione,[3b] **and the naphthoate phenol moiety**. The pH profile of NCS-chrom **1a** suggests the possibility of anchimeric assistance by ionized naphthoate ester moiety **1'**, affording γ-oxo ketene acetal **6** as a potential intermediate in the conversion of NCS-chrom **1a** to cumulene **2** as well as in the presently unknown decomposition pathway(s).[7] The observed rate decrease for genesis of model sulfide **4** from diyne **3** as well as the resultant stereochemistry of sulfide **4** is consistent with the absence of the participatory naphthoate moiety. The strongly diminished reactivity of *N*-nitroso compound **1b** could derive from an equilibrium now favoring the neutral naphthoate form, which is presumably substantially less reactive toward participation.[8] Conversion of intermediate **6**[9] to the observed cumulene **2** presumably is also acid catalyzed, protonation of the carbonyl group providing the neutral naphthoate as a highly-activated leaving group which suffers S_N2 bond formation with thiol at the allylically-activated C-12 position (Scheme II).

Hirama has reported isolating an interesting minor (5%) product from aerobic decomposition of NCS-chrom **1a**.[10] It seems clear from spectral evidence that the product bears cis dioxygenation at C-11,12 (J = 4.6 Hz), resulting in the assignment of structure **7** by Hirama.[11] Alternative structures **7-Alt A** and **7-Alt B** were considered in light of the naphthoate participation mechanism discussed above since the reported ^{1}H NMR data for **7** were obtained in methanol,[11] thereby obviating the ability to

(1) Synthesis Via Vinyl Sulfones. 45. For paper 44, see: Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745.

(2) (a) Goldberg, I. H. *Free Radical Biol. Med.* **1987**, *3*, 41. (b) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688. (c) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191 and references cited therein.

(3) (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. (b) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146.

(4) Myers, A. G.; Harrington, P. K.; Kwon, B.-M. *J. Am. Chem. Soc.* **1992**, *114*, 1086.

(5) (a) Kappen, L. S.; Goldberg, I. H. *Nucleic Acids Res.* **1978**, *5*, 2959. (b) Beerman, T. A.; Poon, R.; Goldberg, I. H. *Biochim. Biophys. Acta* **1977**, *475*, 294. (c) Chin, D.-H.; Goldberg, I. H. *Biochemistry* **1986**, *25*, 1009.

(6) (a) Powirk, L. F.; Goldberg, I. H. *Biochemistry* **1980**, *19*, 4773. (b) Kappen, L. S.; Goldberg, I. H. *Biochemistry* **1980**, *19*, 4786.

(7) This question was originally raised by one of us (P.L.F.) at a seminar presented by Professor Myers at Purdue University, Nov 21, 1991. A spirited debate ensued which centered around the ability of the naphthoate ester carbonyl to assume the spatial orientation required for participation.

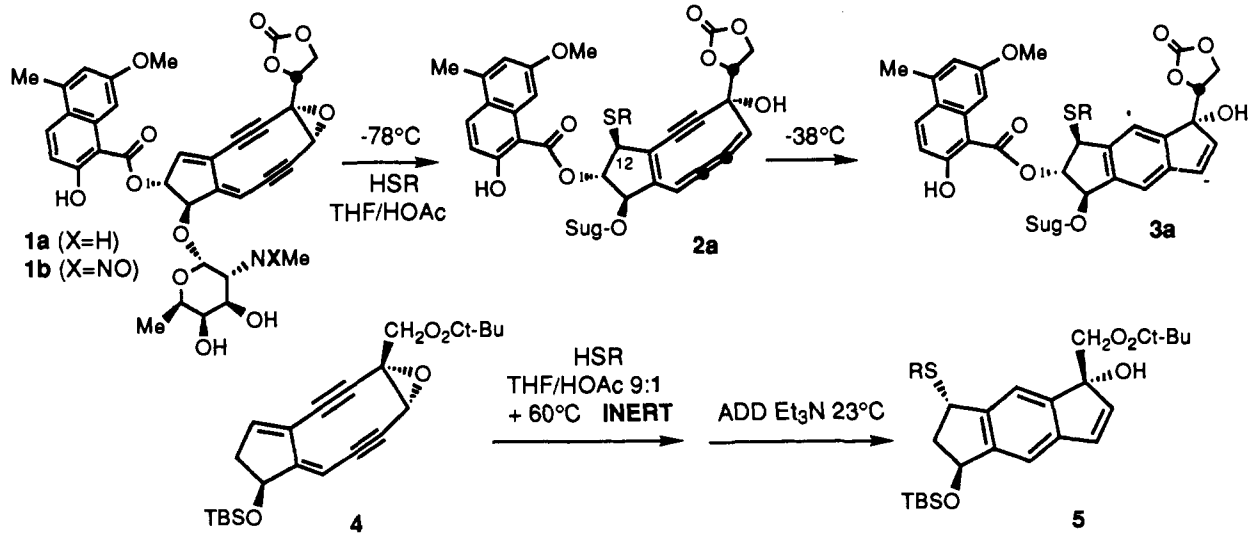
(8) This mechanism implies that the addition of amine or of ammonium acetate to **1b** in acetic acid–tetrahydrofuran in the presence of methyl thioglycolate would again result in formation of **2** at low temperature; conversely, if the participation requires the naphthol to be deprotonated, an alkyl or silyl ether of **1a** should be far less reactive.

(9) Compound **6Z** is arbitrarily shown in the scheme for purposes of simplicity, since MM2 calculations (CAChe v2.8, Textronix) predict it to be the more stable isomer. It should be noted that a conformation of **1** (leading to **6E**) having the naphthol hydrogen within bonding distance of the amine (or, more likely under the Myers reaction conditions, an ammonium acetate ion pair) of the aminoglycoside moiety is calculated to be essentially isoenergetic to the conformation proposed by Myers to explain the intramolecular delivery of thiol.[4]

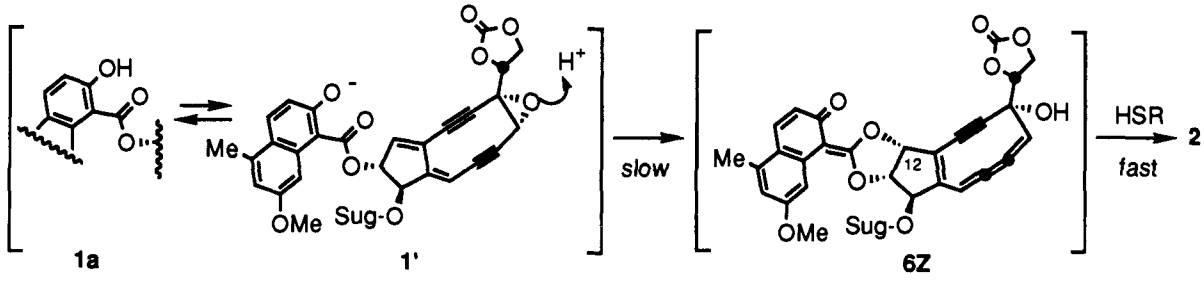
(10) Tanaka, T.; Fujiwara, K.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 5947.

0002-7863/93/1515-4483$04.00/0

Scheme I



Scheme II



directly observe the phenolic proton required for **7** (Scheme III). Formation of **7-Alt A** would involve methanol addition to γ-oxo ketene acetal **8**, giving **9** which could rearrange to orthoacid **10** followed by opening to **7-Alt A**. Alternatively, interception of the γ-oxo ketene acetal intermediate **8** via anchimeric assistance of the aminosugar moiety could provide **11**, which is poised for backside displacement with methanol to afford **7-Alt B**. Communication with Professor Hirama has revealed that compound **7** is most unlikely to have either of the alternative methoxynaphoate structures based upon mass spectrometry and additional ^{1}H NMR evidence.[11] Thus, we are forced to reluctantly conclude that this interesting product is unlikely to be the first example of naphthoate participation in the neocarzinostatin series.

Background on Intramolecular Oxygen Alkylation Resulting in Five-Ring Formation. Prior to initiating a new research program in this area, it was deemed prudent to validate the possibility of anchimeric assistance involving simpler naphthoate esters. It is well known that five-membered ring formation involving intramolecular oxygen alkylation of delocalized ketone (**12**, Y = CH_2)[12] and ester (**12**, Y = O)[13] enolates under kinetic conditions (**12** to **14**) is seen with the almost total exclusion of the thermodynamically-preferred carbon alkylation reaction (**12** to **13**) (Scheme IV). Inspection of enolate **12** reveals that intramolecular alkylation from either the carbon or the oxygen π-orbital of the ambident anion suffers similar geometric difficulty at establishing a collinear transition state for backside displacement at the leaving group–bearing carbon center. Baldwin[12a] has provided a satisfying explanation for the exceptional preference for intramolecular oxygen alkylation which features bond formation via the use of a geometrically more accessible, inplane lone pair on oxygen.

Several apparent exceptions to the rule of intramolecular oxygen alkylation are shown in Scheme V which involve reactions of **12A**,[14] **12B**,[15] and **12C**.[16] In each of these instances, the kinetic intermediates **14A–14C** would be expected to be in ready equilibrium with the starting material, thereby providing an avenue for ultimate formation of the observed carbon-alkylated adducts **13A–13C**.

A bona fide example of five ring formation via kinetic intramolecular carbon alkylation of a ketone enolate involves the base-promoted cyclization of *cis*-allyl halide **15c** (prepared in

(11) Hirama reports (personal communication May 21, 1992) that FABMS of compound **7** showed a small but distinct fragment ion of the naphthoyl ion at *m/e* 215. Additionally, Professor Hirama informed us that under very similar reaction conditions, his collaborator, Professor Mizugaki of the Medical School of Tohoku University, had obtained a similar adduct, devoid of the thioglycolate moiety (see data Scheme III). In addition, the ^{1}H NMR of this latter adduct was obtained in $CDCl_3$, and the naphthoate phenolic proton is clearly observed as a sharp singlet at 11.22 ppm. We sincerely thank Professor Hirama for his instantaneous replies to our two requests (Aug 21, 1992; Feb 5, 1993) for additional information.

(12) (a) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233. (b) House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978**, *43*, 700. (c) Danishefsky, S.; Etheredge, S. J.; Dynak, J.; McCurry, P. *J. Org. Chem.* **1974**, *39*, 2658. (d) Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. *Bull. Soc. Chim. Fr.* **1978**, *78*, 131. (e) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 1173. (f) Mussatto, M. C.; Savoia, D.; Trombini, C.; Umani-Ronchi, *J. Chem. Soc., Perkin Trans. I* **1980**, 260. (g) Pearson, A. J. *J. Chem. Soc., Perkin Trans. I* **1980**, 400. (h) van Tamelen, E. E.; Hwu, J. R.; Leiden, T. M. *J. Chem. Soc., Chem. Commun.* **1983**, 62. (i) Delair, T.; Doutheau, A. *Tetrahedron Lett.* **1986**, *27*, 2859. (j) Lygo, B.; O'Connor, N. *Synlett* **1992**, 529.

(13) (a) Parker, C. O. *J. Am. Chem. Soc.* **1956**, *78*, 4944. (b) Corey, E. J.; Das, J. *Tetrahedron Lett.* **1982**, *23*, 4217. (c) Broadhurst, M. D. *J. Org. Chem.* **1985**, *50*, 1117. (d) Pattenden, G.; Smith, G. F. *Tetrahedron Lett.* **1990**, *31*, 6557. (e) Review: Adams, E.; Hiegemann, M.; Duddeck, H.; Welzel, P. *Tetrahedron* **1990**, *46*, 5975. (f) Review: Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron* **1991**, *47*, 975.

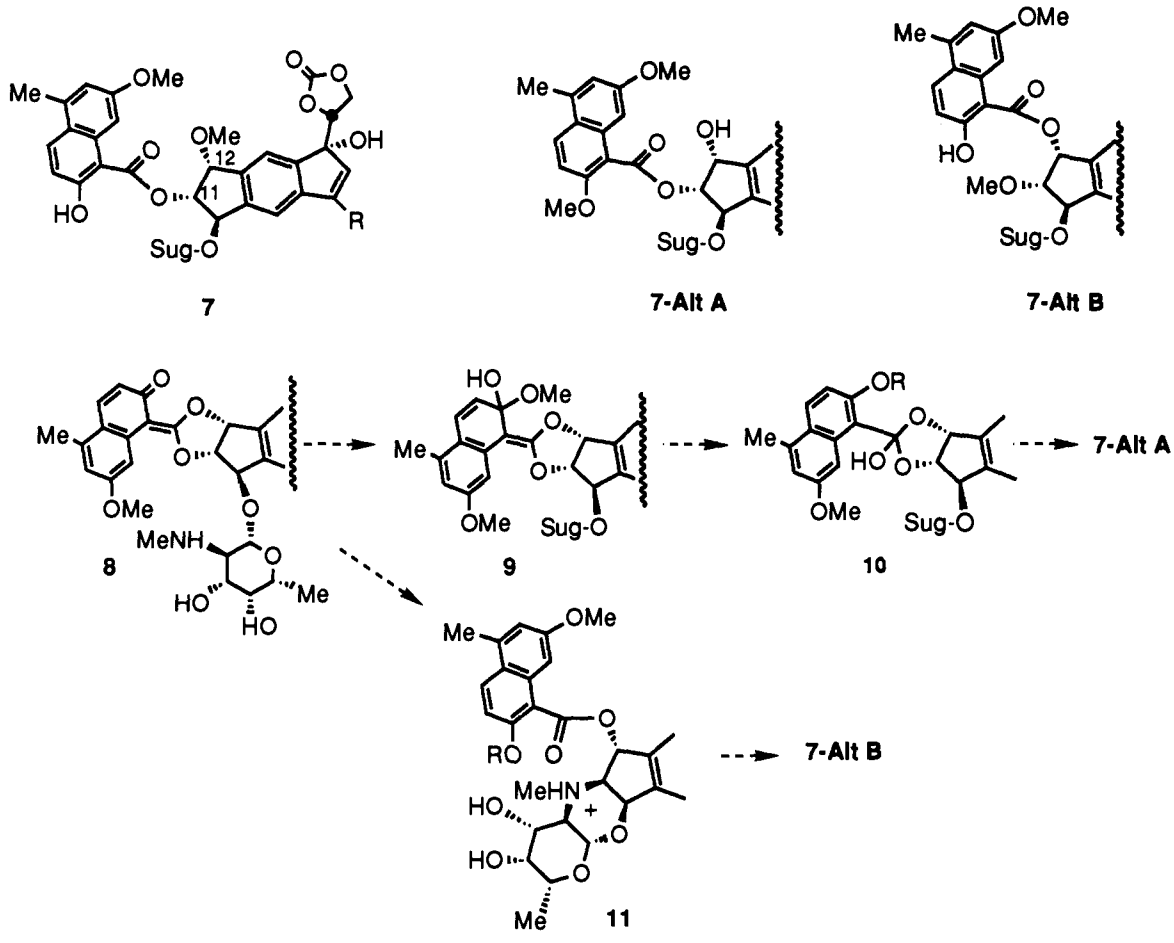
(14) (a) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465. (b) Stork, G.; Saccomano, N. A. *Nouv. J. Chim.* **1986**, *10*, 677. (c) Stork, G.; Saccomano, N. A. *Tetrahedron Lett.* **1987**, *28*, 2087. (d) Kitahara, T.; Mori, K.; Matsui, M.; Iwamoto, M.; Takagi, Y.; Warita, Y. *Agric. Biol. Chem.* **1984**, *48*, 1731.

(15) (a) Li, T.-T.; Wu, Y.-L. *Tetrahedron Lett.* **1988**, *29*, 4039. (b) Somoza, C.; Darias, J.; Ruveda, E. A. *J. Org. Chem.* **1989**, *54*, 1539.

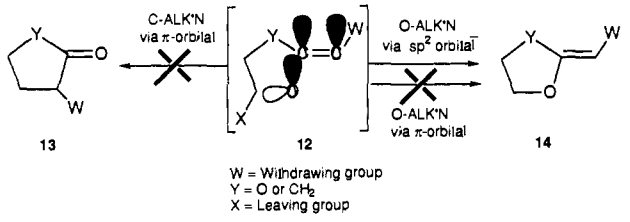
(16) Ager, D. J.; Mole, S. J. *Tetrahedron Lett.* **1988**, *29*, 4807. See also: Reissig, H. L. *Nachr. Chem., Tech. Lab.* **1986**, *34*, 162.

Scheme III

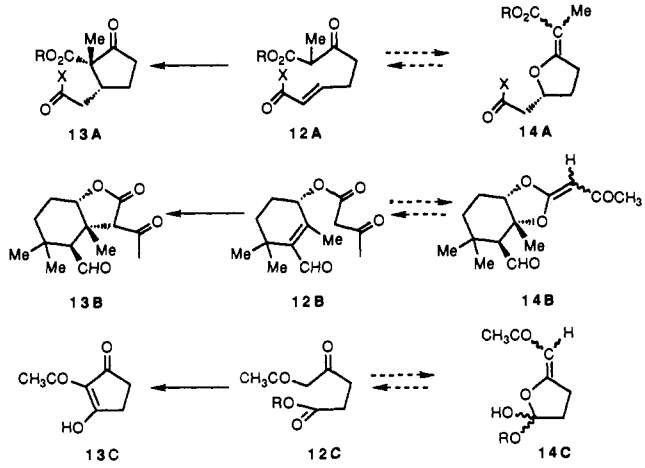
δH_{11}	δH_{12}	NMR solvent	Investigator	R=	J_{10-11}	J_{11-12}
5.87δ	5.31δ	MeOD	Hirama	SCH_2CO_2Me	4.6 Hz	4.6 Hz
5.82δ	5.29δ	$CDCl_3$	Mizugaki	H	5.0 Hz	5.0 Hz



Scheme IV



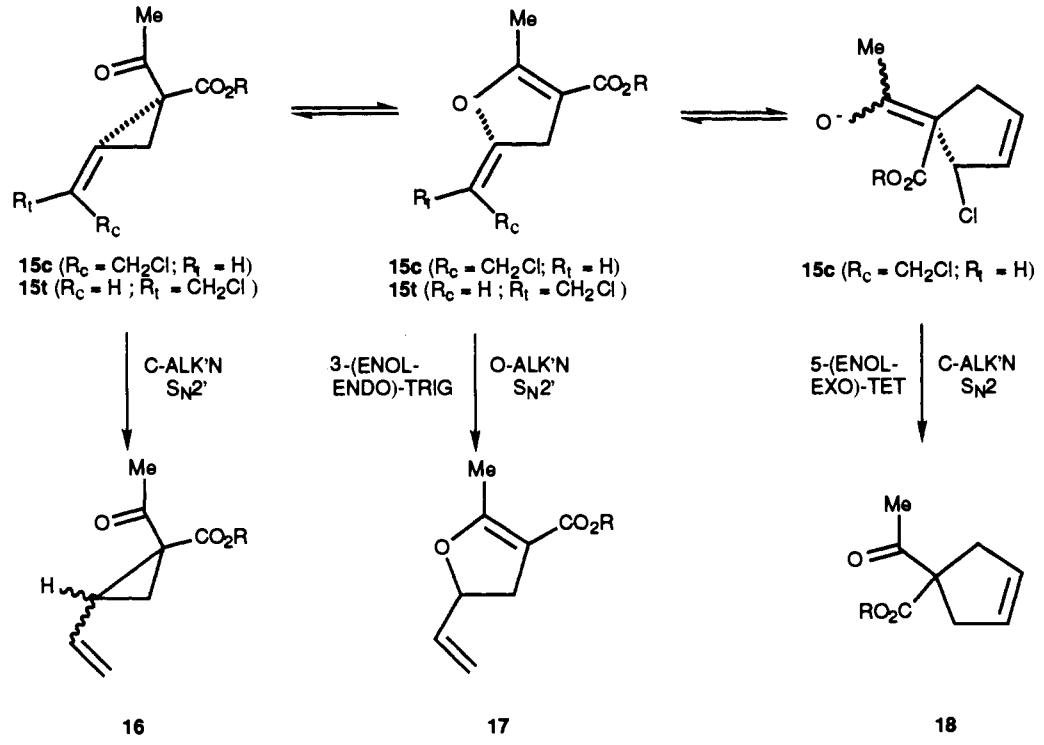
Scheme V



situ from the reaction of acetoacetate and the corresponding ene-1,4 dihalide).[17] Treatment of this material under various conditions provides a mixture of cyclopentene **18** and vinyl cyclopropyl esters **16** in ratios which vary from 97:3 to 3:97 (only traces of the O-alkylation product **17** were isolated) (Scheme VI). Similar reaction of *trans*-allyl halide **15t** affords mixtures of **16** and **17**, production of cyclopentene ester **18** being geometrically impossible.[18] Formation of **18** from **15c** is formally in accord with the Baldwin postulate of preference for a 5-(enol-exo) process over one which is 5-(enol-endo).[19] However, it must also be recognized that *those factors which serve to insure formation of* **14** from **12** *are also present in* **15c**.[20] Therefore, it seems reasonable to consider the fundamental difference between the S_N2 and the S_N2' reactions as a major factor involved in the observed reactivity of **15c**. The (higher energy) S_N2' process requires a more highly ordered transition state which necessitates the π-orbitals of the olefin being *simultaneously well-aligned with both the enolate carbon as well as the departing carbon–*

(17) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928.
(18) (a) Bahurel, Y.; Collonges, F.; Menet, A.; Pautet, F.; Poncet, A.; Descotes, G. *Bull. Soc. Chim. Fr.* **1971**, 2203. (b) Vardapetyan, A. A.; Khachatryan, D. S.; Panosyan, G. A.; Morlyan, N. M. *J. Org. Chem. USSR* **1986**, *22*, 2034.
(19) Baldwin, J. E. *Tetrahedron* **1982**, *38*, 2939.

Scheme VI



chlorine bond. Stated in another way, direct S_N2 bond formation is less geometrically demanding and therefore preferred over polarity-induced (S_N2') bond formation.[21]

Results

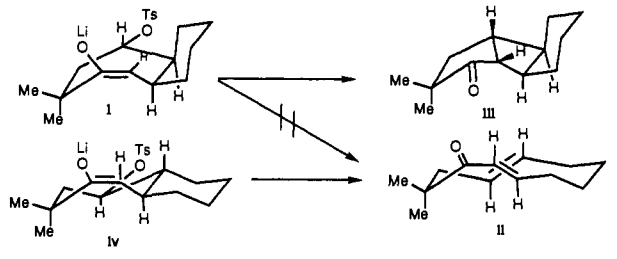
β-Chloroethyl Naphthoate Model System. Activation of the simple naphthoic carboxylates **19** and **22** followed by reaction of 2-chloroethanol afforded 2-chloroethyl 2-hydroxy-1-naphthoate (**20**) and 2-chloroethyl 1-hydroxy-2-naphthoate (**23**), respectively (Scheme VII). The aromatic hydroxynaphthoate esters **20** and **23** appear to be of approximately comparable reactivity to simple β-keto esters.[13] While the tetralone **26** ("dihydro **23**") is converted to isolable γ-oxo ketene acetal **27**[13f] when treated with 4 equiv of potassium carbonate in dimethylformamide for 16 h at 25 °C, naphthoate **20** is transformed to hydroxyethyl ester **21**; isomeric naphthoate ester **23** affords a 1:4 mixture of hydroxyethyl ester **24** and intramolecular oxygen alkylation product **25**. It is likely that hydroxyethyl esters **21** and **24** arise via the addition of adventitious water to intermediates **28** and **29**, respectively. In this instance, independent evidence was not sought to rule out direct displacement by water of the primary chloride, but as will be seen in latter examples, such an event seems far less likely than a mechanism involving intervention of the γ-oxo ketene acetal intermediates **28** and **29**. While it was originally anticipated that these simple β-chloroethyl naphthoates might be *less reactive* than **26** since either carbon or oxygen participation requires disturbing the aromaticity of the phenolic ring, it was also well known that intermolecular carbon alkylation reactions of naphthols is often competitive with oxygen alkylation since the formation of an enone moiety largely offsets the enthalpic cost of aromaticity loss.[22]

Chemistry of Acyclic *cis*- and *trans*-4-Halo-2-buten-1-yl Naphthoate Model Systems under Basic Conditions. Attention was next directed to the chemistry of simple acyclic trans and cis allylic halides **32t-Br** and **32c-Cl**. These materials were easily obtained in high yield simply by treatment of 2-hydroxy-1-naphthoic acid, sodium salt (**19**) with 5 equiv of the appropriate 1,4-dihalo-2-butenes for 15–17 h at room temperature in acetone and DMF, respectively, yielding **32t-Br** and **32c-Cl** in 90% and 95% yields (Scheme VIII).

The outcome of the reaction of **32t-Br** under basic conditions was very solvent dependent. When treated with 2 equiv of sodium hydride in tetrahydrofuran for 3 days, two new products were isolated. Although the crude yield of these materials was 60%, separation on silica was attended by massive material loss. Their proton NMR spectra showed three narrow resonances in the 6.5 to 4 ppm region, each displaying intensity 2H relative to the 1H of the six individual aryl resonances. Exact mass determination ($C_{30}H_{24}O_6$) in conjunction with ^{13}C NMR (15 resonances in $CDCl_3$) was consistent with the dimer structure **33** for the high R_f isomer. The low R_f isomer also exhibited a very similar ^{13}C NMR (15 resonances in $CDCl_3$); however the chemical ionization mass spectrum showed only a weak m/e 481 peak consistent with

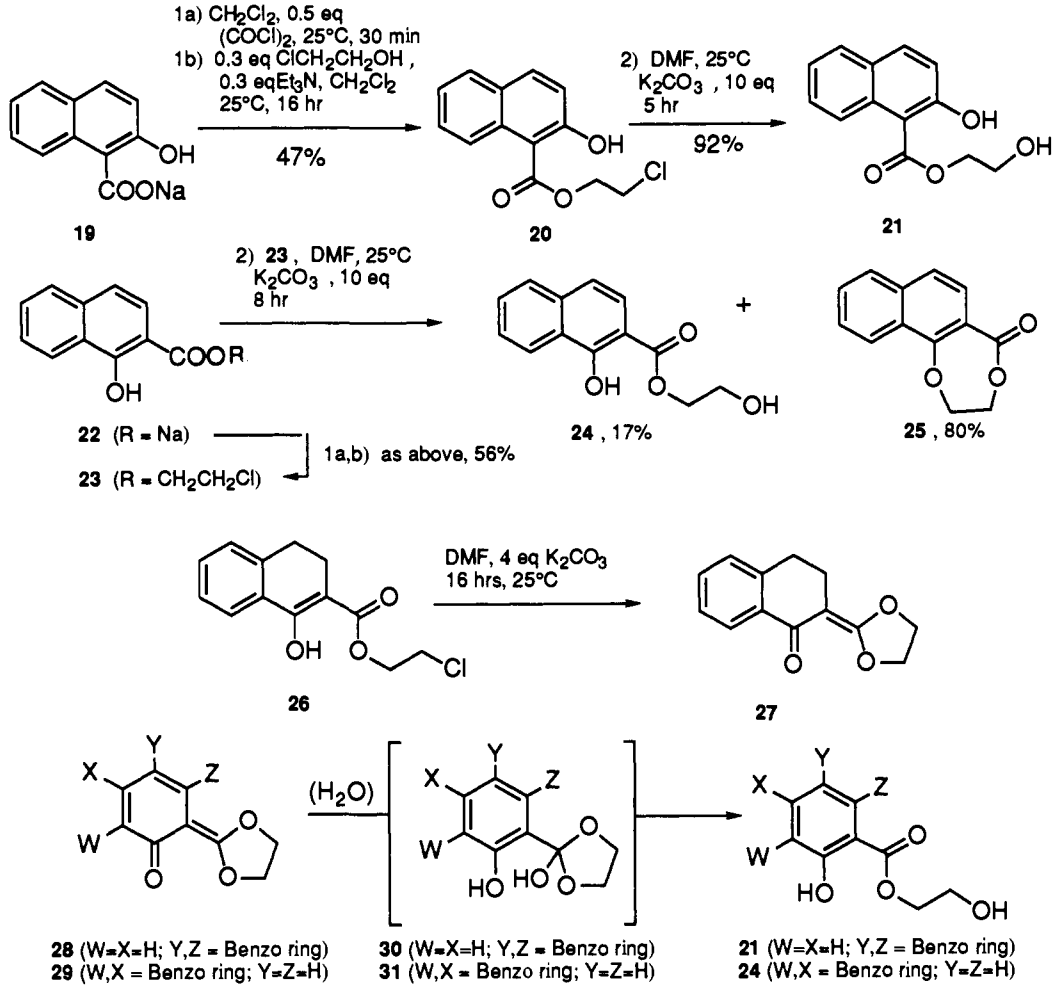
(20) MM2 calculations (CAChe v2.8, Textronix) of the transition states modeled from **15c** favor formation of **17** over **18** by ~25 kcal/mol. While gas-phase calculations of such partially-bonded structures are clearly suspect, it is fair to say that the nonbonding lone pair of enolate **15c** has an excellent approach trajectory, which apparently maintains full delocalization of the extended enolate. The major difficulty in this calculation is its insensitivity to the stereoelectronic requirement of orbital correlation between the carbon–chlorine bond and the olefinic π-system.[22]

(21) A similar situation is seen in the case of enolate-promoted fragmentation reactions (Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567). Compound i bears an appropriate geometry for enolate-promoted fragmentation (a polarity-induced process) to dienone ii. However, since its folded conformation places the participatory orbital in an appropriate spatial location for S_N2 displacement of the tosylate, formation of the cyclobutanone iii is the only reaction observed. Fragmentation is only possible in the case of extended conformer iv, where the enolate orbital is not appropriately alligned for intramolecular alkylation.

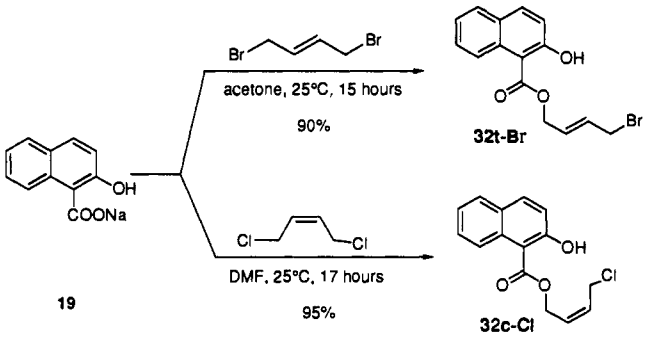


(22) Reutov, O. A.; Kurts, A. L. *Russ. Chem. Rev.* **1977**, *11*, 1040.

Scheme VII



Scheme VIII



the presence of the known 10% contamination of the high R_f isomer with no significant higher m/e peaks. It was originally postulated that the two compounds were atropisomers,[23] with the macrocycle having two low energy conformations separated by a high energy barrier. However, heating these isomers in toluene or xylene at reflux for extended periods of time did not effect their interconversion. Furthermore, manipulation of these structures using either physical or electronic models seemed to effectively dispel the notion that these materials were isolable conformational isomers.

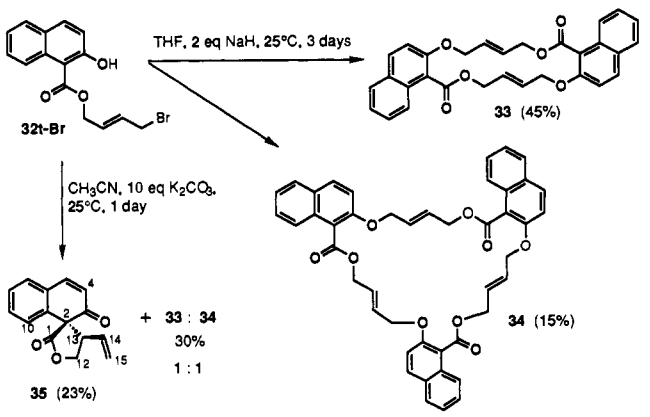
Elucidation of the difference between the two dimeric isomers was hampered by the lack of olefinic coupling information using ^{1}H NMR at 300 MHz in $CDCl_3$. Furthermore, attempts to simplify the spectra of these dimers using europium shift reagents (up to 200 mol %) failed to differentially shift the olefinic protons; shifts were observed, but the olefinic hydrogens of both isomers did not become resolved. A better ^{1}H NMR spectra was obtained on the high R_f dimer using acetone-d_6 at 600 MHz. Under these conditions, the olefins were revealed as a clear X_2ABY_2 pattern (J_{ab} = 15.5 Hz; J_{ax} = 3.7 Hz; J_{by} = 4.3 Hz).[24] Under similar spectral conditions, the low R_f trimer exhibited a poorly-resolved second-order pattern. However, using benzene-d_6, the low R_f trimer was nicely resolved, even at 300 MHz, into a X_2ABY_2 pattern (J_{ab} = 15.6 Hz; J_{ax} = 5.5 Hz; J_{by} = 4.6 Hz).[24] Thus, it was concluded that the high R_f isomer was diolide **33**, and the low R_f isomer was triolide **34**. A new attempt at mass spectrometry using fast atom bombardment revealed a clear m/e 721 ion ($C_{45}H_{36}O_9$ by exact mass measurement), thereby substantiating the assignment of triolide **34**.

By way of comparison, treatment of **32t-Br** in chloroform with potassium carbonate resulted in very slow phenol deprotonation, and the anion produced reacted sluggishly, simply undergoing decomposition after several days. In acetonitrile, reaction of **32t-Br** with 10 equiv of potassium carbonate provided the two macrocycles **33** and **34** in 30% yield (ratio ~1:1) along with 23%

(23) (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694. (b) Elmore, S. W.; Paquette, L. A. *Tetrahedron Lett.* **1991**, *32*, 319. (c) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. *J. Am. Chem. Soc.* **1991**, *113*, 1335. (d) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. (e) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (f) Oki, M. *Top. Stereochem.* **1983**, *14*, 1. (g) Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. *J. Am. Chem. Soc.* **1976**, *98*, 6389. (h) Becker, D.; Hughes, L. R.; Raphael, R. A. *Chem. Soc., Perkin Trans.* **1977**, *77*, 1674.

(24) Copies of the spectra may be found in the supplementary material.
(25) See the conversion of **45-S** to **53/54** for another example.
(26) Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110.

Scheme IX



of C-alkylation product **35** as a single diastereomer (Scheme IX). The stereochemistry of the compound was determined by NOE difference spectroscopy. Strong interactions were observed between H_{10} and H_{13}. *It is believed that this result represents the first example of five-ring formation from a β-keto ester where intramolecular C-alkylation has been observed under kinetic conditions.*[25,26]

Chemistry of Acyclic *cis*- and *trans*-4-Halo-2-buten-1-yl Naphthoate Model Systems under Acidic Conditions. Attention was next turned to chemistry more relevant to the mechanism of the transformations involved with neocarzinostatin under acidic conditions. Allyl halides **32t-Br** and **32c-Cl** were treated with silver fluoroborate in a variety of solvents in order to study the regiochemistry of participation of the naphthoate moiety under conditions where the phenol moiety was presumably present in protonated form.

The silver fluoroborate-promoted chemistry of simple allylic halides **32t-Br** and **32c-Cl** can be understood in terms of the mechanism shown in Scheme X. Activation of the carbon–halogen bond provides an intermediate capable of following two competitive pathways: in the presence of relatively high concentration of nucleophiles, direct substitution can occur at C-4 and/or C-2 via S_N2 and S_N2' reactions, yielding adducts **36t-Nuc** (or **36c-Nuc**) and **37-Nuc**, respectively. However, when the concentration of the nucleophilic partner falls below some critical value, intramolecular alkylation of the ester carbonyl oxygen can compete to afford protonated γ-oxo ketene acetal intermediate **39**. This intermediate is capable of yielding **36t-Nuc** (but presumably not **36c-Nuc**) and **37-Nuc** via S_N2' and S_N2 chemistry but can also undergo hydration to orthoacid **40**, the progenitor of naphthoate alcohols **37-OH** and **38-OH**. While starting with **32t-Br**, the immediate precursor of **36t-Nuc** and **37-Nuc** cannot be ascertained by simple inspection of the product composition, and it appears reasonable to assume that in the case of **32c-Cl**, the **36c-OAc**/**36t-OAc** ratio of 23/15 is indicative of the partitioning between the direct S_N2 reaction at C-4 of **32c-Cl** and the S_N2' addition at C-4 of intermediate **39**. More importantly, it seems assured that **38-OH** *can only arise via the participation mechanism* (appropriate controls insure that **38-OH** is not derived by rearrangement of one of the other products). Furthermore, those reactions which produce **37-OH** *in the absence of* ***36-OH*** are unlikely to have arisen from either S_N2/S_N2' manifold. Additional experiments are summarized in Table I.

Preparation of Cyclopentenyl Models for Testing Fused-Mode Naphthoate Participation. The final set of substrates examined were derived from cyclopentene in order to more closely approximate the environment present in the proposed neocarzinostatin transformation. Sequential treatment of epoxy vinyl sulfone **41**[26] in dichloromethane with six portions of TMSCl over 24 h, followed by stirring an additional 24 h and hydrolysis of the product mixture with 5% hydrochloric acid, provided chloro alcohol **42-Cl** in 78% isolated yield along with 9% of **43-Cl** and 2% of rearrangement product **44**.[27] When the same procedure was applied using TMSBr, the direct S_N2 product **43-Br** was generated in 97% yield. By comparison, when **41** was treated with 1.6 equiv of Li_2NiBr_4,[28] a 42% yield of **42-Br** and **43-Br** was obtained in a ratio of 1:3 (Scheme XI).

Several methods were attempted for the esterification of chloro alcohol **42-Cl**. Activation of 2-hydroxy-1-naphthoic acid, sodium salt was unsuccessful using carbonyl diimidazole[29] in tetrahydrofuran at reflux or triphosgene[30] in dichloromethane or tetrahydrofuran. When the free acid was treated with thionyl chloride in dichloromethane followed by addition of triethylamine along with 2-butanol, no ester was formed. Success was achieved when **19** was treated with 0.5 equiv of oxalyl chloride[31] at room temperature in dichloromethane for 30 min, followed by the addition of 0.3 equiv of **42-Cl** premixed with 0.3 equiv of triethylamine in dichloromethane. After 1 day at room temperature, **45-S** was isolated in 56% yield (Scheme XII).

Synthesis of model **45-H** devoid of the phenyl sulfone moiety was most unsatisfactory. Freshly distilled cyclopentadiene was oxidized via the literature procedure to 3,4-epoxycyclopentene (**46**).[32] A large variety of conditions were examined for the synthesis of cis-chloro alcohol **47**, a representative sample of which is shown in Table II.[33] The high instability of the product made the quality of the transformations difficult to assess. Indeed, **47** could not be stored for extended periods, and heavy decomposition occurred during aqueous workup and chromatography on silica gel. Cyclopentenone **50** is believed to be the main decomposition product; its low boiling point would explain the low recovery in all processes (Scheme XIII).

Eventually the halocuprate reaction (entry 5) was performed on a large scale, producing a 2:1 mixture of **47** and **48** in an isolated yield of 11%. Esterification of the alcohol mixture was accomplished following the same protocol as for the phenyl sulfone analog **45-S**. Compound **45-H** was produced in 40% yield along with 10% of **51**. HPLC was required for isolation of the pure cis isomer (Scheme XIV).

Reaction of Cyclopentenyl Models 45-S and 45-H under Basic and Acidic Conditions. The product composition resulting from reaction of phenyl sulfone **45-S** under basic conditions (Table III), entries 1–4) was highly solvent dependent, with intramolecular phenolate oxygen alkylation being observed for the first time in the production of seven-ring lactone **52-S**. Both diastereomeric spirolactones **53-S** and **54-S** were also characterized as resulting from the very unusual *5-exo-trig* intramolecular carbon alkylation process. No evidence was obtained for the presence of γ-oxo ketene acetal intermediates under these basic conditions.

Phenyl sulfone **45-S** reacted with silver tetrafluoroborate in acetic acid to produce a mixture of alcohols **55-S** and **56-S** as the only products (Table III, entry 5). Reactions which afforded products in the acidic manifold revealed that (1) **45-S** did not react with excess silver fluoroborate in chloroform (control a);

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Scheme X

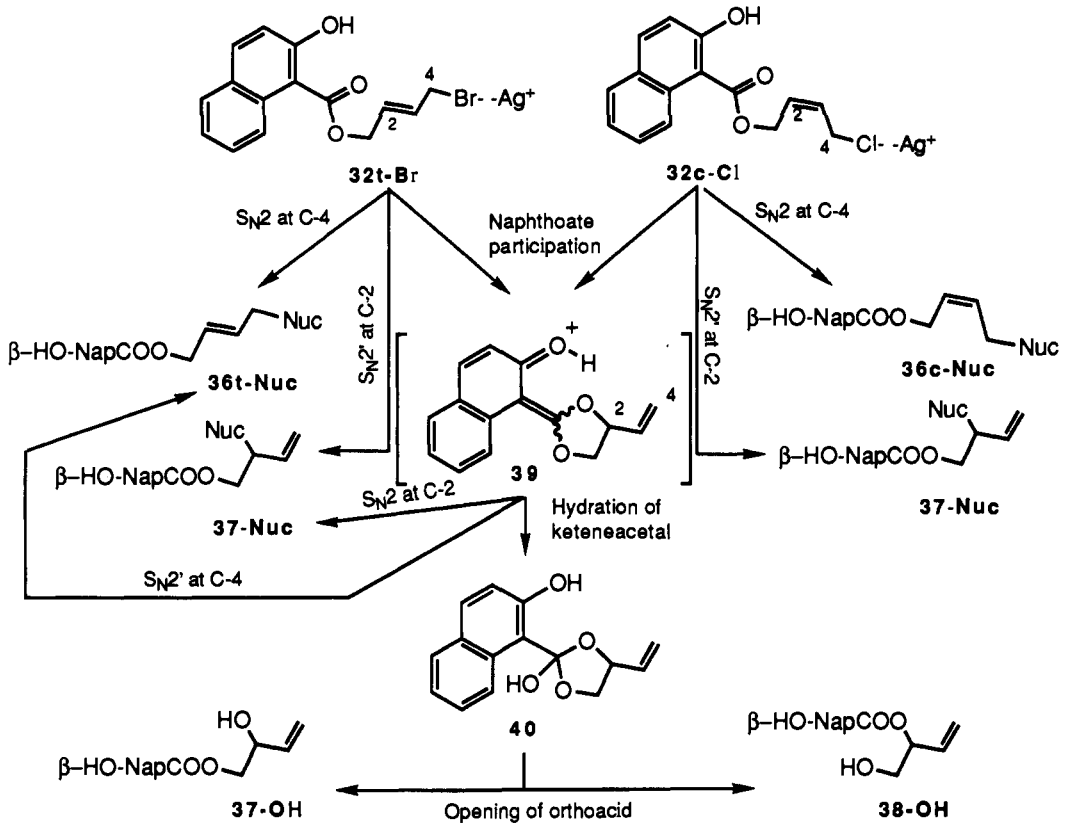


Table I. Reactions of **32-Br** and **32c-Cl** (equiv) under Acidic Conditions

run	SM	solvent	additive	time[a]	products (yield) +/or [NMR ratio]
1t	**32t-Br**	CH_3CO_2H	$AgBF_4$ (2.2)	5 min	**37-OAc** (19%) + **36t-OAc** (43%) + **37-OH** (11%) + **38-OH** (18%) + **36t-OH** (none)
1c	**32c-Cl**	CH_3CO_2H	$AgBF_4$ (2.2)	23 h	**32c-Cl** (12%) + **36c-OAc** (23%) + **36t-OAc** (15%) + **37-OAc** (25%) + **37-OH** (7%) + **38-OH** (4%) + **36c-OH** (none) + **36t-OH** (none)
2c	**32t-Br**	CD_3COCD_3	$AgBF_4$ (2.0)	5 min	**37-OH** (20%) + **38-OH** (20%) + **36t-OH**, (59%)
cntl a	**32t-Br**	CD_3CO_2D	none	7 days	**32t-Br** [quant]
cntl b	**37-OAc**	CH_3CO_2H	$AgBF_4$ (2.2)	15 days	**37-OAc** [quant]
cntl c	**36t-OAc**	CH_3CO_2H	$AgBF_4$ (2.2)	15 days	**36t-OAc** [quant]
cntl d	**36c-OAc**	CH_3CO_2H	$AgBF_4$ (2.2)	7 days	**36c-OAc** [quant]
cntl e	**37-OH**	CH_3CO_2H	$AgBF_4$ (2.2)	9 days	**37-OH** [quant]
cntl f	**38-OH**	CH_3CO_2H	$AgBF_4$ (2.2)	9 days	**38-OH** [quant]
3.1t	**32t-Br**	97.5% CH_3NO_2 2.5% D_2O	$AgBF_4$ (2.0)	5 min	**37-OH** + **38-OH** + **36t-OH** [1:1:0.70]
3.2t	**32t-Br**	99.5% CH_3NO_2 0.5% D_2O	$AgBF_4$ (2.0)	5 min	**37-OH** + **38-OH** + **36t-OH** [1:1:0.35]
3.3t	**32t-Br**	"100%" CH_3NO_2	$AgBF_4$ (2.0)	5 min	**37-OH** + **38-OH** + **36t-OH** [1:1:0], (90%)
3c	**32c-Cl**	"100%" CD_3NO_2	$AgBF_4$ (2.0)	15 h	**32c-Cl** (30%) + **37-OH** + (25%) + **38-OH** (12%) + **36c-OH** (<2%) + **36t-OH** (none)

[a] All reactions are run at 25 °C.

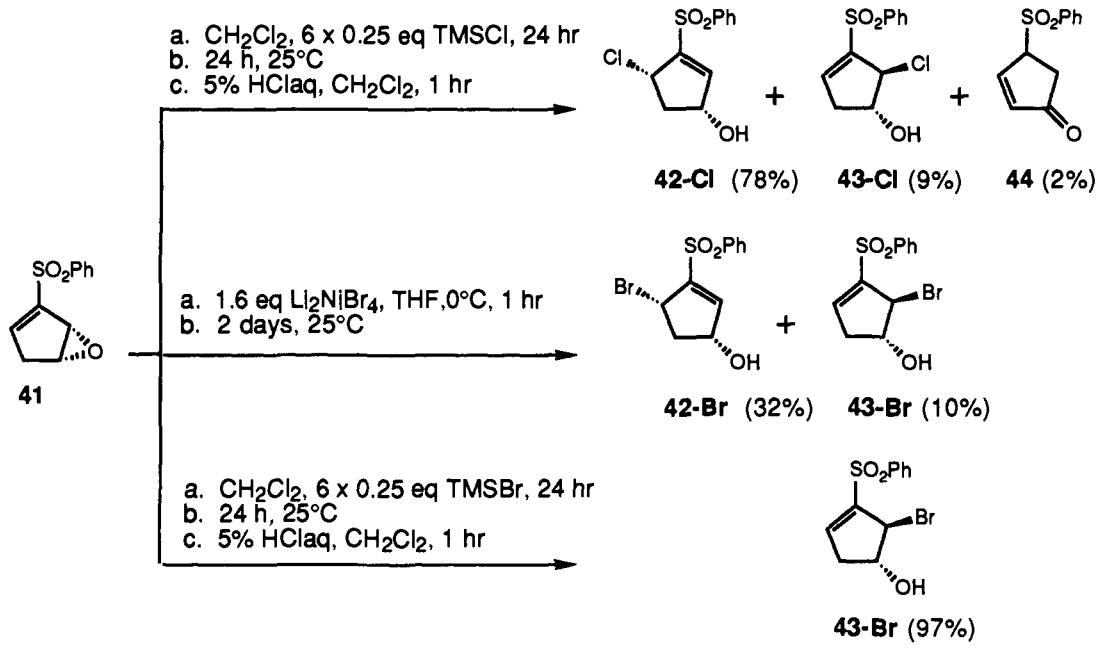
(2) in acetic acid large amounts of silver fluoroborate were necessary to achieve reaction on a reasonable time scale (control b, entry 5); (3) the equilibrium ratio of **55-S** to **56-S** was approximately 3:2 in four different solvents (controls c, d, h, and i, Table III, footnote b); (4) addition of external nucleophile/bases such as sodium acetate or triethylamine did not increase the rate of the reaction (controls f and g); (5) the basic manifold products **52-S**, **53-S**, and **54-S** are not intermediates in the synthesis of **55-S** or **56-S** (controls j–l). It must be stressed that the time scale for establishment of the 3:2 equilibrium ratio of alcohols **55-S** and **56-S** is substantially longer than that of the reaction in acetic acid; therefore, one may confidently conclude that these materials are both formed at the initial stages of the reaction, presumably from hydrolysis of a common γ-oxo ketene acetal intermediate (controls c and d).

Cyclopentene model **45-H** reacted within seconds when treated with 2 equiv of silver tetrafluoroborate in acetic acid at room temperature to produce the acetates **58-H** and **57-H** in 57% and 23% yield, respectively (Table III, entry 6). By comparison, when **45-H** was reacted with 2 equiv of silver tetrafluoroborate in nitromethane, two polar, very unstable compounds were observed by TLC; unfortunately, both decomposed upon chromatography. However, treatment of **45-H** with silver tetrafluoroborate in nitromethane followed by addition of 20 equiv of acetic anhydride and 20 equiv of pyridine provided the diacetates **55-H′** and **56-H′** in 64% and 30% yield, respectively (Table III, entry 7).

Discussion

Interpretation of the Experiments of Table III Using a γ-Oxo ketene acetal Mechanism. The experiments in Table III that generated products in the acidic manifold are in complete accord with a mechanism which requires the presence of γ-oxo ketene acetal intermediate I (Scheme XVI). Naphthoate **45-H**, devoid

Scheme XI



Scheme XII

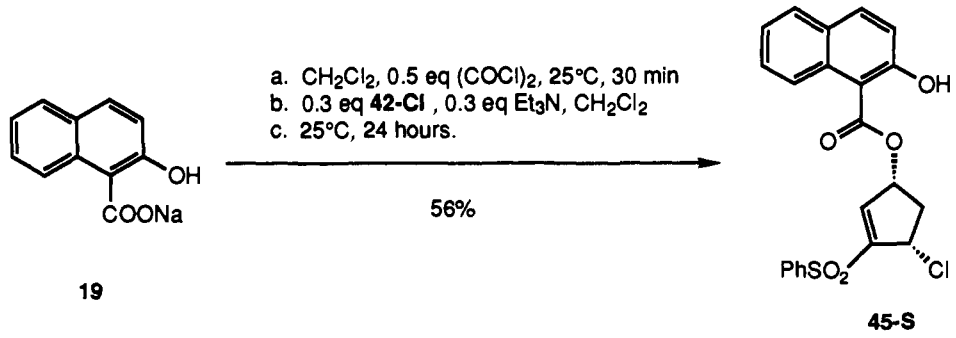


Table II. Partial Survey of Methods for Conversion of **46** to **47**

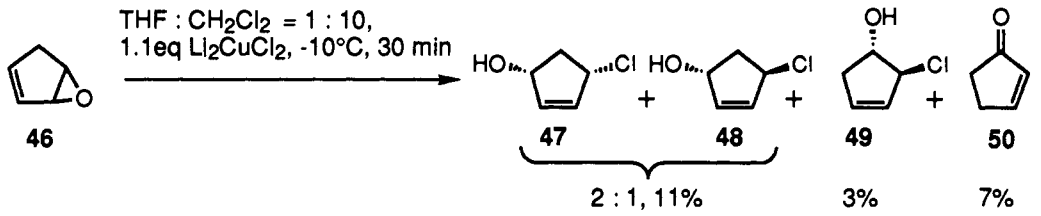
entry	conditions	47:48:49	(yield, %)
1	THF, 0.005 equiv $Pd(PPh_3)_4$, 2 equiv of LiCl, −10 °C[34]	decomposition	
2	THF, 0.005 equiv $Pd(PPh_3)_4$, 2 equiv pyr·HCl, −10 °C	20:15:65	
3	THF, 0.005 equiv $Pd(PPh_3)_4$, 2 equiv TMSCl, 25 °C	45:25:30	
4	THF, 1.1 equiv Li_2CuCl_2, 25 °C[35]	25:20:55	
5	THF:CH_2Cl_2 = 1:10, 1,1 equiv Li_2CuCl_2, −10 °C	55:24:21	(41)
6	THF, 1 equiv $TiCl_4$, 1 equiv LiCl, −78 °C[36]	16:50:34	(56)

of the sulfone moiety, undergoes the most rapid reaction with silver fluoroborate in acetic acid, producing a pair of adducts (**57** and **58**) which have undergone substitution of acetate at C-4. While this is formally in accord with trapping of an allylic cation, it can also be nicely explained by S_N2' reaction of intermediate I with acetic acid. When the reaction of **45-H** is conducted in nominally anhydrous nitromethane, formation of products **55-H'** and **56-H'** (after bis-acetylation to facilitate isolation) would seem to absolutely demand the intermediacy of γ-oxo ketene acetal I. In light of this latter result, it is hard to imagine that an incipient allylic cation intermediate could avoid naphthoate participation. Similarly, formation of **55-S** and **56-S** from reaction of **45-S** and silver fluoroborate in four different solvents is consistent with the proposed mechanism. It is interesting to note that the reaction of **45-S** in acetic acid did not produce any significant amount of the S_N2' adducts **57-S** or **58-S**; apparently, steric shielding of C-4 by the phenyl sulfone moiety outweighs the expected electronic activation.

Attempts to detect γ-oxo ketene acetal I were uniformly unsuccessful. Moreover, all efforts to provide absolutely anhydrous acetic acid, so as to avoid hydration of I to **II-OH**, also failed to generate NMR evidence for γ-oxo ketene acetal I. An anhydrous mechanism for conversion of I to products **55-S**/**56-S** involves addition of acetic acid to I, forming **II-OAc**, which may suffer further attack of acetic acid at the acetyl carbonyl, thereby fragmenting to acetic anhydride and the observed products. Control experiments revealed the futility of attempting to detect a small amount of acetic anhydride in acetic acid solvent by either ^{13}C or ^1H NMR.

Estimation of the Reactivity of Naphthoate-Derived γ-Oxo Ketene Acetal Intermediates. Since both the groups of Konopelski[13f] and Welzel[13e] have been highly successful at preparation of γ-oxo ketene acetals, we began to suspect that the failure to observe or isolate substances akin to I might be specifically related to the added increment of reactivity imparted by the reestablishment of aromaticity during the addition of water or acetic acid to I. In order to address this question, the general method of Konopelski[13f] was employed using β-tetralone as substrate; sequential reaction with dimethyl carbonate followed by exchange with 2-chloroethanol and titanium(IV) isopropoxide gave β-chloroethyl ester **59** in excellent yield (Scheme XVII). Subsequent cyclization to the crystalline γ-oxo ketene acetal **60** again employed the technology[13f] which Konopelski used for the synthesis of the analogous α-tetralone isomer (**26** → **27**).

Scheme XIII



Scheme XIV

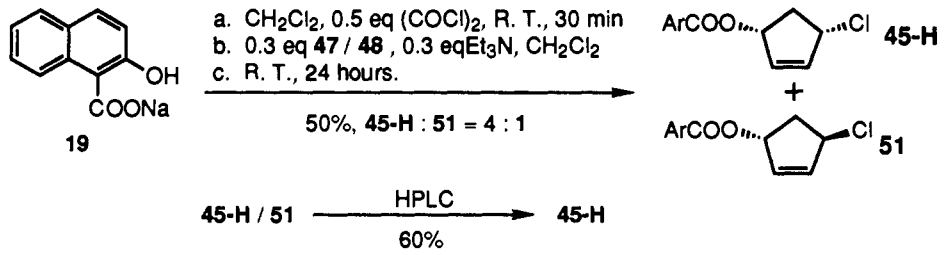


Table III. Reactions of **45-S** and **45-H**

entry	SM	solvent	additive	time	products [NMR ratio] +/or (yield)
1	**45-S**	D_2O/C_5D_5N 10:1	none	5 min	**53-S** + **54-S** [3:2]
2	**45-S**	CH_3CN	K_2CO_3 (10 equiv)	15 h	**52-S** (17%)[a] + **53-S** (19%)[a] + **54-S** (26%)
3	**45-S**	$CHCl_3$	K_2CO_3 (10 equiv)	15 h	**53-S** (59%) + **55-S** (9%) + **56-S** (9%)
4	**45-S**	THF-d_8	NaH	5 min	**53-S** [quant][a]
cntrl a	**45-S**	$CDCl_3$	Ag_2O or $AgBF_4$ (10 equiv)	2 days	**45-S** [quant]
cntrl b	**45-S**	CD_3CO_2D	none	2 days	**45-S** [quant]
5.0	**45-S**	CD_3CO_2D	$AgBF_4$ (2 equiv)	1 h	**45-S** + **55-S** + **56-S** [>95:<5:0]
5.1	**45-S**	CD_3CO_2D	$AgBF_4$ (14 equiv)	70 min	**45-S** + **55-S** + **56-S** [4:1:0]
5.2	**45-S**	CD_3CO_2D	none additional	3 h	**45-S** + **55-S** + **56-S** [1:7:2]
5.3	**45-S**	CD_3CO_2D	none additional	8 h	**45-S** + **55-S** + **56-S** [0:7:3]
5.4	**45-S**	CD_3CO_2D	none additional	27 h	**45-S** + **55-S** + **56-S** [0:3:2][b]
cntrl c	**55-S**	CD_3CO_2D	$AgBF_4$ (10 equiv)	37 days	**55-S** + **56-S** [3:2]
cntrl d	**56-S**	CD_3CO_2D	$AgBF_4$ (10 equiv)	37 days	**55-S** + **56-S** [3:2]
cntrl e	**45-S**	CD_3CO_2D	NaOAc (6 equiv)	9 days	**45-S** [quant]
cntrl f	**45-S**	CD_3CO_2D	NaOAc (1.3 equiv) + $AgBF_4$ (16 equiv)	27 h	**45-S** + **55-S** + **56-S** [0:3:2][b,c]
cntrl g	**45-S**	CD_3CO_2D	Et_3N (1 equiv)/$AgBF_4$ (16 equiv)	27 h	**45-S** + **55-S** + **56-S** [0:3:2][b,c]
cntrl h	**45-S**	CD_3OD	$AgBF_4$ (7 equiv)	48 h	**45-S** + **55-S** + **56-S** [0:3:2][b,c]
cntrl i	**54-S**	CD_3CO_2D	1.6M MeOH	9 days	**45-S** + **55-S** [0:3:2][b,c]
cntrl j	**52-S**	CD_3CO_2D	$AgBF_4$ (10 equiv)	2 days	**52-S** [quant]
cntrl k	**53-S**	CD_3CO_2D	$AgBF_4$ (10 equiv)	2 days	**53-S** [quant]
cntrl l	**54-S**	CD_3CO_2D	$AgBF_4$ (10 equiv)	2 days	**54-S** [quant]
6	**45-H**	CH_3CO_2H	$AgBF_4$ (2 equiv)	5 min	**57-H** (23%) + **58-H** (57%)
7	**45-H**	CH_3NO_2	$AgBF_4$ (2 equiv); then Ac_2O/pyridine	5 min; 15 h	**55-H'** (64%) + **56-H'** (30%)[d]

[a] Structure confirmed by X-ray (see supplementary material). [b] Acetone-d_6 and nitromethane-d_3 plus $AgBF_4$ produce essentially the same equilibrium ratio of **55-S** and **56-S** (3:2). [c] Same reaction rate and product ratio as observed in run 5. [d] The lability of **55-H** and **56-H** precluded chromatographic separation on silica. These materials were immediately derivitized by treatment of the crude reaction mixture with acetic anhydride and pyridine to produce **55-H'** and **56-H'** as the bis-acetylated derivatives.

Treatment of γ-oxo ketene acetal **60** under the standard acetic acid/excess silver fluoroborate conditions revealed some interesting information. While the expected "hydrolysis" product **61** was produced, the reaction required 3.5 h at 25 °C to complete the consumption of the starting material. Comparison of these rates for **60** with the two fastest substrates, **32t-Br** and **45-H**, whose reactions were complete under 5 min under similar conditions, reveals that the presence of the additional double bond in the naphthoate γ-oxo ketene acetal intermediates imparts a factor of at least 40 in greater reactivity, presumably due to the presence of the incipient arene.

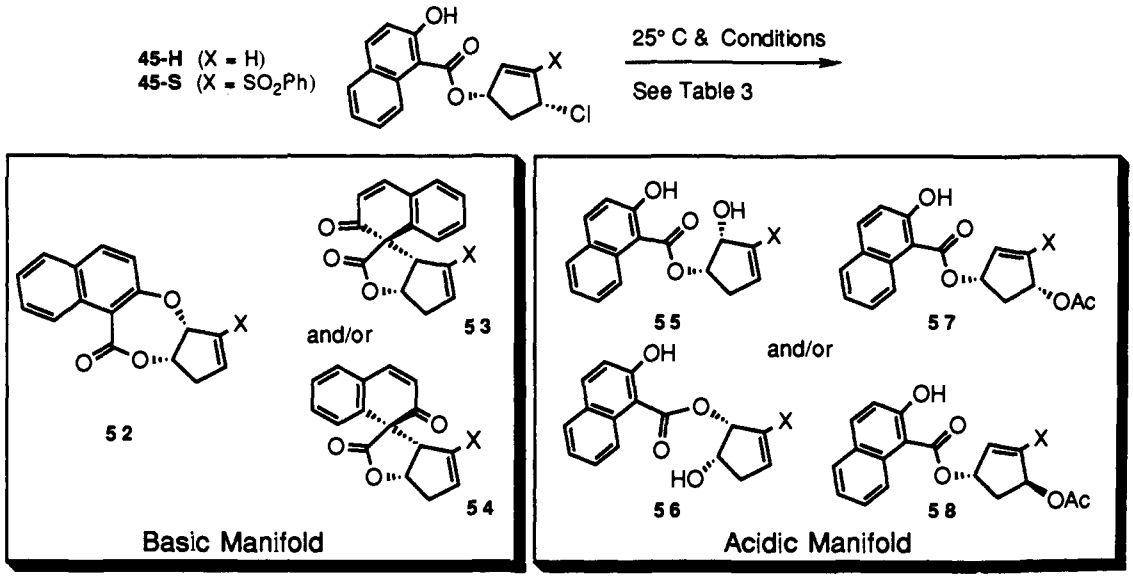
Conclusions

α-Hydroxy naphthoate esters are shown to be capable of undergoing intramolecular alkylation at carbon as well as at both oxygen centers. Basic reaction conditions favor intramolecular alkylation of the phenol moiety in addition to intramolecular carbon alkylation leading to spirolactones. Chemistry in neutral or acidic media appears to proceed via γ-oxo ketene acetal intermediates that are rapidly converted to products formally derived from addition of water and cleavage of the resultant orthoacid. These studies give credence to the proposal that the α-hydroxy naphthoate moiety in neocarzinostatin may participate during the epoxide-opening reaction. Moreover, the diverse set of products which attend the basic reaction conditions suggest a number of possibilities to consider with regard to understanding neocarzinostatin decomposition pathways at high pH. It is noted that the naphthoate moiety of neocarzinostatin contains additional electron-releasing (methyl and methoxy) substituents that would be expected to enhance its reactivity relative to the model naphthoate utilized in this study.

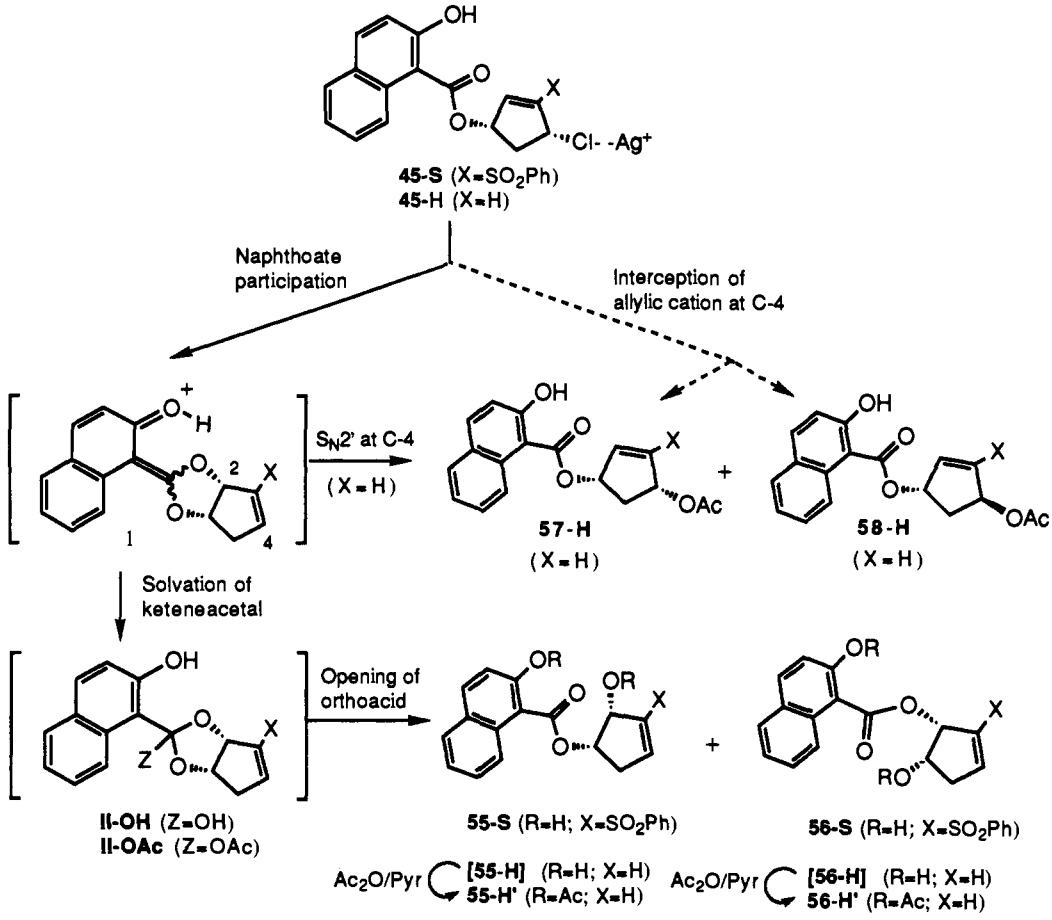
Experimental Section

General Procedures. Powdered anhydrous potassium carbonate was purchased from Mallinckrodt and was used as received. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl; acetonitrile, toluene, and benzene were distilled from calcium hydride, all under argon. Reactions were done under a positive pressure of argon, in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via a syringe. The flasks were flame-dried prior to the reaction. All products were purified by flash

Scheme XV



Scheme XVI



chromatography (unless otherwise stated), using a gradient eluent system.[37] Deactivation of silica gel columns was done by slurry packing with wet acetone, 50% acetone/hexane. All NMR spectra were recorded on a General Electric QE-300, unless otherwise stated. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.26 ppm and 77.00 ppm) unless otherwise indicated. When peak multiplicities are reported, the following abbreviations are used: s (singlet); d (doublet); t (triplet); m (multiplet); br (broadened); dd (doublet of doublets); dt (doublet of triplets). *J* values are reported in hertz. For the carbon spectra, (e) and (o) are used to denote even and odd, respectively.

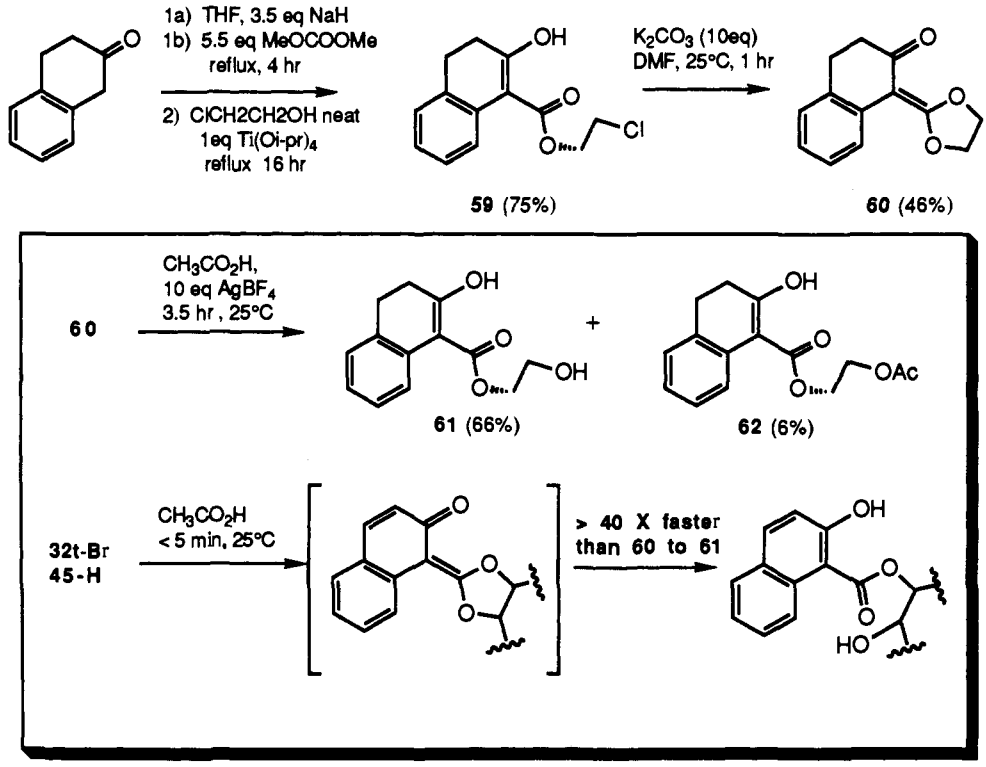
(37) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

General Procedure A: Basic Reactions, Control NMR Experiments. The naphthoate ester was dissolved in the deuterated solvent, and potassium carbonate was added. The NMR tube was sealed with a septum and parafilm. The reaction was then followed by 300 MHz NMR.

General Procedure B: Silver Tetrafluoroborate Reactions, Control NMR Experiments. A standard solution of silver tetrafluoroborate in the deuterated solution was prepared. The naphthoate ester was dissolved in 0.5 mL of solvent, and the NMR tube was sealed with a septum and parafilm prior to the addition of the required quantity of the silver reagent. The reaction was then followed by 300 MHz NMR.

General Procedure C: Preparative Basic Reactions. The naphthoate ester was dissolved in the solvent in a flame-dried flask, under argon

Scheme XVII



atmosphere. The base was then introduced, and the reaction mixture was stirred at 25 °C until the starting material had totally disappeared. After dilution in ether, the solution was washed with saturated ammonium chloride, and dried over magnesium sulfate, and the solvents were removed. Column chromatography using a gradient eluent system (hexane/ethyl acetate) allowed us to separate the different products. The results are given in parentheses as follows: solvent, base, reaction time, yield.

General Procedure D: Preparative Silver Tetrafluoroborate Reactions. A standard solution of the silver tetrafluoroborate in the solvent was prepared. The naphthoate ester was dissolved in the solvent in a flame-dried flask, under argon atmosphere. The silver reactant was then introduced via a syringe, and the reaction mixture was stirred at 25 °C until the starting material had totally disappeared. After dilution in ether, the solution was neutralized using saturated sodium carbonate. The organic phase was separated, washed with brine, and dried over magnesium sulfate, and the solvents were removed. Column chromatography using a gradient eluent system (hexane/ethyl acetate) allowed us to separate the different products. The results are given in parentheses as follows: solvent, reaction time, yield.

2-Chloroethyl 2-Hydroxy-1-naphthoate (20). To a suspension of 2-hydroxy-1-naphthoic acid, sodium salt (3 g, 14.3 mmol) in 100 mL of dichloromethane was added oxalyl chloride (685 μL, 7.1 mmol) at ambient temperature. The solid totally dissolved within minutes, and the reaction was stirred for 30 min prior to the addition of a solution of 2-chloroethanol (0.287 mL, 4.3 mmol) and triethylamine (0.597 mL, 4.3 mM) in 50 mL of dichloromethane. The reaction was stirred for 16 h and then quenched by fast plug through a short column of silica. The solvent was removed, and crude **20** was purified by column chromatography using a gradient eluent system (hexane/ethyl acetate). Compound **20** was isolated in 47% yield (503 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.07 (s, 1H, OH); 8.83 (d, 1H, 8.8 Hz); 7.90 (d, 1H, 9.0 Hz); 7.75 (dd, 1H, 7.9 Hz, 0.9 Hz); 7.59 (ddd, 1H, 8.6 Hz, 7.0 Hz, 1.4 Hz); 7.39 (dd, 1H, 7.0 Hz, 7.9 Hz); 7.17 (d, 1H, 9.0 Hz); 4.76 (t, 1H, 5.5 Hz); 3.94 (t, 1H, 5.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.83 (e); 164.58 (e); 137.27 (o); 131.69 (e); 129.06 (o); 128.68 (o); 128.62 (e); 125.39 (o); 123.77 (o); 119.17 (o); 104.23 (e); 65.27 (e); 41.45 (e). IR ($CDCl_3$) (cm^{-1}): 3018, 1712 (weak), 1652, 1622. High mass calculated for $C_{13}H_{11}ClO_3$ (EI): 250.0397, found 250.0399.

2-Hydroxyethyl 2-Hydroxy-1-naphthoate (21). General procedure C (DMF, 10 equiv of K_2CO_3, 7 h, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.05 (s, 1H, OH); 8.71 (d, 1H, 8.6 Hz); 7.80 (d, 1H, 9.0 Hz); 7.69 (br d, 1H, 8.0 Hz); 7.53 (dd, 1H, 6.9 Hz, 8.6 Hz); 7.33 (dd, 1H, 6.9 Hz, 8.0 Hz); 7.11 (d, 1H, 9.0 Hz); 4.57 (t, 2H, 4.6 Hz); 4.00 (t, 2H, 4.7 Hz); 2.67 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 60.68 (e); 66.90 (e); 104.47 (e); 119.01 (o); 123.56 (o); 125.02 (o); 128.44 (o); 128.49 (e); 128.96 (o); 131.59 (e); 136.84 (o); 163.98 (e); 172.06 (e). High mass calculated for $C_{13}H_{12}O_4$ (EI): 232.0736, found 232.0738.

2-Chloroethyl 1-Hydroxy-2-naphthoate (23). To a suspension of 1-hydroxy-2-naphthoic acid, sodium salt (3 g, 14.3 mmol) in 100 mL of dichloromethane was added oxalyl chloride (685 μL, 7.1 mmol) at ambient temperature. The solid totally dissolved within minutes, and the reaction was stirred for 30 min prior to the addition of a solution of 2-chloroethanol (0.287 mL, 4.3 mmol) and triethylamine (0.597 mL, 4.3 mmol) in 50 mL of dichloromethane. The reaction was stirred for 16 h and then quenched by fast plug through a short column of silica. The solvent was removed, and crude **23** was purified by column chromatography using a gradient eluent system (hexane/ethyl acetate). Compound **23** was isolated in 56% yield (601 mg). Mp: 95–6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.80 (s, 1H, OH); 8.42 (d, 1H, 8.4 Hz); 7.81 (d, 1H, 8.9 Hz); 7.78 (d, 1H, 8.9 Hz); 7.62 (dd, 1H, 7.0 Hz, 8.2 Hz); 7.53 (dd, 1H, 7.0 Hz, 8.2 Hz); 7.30 (d, 1H, 8.8 Hz); 4.65 (t, 1H, 5.7 Hz); 3.86 (t, 1H, 5.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.37 (e); 64.64 (e); 105.13 (e); 118.77 (o); 123.89 (o); 124.13 (o); 124.68 (e); 125.84 (o); 127.47 (o); 129.59 (o); 137.32 (e); 161.23 (e); 170.50 (e). IR ($CDCl_3$) (cm^{-1}): 3028, 1668, 1636. High mass calculated for $C_{13}H_{11}ClO_3$ (EI): 250.0397, found 250.0402. Anal. Calcd: C, 62.24; H, 4.42; Cl, 14.14. Found: C, 62.27; H, 4.38; Cl, 14.09.

2-Hydroxyethyl 2-Hydroxy-1-naphthoate (24). General procedure C (DMF, 10 equiv of K_2CO_3, 5 h, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.89 (s, 1H, OH); 8.40 (br d, 1H, 8.1 Hz); 7.78 (d, 1H, 8.8 Hz); 7.75 (d, 1H, 8.3 Hz); 7.60 (br dd, 1H, 8.1 Hz, 6.9 Hz); 7.52 (br dd, 1H, 6.9 Hz, 8.3 Hz); 7.26 (d, 1H, 8.8 Hz); 4.53 (br t, 2H, 4.6 Hz); 4.01 (br t, 2H, 4.6 Hz); 6.51 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 61.09 (e); 66.78 (e); 105.27 (e); 118.62 (o); 123.84 (o); 124.07 (o); 124.66 (e); 125.78 (o); 127.41 (o); 129.48 (o); 137.20 (e); 161.10 (e); 171.11 (e). High mass calculated for $C_{13}H_{12}O_4$ (EI): 232.0736, found 232.0738.

2-Oxo-1,5-dioxanaphthol[1′,2′-*c*]cycloheptane (25). General proceudre C: (DMF, 10 equiv of K_2CO_3, 5 h, 80%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (d, 1H, 8.6 Hz); 7.97 (d, 1H, 8.9 Hz); 7.83 (d, 1H, 8.0 Hz); 7.58 (dd, 1H, 6.9 Hz, 8.6 Hz); 7.48 (dd, 1H, 6.9 Hz, 8.0 Hz); 7.18 (d, 1H, 8.9 Hz); 4.48 (t, 2H, 4.9 Hz); 4.41 (t, 2H, 4.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 63.72 (e); 71.31 (e); 117.82 (e); 121.08 (o); 125.01 (o); 125.60 (o); 128.19 (o); 128.24 (o); 130.84 (e); 131.73 (e); 134.69 (o); 152.23 (e); 168.44 (e). High mass calculated for $C_{13}H_{10}O_3$ (EI): 214.0630, found 214.0626.

(2*E*)-4-Bromo-2-butenyl 2-Hydroxy-1-naphthoate (32t-Br). A solution of (*E*)-1,4-dibromo-2-butene (6 g, 28 mmol) and 1-hydroxy-2-naphthoic acid, sodium salt (1.2 g, 5.7 mmol) in 40 mL of acetone was stirred for

15 h. Ether (200 mL) was added, and the reaction mixture was washed with brine, dried with magnesium sulfate, and fast plugged through a short silica column. The solvent was removed, and the crude product was purified by column chromatography using a gradient eluent system (hexane/ethyl acetate), yielding 1.46 g (81%) of **32t-Br**. Mp: 64–6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.19 (s, 1H, OH); 8.75 (d, 1H, 8.7 Hz); 7.90 (d, 1H, 9.0 Hz); 7.76 (d, 1H, 8.0 Hz); 7.58 (ddd, 1H, 8.5 Hz, 7.1 Hz, 1.4 Hz); 7.38 (dt, 1H, 7.4 Hz, 0.8 Hz); 7.17 (d, 1H, 9.0 Hz); 6.12 (m, br X_2ABY_2, 2H, 15.5 Hz, 5.2 Hz, 6.7 Hz); 5.03 (d, 1H, 5.2 Hz); 4.00 (d, 1H, 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.07 (e); 64.77 (e); 104.42 (e); 119.25 (o); 123.68 (o); 125.22 (o); 128.11 (o); 128.54 (o); 128.61 (e); 129.10 (o); 131.24 (o); 131.67 (e); 137.05 (o); 164.52 (e); 171.91 (e). IR ($CDCl_3$) (cm^{-1}): 3012, 1718 (weak), 1648, 1622. High mass calculated for $C_{15}H_{13}BrO_3$ (EI): 320.0048, found 320.0045. Anal. Calcd: C, 56.10; H, 4.08; Br, 24.88. Found: C, 55.77; H, 3.86; Br, 25.06.

(2*Z*)-4-Chloro-2-butenyl 2-Hydroxy-1-naphthoate (32c-Cl). A solution of (*Z*)-1,4-dichloro-2-butene (6 mL, 57.4 mmol) and 1-hydroxy-2-naphthoic acid, sodium salt (2.2 g, 10.5 mmol) in 25 mL of DMF was stirred for 17 h. Ether (200 mL) was added, and the reaction mixture was washed with saturated NH_4Cl, dried with magnesium sulfate, and fast plugged through a short silica column. The solvent was removed, and the crude product was purified by column chromatography using a gradient eluent system (hexane/ethyl acetate), yielding 2.76 g (95%) of **32c-Cl**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.21 (s, 1H, OH); 8.73 (d, 1H, 8.6 Hz); 7.89 (d, 1H, 9.0 Hz); 7.74 (br d, 1H, 8.6 Hz); 7.57 (br dd, 1H, 8.6 Hz, 7.0 Hz); 7.38 (br dd, 1H, 8.0 Hz, 7.0 Hz); 7.17 (d, 1H, 9.0 Hz); 5.99 (m, 2H); 5.11 (br d, 2H, 5.4 Hz); 4.26 (br d, 2H, 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.51 (e); 60.31 (e); 104.28 (e); 119.18 (o); 123.62 (o); 125.14 (o); 127.13 (o); 128.47 (o); 128.54 (e); 129.05 (o); 130.73 (o); 131.59 (e); 137.02 (o); 164.50 (e); 171.94 (e). IR (neat) (cm^{-1}): 3042, 1720, 1646, 1622. High mass calculated for $C_{15}H_{13}ClO_3$ (EI): 276.0553, found 276.0550.

(7*E*,16*E*)-Dinaphtho[1′,2′-*c*][1″,2″-*l*]-2,11-dioxo-1,5,10,14-tetraoxacyclooctadeca-7,16-diene (33). General procedure C (THF, 2 equiv of NaH, 2 days, 45%). Mp: 226–7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, 2H, 9.0 Hz); 7.90 (d, 2H, 8.3 Hz); 7.80 (d, 2H, 8.1 Hz); 7.52 (br dd, 2H, 8.3 Hz, 7.0 Hz); 7.39 (br dd, 2H, 7.0 Hz, 8.1 Hz); 7.27 (d, 2H, 9.0 Hz); 6.22 (br s, 4H); 5.03 (d, 4H, 3.6 Hz); 4.74 (d, 4H, 3.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.64 (e); 68.93 (e); 113.76 (o); 117.19 (e); 123.95 (o); 124.28 (o); 126.78 (o); 127.75 (o); 128.09 (o); 128.51 (o); 128.70 (e); 131.24 (e); 132.05 (o); 153.84 (e); 167.49 (e). IR ($CDCl_3$) (cm^{-1}): 1722, 1600. High mass calculated for $C_{30}H_{24}O_6$ (EI): 480.1573, found 480.1563.

(7*E*,16*E*,25*E*)-Trinaphtho[1′,2′-*c*][1″,2″-*l*][1‴,2‴-*u*]-2,11,20-trioxo-1,5,10,14,19,23-hexaoxacycloheptacosa-7,16,25-triene (34). General procedure C (THF, 2 equiv of NaH, 2 days, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 (d, 2H, 9.1 Hz); 7.78 (d, 2H, 8.6 Hz); 7.77 (d, 2H, 8.0 Hz); 7.49 (dd, 2H, 7.0 Hz, 8.6 Hz); 7.37 (dd, 2H, 7.0 Hz, 8.0 Hz); 7.22 (d, 2H, 9.1 Hz); 6.07 (br t, 4H); 4.95 (br d, 4H); 4.68 (br d, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.87 (e); 69.08 (e); 114.79 (o); 118.13 (e); 123.80 (o); 124.36 (o); 126.82 (o); 127.68 (o); 128.05 (o); 128.76 (e); 129.04 (o); 130.98 (e); 131.67 (o); 153.54 (e); 167.58 (e). High mass calculated for $C_{45}H_{36}O_9$ (FAB): 721.2438, found 721.2418.

Spiro[1′,2′-dihydro-2′-oxonaphthalene-1′,2-3-vinyl-4-butanolide] (35). General procedure C (CH_3CN, 10 equiv of K_2CO_3, 1 day, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.5–7.3 (m, 5H); 6.08 (d, 1H, 9.9 Hz); 5.56 (ddd, 1H, 8.4 Hz, 10.2 Hz, 17.0 Hz); 5.04 (d, 1H, 10.2 Hz); 4.92 (d, 1H, 17.0 Hz); 4.56 (dd, 1H, 8.9 Hz, 10.9 Hz); 4.48 (dd, 1H, 8.9 Hz, 8.2 Hz); 3.49 (dt, 1H, 10.9 Hz, 2 × 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 59.32 (o); 65.35 (e); 68.03 (e); 124.37 (o); 128.31 (o); 128.55 (o); 129.37 (o); 129.61 (o); 130.32 (e); 131.00 (o); 138.56 (e); 146.89 (o); 174.76 (e); 195.67 (e). High mass calculated for $C_{15}H_{12}O_3$ (EI): 240.0786, found 240.0788.

(2*E*)-4-(Acetyloxy)-2-butenyl 2-Hydroxy-1-naphthoate (36t-OAc). General procedure D (acetic acid, <5 min, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.21 (s, 1H, OH); 8.76 (d, 1H, 8.8 Hz); 7.90 (d, 1H, 9.0 Hz); 7.75 (d, 1H, 8.0 Hz); 7.57 (dd, 1H, 8.8 Hz, 7.2 Hz); 7.38 (dd, 1H, 7.2 Hz, 8.0 Hz); 7.17 (d, 1H, 9.0 Hz); 6.10 (dd, 1H, 5.0 Hz, 16 Hz); 6.00 (dd, 1H, 5.0 Hz, 16 Hz); 5.04 (d, 2H, 4.5 Hz); 4.64 (d, 2H, 4.4 Hz); 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.83 (o); 63.71 (e); 65.09 (e); 104.44 (e); 119.22 (o); 123.62 (o); 125.22 (o); 127.23 (o); 128.46 (o); 128.59 (e); 129.05 (o); 129.28 (o); 131.68 (e); 136.95 (o); 164.47 (e); 170.55 (e); 171.92 (e). High mass calculated for $C_{15}H_{14}O_5$ (EI): 300.0998, found 300.0995.

(2*E*)-4-Hydroxy-2-butenyl 2-Hydroxy-1-naphthoate (36t-OH). General procedure D (acetone, <5 min, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.25 (s, 1H, OH); 8.77 (d, 1H, 8.8 Hz); 7.89 (d, 1H, 9.0 Hz); 7.75 (d, 1H, 8.0 Hz); 7.56 (dd, 1H, 8.8 Hz, 7.2 Hz); 7.37 (dd, 1H, 7.2 Hz, 8.0 Hz); 7.16 (d, 1H, 9.0 Hz); 6.12 (dd, 1H, 15.5 Hz, 4.0 Hz); 6.04 (dd, 1H, 15.5 Hz, 4.7 Hz); 5.04 (d, 2H, 4.0 Hz); 4.25 (br s, 2H); 1.62 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.48 (e); 65.51 (e); 104.52 (e); 119.18 (o); 123.60 (o); 124.14 (o); 125.22 (o); 128.45 (o); 128.57 (e); 129.03 (o); 131.67 (e); 134.67 (o); 136.90 (o); 164.36 (e); 172.02 (e). High mass calculated for $C_{15}H_{15}O_4$ (CI): 259.0970, found 259.0969.

(2*Z*)-4-(Acetyloxy)-2-butenyl 2-Hydroxy-1-naphthoate (36c-OAc). General procedure D (acetic acid, 23 h, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.21 (s, 1H, OH); 8.74 (d, 1H, 8.6 Hz); 7.90 (d, 1H, 9.0 Hz); 7.75 (br d, 1H, 8.0 Hz); 7.56 (dd, 1H, 8.6 Hz, 7.0 Hz); 7.37 (dd, 1H, 7.0 Hz, 8.0 Hz); 7.16 (d, 1H, 9.0 Hz); 6.02 (br dt, 1H, 11 Hz, 6.5 Hz); 5.89 (br dt, 1H, 11 Hz, 6.5 Hz); 5.13 (d, 2H, 6.5 Hz); 4.79 (d, 2H, 6.5 Hz); 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.84 (o); 59.92 (e); 61.03 (e); 104.44 (e); 119.26 (o); 123.64 (o); 125.21 (o); 127.42 (o); 128.49 (o); 128.61 (e); 129.08 (o); 131.70 (e); 137.00 (o); 164.52 (e); 170.67 (e); 172.02 (e). High mass calculated for $C_{17}H_{16}O_5$ (EI): 300.0998, found 300.0992.

2-(Acetyloxy)-3-butenyl 2-Hydroxy-1-naphthoate (37-OAc). General procedure D (acetic acid, <5 min, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.08 (s, 1H, OH); 8.75 (d, 1H, 8.8 Hz); 7.90 (d, 1H, 9.0 Hz); 7.75 (d, 1H, 8.0 Hz); 7.53 (dd, 1H, 7.0 Hz, 8.8 Hz); 7.37 (dd, 1H, 7.0 Hz, 8.0 Hz); 7.17 (d, 1H, 9.0 Hz); 5.95 (ddd, 1H, 6.3 Hz, 10.5 Hz, 17.2 Hz); 5.79 (m, 1H); 5.50 (d, 1H, 17.2 Hz); 5.39 (d, 1H, 10.5 Hz); 4.70 (dd, 1H, 3.7 Hz, 11.8 Hz); 4.54 (dd, 1H, 6.8 Hz, 11.8 Hz); 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.00 (o); 65.85 (e); 71.73 (o); 104.32 (e); 119.24 (o); 119.39 (e); 123.69 (o); 125.29 (o); 128.41 (o); 128.63 (e); 129.08 (o); 131.74 (e); 132.13 (o); 137.16 (o); 164.54 (e); 169.95 (e); 171.79 (e). High mass calculated for $C_{17}H_{16}O_5$ (EI): 300.0998, found 300.0995.

2-Hydroxy-3-butenyl 2-Hydroxy-1-naphthoate (37-OH). General procedure D (acetic acid, <5 min, 11%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.00 (s, 1H, OH); 8.78 (d, 1H, 8.7 Hz); 7.90 (d, 1H, 9.0 Hz); 7.77 (d, 1H, 7.8 Hz); 7.55 (dd, 1H, 7.0 Hz, 8.7 Hz); 7.37 (dd, 1H, 7.0 Hz, 7.8 Hz); 7.17 (d, 1H, 9.0 Hz); 6.02 (ddd, 1H, 5.5 Hz, 10.5 Hz, 17.2 Hz); 5.52 (d, 1H, 17.2 Hz); 5.35 (d, 1H, 10.5 Hz); 4.63 (m, 2H); 4.48 (dd, 1H, 6.7 Hz, 11.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 68.70 (e); 70.84 (o); 104.62 (e); 117.66 (e); 119.23 (o); 123.71 (o); 125.31 (o); 128.53 (o); 128.64 (e); 129.07 (o); 131.79 (e); 136.17 (o); 137.03 (o); 164.22 (e); 171.99 (e). High mass calculated for $C_{15}H_{14}O_4$ (EI): 258.0892, found 258.0894.

1-Hydroxy-3-buten-2-yl 2-Hydroxy-1-naphthoate (38-OH). General procedure D (acetic acid, <5 min, 18%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.03 (s, 1H, OH); 8.79 (d, 1H, 8.8 Hz); 7.90 (d, 1H, 9.0 Hz); 7.76 (d, 1H, 8.0 Hz); 7.57 (dd, 1H, 7.1 Hz, 8.8 Hz); 7.37 (dd, 1H, 7.1 Hz, 8.0 Hz); 7.16 (d, 1H, 9.0 Hz); 6.04 (ddd, 1H, 6.3 Hz, 10.6 Hz, 17.3 Hz); 5.82 (br q, 1H, 5.1 Hz, 5.1 Hz, 6.3 Hz); 5.53 (br d, 1H, 17.3 Hz); 5.42 (br d, 1H, 10.6 Hz); 3.98 (d, 2H, 5.1 Hz); 2.10 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.25 (e); 77.19 (o); 104.73 (e); 119.29 (o); 119.57 (e); 123.70 (o); 125.12 (o); 128.61 (o); 128.68 (e); 129.14 (o); 131.85 (e); 132.30 (o); 137.01 (o); 164.32 (e); 171.55 (e). High mass calculated for $C_{15}H_{14}O_4$ (EI): 258.0892, found 258.0890.

(3*R*,5*S*)-4-Chloro-1-hydroxy-3-(phenylsulfonyl)cyclopent-2-ene (42-Cl). A solution of 1-epoxy-3-(phenylsulfonyl)-3-cyclopentene (1.5078 g, 6.78 mmol) in 120 mL of dichloromethane was cooled to −78 °C. Five fractions of TMSCl (220 μL/fraction, 1.47 mmol/fraction) were added with a 15-min interval between two additions. The reaction was slowly warmed to ambient temperature. After 3 days at room temperature, the reaction was not completed. Therefore one fraction of TMSCl (220 μL, 1.47 mmol) was added, and the solution was further stirred for 2 days. The products were then hydrolyzed for 30 min with 5% HCl (50 mL). The organic phase was separated, and the aqueous layer was extracted twice with dichloromethane. The organic solutions were combined and dried with magnesium sulfate, and the solvent was removed. Chromatography using a gradient of hexane and ethyl acetate gave 1.3737 g of pure **42-Cl** (78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 (br d, 2H); 7.62 (br dt, 1H); 7.52 (br t, 2H); 6.96 (d, 1H, 2.4 Hz); 4.86 (dd, 1H, 7.4 Hz, 3.5 Hz); 4.80 (m, 1H); 2.17 (d, 1H, OH); 2.96 (dt, 1H, 7.4 Hz, 14.8 Hz); 2.24 (dt, 1H, 3.5 Hz, 14.8 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ: 45.43 (e); 56.89 (o); 73.14 (o); 128.84 (o); 129.15 (o); 133.67 (o); 140.54 (e); 147.34 (o); I47.76 (e). High mass calculated for $C_{11}H_{11}ClO_3S$ (CI): 259.0196, found 259.0193.

(3*R*,5*S*)-2-Bromo-1-hydroxy-3-(phenylsulfonyl)cyclopent-3-one (43-Br). A solution of 1-epoxy-3-(phenylsulfonyl)-3-cyclopentene (100 mg, 0.45 mmol) in 10 mL of dichloromethane was cooled to −78 °C. Two fractions of TMSBr (66 μL/fraction, 0.49 mmol/fraction) were added with a 15-min interval between the additions. The reaction was slowly warmed to ambient temperature. The reaction was then quenched with saturated ammonium chloride. The organic phase was separated, and the aqueous layer was extracted twice with dichloromethane. The organic solutions were combined and dried with magnesium sulfate, and the solvent was removed. Chromatography using a gradient of hexane and ethyl acetate gave 132 mg of pure **43-Br** (97%). Mp: 123–4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (d, 2H, 7.5 Hz); 7.68–7.52 (m, 3H); 7.08 (br s, 1H); 4.74 (s, 1H); 4.64 (d, 1H, 4.8 Hz); 3.02 (br dd, 1H, 4.8 Hz, 19.1 Hz); 2.56 (dd, 1H, 3.2 Hz, 19.1 Hz); 2.8–2.3 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.08 (e); 53.22 (o); 80.59 (o); 128.53 (o); 129.16 (o); 133.96 (o); 139.15 (e); 144.66 (e); 146.78 (o). High mass calculated for $C_{11}H_{11}BrO_3S$ (EI): 302.9690, found 302.9694. Anal. Calcd: C, 43.78; H, 3.66; Br, 26.36; S, 10.57. Found: C, 43.41; H, 3.59; Br, 26.69; S, 10.38.

(3*R*,5*S*)-4-Chloro-3-(phenylsulfonyl)cyclopent-2-enyl 2-Hydroxy-1-naphthoate (45-S). To a suspension of 1-hydroxy-2-naphthoic acid, sodium salt (3.4 g, 15.98 mmol) in 120 mL of dichloromethane was added oxalyl chloride (765 μL, 8.0 mmol) at ambient temperature. The solid totally dissolved within minutes, and the reaction was stirred for 30 min prior to the addition of a solution of **45**-Cl (1.24 g, 4.79 mmol) and triethylamine (0.670 mL, 4.79 mmol) in 60 mL of dichloromethane. The reaction was stirred for 16 h and then quenched by fast plug through a short column of silica. The solvent was removed, and crude **45-S** was purified by column chromatography using a gradient eluent system (hexane/ethyl acetate). Compound **45-S** was isolated in 56% yield (1.1516 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.02 (s, 1H, OH); 8.64 (dd, 1H, 8.6 Hz, 1 Hz); 8.03 (dt, 2H, 7.4 Hz, 1.4 Hz); 7.89 (d, 1H, 9.0 Hz); 7.73 (dd, 1H, 7.7 Hz, 1.3 Hz); 7.69 (tt, 1H, 7.4 Hz, 1.4 Hz); 7.57 (dt, 2H, 7.4 Hz, 1.4 Hz); 7.41 (ddd, 1H, 8.6 Hz, 7.0 Hz, 1.6 Hz); 7.35 (ddd, 1H, 7.0 Hz, 7.6 Hz, 1 Hz); 7.21 (d, 1H, 2.6 Hz); 7.15 (d, 1H, 9.0 Hz); 6.07 (dt, 1H, 2.6 Hz, 2.3 Hz, 7.2 Hz); 5.09 (dd, 1H, 2.0 Hz, 7.2 Hz); 3.21 (dt, 1H, 7.2 Hz, 15.6 Hz); 2.61 (dt, 1H, 2.3 Hz, 2.0 Hz, 15.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.09 (e); 56.17 (o); 75.77 (o); 103.71 (e); 119.13 (o); 123.79 (o); 125.23 (o); 128.52 (e); 128.55 (o); 128.73 (o); 129.08 (o); 129.26 (o); 131.41 (e); 134.28 (o); 137.55 (o); 138.91 (e); 141.49 (o); 151.82 (e); 164.86 (e); 171.34 (e). IR ($CDCl_3$): 1714 (CO ester), 1652 (CO enone). High mass calculated for $C_{22}H_{17}ClO_5S$ (EI): 428.0485, found 428.0476.

(3*R*,5*S*)-4-Chloro-2-cyclopentenyl 2-Hydroxy-1-naphthoate (45-H). The copper reagent was prepared as follows: 10.7 g of lithium chloride (253 mmol) and 17 g of $CuCl_2$ (127 mmol) were dissolved in tetrahydrofuran, at room temperature, and stirred for 30 min. 3,4-Epoxycyclopentene (5 mL, 63.3 mmol) was dissolved in 500 mL of dichloromethane and cooled to −10 °C. The preformed solution of Li_2CuCl_4 was slowly cannulated over a 40-min period. The reaction was quenched by addition of 150 mL of half-saturated ammonium chloride. The layers were separated, and the aqueous phase was extracted once with dichloromethane. The organic solutions were combined, dried with magnesium sulfate, and fast plugged through a short silica column, and the solvent was removed. The product mixture was chromatographed using fine, acetone-deactivated silica and a gradient of hexane and ethyl acetate to yield 826 mg (11%) of a 2:1 mixture of **47** and **48**.

To a suspension of 1-hydroxy-2-naphthoic acid, sodium salt (4.8 g, 22.5 mmol) in 160 mL of dichloromethane was added oxalyl chloride (1.1 mL, 11.2 mmol) at ambient temperature. The solid totally dissolved within minutes, and the reaction was stirred for 30 min prior to the addition of a solution of **47** and **48** (800 mg, 6.7 mmol) and triethylamine (0.940 mL, 6.7 mmol) in 80 mL of dichloromethane. The reaction was stirred for 16 h and then quenched by fast plug through a short column of silica. The solvent was removed, and the crude products (cis and trans isomer ratio, 4:1) were purified by column chromatography using a gradient eluent system (hexane/ethyl acetate), yielding 980 mg (50%). Compound **45-H** was separated from its trans isomer by HPLC, using 8% ethyl acetate in hexane. Compound **45-H** was isolated in 60% yield (498.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.24 (s, 1H, OH); 8.84 (d, 1H, 8.8 Hz); 7.89 (d, 1H, 9.0 Hz); 7.74 (d, 1H, 8.0 Hz); 7.56 (ddd, 1H, 1.3 Hz, 8.8 Hz, 7.1 Hz); 7.37 (ddd, 1H, 0.9 Hz, 8.0 Hz, 7.1 Hz); 7.16 (d, 1H, 9.0 Hz); 6.30 (br s, 2H); 6.03 (ddd, 1H, 1.3 Hz, 2.6 Hz, 7.3 Hz); 4.97 (ddd, 1H, 1.6 Hz, 2.6 Hz, 7.3 Hz); 3.11 (dt, 1H, 15.6 Hz, 7.3 Hz); 2.48 (dt, 1H, 15.6 Hz, 2.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.13 (e); 59.93 (o); 78.66 (o); 104.32 (e); 119.13 (o); 123.65 (o); 125.43 (o); 128.53 (o); 128.56 (e); 128.95 (o); 131.71 (e); 132.20 (o); 137.05 (o); 138.54 (o); 164.50 (e); 171.84 (e). IR ($CDCl_3$) (cm^{-1}): 3014, 1702 (weak), 1648, 1602. High mass calculated for $C_{16}H_{13}ClO_3$ (EI): 288.0553, found 288.0547.

(1*R*,5*R*)-Naphtho[1′,2′-*d*]-3-oxo-2,6-dioxa-10-(phenylsulfonyl)bicyclo-[5.3.0]-9-decene (52). General procedure C (CH_3CN, 10 equiv of K_2CO_3, 15 h, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (dd, 1H, 8.5 Hz, 0.5 Hz); 8.07 (dd, 2H, 8.5 Hz, 1.3 Hz); 8.01 (d, 1H, 8.8 Hz); 7.86 (d, 1H, 7.8 Hz); 7.65–7.49 (m, 4H); 7.27 (d, 1H, 8.8 Hz); 7.08 (br s, 1H, 1.5 Hz, 1 Hz, 15 Hz); 5.46 (br dd, 1H, 5.0 Hz, 1.5 Hz, 1.5 Hz); 4.89 (br t, 1H, 5.0 Hz, 5.5 Hz, 1 Hz); 2.98 (br d, 1H, 1 Hz, 1 Hz, 19.0 Hz); 2.86 (ddt, 1H, 5.5 Hz, 1.5 Hz, 1.5 Hz, 19.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.85 (e); 76.48 (o); 87.16 (o); 119.70 (e); 120.54 (o); 124.99 (o); 126.30 (o); 128.42 (o); 128.45 (o); 128.61 (o); 129.05 (o); 131.68 (e, 2 carbons); 133.86 (o); 135.24 (o); 139.69 (e); 141.86 (e); 144.50 (o); 154.36 (e); 166.55 (e). ^{13}C NMR (75 MHz, C_6D_6:CD_3CN = 1:1) δ: 37.71 (e); 77.74 (o); 88.38 (o); 121.44 (e); 121.84 (o); 126.36 (o); 127.37 (o); 129.47 (o); 129.54 (o); 129.68 (o); 130.33 (o); 132.88 (e); 132.95 (e); 134.94 (o); 136.15 (o); 141.41 (e); 142.44 (e); 146.47 (o); 155.34 (e); 167.35 (e). IR ($CDCl_3$): 1724 (CO). High mass calculated for $C_{22}H_{16}O_5S$ (EI): 392.0718, found 392.0710.

(1*R*,4*S*,5*R*)-3-Oxo-8-(phenylsulfonyl)spiro[1′,2′-dihydro-2′-oxonaphthalene-1′,4-2-oxabicyclo[3.3.0]-7-octene] (53S). General procedure C ($CHCl_3$, 10 equiv of K_2CO_3, 15 h, 59%). Mp: 184–5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (tt, 1H, 1.6 Hz, 7.1 Hz); 7.5–7.3 (m, 8H); 7.14 (br t, 1H); 6.81 (br s, 1H); 6.12 (d, 1H, 9.9 Hz); 5.45 (ddd, 1H, 9.1 Hz, 8.0 Hz, 5.6 Hz); 4.06 (br d, 1H, 9.1 Hz, 2.4 Hz, 1 Hz); 3.32 (ddt, 1H, 2.3 Hz, 5.6 Hz, 2.4 Hz, 18.8 Hz); 3.09 (ddd, 1H, 3.0 Hz, 8.0 Hz, 18.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 39.71 (e); 58.81 (o); 62.01 (e); 80.98 (o); 125.18 (o); 127.20 (o); 128.21 (o); 128.75 (o); 129.22 (o); 130.15 (o); 130.22 (e); 130.56 (o); 133.87 (o); 138.09 (e); 139.54 (e); 140.08 (e); 145.40 (o); 145.42 (o); 173.49 (e); 193.13 (e). IR ($CDCl_3$): 1774 (CO γ-lactone), 1660 (CO enone). High mass calculated for $C_{22}H_{16}O_5S$ (EI): 393.0797, found 393.0789. Anal. Calcd: C, 67.23; H, 4.11; S, 8.17. Found: C, 67.49; H, 4.56; S, 8.03.

(1*R*,4*R*,5*R*)-3-Oxo-8-(phenylsulfonyl)spiro[1′,2′-dihydro-2′-oxonaphthalene-1′,4-2-oxabicyclo[3.3.0]-7-octene (54S). General procedure C (CH_3CN, 10 equiv of K_2CO_3, 15 h, 26%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, 1H, 9.89 Hz); 7.6–7.3 (m, 8H); 6.86 (br d, 1H, 8.0 Hz); 6.66 (m, 1H, 2.10 Hz, 2.91 Hz, 1 Hz); 6.30 (d, 1H, 9.89 Hz); 5.50 (dt, 1H, 8.88 Hz, 8.16 Hz, 3.95 Hz); 4.28 (br d, 1H, 8.88 Hz, 2.22 Hz, 1 Hz); 3.19 (ddd, 1H, 20.3 Hz, 8.16 Hz, 2 91 Hz); 3.02 (ddt, 1H, 20.3 Hz, 3.95 Hz, 2.10 Hz, 2.22 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.13 (e); 58.39 (o); 61.81 (e); 80.13 (o); 123.22 (o); 127.55 (o); 128.89 (o); 129.00 (o); 129.37 (o); 130.19 (o); 130.59 (o); 130.99 (e); 133.77 (o); 136.57 (e); 139.68 (e); 144.11 (e); 144.89 (o); 148.75 (o); 173.90 (e); 197.13 (e). IR ($CDCl_3$): 1776 (CO γ-lactone), 1660 (CO enone). High mass calculated for $C_{22}H_{16}O_5S$ (EI): 392.0718, found 392.0717.

2-Hydroxy-3-(phenylsulfonyl)cyclopent-3-enyl 2-Hydroxy-1-naphthoate (55-S). General procedure D (acetic acid, 20 h, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.50 (s, 1H); 8.65 (d, 1H, 8.7 Hz); 7.98 (d, 2H, 7.8 Hz); 7.87 (d, 1H, 9.0 Hz); 7.72 (d, 1H, 8.0 Hz); 7.65 (t, 1H, 7.35 Hz); 7.55 (t, 2H, 7.5 Hz); 7.47 (dd, 1H, 7.2 Hz, 8.3 Hz); 7.34 (t, 1H, 7.5 Hz); 7.13 (d, 1H, 9.0 Hz); 7.01 (t, 1H, 2.4 Hz); 5.60 (q, 1H, 6.0 Hz); 5.12 (d, 1H, 5.8 Hz); 3.07 (ddd, 1H, 18.7 Hz, 2.7 Hz, 6.7 Hz); 2.98 (ddt, 1H, 18.7 Hz, 2.4 Hz, 5.3 Hz, 1 Hz); 2.89 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.22 (e); 72.43 (o); 74.07 (o); 104.73 (e); 119.14 (o); 123.77 (o); 125.02 (o); 128.09 (o); 128.57 (e); 128.62 (o); 128.92 (o); 129.38 (o); 131.76 (e); 133.93 (o); 136.91 (o); 139.33 (e); 143.12 (o); 145.12 (e); 163.42 (e); 170.60 (e). IR ($CDCl_3$): 3588 (OH), 1718 (CO ester), 1652 (CO enone). High mass calculated for $C_{22}H_{18}O_6S$ (EI): 410.0824, found 410.0820.

(1*R*,2*S*)-1-(Acetyloxy)-4-cyclopenten-2-yl 2-(Acetyloxy)-1-naphthoate (55-H′). General procedure D (acetic acid, <5 min, 30%). Compound **55-H′** was partially separated from **56-H′** by HPLC using a Waters auto 500. Compound **55-H′** was contaminated with 20% of **56-H′**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 (d, 1H, 8.1 Hz); 7.93 (d, 1H, 8.9 Hz); 7.86 (d, 1H, 7.8 Hz); 7.55 (m, 2H); 7.25 (d, 1H, 8.9 Hz); 6.17 (ddd, 1H, 5.2 Hz, 2.4 Hz, 1.8 Hz); 6.03 (m, 2H); 5.50 (ddd, 1H, 6.0 Hz, 7.2 Hz, 4.6 Hz); 2.85 [ddt, 1H, 16.5 Hz (gem), 7.2 Hz, 2.4 Hz (allylic), 1.5 Hz, <1.5 Hz (W)]; 2.53 [ddd, 1H, 16.5 Hz (gem), 4.6 Hz, 1.8 Hz (allylic), 1.5 Hz]; 2.33 (s, 3H); 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.84 (o); 20.92 (o); 36.63 (e); 71.35 (o); 76.93 (o); 121.63 (o); 121.94 (e); 125.18 (o); 126.14 (o); 127.65 (o); 127.96 (o); 128.24 (o); 130.74 (e);

131.49 (e); 131.90 (o); 135.75 (o); 146.77 (e); 165.53 (e); 169.17 (e); 170.60 (e). High mass calculated for $C_{20}H_{18}O_6$ (EI): 354.1103, found 354.1094.

1-Hydroxy-3-(phenylsulfonyl)cyclopent-3-enyl 2-Hydroxy-1-naphthoate (56-S). General procedure D (acetic acid, 20 h, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.42 (s, 1H, OH); 8.17–7.1 (m, 12H); 6.24 (d, 1H, 5.8 Hz); 4.75 (q, 1H, 6.4 Hz); 3.01 (ddd, 1H, 18.5 Hz, 3.1 Hz, 7.1 Hz); 2.75 (ddt, 1H, 18.5 Hz, 1.5 Hz, 1.1 Hz, 6.1 Hz); 2.20 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 38.85 (e); 71.67 (o); 75.05 (o); 104.54 (e); 118.99 (o); 123.64 (o); 125.02 (o); 127.92 (o); 128.43 (e); 128.49 (o); 128.74 (o); 128.95 (o); 131.59 (e); 133.40 (o); 136.97 (o); 138.98 (e); 142.07 (e); 147.25 (o); 163.48 (e); 170.80 (e). IR ($CDCl_3$): 3602 (OH), 1720 (CO ester), 1648 (CO enone). High mass calculated for $C_{22}H_{18}O_6S$ (EI): 410.0824, found 410.0815.

(1*R*,2*S*)-2-(Acetyloxy)-4-cyclopenten-2-yl 2-(Acetyloxy)-1-naphthoate (56-H'). General procedure D (acetic acid, <5 min, 64%). Compound **56-H'** was separated from **55-H'** by HPLC using a Waters auto 500. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, 1H, 8.5 Hz); 7.95 (d, 1H, 8.9 Hz); 7.86 (d, 1H, 8.0 Hz); 7.57 (dd, 1H, 6.9 Hz, 8.5 Hz); 7.51 (dd, 1H, 6.9 Hz, 8.0 Hz); 7.24 (d, 1H, 8.8 Hz); 6.11 (ddd, 1H, 6.0 Hz, 1.2 Hz, 1.6 Hz); 5.91 [($CDCl_3$: m, 2H), (C_6D_6: 5.84, ddd, 1H, 6.0 Hz, 1.5 Hz, 1.2 Hz (W), 5.57, dq, H_1, 6.0 Hz, 1.5 Hz, 2.1 Hz (α allylic), 2.3 Hz (β allylic))]; 5.67 (ddd, 1H, 6.0 Hz, 6.9 Hz, 4.5 Hz); 2.92 [br dt, 1H, 6.9 Hz, 1.2 Hz, 2.3 Hz (allylic), 17.7 Hz, 1.2 Hz (W)]; 2.68 (br ddd, 1H, 1.6 Hz, 2.1 Hz (allylic), 4.5 Hz, 17.7 Hz); 2.34 (s, 3H); 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.89 (o); 20.92 (o); 36.93 (e); 72.90 (o); 75.51 (o); 121.45 (e); 121.64 (o); 125.20 (o); 126.14 (o); 127.71 (o); 128.23 (o); 128.54 (o); 130.78 (e); 131.48 (e); 132.16 (o); 134.22 (o); 147.09 (e); 165.53 (e); 169.20 (e); 170.41 (e). High mass calculated for $C_{20}H_{18}O_6$ (EI): 354.1103, found 354.1099.

(1*R*,4*R*)-4-(Acetyloxy)-2-cyclopentenyl 2-Hydroxy-1-naphthoate (57). General procedure D (acetic acid, <5 min, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.28 (s, 1H, OH); 8.66 (d, 1H, 8.8 Hz); 7.89 (d, 1H, 9.0 Hz); 7.74 (d, 1H, 8.0 Hz); 7.54 (dd, 1H, 7.0 Hz, 8.8 Hz); 7.36 (dd, 1H, 7.0 Hz, 8.0 Hz); 7.16 (d, 1H, 9.0 Hz); 6.38 (ddd, 1H, 7.0 Hz, 1.1 Hz, 2.1 Hz); 6.28 (ddd, 1H, 7.0 Hz, 2.3 Hz, 1.1 Hz); 6.25 (m, 1H); 5.95 (m, 1H, H_1); 2.59 (ddd, 1H, 2.3 Hz, 7.0 Hz, 15.0 Hz); 2.45 (ddd, 1H, 2.1 Hz, 7.0 Hz, 15.0 Hz); 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.09 (o); 37.50 (e); 78.22 (o); 80.20 (o); 104.41 (e); 119.27 (o); 123.66 (o); 125.03 (o); 128.55 (o); 128.62 (e); 129.12 (o); 131.71 (e); 134.88 (o); 136.55 (o); 137.04 (o); 164.59 (e); 170.89 (e); 172.25 (e). High mass calculated for $C_{18}H_{16}O_5$ (EI): 312.0998, found 312.1002.

(1*R*,4*S*)-4-(Acetyloxy)-2-cyclopentenyl 2-Hydroxy-1-naphthoate (58). General procedure D (acetic acid, <5 min, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.24 (s, 1H, OH); 8.78 (d, 1H, 8.7 Hz); 7.90 (d, 1H, 9.0 Hz); 7.75 (d, 1H, 8.0 Hz); 7.53 (dd, 1H, 7.0 Hz, 8.7 Hz); 7.37 (dd, 1H, 7.0 Hz, 8.0 Hz); 7.17 (d, 1H, 9.0 Hz); 6.36 (ddd, 1H, 0.9 Hz, 2.0 Hz, 5.6 Hz); 6.27 (ddd, 1H, 0.9 Hz, 2.1 Hz, 5.6 Hz); 5.98 (m, 1H); 5.67 (m, 1H); 3.04 (dt, 1H, 7.4 Hz, 15.1 Hz); 2.09 (br s, 4H). ^{1}H NMR (300 MHz, C_6D_6) δ: 12.81 (s, 1H, OH); 8.92 (d, 1H, $H_{10'}$, 8.8 Hz); 7.35 (m, 4H); 7.09 (m, 2H); 5.89 (ddd, 1H, H_2, 0.6 Hz, 2.0 Hz, 5.6 Hz); 5.81 (m, 1H, H_3); 5.35 (m, 1H, H_5); 2.47 (dt, 1H, $H_{4\beta}$, 7.4 Hz, 15.1 Hz); 1.83 (dt, 1H, $H_{4\alpha}$, 3.4 Hz, 15 1 Hz); 1.61 (s, 3H, Ac). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.10 (o); 37.41 (e); 78.33 (o, 2 carbons, 2 peaks in C_6D_6); 104.46 (e); 119.32 (o); 123.63 (o); 125.24 (o); 128.41 (o); 128.66 (e); 129.10 (o); 131.82 (e); 134.28 (o); 135.78 (o); 137.02 (o); 164.55 (e); 170.71 (e); 171.85 (e). High mass calculated for $C_{18}H_{16}O_5$ (EI): 312.0998, found 312.0995.

2-Chloroethyl 3,4-Dihydro-2-hydroxy-1-naphthoate (59). Naphthoate ester **59** was prepared following the Eid and Konopelski procedure for the synthesis of 2-chloroethyl 3,4-dihydro-1-hydroxy-2-naphthoate.[13f] A flask containing THF (80 mL) and hexane-washed NaH (6.7 g, 164 mmol) was treated dropwise with a solution of β-tetralone (10.8 mL, 82 mmol) in THF (13 mL). The resulting mixture reacted for 30 min at room temperature before a dropwise addition of dimethyl carbonate (38 mL, 450 mmol) was begun. The reaction was stirred for 20 min and refluxed for 4 h, and after being cooled to room temperature, it was acidified to pH 4 using 3 M acetic acid. The solution was extracted three times with 50 mL of Et_2O, and the combined organic phases were washed with saturated $NaHCO_3$ and brine and dried with $MgSO_4$. Filtration of the drying agent and removal of solvent under vacuum afforded 17 g (100%) of β-keto methyl ester, suitable for further reactions without purification.

The crude β-keto methyl ester, 250 mL of 2-chloroethanol, and 24 mL of titanium tetraisopropoxide (82 mmol) were refluxed overnight. After being cooled to room temperature, the mixture was treated with 5% HCl (50 mL), followed by addition of water and Et_2O (150 mL each). The organic layer was separated, and the aqueous layer was further extracted with Et_2O (3 × 200 mL). The organic layers were combined, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded 21 g of a 7:3 mixture of **59** and the β-keto methyl ester starting material. A 3-g sample of **59** was purified by chromatography using a gradient eluent system. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.16 (s, 1H, OH); 7.79 (d, 1H, 8.0 Hz); 7.07–7.24 (m, 3H); 4.57 (t, 2H, 5.6 Hz); 3.82 (t, 2H, 5.6 Hz); 2.82 (t, 2H, 7.5 Hz); 2.55 (t, 2H, 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.66 (e); 29.58 (e); 41.41 (e); 64.42 (e); 99.61 (e); 125.07 (o); 126.08 (o); 126.50 (o); 127.12 (o); 131.02 (e); 133.08 (e); 171.42 (e); 179.17 (e). IR (neat) (cm^{-1}): 3032, 1718, 1637, 1596. High mass calculated for $C_{13}H_{13}ClO_3$ (EI): 252.0553, found 252.0550.

1-(1,3-Dioxolanylidene)-2-tetralone (60). General procedure C (DMF, 10 equiv of K_2CO_3, 1 h, 46%). Mp: 179–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, 1H, 7.8 Hz); 7.21–7.02 (m, 3H); 4.66 (t, 2H, 7.2 Hz); 4.50 (t, 2H, 7.2 Hz); 2.85 (t, 2H, 6.7 Hz); 2.51 (t, 2H, 6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.18 (e); 39.09 (e); 66.10 (e); 67.66 (e); 90.86 (e); 124.66 (o); 125.89 (o); 126.55 (o); 126.95 (o); 132.96 (e); 135.60 (e); 165.73 (e); 198.24 (e). IR ($CDCl_3$) (cm^{-1}): 2918, 2248, 1672, 1602, 1556. High mass calculated for $C_{13}H_{12}O_3$ (EI): 216.0786, found 216.0788. Anal. Calcd: C, 72.21; H, 5.59. Found: C, 71.90; H, 5.56.

2-Hydroxyethyl 3,4-Dihydro-2-hydroxy-1-naphthoate (61). γ-Oxo ketene acetal **60** (49 mg, 0.22 mmol) was dissolved in 3 mL of acetic acid, under argon atmosphere. The starting material appeared to be totally consumed after 4 days of stirring at room temperature. The solution was diluted in Et_2O, neutralized with saturated sodium bicarbonate, washed with saturated ammonium chloride, and dried over magnesium sulfate, and the solvent was removed. Compound **61** was separated from **62** by chromatography using a gradient eluent system to yield 35 mg of **61** (66%) and 4 mg of **62** (6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.20 (s, 1H); 7.70 (d, 1H, 7.8 Hz); 7.26–7.06 (m, 3H); 4.46 (t, 2H, 4.7 Hz); 3.93 (t, 2H, 4.7 Hz); 2.83 (t, 2H, 7.5 Hz); 2.54 (t, 2H, 7.5 Hz); 2.19 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.65 (e); 29.53 (e); 61.02 (e); 66.40 (e); 99.75 (e); 125.02 (o); 125.76 (o); 126.44 (o); 127.20 (o); 131.28 (e); 133.19 (e); 172.00 (e); 178.88 (e). IR (neat) (cm^{-1}): 3424, 2954, 1718, 1632. High mass calculated for $C_{13}H_{14}O_4$ (EI): 234.0892, found 234.0889.

2-(Acetyloxy)ethyl 3,4-Dihydro-2-hydroxy-1-naphthoate (62). General procedure D on **59** (acetic acid, 7 equiv of $AgBF_4$, 5 days, 49%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.20 (s, 1H); 7.71 (d, 1H, 7.9 Hz); 7.21–7.07 (m, 3H); 4.53 (t, 2H, 4.7 Hz); 4.41 (t, 2H, 4.7 Hz); 2.83 (t, 2H, 7.5 Hz); 2.55 (t, 2H, 7.5 Hz); 2.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.72 (o); 27.61 (e); 29.49 (e); 61.84 (e); 62.33 (e); 99.61 (e); 124.95 (o); 125.80 (o); 126.30 (o); 127.10 (o); 131.13 (e); 133.07 (e); 170.65 (e); 171.49 (e); 178.88 (e). IR (neat) (cm^{-1}): 2956, 1743, 1639, 1600. High mass calculated for $C_{15}H_{16}O_5$ (EI): 276.0998, found 276.1001.

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Supplementary Material Available: ^{1}H and ^{13}C NMR of all compounds described in the Experimental Section and X-ray data for **52** and **53** (100 pages); tables of observed and calculated structure factors (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.