Tandem Pummerer−Diels−Alder Reaction Sequence. A Novel Cascade Process for the Preparation of 1-Arylnaphthalene Lignans†

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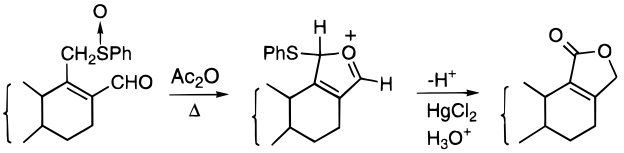
The α-thiocarbocation generated from the Pummerer reaction of an *o*-benzoyl-substituted sulfoxide is intercepted by the adjacent keto group to produce an α-thio isobenzofuran as a transient intermediate which undergoes a subsequent Diels−Alder cycloaddition with added dienophiles. Acid-catalyzed ring-opening of the cycloadduct followed by aromatization gave an arylnaphthalene derivative. With acetylenic dienophiles, the tandem cyclization−cycloaddition sequence provided tetralones which result from a pinacol-type rearrangement of the primary cycloadducts. The versatility of the approach is highlighted through the synthesis of taiwanin C and E and justicidin E. The α-thiocarbocation generated from the Pummerer reaction of benzo[1,3]dioxol-5-yl-[6-[(ethylsulfinyl)methyl]benzo[1,3]dioxol-5-yl)methanone is intercepted by the adjacent keto group to produce an α-thioisobenzofuran as a transient intermediate which undergoes a subsequent Diels−Alder cycloaddition with dimethyl maleate. The initially formed Diels−Alder cycloadduct was readily converted to 5-benzo[1,3]dioxol-5-yl-8-(ethylthio)naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic acid dimethyl ester by loss of water on treatment with *p*-toluenesulfonic acid. Desulfurization of the thionaphthalene with Ra/Ni followed by hydrolysis of the less hindered methyl ester afforded 5-benzo[1,3]dioxol-5-ylnaphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic acid 6-methyl ester which was further transformed into taiwanin C and justicidin E in good yield. Oxidation of the initial Diels−Alder cycloadduct with $NaIO_4$ in the presence of $RuCl_3$ followed by extrusion of ethyl sulfinate gave a naphthol derivative which can be converted into taiwanin E.

The Pummerer rearrangement has been widely studied and has received considerable attention as a synthetically useful process.[1−3] α-Acyl thionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently with nucleophilic carbon species. Bimolecular addition of the cation to various carbon−carbon double bonds is well known.[4] In the realm of natural product synthesis, most success has been achieved using intramolecular Friedel−Crafts cyclization of the Pummerer thionium ion intermediate.[5−20] Far fewer examples exist for heteroatom interception of the Pummerer intermediate.[21,22] De Groot and co-workers[23] recently developed an efficient procedure for butenolide formation in which the key step involves a Pummerer induced cyclization of aldehydic sulfoxides of type **1** into butenolides **3**. It was assumed that the neighboring carbonyl group attacks the initially formed thionium ion to give an oxy-stabilized cation **2** which loses a proton to generate a 2-thio-substituted furan[24] which is subsequently converted to the butenolide upon hydrolysis.



1 **2** **3**

Our interest in the synthesis of 1-arylnaphthalene lignans has prompted us to examine various methods for

† This paper is dedicated to Professor Paul Dowd on the occasion of his 60th birthday.

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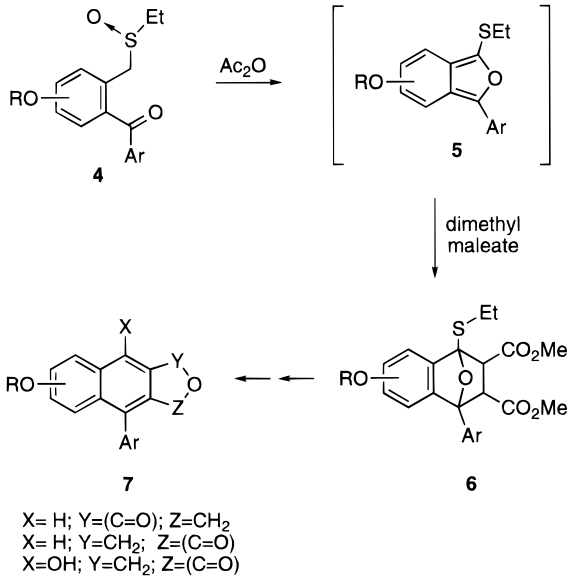
Scheme 1

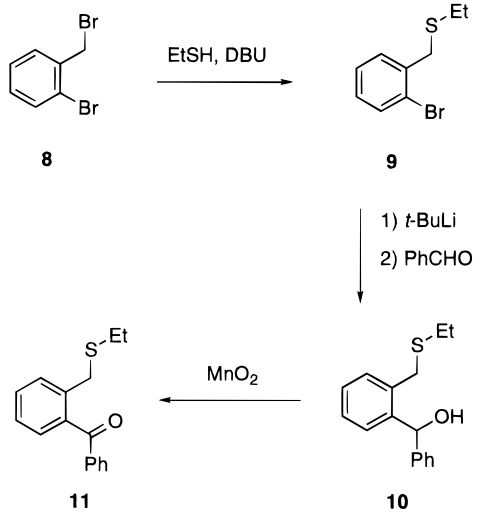


the construction of the phenylnaphthyl skeleton.[25] In particular, we have been interested in the internal trapping of the Pummerer cation with an adjacent carbonyl group (De Groot protocol[23]) as a method to prepare isobenzofurans and subsequently aryl lignans.[26−31] The main features of our strategy are illustrated in Scheme 1. The α-thiocarbocation generated from the Pummerer reaction of an *o*-benzoyl-substituted sulfoxide of type **4** is intercepted by the adjacent keto group to produce an α-thioisobenzofuran **5** as a transient intermediate which undergoes a subsequent Diels−Alder cycloaddition. The resulting cycloadduct **6** should be readily converted to representatives of several arylnaphthalene lignans **7**. In this paper we describe results which verify the underlying viability of this approach to the aryl lignan skeleton.

Results and Discussion

In order to have ready access to the requisite sulfoxides, we have developed three independent routes for their preparation. In the first method (Scheme 2), commercially available 2-bromobenzyl bromide (**8**) was converted to sulfide **9** using ethanethiol and DBU in benzene.[32] Metal−halogen exchange of bromide **9** with *t*-BuLi in THF below −90 °C followed by quenching of the lithiate with benzaldehyde at low temperature produced alcohol **10** in 96% yield. It is important to use these exact experimental conditions since the reaction with *n*-BuLi at −78 °C was sluggish and produced mixtures of starting material, the final product, and miscellaneous side-products. Oxidation of alcohol **10** with MnO_2 in CH_2Cl_2 afforded the desired keto sulfide **11** in quantitative yield.

Scheme 2



An alternative protocol that was also used for the preparation of sulfide **11** is shown in Scheme 3. The readily available 2-(bromomethyl)benzonitrile (**12**)[33] was converted into nitrile **13** by reaction with ethanethiol in the presence of DBU.[32] Further treatment of **13** with phenylmagnesium bromide in toluene provided, after acidic workup, the desired keto sulfide **11** in 95% overall yield from **12**.

In the third method (Scheme 4), commercially available phthalide was allowed to react with sodium ethanethiolate in refluxing ethanol which resulted in the formation of 2-[(ethylthio)methyl]-benzoic acid (**15**) in 90% yield.[34] Conversion of carboxylic acid **15** into the Weinreb amide **16** was accomplished by successive treatment of **15** with thionyl chloride and *N*,*O*-dimethylhydroxylamine in 80% yield.[35] Coupling of amide **16** with phenylmagnesium bromide under the usual reaction conditions[35] produced keto sulfide **11** in 94% yield. The analogous methyl ketone **17** was prepared similarly by treating **16** with methylmagnesium bromide in 96% yield.

This method is particularly useful since carboxylic acid **15** can be prepared in large quantities and can serve as an intermediate for the preparation of other acid analogs (*i.e.* amides, esters) which we have employed in related Pummerer-based transformations.[36] Finally, the oxidation of sulfides **11** and **17** to the desired sulfoxides **18** and **19** was carried out in very high yield using $NaIO_4$ as the oxidizing reagent.[37] To test the viability of the proposed *tandem Pummerer−Diels−Alder cascade* process, sulfoxides **18** and **19** were treated with a suitable dienophile under standard Pummerer reaction conditions.[2] Thus, heating a sample of the sulfoxide at 140 °C with acetic anhydride resulted in the formation of cycloadducts **21**−**24** in 64−87% yield as mixtures of diastereomers. When an unactivated dienophile such as cyclohexene was used (high lying LUMO), the cycloaddition reaction proceeded in low yield. This is presum-

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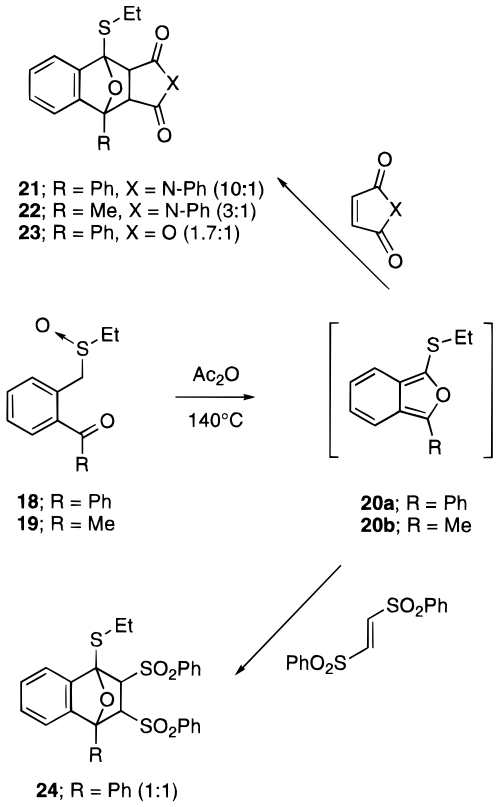
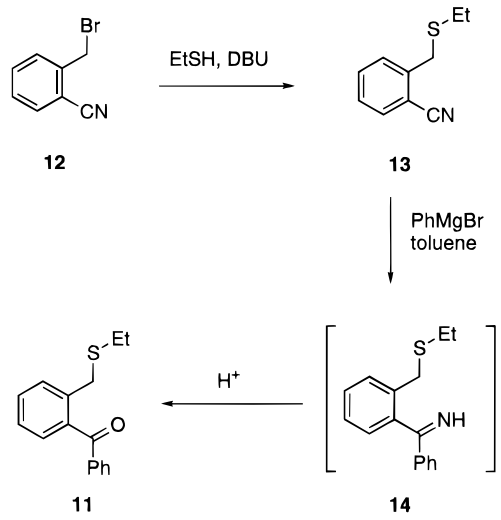
ably due to a poor FMO-matching of the frontier molecular orbitals. Diels–Alder adducts **21**–**24** are stable solids which were isolated and handled in conventional fashion. Prolonged storage or treatment with acid, however, resulted in the formation of aromatized products (*vide infra*).



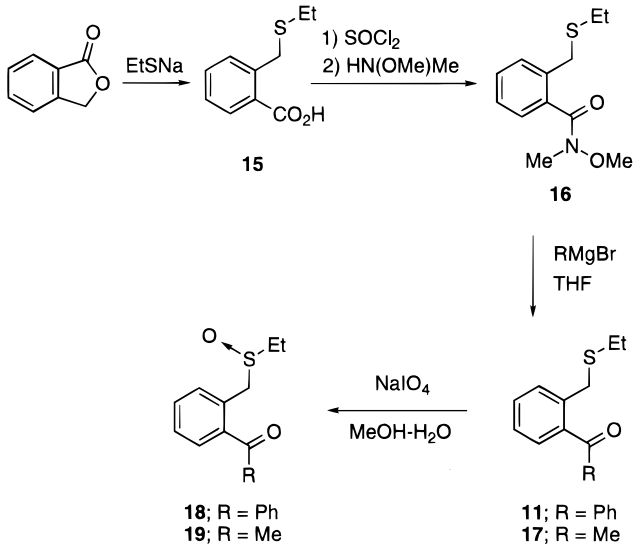
The intermediacy of the highly reactive α-thioisobenzofuran **20** in this reaction was established through the isolation and NMR identification of the phenyl derivative **20a**.[38] By employing somewhat more gentle conditions for triggering the Pummerer reaction (*i.e.* toluene–Ac_2O–*p*-TsOH),[39] we were able to obtain **20a** as a stable intermediate in toluene solution. Addition of *N*-phenylmaleimide to this bright yellow solution at 0 °C resulted in spontaneous decoloration and formation of cycloadduct **21** as a single diastereomer (*endo*) in 82% isolated yield. Isobenzofuran **20a** is sensitive to air and moisture and reacts with oxygen to form ketone **25**.[40]

Since the cycloaddition step of the cascade process proceeds at 0 °C, we attempted to trigger the Pummerer reaction at a lower temperature. Indeed, by using trifluoroacetic anhydride/triethylamine as the Pummerer promotor,[41] we were able to obtain cycloadduct **20a** as the *endo* diastereomer in 80% yield starting from sulfoxide **18** and *N*-phenylmaleimide at 0 °C. When *p*-toluenesulfonic acid was added to the crude reaction mixture, ring-opening followed by aromatization occurred

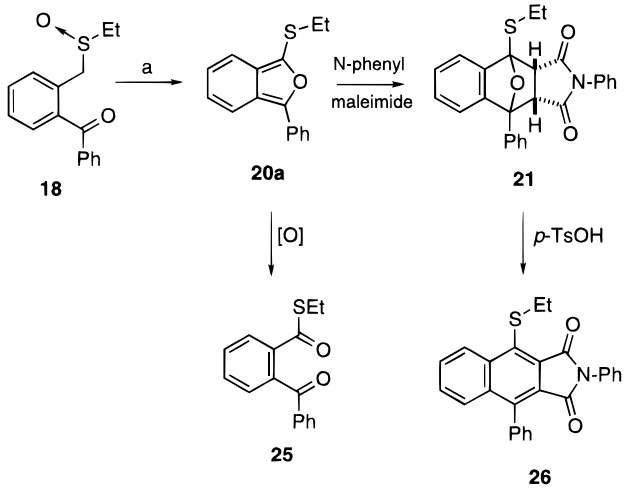
Scheme 3



Scheme 4



to produce the naphthalene derivative **26** in 72% overall yield from sulfoxide **18**.



Key: (a) Ac_2O, *p*-TsOH or $(CF_3CO)_2O$, Et_3N

Acetylenic dienophiles did not give the expected cycloadduct **27** but instead afforded the rearranged tetralone derivative **29** (or **30**). Thus, treatment of **18** with acetic anhydride in the presence of dimethyl acetylenedicarboxylate gave tetralone **29** in 38% isolated yield. An

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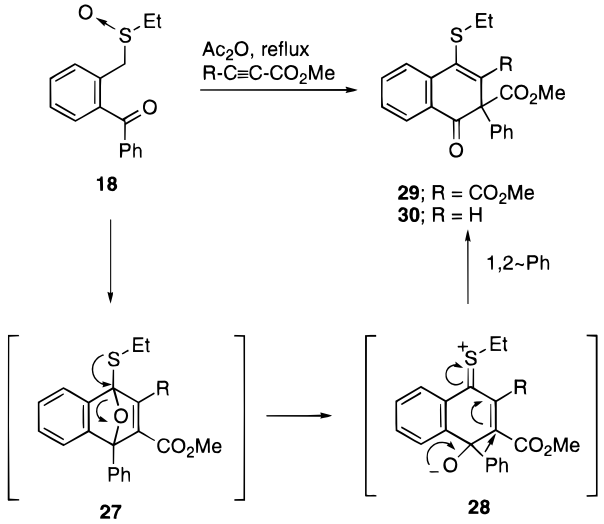
analogous reaction occurred using methyl propiolate producing tetralone **30** as the exclusive product in 51% isolated yield. The structure of **30** was assigned on the basis of its spectral data and was unambiguously established by an X-ray crystal analysis.[42] The mechanism of this unusual reaction has not been unequivocally proven, but one reasonable possibility is outlined below. Here it is proposed that the cyclization−cycloaddition sequence



produces the expected cycloadduct **27** which then rearranges to **29** (or **30**) *via* intermediate **28**. The key step involves oxabicyclic ring opening which is driven by the lone pair of electrons on the sulfur atom, and this is followed by a pinacol type rearrangement of **28** proceeding by way of a 1,2-phenyl shift.[43] The formation of adduct **30** as a single regioisomer is consistent with FMO theory.[44] The most favorable FMO interaction is between the HOMO of the isobenzofuran and the LUMO of methyl propiolate. The atomic coefficient at the ethylthio-substituted position in the isobenzofuran ring is larger than at the phenyl position in the HOMO and this nicely accommodates the high regioselectivity encountered.[45]

The model studies described above clearly demonstrate that the Pummerer reaction of *o*-benzoyl sulfinylmethyl aromatics of type **18** represents an effective method for the preparation of the isobenzofuran ring system. Isobenzofurans are highly reactive dienes for Diels−Alder cycloadditions, and this reactivity has been exploited in the synthesis of biologically active polycyclic aromatic compounds.[46] In this approach, the oxygen bridge in the initially formed cycloadduct can be easily cleaved to produce an aryl naphthalene derivative. Due to their widespread occurrence in nature and broad range of biological activity, aryl-substituted naphthalenes have attracted considerable synthetic attention over the years.[26−31] Much interest has been focused on their effectiveness as antineoplastic agents, and research in this area has revealed several modes of action by which they can regulate the growth of mammalian cells.[47] Over 40 natural arylnaphthalenes, the majority of which are lactones of general type **7**, are known and represent a significant subclass of lignans.[48] Although a wide variety of methods have been utilized for the synthesis of this class of natural products,[49−51] the key step for the construction of the phenylnaphthyl skeleton can be classified roughly into two methodologies. The first relies on assembling the B-ring of the naphthalene nucleus *via* the annulation of a properly substituted benzene derivative followed by an aromatization process.[52] The second approach is the joining of the pertinent aryl and naphthyl units *via* conjugate addition to a butenolide followed by reaction with an aldehyde.[53] These methods generally require a number of steps for construction of the 1-arylnaphthalene skeleton.

The versatility of the *tandem Pummerer−Diels−Alder cascade* approach has been highlighted through the synthesis of taiwanin C and E and justicidin E, naturally occurring arylnaphthalene lignans which possess all the functionality of podophyllotoxin[26] around a central aromatic ring. The requisite ketosulfoxide **34** was synthesized starting from piperonyl alcohol **31** which was converted to 6-bromopiperonyl bromide **32** (92%) using a modified literature procedure.[54] The bromide was treated with ethanethiol and 1,8-diazabicycloundecene (DBU) in benzene to produce the corresponding ethyl sulfide in 93% yield. Metal−halogen exchange took place cleanly with *t*-BuLi below −90 °C producing an orange colored lithiate that was quenched with a THF solution of piperonal to give the expected alcohol **33** in 90% yield. Oxidation to the benzophenone derivative was accomplished using MnO_2 in 92% yield. Further oxidation of the sulfide functionality was carried out with $NaIO_4$ in the usual manner[37] to produce sulfoxide **34** in an overall yield of 62% (five steps). Heating sulfoxide **34** with dimethyl maleate in acetic anhydride at reflux following the standard reaction conditions employed with our model systems led to a dark brown mixture. Extensive silica gel chromatography resulted only in a low yield (<35%) of the aromatized product **36**. The *cascade reaction* sequence, however, could be dramatically improved by slowly adding an acetic anhydride solution of sulfoxide **34** to a refluxing solution of dimethyl maleate in acetic anhydride. Not only were the yields consistently higher (*i.e.* 85%), but also only cycloadduct **35** was obtained and none of the aromatized compound **36** was formed. Further reaction of **35** with *p*-toluenesulfonic acid in CH_2Cl_2 at 25 °C afforded the α-thio-substituted

(42) The authors have deposited coordinates for structure **30** with the Cambridge Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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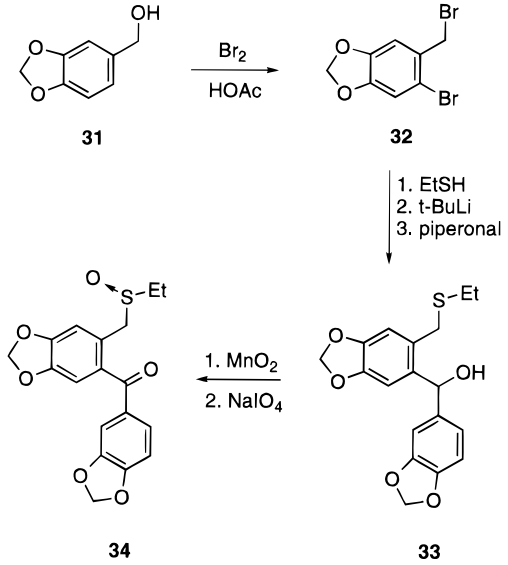
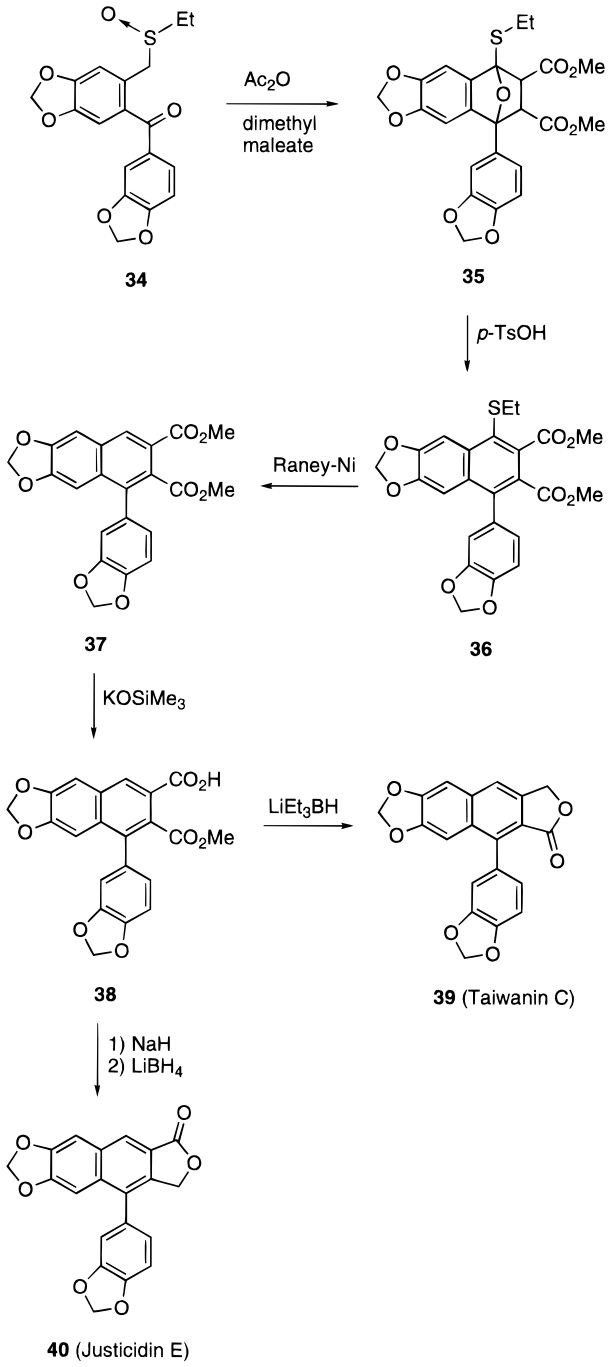


naphthalene **36** in 98% yield. Desulfurization of **36** with Ra−Ni produced naphthalene **37** (>97%), which on treatment with $KOSiMe_3$,[55] resulted in selective attack on the less hindered ester functionality giving rise to the half acid-ester **38** in nearly quantitative yield. Selective reduction of an ester in the presence of a carboxylic acid[56−59] is usually a facile process. We therefore did not expect any difficulty in reducing each functionality in **38** selectively to produce the regioisomeric lignans taiwanin C (**39**) and justicidin E (**40**). The carboxylic acid functionality in **38**, however, proved to be unusually susceptible to reduction. Thus, treatment of the half acid-ester **38** with $LiEt_3BH$ led selectively to the reduction of the carboxylic acid, which after acidic workup, gave taiwanin C (**39**)[60] in 68% yield (56% overall yield from **34**). The carboxylic acid could also be reduced by a variety of other reducing agents including $NaBH_4$ in refluxing dioxane. On the other hand, $LiBH_4$ in dioxane did reduce the ester functionality (albeit with low selectivity) but also led to an over-reduced product (*i.e.* a diol). Selective reduction of the ester functionality was ultimately achieved by an initial deprotonation of **38** using 2 equiv of NaH followed by the addition of 2 equiv of $LiBH_4$ and subsequent heating of the mixture at reflux in dioxane for 2 h. This procedure resulted a 65% yield of a 4:1 mixture of justicidin E (**40**) and taiwanin C (**39**).

The above results prompted us to also investigate the conversion of cycloadduct **35** into taiwanin E (**43**). The selective transformation of cycloadduct **35** to naphthalene **36** is presumably driven by the lone pair of electrons on the sulfur atom which induces regioselective C−O bond cleavage and further loss of a molecule of water. It seemed reasonable to assume that oxidation of the sulfide group in **35** to the corresponding sulfone (*i.e.* **41**) would prevent this type of ring-opening and thereby promote an alternative mode of ring cleavage resulting in the ejection of ethyl sufinate to give naphthol **42**. After some experimentation we found that the oxidation of sulfide **35** to sulfone **41** could best be achieved using $NaIO_4$ containing a catalytic amount of $RuCl_3$ at 0 °C.[61] This



procedure worked exceedingly well for our system producing sulfone **41** in essentially quantitative yield. Treatment of the crude sulfone **41** with *p*-TsOH in CH_2Cl_2 promoted the desired elimination to give naphthol **42** in 65% overall yield from sulfoxide **34**. The synthesis of naphthol **42** completes the formal synthesis of taiwanin E (**43**), since **42** can be readily converted to the natural product in one step using $NaBH_4$.[62]

In conclusion, we have demonstrated that the *tandem Pummerer−Diels−Alder cyclization−cycloaddition sequence* is well suited for the preparation of a variety of naturally occurring 1-arylnaphthalene lignans. The required sulfoxide precursors can be obtained in high overall yield by several routes and different methods for triggering the desired Pummerer reaction may be employed. The combination of these factors makes the cascade process extremely useful. Further work utilizing

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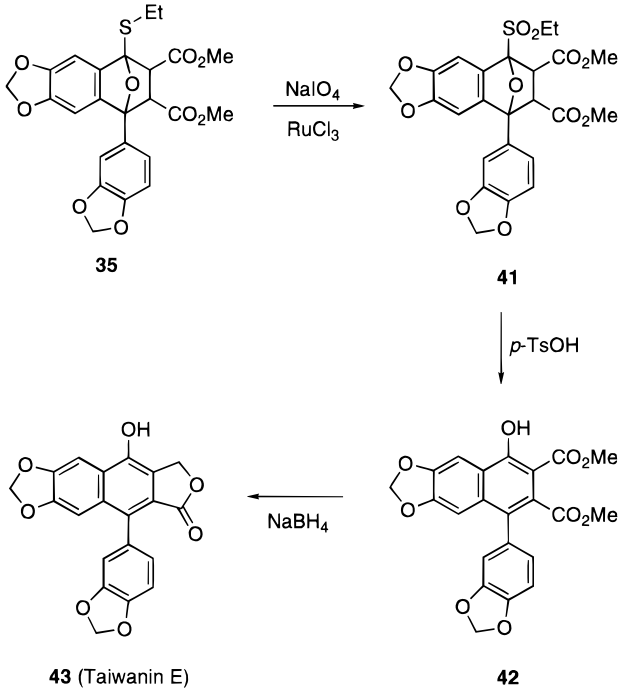

these thioisobenzofuran-derived cycloadducts as low cytotoxicity precursors of intercalating agents is in progress, and the results of these studies will be reported in due course. We are also investigating the generality of the cascade process for the construction of aza-polycyclic ring systems and its further application in target-oriented synthesis.

Experimental Section

Diethyl ether, tetrahydrofuran, benzene, toluene, and xylene were distilled from sodium benzophenone ketyl prior to use. Dichloromethane and triethylamine were distilled from CaH_2 prior to use. All reactions were performed under an atmosphere of dried argon unless otherwise noted.

General Procedure for Tandem Pummerer Cyclization Diels−Alder Cycloaddition Sequence. In a 250 mL, flame-dried, round-bottomed flask, a sample of Weinreb's amide **16** (*vide infra*) was dissolved in THF. The solution was cooled to 0 °C, and an excess of the appropriate Grignard reagent in THF was added dropwise. The solution was stirred overnight, poured into 5% HCl, and extracted with a 50% mixture of Et_2O/CH_2Cl_2. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel to give the appropriate thio-substituted ketone, **11** or **17**. This compound was dissolved in methanol, and the mixture was added to a solution of $NaIO_4$ in H_2O at 0 °C. The mixture was stirred for 1 h at 0 °C and then at rt until the starting material was no longer evident by TLC. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure to give the crude sulfoxide. The sulfoxide was purified by silica gel chromatography. The appropriate sulfoxide was dissolved in acetic anhydride in a flame-dried, 25 mL, round-bottomed flask. The dienophile was added and the mixture was heated at reflux under an inert atmosphere. The solution was cooled and concentrated under reduced pressure, and the residue was taken up in CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the resulting crude cycloadduct was chromatographed on silica gel with 1% Et_3N added.

Preparation of [2-[(Ethylsulfinyl)methyl]phenyl]-phenylmethanone (18). In a 250 mL, flame-dried, round-bottomed flask equipped with a dropping funnel was placed 3.90 mL (52.7 mmol) of ethanethiol in 100 mL of benzene. To this solution was added 7.20 mL (48.1 mmol) of 1,8-diazabicyclo-[5.4.0]un-dec-7-ene, and then a solution of 12.4 g (49.7 mmol) of 2-bromobenzyl bromide in 100 mL of benzene was added dropwise. The mixture was stirred overnight at rt, diluted with benzene, and poured into 5% HCl. The aqueous layer was extracted with benzene, the resulting solution was dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was chromatographed on silica gel to give 10.8 g (94%) of 2-[(ethylthio)methyl]bromobenzene (**9**) as a colorless oil: IR (neat) 3058, 2970, 1569, 1468, 1439 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.4 Hz), 2.50 (q, 2H, J = 7.4 Hz), 3.84 (s, 2H), 7.09 (td, 1H, J = 7.7 and 1.6 Hz), 7.25 (ddd, 1H, J = 7.7, 7.4, and 1.0 Hz), 7.36 (dd, 1H, J = 7.4 and 1.6 Hz), and 7.55 (dd, 1H, J = 7.7 and 1.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5, 25.6, 36.1, 124.4, 127.3, 128.4, 130.6, 132.0, 138.0. HRMS Calcd for $C_9H_{11}BrS$: 229.9765. Found: 229.9761.

In a 250 mL, flame-dried, round-bottomed, three-necked flask equipped with a low temperature thermometer was dissolved 10.4 g (45.0 mmol) of the above bromide in 70 mL of THF. The solution was cooled to −90 °C and 40 mL of 1.2 M t-BuLi solution (66.0 mmol) was added maintaining the temperature at −90 °C. The solution was stirred for 15 min at −90 °C, and then a solution of 4.6 mL (45.3 mmol) of benzaldehyde in 20 mL of THF was added to the mixture. The solution was stirred overnight at 25 °C, concentrated under reduced pressure, poured into a 5% HCl solution, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to give 11.18 g (96%) of [2-[(ethylthio)methyl]phenyl]phenylmethanol (**10**) as a light yellow oil: IR (neat) 3406, 3062, 1602, 1493, 1451 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, 3H, J = 7.4 Hz), 2.44 (q, 2H, J = 7.4 Hz), 3.23 (d, 1H, J = 3.4 Hz), 3.67 (d, 2H, J = 13.0 Hz), 3.74 (d, 2H, J = 13.0 Hz), 6.20 (d, 1H, J = 3.4 Hz), 7.18−7.37 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.4, 25.7, 33.4, 72.4, 126.6, 127.2, 127.5, 127.6, 128.2, 128.6, 130.4, 135.4, 142.1, 142.8. HRMS (FAB) Calcd for $C_{16}H_{18}OS$: 265.1238. Found: 265.1233 (M + Li).

In a 250 mL, flame-dried, round-bottomed flask was dissolved 9.55 g (40.0 mmol) of the above alcohol in 100 mL of CH_2Cl_2. To this solution was added 31.9 g (313 mmol) of activated MnO_2 (85%), and the black slurry was stirred for 3 days. The mixture was filtered through a plug of silica gel, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on silica gel to give 8.79 g (93%) of [2-[(ethylthio)methyl]phenyl]phenylmethanone (**11**) as a pale yellow oil: IR (neat) 3062, 2927, 1665, 1598, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, 3H, J = 7.4 Hz), 2.37 (q, 2H, J = 7.4 Hz), 3.87 (s, 2H), 7.25−7.33 (m, 2H), 7.39−7.47 (m, 4H), 7.55−7.60 (m, 1H), 7.79−7.83 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 25.7, 33.1, 126.2, 128.3, 129.2, 130.1, 130.2, 130.5, 133.0, 137.8, 138.4, 138.6, 198.0. HRMS (FAB) Calcd for $C_{16}H_{16}OS$: 263.1082. Found: 263.1083 (M + Li).

A sample of sulfide **11** was also prepared from 2-[(ethylthio)-methyl]benzonitrile (**13**). A mixture containing 2.83 g (18.0 mmol) of DBU, and 1.12 g (18.0 mmol) of ethanethiol in 10 mL of THF was added to a solution of 2.91 g (14.8 mmol) of 2-(bromomethyl)benzonitrile (**12**)[33] in 20 mL of THF. After stirring for 5 h, the precipitate that formed was filtered and the filtrate was passed through a plug of silica gel to give 2.60 g (99%) of **13** as a colorless oil: IR (neat) 3065, 2225, 1598, 1485 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.4 Hz), 2.49 (q, 2H, J = 7.4 Hz), 3.90 (s, 2H), 7.32−7.63 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 25.5, 33.7, 112.1, 117.3, 127.2, 129.7, 132.5, 132.5, 142.6. A solution of phenylmagnesium bromide in 20 mL of ether was prepared from 486 mg (20.0 mmol) of Mg powder and 3.14 g (20.0 mmol) of bromobenzene. Most of the solvent was removed under reduced pressure, and this was followed by the addition of 10 mL of toluene. A solution of 2.46 g (13.9 mmol) of nitrile **13** in 5 mL of toluene was added to the hot solution, and the mixture was heated at reflux for 15 min. After cooling to rt, 3 mL of H_2O followed by 10 mL of 2 N H_2SO_4 was added, and the mixture was heated at reflux for 1 h in order to hydrolyze the initially formed imine. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with 2 N NaOH, brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography gave 3.42 g (96%) of sulfide **11**.

A 1.28 g (5.00 mmol) sample of sulfide **11** was treated with 1.18 g (5.51 mmol) of $NaIO_4$ dissolved in 25 mL of CH_3OH and 25 mL of water to give 1.55 g (99%) of [2-[(ethylsulfinyl)methyl]-phenyl]phenylmethanone (**18**) as a colorless oil: IR (neat) 2948, 1667, 1599, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.5 Hz), 2.61−2.79 (m, 2H), 4.20 (d, 1H, J = 12.7 Hz), 4.38 (d, 1H, J = 12.7 Hz), 7.33−7.61 (m, 3H), 7.79 (dd, 1H, J = 8.1 and 1.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 6.5, 45.1, 55.1, 127.2, 128.1, 130.0, 130.3, 130.8, 131.0, 132.2, 132.9, 137.5, 137.7, 197.4. HRMS Calcd for $C_{16}H_{16}OS$: 273.0946. Found: 273.0934.

Preparation of 1-[2-[(Ethylsulfinyl)methyl]phenyl]-ethanone (19). In a 1 L round-bottomed flask was placed 22.1 g (165 mmol) of phthalide in 400 mL of 95% ethanol. To this solution was added 14 g (166 mmol) of sodium ethanethiolate, and the mixture was heated at reflux for 3 h. The solution was concentrated under reduced pressure, and the resulting solid was dissolved in a saturated $NaHCO_3$ solution and washed with ethyl acetate. The aqueous layer was acidified with concentrated HCl, and the solid was filtered, washed with water, and dried to give 28.3 g (90%) of pure **15** as a white solid: mp 105−106 °C; IR (KBr) 2961, 1674, 1567, 1389 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.4 Hz), 2.48 (q, 2H, J = 7.4 Hz), 4.20 (s, 2H), 7.32−7.40 (m, 2H), 7.49 (td, 1H, J = 7.4 and 1.3 Hz), 8.08 (dd, 1H, J = 7.2 and 0.9 Hz), 11.85 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.4, 25.7, 34.2, 127.0, 128.0, 131.1, 132.0, 132.7, 141.8, 173.2. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.17. Found: C, 60.97; H, 6.21.

In a 250 mL, flame-dried, round-bottomed flask was placed a mixture of 9.82 g (50.04 mmol) of the above acid in 100 mL of benzene, and then 7.3 mL (100.1 mmol) of thionyl chloride was added and the mixture was stirred at rt for 12 h. The solvent was removed under reduced pressure, and the resulting oil was dissolved in 200 mL of CH_2Cl_2 and 5.48 g (55.05 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride was added. The mixture was cooled to 0 °C, and 9.30 g (115.0 mmol) of pyridine was added dropwise. After stirring at 25 °C for 3 h, the mixture was extracted with ether and washed with brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel to give 9.62 g (80%) of *N*-methoxy-*N*-methyl 2-[(ethylthio)methyl]-benzamide (**16**) as a colorless oil: IR (neat) 2925, 1645, 1595, 1445, 1410 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, 3H, J = 7.4 Hz), 2.44 (q, 2H, J = 7.4 Hz), 3.30 (brs, 3H), 3.55 (br s, 3H), 3.85 (s, 2H), 7.23−7.39 (m, 4H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.2, 25.5, 32.9, 60.6, 126.3, 126.9, 129.1, 129.8, 134.6, 136.4. HRMS Calcd for $C_{12}H_{17}NO_2S$: 239.0980. Found: 239.0979.

A 2.39 g (10.0 mmol) sample of amide **16** in 70 mL of THF was treated with 10.0 mL (30.0 mmol) of a 3.0 M MeMgBr solution to give 1.86 g (96%) of 1-[2-[(ethylthio)methyl]phenyl]-ethanone (**17**) as a colorless oil: IR (neat) 3061, 2869, 1681, 1595, 1567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, 3H, J = 7.4 Hz), 2.43 (q, 2H, J = 7.4 Hz), 2.59 (s, 3H), 4.03 (s, 2H), 7.30−7.38 (m, 3H), 7.65 (d, 1H, J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 25.7, 29.6, 33.5, 126.7, 129.1, 130.9, 130.9, 137.7, 138.7, 201.9. HRMS Calcd for $C_{11}H_{14}OS$: 194.0765. Found: 194.0775.

A 1.46 g (7.50 mmol) sample of the above sulfide was treated with 1.76 g (8.21 mmol) of $NaIO_4$ in 40 mL of CH_3OH and 40 mL of H_2O to give 1.55 g (98%) of 1-[2-[(ethylsulfinyl)methyl]-phenyl]ethanone (**19**) as a colorless oil: IR (neat) 2968, 1681, 1595, 1567 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, 3H, J = 7.5 Hz), 2.60 (s, 3H), 2.70−2.85 (m, 2H), 4.00 (d, 1H, J = 12.1 Hz), 4.38 (d, 1H, J = 12.1 Hz), 7.38−7.50 (m, 3H), 7.86 (d, 1H, J = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 6.3, 28.6, 45.0, 56.5, 127.9, 129.9, 130.9, 131.7, 132.7, 136.2, 200.7. HRMS (FAB) Calcd for $C_{11}H_{14}O_2S$: 211.0793. Found: 211.0796.

Generation and Trapping of 1-(Ethylthio)-3-phenyl-isobenzofuran (20a). A mixture containing 20 mL of dry toluene and 1 mL of acetic anhydride containing 2 mg of *p*-toluenesulfonic acid was heated at reflux under argon. To this mixture, was added 272 mg (1 mmol) of sulfoxide **18** in 5 mL of toluene dropwise *via* syringe over a 10 min period. After the addition was complete, the yellow solution was heated at reflux under argon for an additional 20 min. The bright yellow solution was cooled in an ice-bath, and then 190 mg (1.1 mmol) of *N*-phenylmaleimide in 5 mL of toluene was added. The resulting mixture was stirred for 10 min at 0 °C and was then *immediately* washed with a saturated aqueous $NaHCO_3$ solution. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give 350 mg (82%) of 1-(ethylthio)-8,11-diphenyl-11-aza-14-oxatetracyclo[6.5.1.$0^{2,7}0^{9,13}$]-tetradeca-2,4,6-triene-10,12-dione (**21**) as a white solid after chromatographic purification: mp 180−181 °C; IR (neat) 3067, 1779, 1717, 1598, 1501 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, 3H, J = 7.5 Hz), 2.81−2.98 (m, 2H), 3.96 (d, 1H, J = 8.4 Hz), 4.16 (d, 1H, J = 8.4 Hz), 6.46−6.49 (m, 2H), 7.04 (d, 1H, J = 7.3 Hz), 7.23−7.27 (m, 3H), 7.29 (td, 1H, J = 7.3 Hz and 1.2 Hz), 7.38 (td, 1H, J = 7.3 Hz and 0.9 Hz), 7.46−7.53 (m, 4H), 7.93−7.97 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.4, 24.4, 54.3, 54.8, 90.6, 95.0, 121.2, 121.5, 126.2, 127.0, 128.4, 128.6, 128.6, 128.7, 128.8, 135.9, 140.3, 144.6, 171.4, 172.9. HRMS (FAB) Calcd for $C_{26}H_{22}NO_3S$: 428.1320. Found: 428.1326 (M + H^+).

An NMR spectrum of 1-(ethylthio)-3-phenylisobenzofuran (**20a**) could be obtained by subjecting the bright yellow solution of **20a** obtained above to rapid flash chromatogaphy followed by removal of the solvent under reduced pressure. The resulting yellow oil (95%) obtained by this procedure can be stored under an argon atmosphere in solution for several hours before decomposition occurs: ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 2.83 (q, 2H, J = 7.2 Hz), 6.97 (m, 2H), 7.28 (dd, 1H, J = 7.6 Hz), 7.45 (dd, 2H, J = 7.6 Hz), 7.50 (m, 1H), 7.61 (m, 1H), 7.89 (dd, 2H, J = 7.6 and 1.2 Hz); ^{13}C-NMR ($CDCl_3$) δ 15.6, 31.5, 119.6, 119.9, 121.1, 124.9, 125.0, 125.1, 127.2, 128.8, 131.0, 131.4, 136.5, 147.6. On prolonged exposure to atmospheric conditions, the transient isobenzofuran **20a** was converted into 2-benzoylthiobenzoic acid *S*-ethyl ester (**25**). Purification by flash silica gel chromatography afforded 167 mg (62%) of pure **25** as a colorless oil: IR ($CDCl_3$) 1771, 1665, 1282, 1207 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, 3H, J = 7.5 Hz), 2.87 (q, 2H, J = 7.5 Hz), 7.36−7.97 (m, 9H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.3, 23.8, 128.2, 128.3, 128.4, 129.4, 129.8, 132.2, 133.0, 137.0, 137.2, 139.3, 192.0, 196.9. HRMS (FAB) Calcd for $C_{16}H_{15}O_2S$: 271.0793. Found: 271.0805 (M + H^+).

Preparation of 1-(Ethylthio)-8-methyl-11-phenyl-11-aza-14-oxatetracyclo[6.5.1.$0^{2,7}0^{9,13}$]tetradeca-2,4,6-triene-10,12-dione (22). A 526 mg (2.50 mmol) sample of sulfoxide **19** was treated with 433 mg (2.50 mmol) of *N*-phenylmaleimide in 3 mL of Ac_2O to give 584 mg (64%) of cycloadduct **22** as a white solid: mp 181−182 °C; IR (neat) 2977, 2933, 1715, 1499, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz), δ 1.32 (t, 3H, J = 7.5 Hz), 2.07 (s, 3H), 2.80 (m, 2H), 3.63 (d, 1H, J = 8.4 Hz), 3.81 (d, 1H, J = 8.4 Hz), 6.39−6.42 (m, 2H), 7.22−7.29 (m, 4H), 7.37 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.1, 17.5, 24.2, 54.8, 86.9, 95.1, 120.2, 121.5, 123.9, 126.1, 126.4, 128.3, 128.5, 128.6, 128.7, 129.0, 141.0, 143.7, 171.7, 172.8. HRMS (FAB) Calcd for $C_{21}H_{20}NO_3S$: 366.1164. Found: 366.1177 (M + H^+).

Preparation of 1-(Ethylthio)-8-phenyl-11,14-dioxa-tetracyclo[6.5.1.$0^{2,7}0^{9,13}$]tetradeca-2,4,6-triene-10,12-dione (23). A 595 mg (2.18 mmol) sample of sulfoxide **18** was treated with 217 mg (2.21 mmol) of maleic anhydride in 4 mL of Ac_2O to give 670 mg (87%) of cycloadduct **23** as a white solid after chromatographic purification: mp 179−180 °C; IR (neat) 3068, 1866, 1785, 1461 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, J = 7.4 Hz), 1.38 (t, 3H, J = 7.4 Hz), 2.70−2.95 (m, 4H), 3.43 (d, 1H, J = 6.6 Hz), 3.70 (d, 1H, J = 6.6 Hz), 4.06 (d, 1H, J = 8.8 Hz), 4.27 (d, 1H, J = 8.8 Hz), 7.03 (brd, 1H, J = 7.1 Hz), 7.21 (brd, 1H, J = 7.0 Hz), 7.28−7.55 (m, 16H), 7.58−7.62 (m, 2H), 7.80−7.83 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.1, 15.2, 15.3, 24.5, 24.6, 54.8, 55.1, 55.9, 56.3, 90.8, 91.3, 95.2, 95.7, 91.3, 95.7, 119.9−122.3, 125.0−129.9, 134.9, 139.4, 142.4, 143.7, 146.0, 166.1, 166.7, 166.6. HRMS (FAB) Calcd for $C_{20}H_{17}O_4S$: 353.0848. Found: 353.0837 (M + H^+).

Preparation of 9,10-Bis(phenylsulfonyl)-1-(ethylthio)-8-phenyl-11-oxatricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6-triene (24). A 396 mg (1.45 mmol) sample of sulfoxide **18** was treated with 459 mg (1.49 mmol) of *trans*-bis(phenylsulfonyl)ethene in 3 mL of Ac_2O to give 559 mg (69%) of a 1:1 mixture of diastereomers. Recrystallization from $CHCl_3$ provided one of the diastereo-

mers as a white solid: mp 144−145 °C; IR (neat) 3066, 1461, 1449, 1323, 1152 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, 3H, J = 7.5 Hz), 2.83 (t, 2H, J = 7.5Hz), 4.52 (d, 2H, J = 4.3 Hz), 4.86 (d, 2H, J = 4.3 Hz), 7.07−7.71 (m, 17H), 7.03 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 15.2, 24.4, 71.8, 73.7, 89.3, 93.4, 120.1, 123.7, 126.2, 127.9, 128.0, 128.1, 128.5, 128.6, 128.6, 128.8, 129.1, 133.3, 134.2, 138.7, 139.9, 141.6, 145.1, 148.6. HRMS (FAB) Calcd for $C_{30}H_{26}O_5S_3$: 563.1021. Found: 563.1033 (M + H^+).

Preparation of 4-(Ethylthio)-2,9-diphenylbenzo[*f*]isoindole-1,3-dione (26). Cycloadduct **21** was also obtained using trifluoroacetic anhydride as the Pummerer promotor at 25 °C. To a solution of 1.15 g (4.22 mmol) of sulfoxide **18**, 1.06 g (6.12 mmol) of *N*-phenylmaleimide, and 0.69 g (6.77 mmol) of triethylamine in 15 mL of CH_2Cl_2 was added dropwise a solution of 1.30 g (6.19 mmol) of trifluoroacetic anhydride in 3 mL of CH_2Cl_2 at 0 °C. After stirring at rt for 1 h, the mixture was washed successively with 2 N HCl and H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to leave cycloadduct **21** as a single diastereomer. Treatment of a sample of **21** with 5 mg of *p*-TsOH in CH_2Cl_2 for 18 h at rt resulted in the loss of water producing 4-(ethylthio)-2,9-diphenylbenzo[*f*]isoindole-1,3-dione (**26**) (72%) as pale yellow solid: mp 169−170 °C; IR (KBr) 3050, 1764, 1718, 1490, 1375 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.4 Hz), 3.22 (q, 2H, J = 7.4 Hz), 7.32−7.83 (m, 13H), 9.13 (d, 1H, J = 8.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 15.2, 31.5, 124.1, 126.7, 127.9, 128.0, 128.1, 128.4, 128.4, 128.7, 128.9, 129.3, 129.4, 129.6, 131.7, 134.5, 135.6, 138.3, 140.6, 165.6. Anal. Calcd for $C_{26}H_{19}NO_2S$: C, 76.26; H, 4.68; N, 3.42. Found: C, 75.98; H, 4.71; N, 3.32.

Preparation of 4-(Ethylthio)-1-oxo-2-phenyl-1,2-dihydronaphthalene-2,3-dicarboxylic Acid Dimethyl Ester (29). A 421 mg (1.55 mmol) sample of sulfoxide **18** was treated with 950 μL (7.73 mmol) of DMAD in 3 mL of Ac_2O to give 230 mg (38%) of cycloadduct **29** as a yellow oil: IR (neat) 3064, 1771, 1740, 1719, 1669, 1447 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, 3H, J = 7.4 Hz), 2.86 (q, 2H, J = 7.4 Hz), 3.35 (s, 3H), 3.87 (s, 3H), 7.09 (d, 1H, J = 7.7 Hz), 7.17 (d, 1H, J = 7.3 Hz), 7.30−7.55 (m, 5H), 7.80 (d, 1H, J = 7.7 Hz), 8.45 (d, 1H, J = 7.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5, 30.6, 52.2, 64.6, 68.8, 127.7, 128.1, 128.2, 128.4, 128.6, 129.3, 129.4, 129.5, 130.9, 131.8, 133.8, 134.1, 134.4, 140.1, 166.1, 166.7. HRMS (FAB) Calcd for $C_{22}H_{21}O_5S$: 397.1110. Found: 397.1108 (M + H^+).

Preparation of 4-(Ethylthio)-1-oxo-2-phenyl-1,2-dihydronaphthalene-2-carboxylic Acid Methyl Ester (30). A 436 mg (1.60 mmol) sample of sulfoxide **18** was treated with 0.8 μL (9.57 mmol) of methyl propiolate in 2 mL of Ac_2O to give 276 mg (51%) of cycloadduct **30** as pale yellow solid: mp 99−100 °C; IR (neat) 3064, 1777, 1740, 1593, 1684 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, 3H, J = 7.4 Hz), 2.94 (q, 2H, J = 7.4 Hz), 3.76 (s, 3H), 6.35 (s, 1H), 7.27−7.49 (m, 6H), 7.63 (td, 1H, J = 7.4 and 1.0 Hz), 7.83 (d, 1H, J = 8.0 Hz), 8.02 (dd, 1H, J = 8.0 and 1.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 13.6, 26.4, 53.2, 65.9, 125.2, 127.1, 127.8, 127.8, 127.9, 128.1, 128.3, 128.4, 129.1, 132.5, 134.7, 136.1, 136.4, 170.2, 193.4. HRMS (FAB) Calcd for $C_{20}H_{19}O_3S$: 339.1055. Found: 339.1069 (M + H^+). Anal. Calcd for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36. Found: C, 70.73; H, 5.43. The X-ray structure of **30** was solved by direct methods using the SHELXTL program.[42]

Preparation of Benzo[1,3]dioxol-5-yl-[6-[(ethylsulfinyl)-methyl]benzo[1,3]dioxol-5-yl)methanone (34). In a 100 mL round-bottomed flask was dissolved 5.0 g (3.29 mmol) of piperonyl alcohol (**31**) in 10 mL of acetic acid. The flask was cooled in an ice-bath, and a mixture of 2.0 mL of bromine (38.8 mmol) and 6 mL of acetic acid was added dropwise. The reaction mixture was stirred at rt overnight during which time a white solid precipitated. The mixture was filtered, and the filtercake was washed with water. The solid was dried *in vacuo* to give 7.62 g of 5-bromo-6-(bromomethyl)benzo[1,3]-dioxole (**32**). The filtrate was extracted with CH_2Cl_2, and the extracts were dried over Na_2SO_4, concentrated, and chromatographed to afford an additional 1.42 g (92% total) of dibromide **32** as a white solid: mp 88−89 °C (lit.[54] 91−92 °C); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.55 (s, 2H), 5.99 (s, 2H), 6.91 (s, 1H), 7.01 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 34.1, 102.1, 110.5, 113.1, 115.6, 129.9, 147.6, 148.8.

In a flame-dried 250 mL round-bottomed flask equipped with an addition funnel, was dissolved 4.4 mL (29.4 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 100 mL of benzene. A 2.2 mL (29.7 mmol) sample of ethanethiol was added to the colorless solution. To this mixture was added dropwise a solution of 8.60 g (29.3 mmol) of dibromide **32** in 50 mL of benzene which caused the precipitation of the DBU hydrobromide salt. The mixture was stirred overnight, diluted with H_2O, and extracted with CH_2Cl_2. The organic extracts were washed with 10% NaOH, dried over Na_2SO_4, and concentrated under reduced pressure to give 7.90 g (98%) of 5-bromo-6-ethylthiomethylbenzo[1,3]dioxole as a clear light yellow oil: IR (neat) 2970, 2925, 1503, 1450, 1231 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.3 Hz), 2.51 (q, 2H, J = 7.3 Hz), 3.77 (s, 1H), 5.96 (s, 1H), 6.89 (s, 1H), 6.99 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.6, 25.6, 36.0, 101.7, 110.1, 112.7, 114.6, 131.1, 147.1, 147.3.

In a flame-dried, 250 mL, three-necked, round-bottomed flask equipped with a low temperature thermometer and septa was dissolved 7.51 g (27.3 mmol) of the above sulfide in 50 mL of THF. The solution was cooled below −90 °C using a liquid N_2−Et_2O bath, and 34 mL (57.8 mmol) of 1.7 M t-BuLi solution was added dropwise. In a separate 25 mL, flame-dried, round-bottomed flask was dissolved 4.10 g (27.3 mmol) of piperonal in 20 mL of THF. After addition of the t-BuLi solution to the sulfide was complete, the solution was stirred for 30 min below −90 °C, and the piperonal solution was added to the dark reddish-orange lithiate solution. The solution was stirred overnight, acidified with 5% HCl solution, and extracted with CH_2Cl_2. The organic extracts were washed with a saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 8.51 g (90%) of benzo[1,3]dioxol-5-yl-[6-[(ethylthio)methyl]benzo[1,3]dioxol-5-yl)methanol (**33**) as a light yellow oil: IR (neat) 3408, 2898, 1486, 1241, 1040 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, J = 7.4 Hz), 2.48 (q, 2H, J = 7.4 Hz), 2.86 (d, 1H, J = 3.7 Hz), 3.62 (d, 1H, J = 13.1 Hz), 3.72 (d, 1H, J = 13.1 Hz), 5.90 (d, 2H, J = 1.4 Hz), 5.92 (s, 2H), 6.06 (d, 1H, J = 3.7 Hz), 6.69 (s, 1H), 6.75 (d, 1H, J = 8.5 Hz), 6.81 (s, 1H), 6.82−6.84 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5, 25.9, 33.5, 71.6, 101.0, 101.1, 107.3, 108.0, 108.6, 110.3, 119.9, 129.0, 136.2, 137.0, 146.7, 147.1, 147.2, 147.7.

In a flame-dried, 500 mL, round-bottomed flask was dissolved 8.34 g (24.1 mmol) of alcohol **33** in 75 mL of CH_2Cl_2. To the yellow solution was added 10.18 g (117 mmol) of activated MnO_2 (85%). The mixture was stirred at rt for 24 h, filtered over Celite and concentrated under reduced pressure to give 7.62 g (92%) of benzo[1,3]dioxol-5-yl-[6-[(ethylthio)methyl]-benzo[1,3]dioxol-5-yl)methanone as a light yellow oil: IR (neat) 2905, 1654, 1603, 1485 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, 3H, J = 7.4 Hz), 2.39 (q, 2H, J = 7.4 Hz), 3.77 (s, 2H), 6.02 (s, 2H), 6.06 (s, 2H), 6.77 (s, 1H), 6.82 (d, 1H, J = 8.1 Hz), 6.98 (s, 1H), 7.32 (dd, 1H, J = 8.1 and 1.7 Hz), 7.35 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.5, 25.8, 33.1, 101.6, 101.9, 107.7, 109.2, 109.5, 110.6, 127.1, 132.2, 132.6, 133.5, 145.7, 148.0, 149.0, 151.9, 195.2. HRMS (FAB) Calcd for $C_{18}H_{16}O_5S$: 345.0797. Found: 345.0793.

In a 250 mL round-bottomed flask equipped with an addition funnel was dissolved 12.9 g (60.5 mmol) of $NaIO_4$ in 100 mL of H_2O, and the mixture was cooled in an ice-bath. A 19.8 g (57.4 mmol) sample of the above sulfide was dissolved in 100 mL of 1,4-dioxane and added dropwise to the aqueous solution which resulted in the eventual precipitation of a white solid. The ice-bath was removed, and the mixture was stirred overnight, diluted with water, and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 17.47 g (88%) of benzo[1,3]-diox-ol-5-yl-[6-[(ethylsulfinyl)methyl]benzo[1,3]dioxol-5-yl)-methanone (**34**) as a colorless oil: IR (neat) 2910, 1650, 1603, 1487 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, J = 7.6 Hz), 2.70 (m, 2H), 3.87 (d, 2H, J = 12.8 Hz), 4.27 (d, 2H, J = 12.8 Hz), 6.04−6.06 (m, 4H), 6.82−6.85 (m, 1H), 6.90 (s, 1H), 6.99, (s, 1H), 7.28−7.33 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 6.7, 45.3, 55.5, 101.9, 102.0, 107.7, 109.6, 110.5, 112.2, 126.2, 127.2, 132.1, 132.4, 146.8, 148.0, 149.6, 152.0, 194.8. HRMS (FAB) Calcd for $C_{18}H_{16}O_5S$: 345.0797. Found: 345.0793.

Preparation of 5-Benzo[1,3]dioxol-5-yl-8-(ethylthio)-naphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic Acid Dimethyl Ester (36). In a flame-dried, three-necked, 500 mL, round-bottomed flask was dissolved 5.0 mL (40 mmol) of dimethyl maleate in 250 mL of Ac_2O, and the mixture was heated at reflux. A 7.11 g (19.7 mmol) sample of sulfoxide **34** was dissolved in 30 mL of Ac_2O and this was added dropwise to the hot Ac_2O solution. After all of the sulfoxide solution had been added, the reaction was heated at reflux for an additional 30 min. The yellow solution was concentrated under reduced pressure, and the orange residue was taken up in CH_2Cl_2. The organic solution was washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure to give 8.17 g (85%) of cycloadduct **35**. The solid was dissolved in 200 mL of CH_2Cl_2, and 200 mg (1.05 mmol) of *p*-toluenesulfonic acid was added. The reaction was heated overnight at reflux, cooled and washed with a saturated aqueous $NaHCO_3$ solution, concentrated, and chromatographed to afford 7.58 g (82%) of naphthalene sulfide **36** as a white solid: mp 219−220 °C; IR (KBr) 1739, 1719, 1443, 1216, 1038 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, 3H, J = 7.4 Hz), 2.86 (q, 2H, J = 7.4 Hz), 3.49 (s, 3H), 3.84 (s, 3H), 6.12 (d, 2H, J = 5.9 Hz), 6.23 (d, 2H, J = 2.3 Hz), 6.68 (dd, 1H, J = 7.9 and 1.4 Hz), 6.86 (s, 1H), 6.87 (d, 1H, J = 1.4 Hz), 7.03 (d, 1H, J = 7.9 Hz), 7.99 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.7, 30.7, 52.3, 52.5, 101.4, 102.6, 103.2, 108.3, 110.1, 122.9, 126.9, 127.4, 129.9, 130.1, 130.6, 133.0, 135.7, 138.9, 147.1, 147.3, 149.3, 150.3, 167.3, 167.7. HRMS Calcd for $C_{18}H_{16}O_6S$: 361.0746. Found: 361.0744.

Preparation of 5-Benzo[1,3]dioxol-5-ylnaphtho[2,3-*d*]-[1,3]dioxole-6,7-dicarboxylic Acid Dimethyl Ester (37). In a 250 mL round-bottomed flask was placed 4.35 g (9.28 mmol) of naphthalene **36** in 85 mL of THF. To this mixture was added 24 g (408 mmol) of wet Ra−Ni, and the mixture was heated at reflux until the starting material had disappeared. The hot mixture was filtered over a pad of SiO_2 and was eluted with THF. Evaporation of the filtrate afforded 3.79 g (100%) of **37** as a white solid: mp 218−219 °C; IR (KBr) 3017, 2948, 2917, 1727, 1713 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.66 (s, 3H), 3.93 (s, 3H), 6.03−6.06 (m, 4H), 6.77 (dd, 1H, J = 8.1 and 1.2 Hz), 6.79 (d, 1H, J = 1.2 Hz), 6.88 (s, 1H), 6.89 (d, 1H, J = 7.5 Hz), 7.22 (s, 1H), 8.38 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 52.2, 52.5, 101.2, 101.7, 103.3, 104.8, 108.1, 110.8, 122.9, 123.7, 129.8, 129.9, 130.4, 132.3, 137.0, 147.4, 148.7, 150.3, 166.3, 169.5.

Preparation of 5-Benzo[1,3]dioxol-5-ylnaphtho[2,3-*d*]-[1,3]dioxole-6,7-dicarboxylic Acid 6-Methyl Ester (38). In a flame-dried, 100 mL, round-bottomed flask was placed 2.26 g (5.55 mmol) of diester **37** in 60 mL of THF. To the mixture was added 3.14 g (24.5 mmol) of potassium trimethylsilanolate. The reaction was stirred at rt for 15 min and then acidified with 5% HCl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 2.23 g (100%) of the mono-acid ester **38** as a white solid: mp 243−244 °C; IR (KBr) 3428, 1737, 1690, 1487, 1238 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.50 (s, 3H), 6.10−6.18 (m, 4H), 6.68 (dd, 1H, J = 7.8 and 1.3 Hz), 6.72 (s, 1H), 6.80 (d, 1H, J = 1.3 Hz), 7.02 (d, 1H, J = 7.8 Hz), 7.62 (s, 1H), 8.45 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.8, 101.2, 102.0, 102.2, 104.9, 108.1, 110.3, 123.3, 123.8, 129.6, 130.1, 131.2, 136.2, 146.9, 147.0, 148.5, 150.1, 166.9, 168.5. Anal. Calcd for $C_{21}H_{14}O_8$: C, 63.96; H, 3.58. Found: C, 63.79; H, 3.68.

Preparation of Taiwanin C (39). In a flame-dried 50 mL round-bottomed flask was placed 550 mg (1.39 mmol) of half ester-acid **38** in 25 mL of THF. A 5 mL sample of $LiEt_3BH$ (1.0 M solution in THF, 5.0 mmol) was added which resulted in immediate gas evolution. The mixture was heated at reflux overnight, cooled, acidified with 5% HCl and then heated to reflux for 2 h. A white precipitate appeared during the heating period. The reaction mixture was poured into a 5% $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 450 mg (93%) of taiwanin C (**39**) as a white solid, mp 272−273 °C, whose spectral characteristics were identical with those previously reported:[60] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.38 (s, 2H), 6.07 (s, 4H), 6.78 (dd, 1H, J = 8.0 and 1.0 Hz), 6.82 (d, 1H, J = 1.0 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.13 (s, 1H), 7.20 (s, 1H), 7.69 (s, 1H).

Preparation of Justicidin E (40). In a 50 mL, flame-dried, round-bottomed flask was dissolved 506 mg of the half acid-ester **38** in 20 mL of anhydrous 1,4-dioxane. A 202 mg sample of NaH (8.42 mmol) was added in one portion, then 3.0 mL of $LiBH_4$ (2.0 M in THF, 6.0 mmol) was added, and the mixture was heated at reflux for 2 h. The solution was cooled, acidified with 5% HCl, and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give 560 mg of a white solid that was shown by ^{1}H-NMR spectroscopy to consist of a 4:1 mixture of justicidin E (**40**) and taiwanin C (**39**). The mixture was chromatographed on silica gel (90% CH_2Cl_2:hexane) to afford 233 mg (51%) of justicidin E whose spectral properties were identical with those previously reported:[60] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.17 (s, 2H), 6.07 (s, 4H), 6.77 (dd, 1H, J = 8.0 and 1.0 Hz), 6.82 (d, 1H, J = 1.0 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.10 (s, 1H), 7.32 (s, 1H), 8.27 (s, 1H).

Preparation of 5-Benzo[1,3]dioxol-5-yl-8-hydroxynaphtho[2,3-*d*][1,3]dioxole-6,7-dicarboxylic Acid Dimethyl Ester (42). In a flame-dried, three-necked, 500 mL, round-bottomed flask was dissolved 5.0 mL (40 mmol) of dimethyl maleate in 250 mL of Ac_2O, and the mixture was heated at reflux. A 7.11 g (19.7 mmol) sample of sulfoxide **34** was dissolved in 30 mL of Ac_2O and was added dropwise to the hot Ac_2O solution. After all of the sulfoxide solution had been added, the reaction was heated at reflux until all of the starting sulfoxide had been consumed. The resulting yellow solution was concentrated under reduced pressure, and the orange residue was taken up in CH_2Cl_2. The mixture was washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to give 1.53 g of a yellow oil. The oil was immediately dissolved in 100 mL of 70% mixture of 1,4-dioxane/CH_3CN and added to a solution of 1.51 g (7.0 mmol) of $NaIO_4$ in H_2O. A catalytic amount of $RuCl_3$ (77 mg, 371 μmol) was added, and the mixture was stirred overnight. The olive green mixture was poured into H_2O and extracted with CH_2Cl_2. The organic extracts were washed with a saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to give 1.73 g of sulfone **41**. This material was dissolved in 20 mL of CH_2Cl_2, 200 mg of *p*-toluenesulfonic acid was added, and the mixture was stirred for 5 min at rt. The solution was washed with a saturated aqueous $NaHCO_3$ solution and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 0.82 g (65%) of naphthol **42** as a pale, yellow solid: mp 172−173 °C; IR (KBr) 3010, 2906, 1737, 1663, 1462 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.59 (s, 3H), 3.92 (s, 3H), 6.02 (s, 2H), 6.03 (s, 2H), 6.70−6.78 (m, 3H), 6.86 (d, 1H, J = 7.8 Hz), 7.69 (s, 1H), 12.2 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 51.9, 52.7, 100.7, 101.1, 101.7, 103.6, 107.9, 111.2, 121.2, 124.1, 128.0, 128.9, 129.7, 130.4, 133.9, 147.1, 147.2, 148.0, 150.9, 159.6, 169.1, 170.3. Anal. Calcd for $C_{22}H_{16}O_9$: C, 62.26; H, 3.81. Found: C, 62.15; H, 3.87.

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Supporting Information Available: ^{1}H-NMR and ^{13}C-NMR spectra for all compounds with high-resolution mass spectra together with an ORTEP drawing for cycloadduct **30** (17 pages). This material is contained in 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.

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