Ultrasound-Promoted Cycloadditions in the Synthesis of *Salvia miltiorrhiza* Abietanoid *o*-Quinones[1]

Junning Lee and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Ave., Boston, Massachusetts 02215

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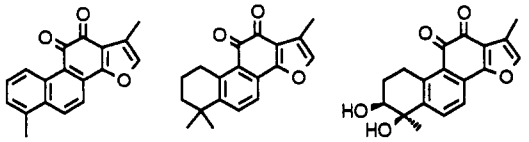
The ultrasound-promoted Diels–Alder reaction of 3-methyl-4,5-benzofurandione with appropriately substituted vinylcyclohexenes has led to the synthesis of tanshinone IIA, nortanshinone, tanshindiol B, methyl tanshinonate, and tanshinone IIB, biologically active metabolites of the Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge. Methyltanshinquinone, the dihydro derivative of the natural product, methylenetanshinquinone, was similarly prepared. The effect of ultrasound in promoting the cycloadditions parallels that of high pressure and improved the regioselectivity in favor of the natural isomers.

Introduction

The roots of various species of sage, *Salvia* spp. (Labiatae), are used throughout the world in folk medicine to treat a wide variety of ailments.[2] One of the more thoroughly investigated species, the Chinese sage, *Salvia miltiorrhiza* Bunge,[3] still attracts considerable attention due to its remarkable array of biological activities,[3,4] usually attributed to a series of quinoidal abietane-derived diterpenes.[4a,g,5] Similar abietanes with the benzofuran *o*-quinone moiety have also been found in the roots of a related species, *S. przewalskii*, locally used as a substitute for *S. miltiorrhiza* in the preparation of Dan Shen.[6] Phytochemical investigations of the minor metabolites of the root of *S. miltiorrhiza* continue in order to identify more potently active constituents since the activity of the crude medicinal preparation, known as Dan Shen or the "tanshinone mixture" often exceeds that of the identified natural products.[4d,5l]

There have been only a few synthetic efforts to data with the Dan Shen metabolites as the target, with most of this work directed toward tanshinone I (**1**)[7] and tanshinone IIA (**2**).[7b,c,8] We initiated our work in this area with the goal of preparing the minor metabolite, tanshindiol B (**3**), in sufficient quantity for biological testing. We had also planned to prepare **3** asymmetrically from an optically pure intermediate of defined chirality in order to assign the absolute stereochemistry. We have since expanded this goal to include five additional related natural products.



1 **2** **3**

A simple dissection of **3** immediately suggested a cycloaddition route utilizing an *o*-quinone dienophile, **4**, and a suitably substituted vinylcyclohexene diene unit (Scheme I). The approach for preparing other abietanoid metabolites would then be a relatively straightforward matter of adjusting the substituents on the diene and dienophile. A similar approach to related diterpenes was reported by Knapp in the preparation of miltirone[9] and more recently by Engler and co-workers in a formal synthesis of taxodione and royleanone.[10] In a preliminary paper[11] we described the use of ultrasound to promote the Diels–Alder reaction of **4** with 1-vinylcyclohexene derivatives in the syntheses of the natural products tanshinone IIA (**2**),[5g] nortanshinone (**5**),[5n] and tanshindiol B (**3**).[5n] We now report the full details of this work and the further application of this approach to the syntheses of the related

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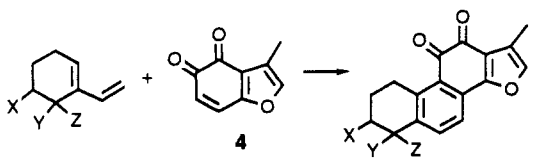
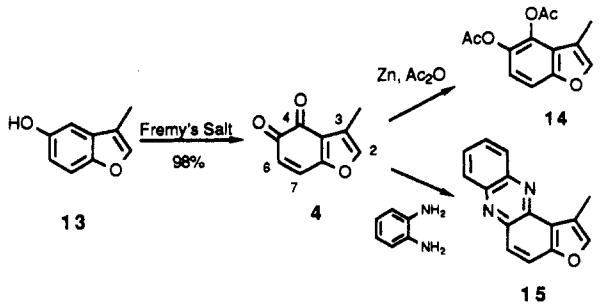
0022-3263/90/1955-4995$02.50/0

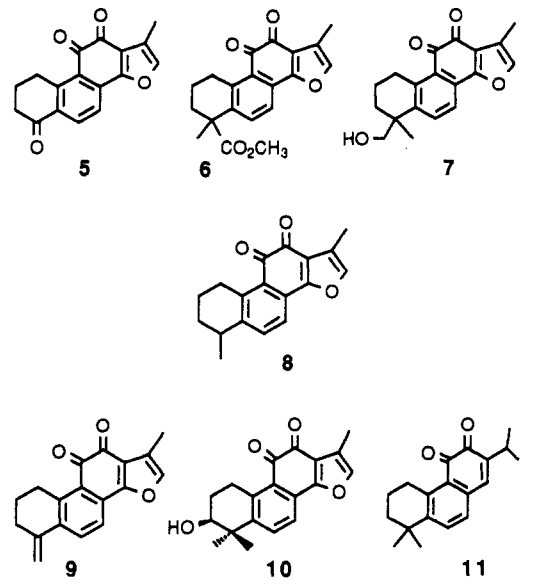
Scheme I



Scheme II



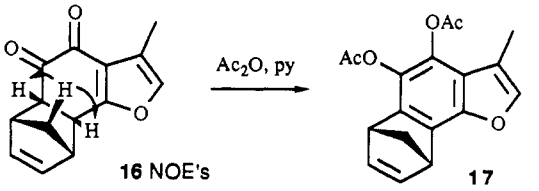
natural products, methyl tanshinonate (**6**),[5h] tanshinone IIB (**7**),[7a] and methyltanshinquinone (**8**), the hydrogenation product of methylenetanshinquinone (**9**).[4a] In the following paper we describe the asymmetric synthesis of **3**, **6**, and **7**, as well as that of 3-hydroxytanshinone IIA (**10**).[12] In the final paper of this series, the preparation of miltirone (**11**)[5j] from the ultrasound-promoted cycloaddition using 3-isopropyl-1,2-benzoquinone as the dienophile according to the strategy of Knapp[9] is presented.



Results and Discussion

Preparation of 4. The benzofuran-4,5-dione dienophile, **4**, was prepared in three steps from *p*-benzoquinone and 1-(*N*-morpholino)propene in good overall yield (96%) as previously reported.[13,14] Reductive acetylation of **4** gave diacetate **14**, and reaction of **4** with *o*-phenylenediamine produced quinoxaline **15**, confirming the *o*-quinone structure (Scheme II). Given the relative instability of **4**, its precursor, **13**, was prepared in large quantities and oxidized to **4** immediately before use. The yields of the oxidation noticeably decreased with the age of the potassium nitrosodisulfonate (Fremy's salt). Consequently, the Fremy's salt was recrystallized from water by the addition of saturated KCl solution immediately before use.[15]

Model Studies.[13] In model studies, **4** was found to smoothly participate in cycloadditions with reactive dienes such as cyclopentadiene, 1-acetoxy-1,3-butadiene, and 1-(trimethylsiloxy)-1,3-butadiene (Table I, items 1–3). Best yields were obtained when **4** was isolated by extraction following its preparation from **13**. In situ generation of **4** from **13** by Fremy's salt oxidation in the presence of the dienes gave greatly reduced yields of cycloadducts. The reaction of **4** with cyclopentadiene gave an excellent yield of cycloadduct **16** as the sole product under mild conditions. This adduct was identified as the endo isomer by NOE's observed between the bridging methylene hydrogen syn to the dione ring and the cyclohex-3-ene-1,2-dione bridgehead methines. Warming **16** in acetic anhydride in the presence of pyridine produced the diacetate **17**.



Aromatized cycloadduct **18** was produced in comparable yields in the thermally promoted reactions of **4** with 1-acetoxybutadiene and 1-(trimethylsiloxy)butadiene (Table I, items 2 and 3). While the initially formed adduct could be detected in the crude reaction mixture, attempted isolation by silica gel chromatography led only to **18**. In the reaction of **4** with 1-acetoxybutadiene, diacetate **14** was also isolated in 13% yield. Presumably unreacted **4** functions as a dehydrogenation agent toward the initial cycloadduct with the 1-acetoxybutadiene, producing the reduced catechol of **4**, which is subsequently acetylated by the excess diene. This cycloaddition between **4** and 1-acetoxybutadiene was the only reaction in which a reduced derivative of **4** was detected. Engler et al., who used *p*-quinones as dienophiles in their studies, also reported the dehydrogenation of the initial cycloadducts by the *p*-quinones.[10] Conducting the cycloaddition with 1-(trimethylsiloxy)-1,3-butadiene under high-pressure conditions (11 kBar) did not improve the yield of cycloadducts (item 3), though under these conditions, more of the nonaromatized cycloadducts were detected in the product mixture by NMR in comparison to the thermally promoted reaction. All attempts to isolate these nonaromatized intermediates gave only **18**.

The dienophilicity of **4** toward less reactive dienes such as isoprene and butadiene, however, was poor (Table I, items 4 and 5). With the crucial model 1-vinylcyclohexene (**21**, item 6) the yields of cycloadducts (**22** and **23**) were poor (<40%) under either thermal promotion or Lewis acid catalysis, $Eu(fod)_3$,[16] due to the instability of **4**, though in

(9) (a) Knapp, S.; Sharma, S. *J. Org. Chem.* **1985**, *50*, 4996. These workers referred to miltirone as rosmariquinone as it was termed upon isolation from rosemary leaves: (b) Houlihan, C. M.; Ho, C.-T.; Chang, S. S. *J. Am. Oil Chem. Soc.* **1985**, *62*, 96. These latter workers were apparently unaware of the original isolation of this compound by Kakisawa and coworkers (ref 5j) from *S. miltiorrhiza* and the original synthesis of miltirone: (c) Nasipuri, D.; Mitra, A. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 285.

(10) (a) Engler, T. A.; Naganathan, S. *Tetrahedron Lett.* **1986**, *27*, 1015. (b) Engler, T. A.; Sampath, U.; Naganathan, S.; Velde, D. V.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712.

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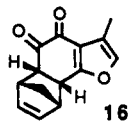
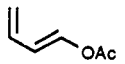
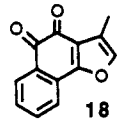
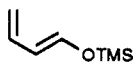
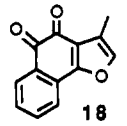
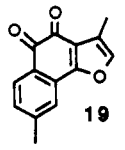
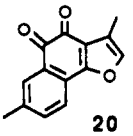
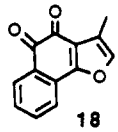
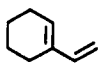
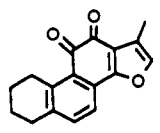
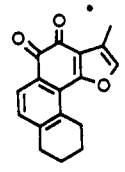
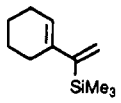
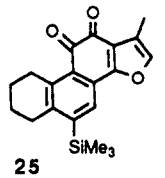
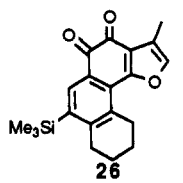
(16) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.

Table I. Cycloadditions of *o*-Quinone 4

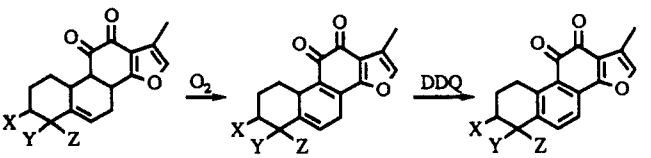
item	diene	conditions	product(s)	yields,[a] %
1		−78 °C to 0 °C, benzene, 1.5 h	 **16**	91
2		reflux, benzene, 16 h	 **18**	62
3		1. reflux, toluene, 20 h 2. 11 kBar, toluene, 2 h, rt	 **18**	1. 60 2. 61
4		1. reflux, benzene, 4 h 2. ultrasound, MeOH, 2 h, 45 °C	 **19**  **20**	1. 15 (1:1) 2. 38 (5:4)
5		neat, −78 °C to rt	 **18**	<10
6	 **21**	1. 110 °C, benzene, 12 h, sealed tube 2. reflux, MeOH, 16 h 3. 11 kBar, MeOH, 2 h, rt 4. $Eu(fod)_3$, 0.08 equiv, benzene 5. $Eu(fod)_3$, 0.08 equiv, MeOH 6. ultrasound, neat, 45 °C, 2 h	 **22**  **23**	1. <10 2. 40 (2.5:1) 3. 67 (6:1) 4. 31 (10:1) 5. 20 (10:1) 6. 65 (7:2)
7	 **24**	1. reflux, benzene, 12 h 2. reflux, MeOH, 4 h 3. 11 kBar, MeOH, 2 h, rt 4. ultrasound, neat, 45 °C	 **25**  **26**	1. 18 (1:6) 2. 28 (1:2.5) 3. 62 (1:3.5) 4. 57 (1:5)

[a] Yields for items 4–7 are after DDQ aromatization.

the latter case, the regioselectivity was greatly improved in favor of the desired regioisomer **22** (10:1). The use of high pressure (11 kBar) did succeed in providing acceptable yields of cycloadducts and very gratifyingly improved the regioselectivity in comparison to the thermally promoted reaction. In an attempt to promote the cycloaddition by placing a donor substituent at the α-position of the vinyl group which could be easily removed after the cycloaddition, [α-(trimethylsilyl)vinyl]cyclohexene (**24**) was prepared.[17] The yields of the cycloaddition using this diene were not improved by this substitution (Table I, item 7), and the regioselectivity was reversed in comparison to that observed with **21** (Table I, item 6).

While the initially formed, nonaromatized cycloadducts could be detected in the NMR spectrum of the crude reaction mixtures, exposure to air led to oxidation to the intermediate didehydro-*o*-quinones, presumably via an initial, rapid tautomerization to the corresponding catechol. This rapid regeneration of the *o*-quinone functionality in the cycloadduct eliminated the stereochemical label of the cycloaddition transition state (Scheme III). The sole exception was the cyclopentadiene adduct **16**, which was quite stable.

Scheme III



Assuming an endo transition state for the remaining cycloadditions as established for **16**, the reversal of the regioselectivity in the reaction of **4** with **21** compared with the α-silylated derivative **24** may be a consequence of the steric interaction between the trimethylsilyl substituent and the furanomethyl group favoring the "unnatural" regioisomer **26** in the latter reaction (Figure 1, X = TMS). With **21**, the greatly reduced interaction between the vinyl proton and the furanomethyl group leads to the "natural" regioisomer, **22**. Subsequent aromatization of the dehydro cycloadducts occurred slowly upon prolonged standing in air, or more rapidly upon chromatography on silica gel. The cycloadduct mixture containing the initially formed tetrahydro adducts and the dihydro intermediates could be conveniently converted to the fully aromatized products by refluxing in benzene or toluene in the presence of DDQ.

(17) Internally silylated dienes (2- or 3-position) have been reported to undergo cycloadditions in excellent yields: (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, 3323.

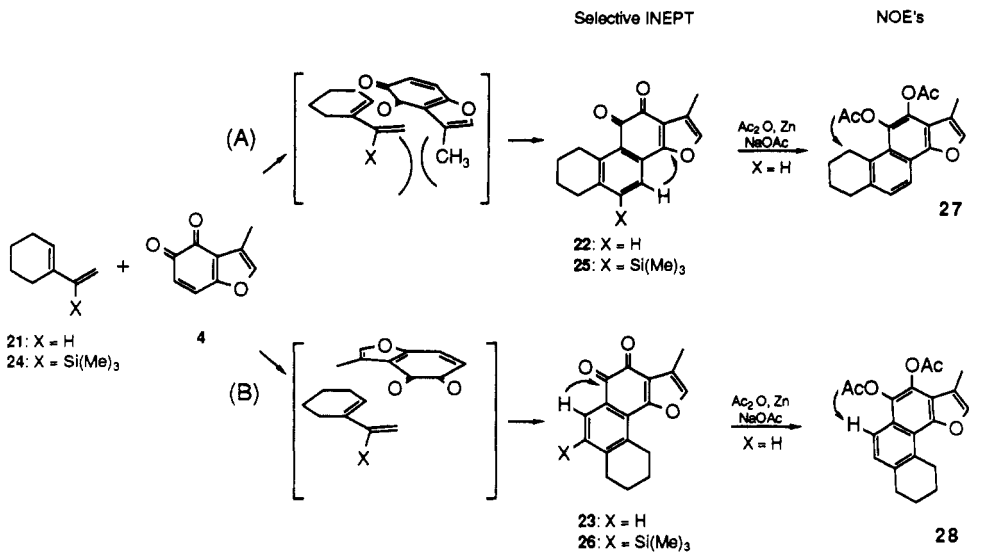
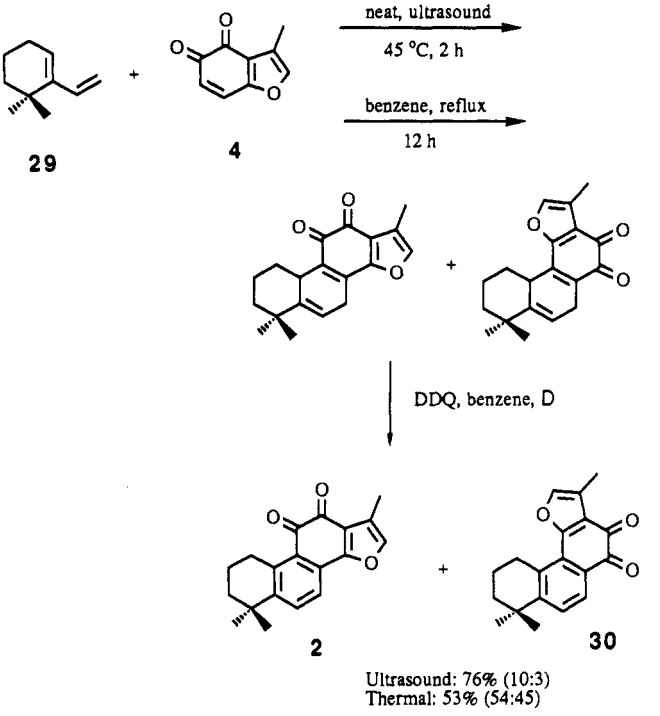


Figure 1. Comparison of endo transition states leading to natural regioisomer (A) and unnatural regioisomer (B) in the cycloaddition of **4** with **21** and **24**; regioisomers were assigned by selective INEPT studies on cycloadducts, and by NOE studies on reduced diacetates of cycloadducts.

With the aromatized products from these model studies in hand, the NMR protocols were established which enabled assignment of the regioisomers from subsequent cycloadditions (Figure 1). The lower field aromatic doublet of each aromatic pair was assumed to be peri to an oxygen: either the carbonyl oxygen or the furan oxygen. This assumption was confirmed, and the regioisomers were distinguished by selective INEPT experiments.[18] Thus, saturation of each lower field doublet led to an enhancement via a three-bond polarization transfer to either the oxygenated furan carbon (δ 161.8, **22**, natural regioisomer) or the carbonyl carbon (δ 176.3, **23**, unnatural regioisomer). The assignments of **22** and **23** were further confirmed by reductive acetylation to the diacetates, **27** and **28**, and the observation of NOE's from the acetyl methyl group to either a cyclohexene methylene proton (**27**) or an aromatic proton (**28**). The outcome of these studies revealed that the lower field doublet of the natural regioisomer was at higher field than the lower field doublet of the unnatural regioisomer. Thus, the deshielding effect of the carbonyl group is greater than that of the furan oxygen.[19] Ultimately the assignments of the regioisomers of the target natural products were confirmed by comparison with authentic samples or reported literature NMR data.

Other means of promoting the cycloaddition of **4** with the vinylcyclohexenes rather than high pressure were sought. Subsequently it was discovered that the cycloaddition could be conveniently achieved using ultrasonication (Table I, items 4, 6, and 7).[11] The yields of cycloadducts were optimized by mixing **4** in an excess of diene (3–5 equiv) in the absence of solvent. In a control experiment under the same conditions (45 °C, 3-fold excess of diene in the absence of solvent), no reaction ensued between **4** and **21** without ultrasonication. For the reaction with isoprene, a small amount of methanol was used in order to solubilize **4** in the isoprene. Ultrasonication of a suspension of **4** in isoprene alone gave only trace amounts of cycloadducts **19** and **20**. Regioisomers **19** and **20** were extremely difficult to separate. While **19** was obtained in

Scheme IV



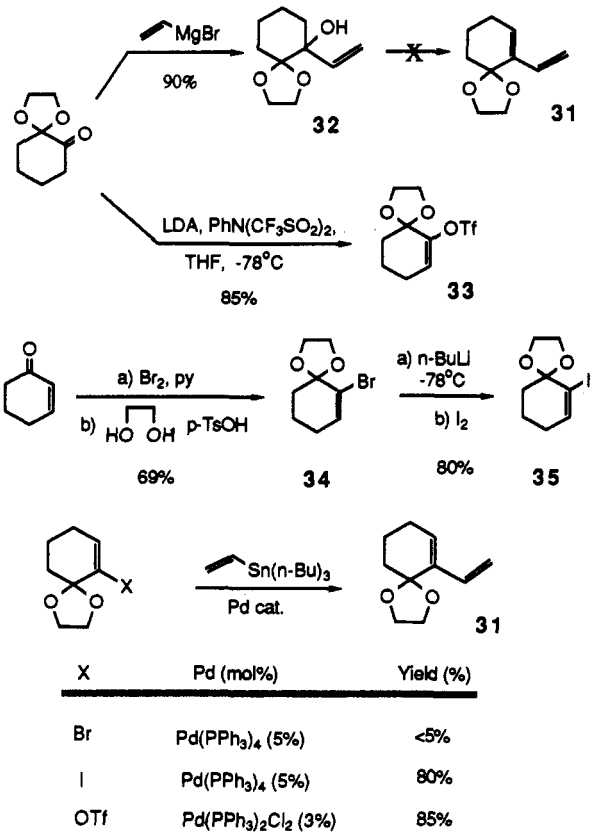
crystalline form after two flash columns, **20** was only enriched to 85% purity. In all cases, the yields of cycloadducts produced by ultrasonication in comparison to thermal promotion increased and the regioselectivity was improved, often dramatically, in favor of the natural regioisomer. These observations parallelled the results obtained in the pressure-promoted cycloadditions. The optimal methodology for applying the Diels–Alder approach to the preparation of the desired natural products as established by the model studies thus called for an ultrasound-promoted Diels–Alder reaction of **4** with the vinylcyclohexene derivative followed by DDQ-promoted aromatization of the cycloadducts.

Tanshinone IIA (2). 6,6-Dimethyl-1-vinylcyclohexene, **29**, required for the preparation of **2**, was prepared as previously reported.[9a] When the cycloaddition of **29** with **4** was carried out in refluxing benzene (12 h) with subsequent DDQ oxidation, a 53% yield of cycloadducts **2** and

(18) (a) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314. (b) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. M. *J. Org. Chem.* **1985**, *50*, 3029.

(19) The sole exception to this generality was observed with nortanshinone (**5**) and the regioisomer **38**. In this example, **5** had the lower field aromatic doublet, though this doublet was assigned to H-5 and thus is still peri to a carbonyl oxygen.

Scheme V



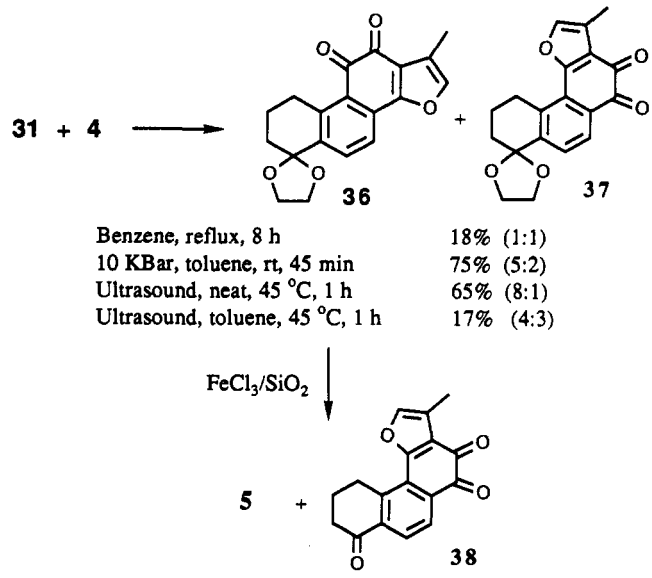
X	Pd (mol%)	Yield (%)
Br	$Pd(PPh_3)_4$ (5%)	<5%
I	$Pd(PPh_3)_4$ (5%)	80%
OTf	$Pd(PPh_3)_2Cl_2$ (3%)	85%

30 with poor regioselectivity (54:46) was obtained. In contrast, the ultrasound-promoted cycloaddition proceeded smoothly with subsequent aromatization to give a 76% yield of cycloadducts favoring the natural regioisomer (2:30, 10:3, Scheme IV). The regioisomers were separated by flash chromatography to give pure 2.

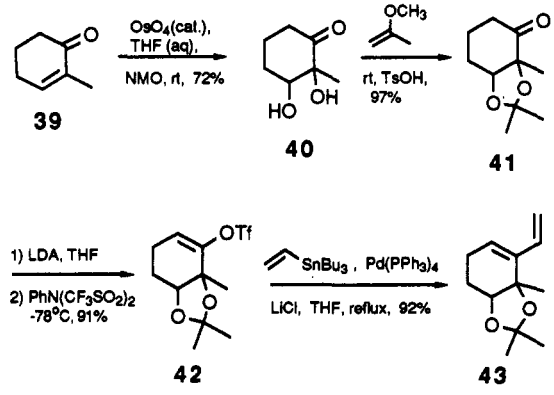
Nortanshinone (5). All efforts to prepare vinylcyclohexene ketal 31, required for the synthesis of 5, by adapting the procedure used to prepare 29 failed due to the inability to affect the dehydration of allylic alcohol 32 subsequent to the vinyl Grignard addition (Scheme V). The preparation of 31 was accomplished by the palladium-catalyzed coupling of either the vinyl triflate (33) or vinyl iodide (35) with tri-*n*-butylvinylstannane as described by Stille.[20] The overall yield of 31 beginning with 1-methoxycyclohexene via vinyl triflate 33 was 45%, beginning with cyclohexenone via vinyl iodide 35 was 44%.

The cycloaddition between vinylcyclohexene derivative 31 and 4 was examined under several conditions (Scheme VI). The best results in terms of yield and regioselectivity were obtained by the ultrasound-promoted cycloaddition in the absence of solvent (65%, 36:37, 8:1, after aromatization). When the ultrasound-promoted cycloaddition was run in toluene, both the yield and the regioselectivity decreased. Aromatization by DDQ oxidation followed by deprotection of the inseparable mixture of 36 and 37 by passage through a column of $FeCl_3$-impregnated silica gel[21] gave 5 and its regioisomer 38. Nortanshinone, 5, which proved to be very insoluble in most organic solvents, was obtained in pure form by recrystallization from acetone. Regioisomer 38 was obtained from the mother liquors in

Scheme VI



Scheme VII



90% purity, but could not be further purified by recrystallization or chromatography.

Tanshindiol B (3), Methyl Tanshinonate (6), Tanshinone IIB (7), and Methyltanshinquinone (8). With the completion of the synthesis of 5, the strategy was thereby established for the preparations of the vinylcyclohexene derivatives required in the syntheses of the remainder of the Dan Shen metabolites. Thus, the appropriate vinylcyclohexene was prepared by the palladium-catalyzed coupling of the vinyl triflate with the vinylstannane followed by the ultrasound-promoted cycloaddition with 4 and DDQ aromatization. The preparations of the vinyl triflates proceeded according to known or routine procedures from simple cyclohexanone derivatives. The palladium-catalyzed coupling reaction with the vinylstannane gave the desired vinylcyclohexene dienes in excellent yields (>80%).

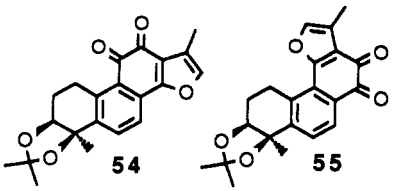
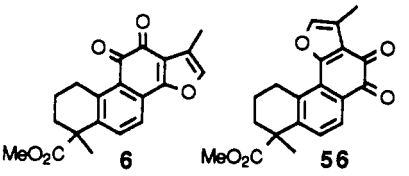
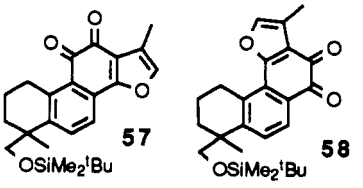
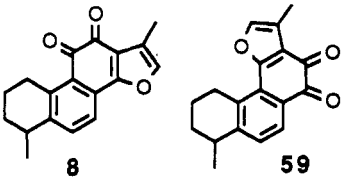
The preparation of protected diol diene 43, for the synthesis of 3 (Scheme VII), proceeded from either 2-methylcyclohexanone or 2-vinylpyridine in comparable yields. The latter route, which proceeds via a Birch reduction with subsequent base-catalyzed aldol condensation according to the method of Danishefsky,[22] was preferred due to the one-pot preparation of 2-methylcyclohexenone (39). Catalytic osmium tetroxide dihydroxylation of 39 with subsequent protection and vinyl triflate formation produced 42. The palladium-catalyzed vinyl coupling of

(20) (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. Review: (c) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.

(21) (a) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404. (b) Fadel, A.; Yefsah, R.; Salaun, J. *Synthesis* **1987**, 37.

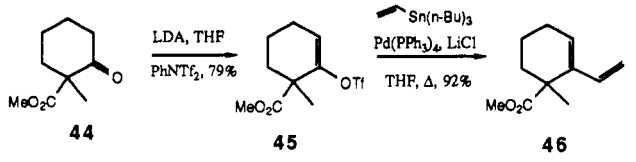
(22) Danishefsky, S.; Cain, P. *J. Org. Chem.* **1975**, *40*, 3606.

Table II. Cycloadditions of *o*-Quinone 4 Leading to 3, 6, 7, 8, and 9

item	diene	conditions	product(s)[a]	yields,[a] %
1	43	1. benzene, reflux, 8 h 2. toluene, 10 kBar, 1 h 3. ultrasound, neat, 1 h, 45 °C	 54 55	1. 15 (1:1) 2. 73 (7:1) 3. 66 (5:1)
2	46	ultrasound, neat, 2 h, 45 °C	 6 56	66 (8:1)
3	51	ultrasound, MeOH, 1.5 h, 45 °C	 57 58	71 (12:1)
4	53	1. benzene, reflux, 6 h 2. ultrasound, neat, 2 h, 45 °C	 8 59	1. 11 (10:1) 2. 56 (20:1)

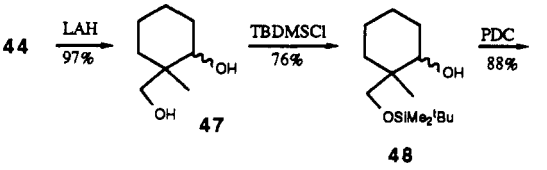
[a] Products and yields after DDQ aromatization.

Scheme VIII

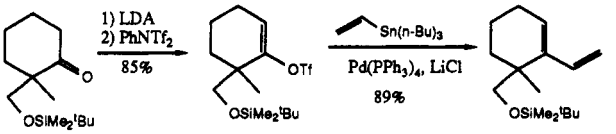


44 45 46

Scheme IX

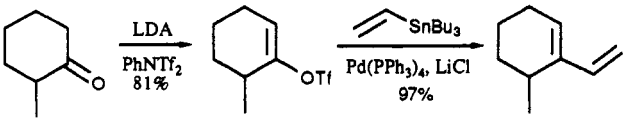


47 48



49 50 51

Scheme X



52 53

42 then gave diene 43 in an overall yield of 44% beginning with vinylpyridine (49% from 39).

Dienes 46 and 51, needed for the syntheses of methyl tanshinonate (6) and tanshinone IIB (7), respectively, were both prepared from β-keto ester 44 (Schemes VIII and IX). In the preparation of cyclohexanone 49 required for diene 51, the diastereomeric diols, 47, from the LAH reduction of 44 were not separated but carried through the diastereomeric silyl ethers 48 as a mixture, giving ketone 49 upon oxidation. Following the palladium-catalyzed vinyl-coupling reactions of triflates 45 and 50, dienes 46 and 51 were obtained in overall yields of 64% and 43%, respectively, each beginning with cyclohexanone. 6-Methyl-1-vinylcyclohexene (53) required in the synthesis of 8 was prepared from 2-methylcyclohexanone via the known vinyl triflate 52 (Scheme X).[23]

When a mixture of freshly prepared *o*-quinone 4 in an excess of the vinylcyclohexenes (3–5 equiv) was subjected to ultrasonication at 45 °C, smooth cycloadditions resulted (Table II). Due to the miscibility of 4 in dienes 43, 46, and 53, these cycloadditions were run under neat conditions. For the cycloaddition with diene 51, small amounts of methanol were added in order to solubilize 4. As with the isoprene reaction, the immiscibility of 4 in this diene severely limited the cycloaddition which occurred upon ultrasonication if methanol was not added. When increasing amounts of methanol were added, however, the yields of cycloadducts decreased as previously noted.[11] Unnatural regioisomer 56 could only be purified to 85% enrichment, while unnatural regioisomers 58 and 59 were only detected in the cycloadduct mixture following DDQ aromatization, but could not be purified; thus the structure assignment of these latter two must be regarded as tenative.

In those cases where parallel reactions were run in comparison to thermal promotion, the ultrasound-promoted reactions proceeded in significantly higher yields and with greater regioselectivity (Table II, items 2 and 4). Aromatization was accomplished by DDQ dehydrogenation in refluxing benzene or toluene, and the natural regioi-

(23) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

Table III. Summary of Syntheses via Ultrasound-Promoted Cycloadditions

target	starting material[a]	no. steps[b]	overall yield,[c] %
tanshinone IIA (2)		8	31
tanshindiol B (3)		12	30
nortanshinone (5)		10	26
methyl tanshinonate (6)		9	37
tanshinone IIB (7)		13	26
methyltanshinquinone (8)		7	40

[a] Diene starting material; starting material for 4 is *p*-benzoquinone. [b] Number of steps includes three steps to make 4. [c] Overall yield includes 96% overall yield to make 4. All yields are isolated yields.

somer was isolated by either flash chromatography or recrystallization. Methyl tanshinonate (6) and methyltanshinquinone (8) were produced directly in good yields and with high regioselectivities by the cycloaddition followed by aromatization and purification. Tanshindiol B (3) and tanshinone IIB (7) were produced following deprotection steps. Thus, deprotection of 54 by acid-catalyzed hydrolysis (Dowex-50, H^+ form) gave 3, and cleavage of the silyl ether in 57 (HF) produced 7.

As a result of the synthesis of 3, the original structural assignment of tanshindiols B and C was reversed as previously noted.[11] Enhancement of the H-3 resonance upon saturation of the H-18 methyl protons (NOEDS) in the protected diol 54 confirmed the retention of the cis relationship in the cycloadduct. Comparison of synthetic 2, 3, and 5 with authentic samples confirmed the identities of these natural products. The identities of synthetic 6, 7, and 8 were confirmed upon comparison of the spectroscopic data with that reported in the literature. Tanshindiol B (3) was very insoluble in all solvents examined, thus the ^{13}C NMR spectrum was difficult to record, and one carbonyl resonance was not observed. This insolubility of 3 in all NMR solvents is presumably the reason the ^{13}C NMR spectrum of 3 was not reported in the original isolation report.[5n]

Summary

An ultrasound-promoted cycloaddition was used to prepare several biologically active metabolites of the Chinese traditional medicine, Dan Shen, the roots of *Salvia miltiorrhiza*, exploiting the dienophilicity of *o*-quinone (4) in an ultrasound-promoted Diels–Alder reaction. The value of this route is seen in the relatively high overall yields (Table III), beginning with *p*-benzoquinone to prepare 4 and simple cyclohexanone derivatives. Of particular note is a comparison of the regioselectivity in the thermal, high-pressure, and ultrasound-promoted cycloadditions. In all examples, the regioselectivity improved significantly in favor of the natural product regioisomers under high pressure or ultrasonication. Indeed the regioselectivity of the ultrasound-promoted cycloadditions quite nicely paralleled that of the high-pressure promotions.

Experimental Section

General. The NMR spectra were recorded on a Varian XL-400 (93.93 kG, 400 MHz for ^1H, 100 MHz for ^{13}C) in $CDCl_3$ unless otherwise noted. Residual $CHCl_3$ (δ 7.24 ppm), and $^{13}CDCl_3$ (δ 77.0 ppm) were used as internal references for ^1H and ^{13}C, respectively. Assignments of "OH" protons were confirmed by D_2O exchange. All compounds were shown to be >98% pure by ^1H NMR data. Mass spectra (medium and high resolution) were run on a Finnigan MAT-90 as indicated; IR spectra were recorded on a Perkin-Elmer 1800 FTIR or a Perkin-Elmer 1300 IR spectrometer. Melting points are uncorrected. All solvents were purified and dried prior to use according to standard procedures.[24] "Petroleum ether" refers to petroleum ether bp 35–60 °C; "ether" refers to diethyl ether. *o*-Quinone 4 was freshly prepared immediately before use; a "silica gel plug" refers to either a disposable Pasteur pipet or a 10-mm i.d. flash column filled with approximately 2 in. of flash silica gel.

General Procedure A. Preparation of Enol Triflates.[23] Freshly generated LDA solution in THF was cooled to −78 °C, and the ketone (1 eq) in anhydrous THF was added dropwise via syringe. The reaction was stirred at −78 °C for 2 h, and solid N-phenyltriflimide[25] (1.5 eq) was added. The solution was stirred at 0 °C for 3 h, and then at room temperature overnight. After the solvent was removed in vacuo, the enol triflate was purified by flash chromatography on silica gel.

General Procedure B. Palladium-Catalyzed Couplings of Enol Triflates with Tri-*n*-butylvinylstannane.[20a] To a slurry of LiCl (3–5 equiv) and $Pd(PPh_3)_4$ in anhydrous THF (10 mL) was added a solution of enol triflate (1 equiv) in THF (5 mL) and tri-*n*-butylvinylstannane (1 equiv). The solution was refluxed overnight (12 h), cooled to room temperature, and diluted with petroleum ether (30 mL). The resultant solution was washed with 10% NH_4OH solution (15 mL), water (15 mL), and saturated NaCl solution (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel.

General Procedure C. Ultrasound-Promoted Cycloadditions. Freshly prepared 4 (typically 100 mg, 0.62 mmol) was placed in a conical reaction vial with the diene (typically 3–7 equiv); the vial was sealed and placed in an ultrasound cleaner (Cole-Parmer 8851, 50/60 kHz, 125 W) and subjected to ultrasonication for the time periods as indicated. The temperature of the water bath was maintained at 45 °C. The resulting product mixture was diluted with CH_2Cl_2 (10 mL) and loaded onto a plug of silica gel. Elution with petroleum ether removed unreacted diene which was recycled. Subsequent elution with CH_2Cl_2 gave the mixture of cycloadducts as the tetrahydro, dihydro, and aromatized products. Without further purification this mixture was aromatized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene or toluene.

1-Morpholinopropene. The procedure of Yamashita[26] was followed using morpholine (65 g, 0.75 mol) freshly distilled from CaH_2 and freshly distilled propionaldehyde (20 g, 0.34 mol). 1-Morpholinopropene was purified by two distillations in vacuo, upon which the product was shown to be free of morpholine by ^1H NMR analysis to give 22.5 g (52% yield, >95% *E* isomer) of a colorless oil: bp 70 °C (25 mmHg); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.78 (dq, J = 14.0, 1.4 Hz, 1 H), 4.46 (dq, J = 14, 6.4 Hz, 1 H), 3.71 (br m, 4 H), 2.82 (t, J = 4.7 Hz, 2 H), 2.71 (t, J = 4.8 Hz, 2 H), 1.58 (dd, J = 6.4, 1.4 Hz, 3 H). The IR spectrum was identical with that reported in the literature.[26]

2,3-Dihydro-5-hydroxy-2-morpholino-3-methylbenzo[1,2-*b*]furan (12). The procedure of Domschke[14] was followed with modifications. To a solution of *p*-benzoquinone (5 g, 46.25 mmol) in anhydrous CH_2Cl_2 (150 mL) cooled to −5 °C under argon was added dropwise via syringe a solution of freshly distilled 1-

(24) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, 1980.
(25) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335.
(26) Tanaka, A.; Nakata, T.; Yamashita, K. *Agr. Biol. Chem.* **1973**, *37*, 1365.

morpholinopropene (5.88 g, 46.25 mmol) in anhydrous CH_2Cl_2 (50 mL) previously cooled to −5 °C. (*NOTE*: Optimal yields were achieved only when excess morpholine was removed from the enamine by careful distillation.) The resultant wine-red solution was stirred at 0 °C for 3 h and then at room temperature overnight (12 h). (For smaller scale reactions, stirring at 0 °C was continued until the color disappeared.) The white solid (10.88 g, 46.25 mmol, 100% yield of crude **12**) obtained upon removal of the solvent in vacuo was used in the next step without further purification. The ^1H NMR spectrum of this crude sample indicated >95% trans isomer. A sample of **12** was purified by recrystallization from ether/petroleum ether to give pure trans **12** for characterization: mp 128–129 °C; IR (KBr) 3100, 2950, 2850, 1600, 1580, 1540, 1352, 1235, 1180, 895, 805, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.50 (m, 3 H), 5.39 (br s, OH), 4.83 (d, J = 4.9 Hz, 1 H), 3.62 (t, J = 4.6 Hz, 4 H), 3.19 (m, 1 H), 2.76 (m, 2 H), 2.58 (m, 2 H), 1.23 (d, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 152.2, 150.0, 131.9, 114.6, 110.9, 108.8, 106.6, 67.6, 66.9, 47.8, 45.9, 39.3, 20.1; LRMS (EI, 70 eV) m/z (relative intensity) 235 (M^+, 98). The trans stereochemistry was confirmed by NOE's between the furanomethyl group and H-2 and between the morpholino H-2′ protons and the dihydrofuran H-3.

5-Hydroxy-3-methylbenzo[1,2-*b*]furan (13). The procedure of Domschke[14] was followed beginning with **12** (2.0 g, 8.5 mmol) to give **13** as white crystals in 98% yield: mp 93–94 °C [lit.[14,27] mp 92 °C]; IR (KBr) 3290, 1600, 1480, 1445, 1240, 1178, 1085, 840, 795, 628 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36 (br s, 1 H), 7.28 (d, J = 8.8 Hz, 1 H), 6.90 (d, J = 2.7 Hz, 1 H) 6.77 (dd, J = 8.8, 2.7 Hz, 1 H), 4.85 (br s, OH), 2.17 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1, 150.3, 142.5, 129.9, 115.5, 112.6, 111.7, 104.6, 7.9; LRMS (EI, 70 eV) m/z (relative intensity) 148 (M^+, 98).

4,5-Dihydro-3-methylbenzo[1,2-*b*]furan-4,5-dione (4). A solution of **13** (300 mg, 2.03 mmol) in MeOH (9 mL) was cooled to 0 °C in an ice bath, and an ice-cooled aqueous buffered solution of freshly recrystallized Fremy's salt[15] (1.8 g dissolved in 100 mL of a 0.07 M KH_2PO_4 buffer adjusted to pH 7) was added dropwise with stirring, maintaining the temperature at 0 °C. After completion of the addition, the dark red solution was stirred at 0 °C for 1 h. The red precipitate (**4**, 280 mg) was collected by filtration. The filtrate was extracted with ethyl acetate (2 × 40 mL), and the combined extracts washed with water (2 × 30 mL) and saturated brine (30 mL) and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave additional **4** as a red solid (42 mg), overall yield 98%: mp 92–93 °C; IR (KBr) 1682 (C=O), 1655 (C=O), 1520, 1385, 1215, 920, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27 (br s, H-2), 7.24 (d, J = 10.3 Hz, H-7), 6.14 (d, J = 10.3 Hz, H-6), 2.24 (br s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.9 (C-5), 174.1 (C-4), 159.6 (C-7a), 143.2 (C-2), 131.5 (C-7), 125.7 (C-6), 123.0 (C-3a), 122.7 (C-3), 8.78 (CH_3); UV λmax (MeOH) 225 nm (ϵ 19100), 295 (1280), 460 (2130); HRMS (EI, 70 eV) m/z 162.0316 (M^+, calcd for $C_9H_6O_3$, 162.0316).

Reductive Acetylation of 4: 4,5-Diacetoxy-3-methylbenzo[1,2-*b*]furan (14). A mixture of **4** (50 mg, 0.31 mmol), zinc dust (300 mg, 4.6 mmol), and sodium acetate (100 mg, 1.2 mmol) in freshly distilled acetic anhydride (15 mL) was refluxed for 1 h. After filtration and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/petroleum ether, 2:1) to give **14** (46 mg, 60% yield) as a white solid: mp 89–91 °C; IR (KBr) 3120, 2949, 2923, 1759, 1642, 1604, 1490, 1443, 1371, 1330, 1211, 1034, 1020, 956, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (br s, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 2.36 (s, 3 H), 2.30 (s, 3 H), 2.22 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.4, 154.0, 142.9, 137.4, 135.3, 123.0, 118.9, 114.8, 109.5, 20.5, 20.2, 8.7; LRMS (EI, 70 eV) m/z (relative intensity) 248 (M^+, 19), 206 (17), 164 (100); HRMS (EI, 70 eV) m/z 248.0699 (M^+, calcd for $C_{13}H_{12}O_5$, 248.0687).

Reaction of 4 with *o*-Phenylenediamine: Quinoxaline 15. A solution of **4** (50 mg, 0.31 mmol), *o*-phenylenediamine (66 mg, 0.61 mmol), and anhydrous K_2CO_3 (84 mg, 0.61 mmol) were refluxed in anhydrous benzene (15 mL) for 2 h. After cooling and removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (CH_2Cl_2/ethyl acetate, 10:1) to give **15** (37 mg, 52% yield) as a yellow solid: mp 120–121 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.31 (m, 2 H), 8.03 (AB, J_{AB} = 8.3 Hz, 2 H), 7.87 (m, 2 H), 7.29 (br s, 1 H), 2.86 (d, J = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.68, 142.32, 142.07, 142.01, 141.64, 141.07, 129.86, 129.63, 129.54, 129.37, 125.86, 120.32, 120.14, 119.09, 10.41; LRMS (EI, 70 eV) m/z (relative intensity) 235 ([M + 1]$^+$, 16), 234 (M^+, 100), 206 (13), 205 (76), 148 (64), 147 (50); HRMS (EI, 70 eV) m/z 234.0795 (M^+, calcd for $C_{15}H_{10}N_2O$, 234.0793).

Cycloaddition of 4 with Cyclopentadiene: 6,9-Dihydro-6,9-methano-3-methylnaphtho[1,2-*b*]furan-4,5-dione (16). To a solution of **4** (50 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (10 mL) cooled to −78 °C was added excess freshly distilled cyclopentadiene through a cold finger condenser filled with dry ice/acetone. After being stirred for 1 h at −78 °C, the reaction mixture was allowed to warm to 0 °C, and stirring was continued for an additional 2 h until the red color disappeared. The solvent was removed in vacuo to give a yellow residue (71 mg). Recrystallization (ether/petroleum ether) gave pure **16** as a yellow solid (64 mg, 91% yield): mp 101–104 °C; IR (KBr) 1705, 1670, 1555, 1430, 1145, 1071, 1051, 930, 791, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.16 (br s, 1 H), 6.12 (dd, J = 5.6, 2.6 Hz, 1 H), 5.79 (dd, J = 5.6, 2.9 Hz, 1 H), 3.79 (dd, J = 7.6, 4.0 Hz, 1 H), 3.58 (br s, 1 H), 3.48 (br s, 1 H), 3.32 (dd, 7.6, 4.0, 1 H), 2.21 (s, 3 H), 1.72 (dt, J = 8.7, 1.8, 1.8, 1 H), 1.63 (br d, J = 8.7, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6, 169.8, 160.5, 140.5, 135.1, 134.8, 124.0, 119.3, 49.2, 49.0, 48.9, 47.6, 38.7, 8.7; LRMS (EI, 70 eV) m/z (relative intensity) 228 (M^+, 47), 163 (100), 134 (92), 66 (23); HRMS (EI, 70 eV) m/z 228.0794 (M^+, calcd for $C_{14}H_{12}O_3$, 228.0786).

Acetylation of 16: 4,5-Diacetoxy-8,11-dihydro-8,11-methano-3-methylnaphtho[1,2-*b*]furan (17). A mixture of **16** (63 mg, 0.28 mmol), anhydrous pyridine (0.05 mL), and acetic anhydride (2.5 mL) was heated at 80–90 °C for 2 h. The excess pyridine and acetic anhydride were removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/CH_2Cl_2, 1:2) to give **17** (65 mg, 74%) as white crystals: mp 144–146 °C; IR (KBr) 2910, 1760, 1630, 1445, 1360, 1210, 1160, 1020, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (br s, 1 H), 6.85 (s, 2 H), 4.34 (br s, 1 H), 3.94 (br s, 1 H), 2.33 (s, 6 H), 2.25 (br s, 2 H), 2.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.5, 147.8, 143.2, 142.5, 142.1, 141.9, 132.7, 132.2, 131.3, 120.4, 114.8, 70.2, 48.5, 47.2, 20.6, 20.4, 8.9; LRMS (EI, 70 eV) m/z (relative intensity) 312 (M^+, 27), 270 (55), 228 (100); HRMS (EI, 70 eV) m/z 312.0954 (M^+, calcd for $C_{18}H_{16}O_5$, 312.0998).

3-Methyl-4,5-dihydronaphtho[1,2-*b*]furan-4,5-dione (18).[7e] **Method A: Cycloaddition of 4 with 1-Acetoxy-1,3-butadiene.** A solution of **4** (50 mg, 0.31 mmol) and 1-acetoxy-1,3-butadiene[28] (105 mg, 0.94 mmol) in anhydrous benzene (15 mL) was refluxed overnight (12 h). After cooling, the solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give **14** (10 mg, 13% yield) and **18** (40 mg, 62% yield) as red crystals: mp 170–172 °C; IR (KBr) 2940, 1670, 1585, 1540, 1220, 905, 775, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 8.0 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.64 (t, J = 8.0, 8.0 Hz, 1 H), 7.43 (t, J = 8.0, 8.0 Hz), 7.26 (q, J = 1.2 Hz, 1 H), 2.28 (d, J = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 175.5, 160.6, 141.6, 135.3, 130.4, 129.9, 128.8, 128.7, 122.2, 121.7, 121.2, 8.8; LRMS (EI, 70 eV) m/z (relative intensity) 212 (M^+, 98), 184 (100), 128 (63).

Method B: Cycloaddition of 4 with 1-(Trimethylsiloxy)-1,3-butadiene. A solution of **4** (50 mg, 0.31 mmol) and 1-(trimethylsiloxy)-1,3-butadiene[29] (100 mg, 0.70 mmol) in anhydrous toluene (15 mL) was refluxed for 20 h. After cooling, the solvent was removed in vacuo, and the residue was purified (method A) to give **18** (39.3 mg, 60% yield).

Method C. A mixture of **4** (100 mg, 0.62 mmol) and 1-(trimethylsiloxy)-1,3-butadiene[29] (250 mg, 1.76 mmol) in anhydrous toluene (10 mL) was placed into a 10-mL compressible syringe and subjected to 160000 psi (11 kBar) at room temperature for 2 h. The solvent was removed in vacuo, and the residue was purified (method A) to give **18** (79.8 mg, 61% yield).

1-Vinylcyclohexene (21). 1-Vinylcyclohexene was prepared according to the literature[30] using $KHSO_4$ by Kugelrohr distillation

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at 150 °C for 15 min to affect the dehydration. Flash chromatography (CH_2Cl_2/petroleum ether, 1:5) of the residue on silica gel afforded **21** (2.3 g, 52% overall yield).

1-[α-(Trimethylsilyl)vinyl]cyclohexene (24). To a solution of 1-(trimethylsilyl)-1-bromoethylene[31] (1.8 g, 10 mmol) in anhydrous ether (28 mL) cooled to −78 °C was added dropwise *t*-BuLi (1.7 M in pentane, 6.7 mL) with stirring under nitrogen. Stirring was continued at −62 °C for 1.5 h, and then a solution of cyclohexanone (0.9 g, 8 mmol) in anhydrous ether (15 mL) was added dropwise. The resulting mixture was stirred for 1 h at −62 °C and at −30 °C for an additional hour. The reaction was quenched with saturated $NaHCO_3$ solution (10 mL), and the ether layer was separated. The aqueous layer was extracted with ether (3 × 10 mL); the ether layers were combined, washed with water and saturated brine, and then dried ($MgSO_4$). The ether was removed in vacuo, and 1-[(α-trimethylsilyl)vinyl]cyclohexan-1-ol was purified by flash chromatography on silica gel (CH_2Cl_2) to give a colorless oil (1.05 g, 66% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 5.71 (br s, 1 H), 5.39 (br s, 1 H), 3.58 (br s, OH), 1.50–1.65 (m, 10 H), 0.17 (s, 9 H). The alcohol was subsequently acylated with trifluoroacetic anhydride and dehydrated to give **24** as a colorless oil according to the literature[31] (54% overall yield from cyclohexanone): ^1H NMR ($CDCl_3$, 400 MHz) δ 5.70 (br s, 1 H), 5.66 (d, *J* = 2.8 Hz, 1 H), 5.31 (d, *J* = 2.8 Hz, 1 H), 2.13 (m, 4 H), 1.68 (m, 2 H), 1.59 (m, 2 H), 0.16 (s, 9 H).

Cycloaddition of 4 with Isoprene: 3,7-Dimethyl-4,5-dihydronaphtho[1,2-*b*]furan-4,5-dione (19) and 3,8-Dimethyl-4,5-dihydronaphtho[1,2-*b*]furan-4,5-dione (20). Method A. A solution of isoprene (2 g, 29.3 mmol) and **4** (100 mg, 0.62 mmol) was refluxed in anhydrous benzene (35 mL) for 4 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug (CH_2Cl_2) to give a mixture of aromatized and dihydro adducts. This mixture was fully aromatized by refluxing overnight (10 h) in toluene (30 mL) with DDQ (150 mg, 0.67 mmol). Passage through another silica gel plug gave the mixture of **19** and **20** (21 mg, 15% yield, **19:20**, 1:1, from ^1H NMR). Aromatized adducts **19** and **20** were purified by flash chromatography on silica gel (CH_2Cl_2) to give **19** and **20** as enriched mixtures. A second flash column (CH_2Cl_2) gave pure **19** as red crystals: mp 175–176 °C; IR (KBr) 2963, 1690, 1674, 1614, 1588, 1546, 1261, 1020, 912, 801 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, *J* = 8.0 Hz, 1 H), 7.48 (s, 1 H), 7.23 (m, 2 H), 2.46 (s, 3 H), 2.28 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4, 175.8, 160.7, 146.8, 141.5, 130.7, 130.6, 128.6, 126.6, 122.7, 121.6, 121.1, 22.0, 8.5; LRMS (EI, 70 eV) *m/z* (relative intensity) 226 (M^+, 95), 198 (100), 181 (22), 169 (18), 141 (57), 69 (74); HRMS (EI, 70 eV) *m/z* 226.0621 (M^+, calcd for $C_{14}H_{10}O_3$, 226.0629). Compound **20** could not be purified by flash chromatography, and its ^1H NMR shifts were recorded on an 85% enriched sample still containing **19**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (s, 1 H), 7.57 (d, *J* = 8.1 Hz, 1 H), 7.42 (d, *J* = 8.1 Hz, 1 H), 7.21 (q, *J* = 1.2 Hz, 1 H), 2.40 (s, 3 H), 2.28 (d, *J* = 1.2 Hz, 3 H).

Method B. A mixture of **4** (100 mg, 0.62 mmol), isoprene (2 g, 29.4 mmol), and methanol (1.0 mL) were subjected to ultrasonication for 2 h, and the mixture of cycloadducts was isolated and aromatized (method A) to give a mixture of **19** and **20** (53 mg, 38% overall yield, **19:20**, 5:4 from ^1H NMR).

Cycloaddition of 4 with 21: 1-Methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione (22) and 1-Methyl-8,9,10,11-tetrahydrophenanthro[4,3-*b*]furan-4,5-dione (23). Method A. A solution of **21** (230 mg, 2.13 mmol) and **4** (100 mg, 0.62 mmol) was refluxed in anhydrous MeOH (15 mL) for 16 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with CH_2Cl_2/petroleum ether (1:2) to recover unreacted **21**, and then with CH_2Cl_2 to give a mixture of aromatized and dihydro adducts. This mixture was fully aromatized by refluxing overnight (12 h) in benzene (30 mL) with DDQ (150 mg, 0.67 mmol). Aromatized adducts **22** and **23** (66 mg, 40% yield, **22:23**, 2.5:1, from ^1H NMR) were purified by flash chromatography on silica gel (CH_2Cl_2/petroleum ether, 2:1) to give **22** and **23** as enriched mixtures. A second flash column with the same solvent system gave pure **22** and **23**; **22** is a red solid: mp 205–207 °C; IR (KBr) 2920, 1690, 1665, 1540, 1405, 1285, 1175, 1078, 972, 811, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.21 (q, *J* = 1.2 Hz, 1 H), 3.20 (t, *J* = 7.0 Hz, 2 H), 2.82 (t, *J* = 6.0 Hz, 2 H), 2.27 (d, *J* = 1.2 Hz, 3 H), 1.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.4, 175.5, 161.8, 145.1, 141.4, 141.2, 135.6, 127.6, 126.4, 121.1, 119.9, 119.7, 30.7, 28.8, 22.9, 21.9, 8.8; LRMS (EI, 70 eV) *m/z* (relative intensity) 266 (M^+, 65), 251 (69), 238 (97), 223 (89), 210 (55), 195 (43), 167 (68), 165 (100), 152 (74), 128 (27); HRMS (EI, 70 eV) *m/z* 266.0942 (M^+, calcd for $C_{17}H_{14}O_3$, 266.0943). **23** is a red solid: mp 190–191 °C; IR (KBr) 3135, 2924, 1692, 1667, 1535, 1426, 1382, 1284, 943, 808 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.0 Hz, 1 H), 7.28 (br s, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 3.16 (t, *J* = 6.5 Hz, 2 H), 2.83 (t, *J* = 6.5 Hz, 2 H), 2.28 (br s, 3 H), 1.86 (m, 2 H), 1.79 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 176.3, 162.4, 147.1, 141.1, 135.0, 130.8, 128.2, 127.9, 127.0, 121.6, 121.3, 31.2, 27.8, 22.9, 21.7, 8.9; LRMS (EI, 70 eV) *m/z* (relative intensity) 266 (M^+, 100) 238 (44), 223 (11), 181 (7), 165 (11); HRMS (EI, 70 eV) *m/z* 266.0985 (M^+, calcd for $C_{17}H_{14}O_3$, 266.0943).

Method B. A mixture of **4** (100 mg, 0.62 mmol) and **21** (200 mg, 1.85 mmol) in anhydrous MeOH (10 mL) was placed into a 10-mL compressible syringe and subjected to 160 000 psi (11 kBar) at room temperature for 2 h. The solvent was removed in vacuo, and the residue was passed through a silica gel plug to recover unreacted **21** and the mixture of cycloadducts (method A). The cycloadduct mixture was oxidized with DDQ (method A) to give a mixture of **22** and **23** (110 mg, 67% overall yield, **22:23**, 6:1, by ^1H NMR). Compounds **22** and **23** were purified by flash chromatography (method A).

Method C. A mixture of **4** (100 mg, 0.62 mmol) and **21** (200, 1.85 mmol) were subjected to ultrasonication for 2 h, and the mixture of cycloadducts was isolated (General Procedure) and aromatized with DDQ (method A) to give a mixture of **22** and **23** (107 mg, 65% overall yield, **22:23**, 7:2, by ^1H NMR). Compounds **22** and **23** were purified by flash chromatography (method A).

Reductive Acetylation of 22. The same procedure was used as employed for the reductive acetylation of **4** beginning with **22** (40 mg, 0.15 mmol). Flash chromatography on silica gel (CH_2Cl_2/petroleum ether, 5:1) gave **27** (39 mg, 74% yield) as white crystals: mp 182–183 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 8.5 Hz, 1 H), 7.46 (br s, 1 H), 7.25 (d, *J* = 8.5 Hz), 3.23 (m, 2 H), 2.94 (t, *J* = 5.9 Hz, 2 H), 2.40 (s, 3 H), 2.39 (s, 3 H), 2.26 (br s, 3 H), 1.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 168.8, 160.1, 150.4, 141.5, 135.8, 134.6, 131.9, 129.3, 124.4, 119.7, 118.0, 117.3, 115.5, 31.3, 28.3, 23.8, 22.0, 21.1, 20.5, 8.9; LRMS (EI, 70 eV) *m/z* (relative intensity) 352 (M^+, 22), 310 (25), 268 (100), 221 (4); HRMS (EI 70 eV) *m/z* 352.1309 (M^+, calcd for $C_{21}H_{20}O_5$, 352.1311).

Reductive Acetylation of 23. The same procedure was used as employed for the reductive acetylation of **4** beginning with **23** (35 mg, 0.13 mmol). Flash chromatography on silica gel (CH_2Cl_2/petroleum ether, 5:1) gave **28** (37 mg, 79% yield) as white crystals: mp 134–135 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 8.6 Hz, 1 H), 7.53 (q, *J* = 1.2 Hz, 1 H), 7.23 (d, *J* = 8.6 Hz, 1 H), 3.53 (t, *J* = 6.0 Hz, 2 H), 2.95 (t, *J* = 6.0 Hz, 2 H), 2.46 (s, 3 H), 2.41 (s, 3 H), 2.30 (d, *J* = 1.2 Hz, 3 H), 1.95 (m, 2 H), 1.86 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.7, 150.7, 141.4, 135.6, 133.4, 133.0, 131.6, 128.4, 124.1, 120.5, 119.1, 118.7, 115.2, 30.7, 28.5, 23.4, 22.4, 20.5, 8.9; HRMS (EI, 70 eV) *m/z* 352.1307 (M^+, calcd for $C_{21}H_{20}O_5$, 352.1311).

Cycloaddition of 4 with 24: 3-Methyl-7-(trimethylsilyl)-8,9,10,11-tetrahydrophenanthro[4,3-*b*]furan-4,5-dione (25) and 1-Methyl-5-(trimethylsilyl)-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione (26). Method A. A solution of **24** (125 mg, 0.69 mmol) and **4** (100 mg, 0.62 mmol) in anhydrous benzene (20 mL) was refluxed for 12 h under nitrogen. The reaction was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with CH_2Cl_2/petroleum ether (1:2) to recover unreacted **24**, and then with CH_2Cl_2 to give a mixture of aromatized and dihydro adducts, which was fully aromatized by refluxing overnight (12 h) in benzene (30 mL) with DDQ (150 mg, 0.67 mmol). Adducts **25** and **26** (48 mg, 23% yield, **25:26**, 1:2.5,

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from ^1H NMR) were purified by flash chromatography on silica gel (CH_2Cl_2) to give **25** and **26**. Recrystallization from ether/petroleum ether (5:1) gave pure **26** as red crystals: mp 182–184 °C; IR (KBr) 2928, 1693, 1671, 1247, 865, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1 H), 7.31 (s, 1 H), 3.21 (t, J = 6.0 Hz, 2 H), 2.93 (t, J = 6.0 Hz, 2 H), 2.30 (s, 3 H), 1.87 (m, 4 H), 0.37 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.5, 176.4, 162.3, 153.0, 141.5, 134.4, 130.9, 128.8, 127.4, 126.4, 122.0, 121.3, 32.3, 28.2, 22.4, 22.0, 8.9, –0.01 (3 C); LRMS (EI, 70 eV) m/z (relative intensity) 338 (M^+, 12), 307 (24), 296 (80), 281 (95), 253 (26), 149 (100); HRMS (EI, 70 eV) m/z 338.1333 (M^+, calcd for $C_{20}H_{22}O_3Si$, 338.1338). Compound **25** was obtained as an enriched mixture (40% **25**) on which the ^1H NMR was recorded: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1 H), 7.21 (s, 1 H), 3.3 (m, 2 H), 3.0 (m, 2 H), 2.25 (s, 3 H), 1.86 (m, 4 H), 0.38 (s, 9 H).

Method B. A mixture of **4** (70 mg, 0.43 mmol) and **24** (200 mg, 1.11 mmol) in anhydrous methanol (10 mL) was placed in a 10-mL compressible syringe and subjected to 160 000 psi (11 kBar) at room temperature for 2 h. The solvent was removed in vacuo, and the residue was passed through a silica gel plug to recover unreacted **24** and the mixture of cycloadducts (method A). The cycloadduct mixture was oxidized with DDQ (method A) to give a mixture of **25** and **26** (90 mg, 62% overall yield, **25:26**, 1:3.5, by ^1H NMR). Compound **26** was purified as described in method A.

Method C. A mixture of **4** (100 mg, 0.62 mmol) and **24** (310 mg, 1.67 mmol) was subjected to ultrasonication for 2 h, and the mixture of cycloadducts was isolated (General Procedure) and aromatized with DDQ (method A) to give a mixture of **25** and **26** (119 mg, 57% overall yield, **25:26**, 5:1, by ^1H NMR). Compound **26** was purified as described in method A.

6,6-Dimethyl-1-vinylcyclohexene (29). 2,2-Dimethylcyclohexanone, prepared from 2-methylcyclohexanone in 80% yield according to the method of Negishi,[32] was converted to **29** according to the literature in 69% yield.[9a]

Cycloaddition of 4 and 29: Tanshinone IIA (2) and 30. Method A. A solution of **29** (170 mg, 1.25 mmol) and **4** (100 mg, 0.62 mmol) in anhydrous benzene (20 mL) was refluxed for 12 h. The reaction was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with CH_2Cl_2/petroleum ether (1:2) to recover unreacted **29** (48 mg, 56% recovery) and then with CH_2Cl_2 to give a mixture of aromatized and dihydro adducts, which was fully aromatized by refluxing overnight (12 h) in benzene (30 mL) with DDQ (150 mg, 0.67 mmol). Adducts **2** and **30** (96 mg, 53% yield, **2:30**, 54:45, from ^1H NMR) were purified by flash chromatography on silica gel (CH_2Cl_2/petroleum ether, 4:1) to give **2** and **30**. Recrystallization of **2** from EtOH (95%) gave pure **2** (55 mg, 29% overall) as red crystals: mp 206–207 °C; IR (KBr) 3328, 3128, 2976, 2954, 2924, 2870, 1692 1670, 1582, 1536, 1460, 1428, 1382, 1326, 1284, 1192, 1160, 1144, 1074, 992, 958, 836, 794, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J = 8.1 Hz), 7.53 (d, J = 8.1 Hz), 7.20 (q, J = 1.3 Hz), 3.16 (t, J = 6.5 Hz, 2 H), 2.24 (d, J = 1.3 Hz, 3 H), 1.77 (m, 2 H), 1.63 (m, 2 H), 1.28 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.7, 175.8, 161.8, 150.1, 144.5, 141.3, 133.5, 127.5, 126.5, 121.1, 120.3, 119.9, 37.8, 34.7, 31.8 (2 C), 29.9, 19.1, 8.8; LRMS (CI, isobutane) m/z (relative intensity) 295 ($[M + 1]^+$, 100); HRMS (EI, 70 eV) 294.1248 (M^+, calcd for $C_{19}H_{18}O_3$ 294.1255). Compound **30** was isolated as red crystals (41 mg, 24% overall yield): mp 194–195 °C; IR (KBr) 3132, 2938, 2858, 1691, 1667, 1565, 1530, 1467, 1383, 1290, 1259, 931, 847, 809 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, J = 8.3 Hz, 1 H), 7.40 (d, J = 8.3 Hz, 1 H), 7.26 (q, J = 1.2 Hz, 1 H), 3.15 (t, J = 6.5 Hz, 2 H), 2.26 (d, J = 1.2 Hz, 3 H), 1.85 (m, 2 H), 1.66 (m, 2 H), 1.30 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 176.3, 162.5, 155.6, 141.0, 134.5, 130.0, 128.5, 128.3, 127.5, 126.9, 121.2, 37.6, 35.1, 31.5 (2 C), 28.9, 18.9, 8.8; LRMS (EI, 70 eV) m/z (relative intensity) 294 (M^+, 71), 266 (57), 251 (62), 165 (22), 129 (19), 83 (80), 49 (60), 45 (100); HRMS (EI, 70 eV) m/z 294.1240 (M^+, calcd for $C_{19}H_{18}O_3$ 294.1256).

Method B. A mixture of **4** (80 mg, 0.50 mmol) and **29** (465 mg, 3.42 mmol) was subjected to ultrasonication for 2 h, and unreacted **29** (360 mg, 91% recovery) and the mixture of cycloadducts were isolated. Oxidation with DDQ (120 mg, 0.53 mmol, method A) gave a mixture of **2** and **30** (111 mg, 76% overall yield, **2:30**, 10:3, by ^1H NMR). The cycloadducts were purified as described in method A.

2-Hydroxycyclohexanone Ethylene Glycol Ketal. A mixture of 2-hydroxycyclohexanone dimethyl acetal[33] (13.64 g, 85 mmol), ethylene glycol (5.27 g, 85 mmol), and a catalytic amount of camphorsulfonic acid (200 mg) were placed in a 100-mL round-bottom flask, and the flask was placed on a rotary evaporator.[34] The flask was warmed to 30 °C with a water bath under reduced pressure (water aspirator, 17 mmHg) with rotation for 4 h to give the crude ketal, which was used in the next step without further purification (13.09 g, 97% crude yield, >98% pure by ^1H NMR). A small sample was purified by flash chromatography on silica gel (CH_2Cl_2) to give a colorless oil: IR (NaCl) 2935, 2882, 1724, 1196, 1018, 949, 900, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.98 (m, 4 H), 3.54 (m, 1 H), 2.28 (br s, OH), 1.97 (m, 2 H), 1.15 – 1.61 (m, 6 H) in agreement with that reported in the literature.[35]

Cyclohexane-1,2-dione Ethylene Glycol Monoketal. To a solution of 2-hydroxycyclohexanone ethylene glycol ketal (2.1 g, 13.3 mmol) in anhydrous CH_2Cl_2 (100 mL) at room temperature was added pyridinium chlorochromate (4.3 g, 20 mmol) with stirring. The mixture was stirred until the reaction was complete (3 days), and then the mixture was passed through a pad of Florisil. The solvent was removed in vacuo to give a crude oil. Flash chromatography on silica gel afforded the pure ketone (1.64 g, 79%) as a colorless oil: IR (NaCl) 2935, 1725, 1195, 1020, 950, 900, 805 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (m, 4 H), 2.50 (m, 2 H), 1.92 (m, 2 H), 1.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.5, 106.8, 65.2 (2 C), 39.7, 36.9, 26.2, 22.7. (The IR, boiling point, and ^1H NMR in CCl_4 have been previously reported.)[36]

2-Hydroxy-2-vinylcyclohexanone Ethylene Glycol Ketal (32). Cyclohexane-1,2-dione monoethylene glycol ketal (700 mg, 4.5 mmol) was dissolved in anhydrous THF (20 mL) and cooled to –78 °C. Vinylmagnesium bromide (1.0 M in THF, 8 mL, 8 mmol) was added dropwise with stirring, and the stirring was continued at –78 °C for 2 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL), and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (20 mL) and saturated NaCl (20 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give **32** (750 mg, 90% yield) as a colorless oil: IR (NaCl) 3494, 3086, 2938, 2888, 1640, 1435, 1357, 1276, 1185, 1106, 1081, 990, 889 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.13 (dd, J = 17.5, 11.0 Hz, 1 H), 5.39 (dd, J = 17.5, 1.5 Hz, 1 H), 5.17 (dd, J = 11.0, 1.5 Hz, 1 H), 3.87–4.04 (m, 4 H), 2.25 (br s, OH), 1.90 (m, 1 H), 1.53–1.75 (m, 7 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 140.7, 113.8, 110.6, 75.9, 65.6, 65.1, 35.6, 31.7, 23.1, 20.5.

2-Hydroxy-2-cyclohexen-1-one 2-Triflate Ethylene Glycol Ketal (33). From cyclohexane-1,2-dione monoethylene glycol ketal (200 mg, 1.28 mmol), general procedure A, as a colorless oil (307 mg, 85% yield): IR (NaCl) 1682, 1420, 1215, 1145 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.97 (t, J = 4 Hz, 1 H), 4.12 (m, 2 H), 3.95 (m, 2 H), 2.25 (m, 2 H), 1.93 (m, 2 H), 1.81 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.1, 124.2, 118.4 (q, $J_{^{13}C^{19}F}$ = 319 Hz), 104.3, 65.8 (2 C), 35.1, 24.2, 20.1; LRMS (EI, 70 eV) m/z (relative intensity) 288 (M^+, 4), 262 (21), 244 (86), 152 (100), 127 (47), 93 (32), 73 (50).

2-Iodo-2-cyclohexen-1-one Ethylene Glycol Ketal (35). To a solution of 2-bromo-2-cyclohexen-1-one (**34**)[37] (1.40 g, 6.4 mmol) in anhydrous THF (60 mL) cooled to –78 °C was dropwise added a solution of n-BuLi in hexane (10 M, 0.78 mL) with stirring. Stirring was continued at –78 °C for 2.5 h, and a solution of I_2 (1.99 g, 7.8 mmol) in anhydrous THF (20 mL) was subsequently added, also at –78 °C. Stirring was continued for an additional

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2.5 h at −78 °C, the solution was diluted with ether (20 mL), and the reaction was quenched with 1 N HCl (25 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with 10% sodium bisulfite solution (20 mL, to remove excess I_2), water (2 × 20 mL), and saturated NaCl (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give **35** as a colorless oil (1.36 g, 80% yield): IR (NaCl) 2943, 2886, 1624, 1436, 1350, 1174, 1145, 1110, 1067, 1024, 946, 876, 805, 776, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.64 (t, J = 4 Hz, 1 H), 4.17 (m, 2 H), 3.95 (m, 2 H), 2.06 (m, 2 H), 1.89 (m, 2 H), 1.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.6, 106.0, 103.3, 65.5 (2 C), 34.3, 29.1, 20.2; LRMS (CI, isobutane) m/z (relative intensity) 267 ([M + 1]$^+$, 100).

2-Vinylcyclohex-2-en-1-one Ethylene Glycol Ketal (31). Method A: From Vinyl Iodide 35. The general procedure of Stille was followed[20b] using vinyl iodide **35** (700 mg, 2.63 mmol), tri-*n*-butylvinylstannane (830 mg, 2.63 mmol), and $Pd(PPh_3)_2Cl_2$ (37 mg, 0.05 mmol) in anhydrous DMF (10 mL). Diene **31** was purified by flash chromatography on silica gel (petroleum ether/CH_2Cl_2, 5:1) as a colorless oil (350 mg, 80% yield): IR (NaCl) 2944, 2883, 2831, 1640, 1614, 1574, 1439, 1265, 1227, 1175, 1020, 943 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.30 (dd, J = 17.5, 11 Hz, 1 H), 6.18 (t, J = 4 Hz, 1 H), 5.40 (br d, J = 17.5 Hz, 1 H), 5.03 (br d, J = 11 Hz, 1 H), 4.04 (m, 4 H), 2.13 (m, 2 H), 1.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9, 133.7, 130.7, 113.9, 107.0, 65.0 (2 C), 33.6, 25.5, 20.4; LRMS (EI, 70 eV) m/z (relative intensity) 166 (M$^+$, 28), 138 (48), 99 (100); HRMS (EI, 70 eV) m/z 166.0998 (M$^+$, calcd for $C_{10}H_{14}O_2$ 166.0994).

Method B. Diene **31** (236 mg, 85% yield) was obtained from **33** (470 mg, 1.67 mmol) using the general procedure of Stille[20a] as described above and purified as described in method A.

Cycloaddition of 4 and 31: Nortanshinone (5) and 38. Method A. A solution of **31** (158 mg, 0.95 mmol) and **4** (100 mg, 0.62 mmol) in anhydrous benzene (15 mL) was refluxed for 8 h. The reaction was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with petroleum ether to recover unreacted **31** (35 mg, 63% recovery), and then with CH_2Cl_2/ethyl acetate (8:1) to give a mixture of aromatized and dihydro adducts. This mixture was fully aromatized by refluxing overnight (12 h) in benzene (30 mL) with DDQ (150 mg, 0.67 mmol) to give a mixture of **36** and **37** (32 mg, 18%, **36:37**, 1:1, from ^1H NMR). Aromatized adducts **36** and **37** were deprotected by passage through a column of silica gel impregnated with $FeCl_3$,[21] eluting with CH_2Cl_2/ethyl acetate/MeOH (15:5:1). Recrystallization from acetone gave pure **5** (14 mg, deprotection: 100% yield) as orange red crystals: mp 232–233 °C; IR (KBr) 3120, 1660, 1570, 1530 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (d, J = 8.0 Hz, 1 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.24 (q, J = 1.2 Hz, 1 H), 3.45 (t, J = 6.2 Hz, 2 H), 2.68 (t, J = 6.5 Hz, 2 H), 2.28 (d, J = 1.2 Hz, 3 H), 2.13 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.8, 182.7, 175.4, 159.8, 150.3, 142.9, 134.5, 134.1, 133.8, 133.4, 125.8, 121.9, 120.7, 38.2, 28.3, 22.1, 8.8; LRMS (EI, 70 eV) m/z (relative intensity) 280 (M$^+$, 27), 265 (20), 252 (74), 224 (60), 196 (60), 152 (39), 139 (100); HRMS (EI, 70 eV) m/z 280.0733 (M$^+$, calcd for $C_{17}H_{12}O_4$, 280.0735).

Method B. A mixture of **4** (100 mg, 0.62 mmol) and **31** (250 mg, 1.5 mmol) were subjected to ultrasonication for 1 h, and unreacted **31** (130 mg, 89% recovery) and the mixture of cycloadducts were isolated. Oxidation with DDQ (150 mg, 0.67 mmol, method A) gave a mixture of **36** and **37** (274 mg, 65% overall yield, **36:37**, 8:1, by ^1H NMR). The cycloadducts were deprotected and purified (method A). After recrystallization of **5**, from the mother liquor, **38** was obtained as a red solid (90% purity by ^1H NMR): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, J = 8.0 Hz), 8.06 (d, J = 8.0 Hz, 1 H), 7.37 (q, J = 1.2 Hz, 1 H), 3.46 (t, J = 6.1 Hz, 2 H), 2.73 (t, J = 6.2 Hz, 2 H), 2.32 (d, J = 1.2 Hz, 3 H), 2.23 (m, 2 H).

Method C. A mixture of **4** (106 mg, 0.65 mmol) and **31** (200 mg, 1.20 mmol) in anhydrous toluene (5 mL) was placed into a 10-mL compressible syringe and subjected to 160 000 psi (11 kBar) at room temperature for 45 min. The solvent was removed in vacuo, and workup proceeded as described in method A to give unreacted **31** (87 mg, 95% recovery) and the cycloadduct mixture, which was subsequently oxidized with DDQ, deprotected, and purified (method A). Yield of aromatized cycloadducts: 160 mg, 75% **36:37**, 5:2, by ^1H NMR.

2-Methylcyclohex-2-enone (39). Method A. Ketone **39** was prepared from 2-vinylpyridine (4 g, 38 mmol) in 76% yield according to the literature.[22]

Method B. The literature procedure was followed with modifications.[38] A mixture of 2-bromo-2-methylcyclohexanone (6.52 g, 32.7 mmol), anhydrous LiCl (7 g, 160 mmol), and anhydrous Li_2CO_3 (12 g, 162 mmol) in anhydrous DMF (200 mL) was heated to 200 °C for 12 h and then cooled to room temperature. Water (50 mL) was added, and the aqueous layer extracted with ether (3 × 40 mL). the combined ether extracts were washed with water (40 mL) and saturated NaCl (20 mL) and dried (Na_2SO_4). The solution was filtered, and the solvent was removed in vacuo. Kugelrohr distillation gave pure **39** (3.2 g, 89% yield): bp 84 °C (20 mmHg).

2,3-Dihydroxy-2-methylcyclohexanone (40). To a solution of triethylamine (1 mL) in aqueous *t*-BuOH (30 mL, 1:1, v/v) was added **39** (1.6 g, 14.5 mmol) and trimethylamine *N*-oxide dihydrate (1.98 g, 17.5 mmol). The solution was cooled to −5 °C, and a solution of OsO_4 in *t*-BuOH (4.65 mL, 0.157 M, 0.73 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 1 h and then maintained at room temperature for 48 h. An aqueous solution of sodium bisulfite (10%, 10 mL) was added, and the mixture was stirred for 30 min at room temperature. Sodium chloride was then added until the solution was saturated, and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water (20 mL) and saturated NaCl (20 mL), dried (Na_2SO_4), and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, increasing ethyl acetate from 15% to 80%) to afford **40** as white crystals (1.5 g, 72%): mp 150 °C; IR (KBr) 3850, 3425, 2974, 2941, 1798, 1719, 1465, 1389, 1363, 1341, 1254, 1197, 1086, 1053, 1017, 1002, 879, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.27 (br s, OH), 4.06 (br s, 1 H), 2.91 (br s, OH), 2.54 (m, 1 H), 2.48 (m, 1 H), 1.93–2.20 (m, 4 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.1, 78.6, 76.8, 36.9, 27.7, 23.4, 21.4.

2,3-Dihydroxy-2-methylcyclohexan-1-one 2,3-Acetonide (41). A solution of **40** (1.2 g, 8.33 mmol), 2-methoxypropene[39] (3.5 g, 48.6 mmol), and *p*-TsOH (150 mg) in anhydrous benzene (100 mL) was stirred overnight (12 h) at room temperature in the presence of 3-Å molecular sieves (1.5 g). After removal of the solvent in vacuo, the resulting oil was chromatographed on flash silica gel (CH_2Cl_2/ethyl acetate, 10:1) to afford acetonide **41** (1.49 g, 97%) as a colorless oil: IR (NaCl) 2950, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.18 (br s, 1 H), 2.48, m (1 H), 2.37 (m, 1 H), 2.25 (m, 1 H), 2.04 (m, 1 H), 1.86–1.99 (m, 2 H), 1.40 (s, 9 H); ^1H NMR (benzene-d_6, 400 MHz) δ 3.75 (br s, 1 H), 2.22 (m, 1 H), 1.72–1.89 (m, 3 H), 1.49 (s, 3 H), 1.32 (s, 3 H), 1.25 (m, 2 H), 1.04 (s, 3 H).

1,5,6-Trihydroxy-6-methylcyclohexene 5,6-Acetonide 1-Triflate (42). From **41** (500 mg, 2.7 mmol), general procedure A, as a colorless oil (781 mg, 91% yield): IR (NaCl) 2990, 2930, 2880, 1415, 1210, 1145, 1045, 990, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72 (dd, J = 5.4, 5 Hz, 1 H), 4.17 (d, J = 1.8 Hz), 2.50 (m, 1 H), 2.09–2.16 (m, 2 H), 1.72 (m, 1 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 117.7, 109.3, 79.8, 77.4, 27.1, 27.0, 23.1, 21.7, 19.7 ($^{13}CF_3$ not observed); LRMS (CI, isobutane) m/z (relative intensity) 317 ([M + 1]$^+$, 100).

1-Vinyl-5,6-dihydroxy-6-methylcyclohexene 5,6-Acetonide (43). General procedure A[20a] using vinyltriflate **42** (640 mg, 2 mmol), tri-*n*-butylvinylstannane (650 mg, 2 mmol), LiCl (300 mg, 6 mmol), and $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) in anhydrous THF (35 mL), as a colorless oil (360 mg, 92% yield): IR (NaCl) 2985, 2935, 2870, 1635, 1600, 1415, 1365, 1205, 1099, 1000, 920, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.23 (dd, J = 17.3, 11 Hz, 1 H), 5.75 (br d, J = 3.3 Hz, 1 H), 5.43 (d, J = 17.3 Hz, 1 H), 4.99 (d, J = 11 Hz, 1 H), 3.96 (br s, 1 H), 2.31 (m, 1 H), 2.07 (m, 1 H), 2.00 (m, 1 H), 1.67 (m, 1 H), 1.37 (s, 6 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 135.9, 125.5, 114.1, 107.8, 79.1, 78.4, 27.8, 27.1, 23.6, 22.8, 20.4; LRMS (CI, isobutane) m/z (relative intensity) 195 ([M + 1]$^+$, 100).

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Methyl 2-Methyl-1-oxocyclohexane-2-carboxylate (44). Beginning with methyl cyclohexanone-2-carboxylate[40] (3.12 g, 20 mmol), the procedure of Piers and Friesen[41] was modified subjecting the reaction mixture to ultrasonication for 5 h. After workup, the resulting oil was purified by Kugelrohr distillation to give **44** as a colorless oil (3.05 g, >95% yield): bp 65 °C (0.3 mmHg); IR (NaCl) 2930, 2850, 1705, 1446, 1255, 1209, 1154, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.73 (s, 3 H), 2.44–2.53 (m, 3 H), 2.01 (m, 1 H), 1.62–1.75 (m, 3 H), 1.46 (m, 1 H), 1.29 (s, 3 H).

Methyl 1-Hydroxy-6-methylcyclohexene-6-carboxylate 1-Triflate (45). From **44** (500 mg, 3.13 mmol), general procedure A, as a colorless oil (746 mg, 79% yield): IR (NaCl) 2960, 1740, 1680, 1415, 1210, 1145, 1040, 960, 900, 860, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.87 (dd, J = 4.0, 4.0 Hz, 1 H), 3.75 (s, 3 H), 2.26 (m, 3 H), 1.66 (m, 3 H), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 149.0, 119.1, 117.9 (q, $J_{^{13}C^{19}F}$ = 319 Hz), 52.3, 46.7, 35.9, 24.4, 22.1, 18.5; LRMS (CI, isobutane) m/z (relative intensity) 303 ([M + 1]$^+$, 100); LRMS (EI, 70 eV) m/z (relative intensity) 302 (M$^+$, 20), 252 (74), 243 (45), 225 (25), 169 (100), 119 (57), 109 (67), 93 (50).

Methyl 6-Methyl-1-vinylcyclohexene-6-carboxylate (46). General procedure A[20a] using **45** (640 mg, 2.1 mmol), tri-*n*-butylvinylstannane (705 mg, 2.2 mmol), LiCl (420 mg, 8.5 mmol), and $Pd(PPh_3)_4$ (74 mg, 0.06 mmol) in anhydrous THF (40 mL), as a colorless oil (350 mg, 92% yield): IR (NaCl) 2930, 1720, 1630, 1600, 1450, 1430, 1250, 1180, 1100, 980, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.14 (dd, J = 17.8, 11.3 Hz, 1 H), 5.93 (dd, J = 4.2, 4.2, 1 H), 5.02 (d, J = 17.8 Hz, 1 H), 4.90 (d, J = 11.3 Hz, 1 H), 3.67 (s, 3 H), 2.16 (m, 2 H), 1.98 (m, 1 H), 1.65 (m, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.1, 138.5, 137.6, 129.4, 111.9, 52.1, 44.7, 35.9, 25.6, 23.2, 18.3; LRMS (CI, isobutane) m/z (relative intensity) 181 ([M + 1]$^+$, 100).

2-(Hydroxymethyl)-2-methylcyclohexanol (47). In a three-necked round-bottom flask (100 mL) was placed $LiAlH_4$ (760 mg, 20 mmol) and anhydrous THF (40 mL). The suspension was refluxed for 15 min, and then cooled to room temperature. A solution of **44** (1.6 g, 10 mmol) in anhydrous THF (20 mL) was added through a dropping funnel under nitrogen at such a rate as to maintain gentle reflux. After the addition was complete, the resulting mixture was refluxed for 1 h and then cooled to room temperature. Excess $LiAlH_4$ was quenched by the careful addition of aqueous KOH solution (20 mg in 3 mL).[42] The mixture was refluxed for 15 min, and the hot solution was suction filtered. Upon cooling, a precipitate formed which was collected by suction filtration, refluxed with additional THF (30 mL, 1 h), cooled, and filtered by suction. After removal of the solvent from the combined filtrates in vacuo, the resulting oil was chromatographed on flash silica gel (CH_2Cl_2/ethyl acetate, 1:1), giving a mixture of diastereomeric diols **47** as a colorless oil (1.4 g, 97%), which was used in the next step without further purification; IR and ^1H NMR spectral data were identical with that reported in literature.[43]

2-[[(Dimethyl-*tert*-butylsilyl)oxy]methyl]-2-methylcyclohexanol (48). To a solution of diastereomeric diols **47** (600 mg, 4.2 mmol), triethylamine (470 mg, 4.6 mmol), and 4-(dimethylamino)pyridine (DMAP, 21 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (30 mL) was added a solution of *tert*-butyldimethylsilyl chloride (660 mg, 4.4 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred at room temperature under argon overnight (12 h). After removal of the solvent in vacuo, the resulting oil was chromatographed on flash silica gel (CH_2Cl_2) to give a colorless oil, **48**, as a mixture of diastereomers (820 mg, 76% yield), which was used in the next step without further purification.

2-[[(Dimethyl-*tert*-butylsilyl)oxy]methyl]-2-methylcyclohexanone (49). To a solution of diastereomeric cylohexanols **48** (780 mg, 3 mmol) in anhydrous CH_2Cl_2 (35 mL) at room temperature was added pyridinium dichromate[44] (1.7 g, 4.5 mmol) with stirring. Stirring was continued until the reaction was complete (16 h), and the reaction mixture was then passed through a pad of Florisil. After removal of the solvent in vacuo, the resulting oil was chromatographed on flash silica gel (CH_2Cl_2) to give **49** as a colorless oil (680 mg, 88%): IR (NaCl) 2930, 2865, 1713, 1439, 1370, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.65 (s, 2H), 2.38 (m, 2H), 1.83 (m, 3H), 1.69 (m, 3H), 1.08 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.9, 68.3, 50.5, 39.3, 35.9, 27.0, 25.8 (3 C), 21.2, 20.6, 18.2, -5.6 (2 C); LRMS (CI, isobutane) m/z (relative intensity) 257 ([M + 1]$^+$, 100).

6-[[(Dimethyl-*tert*-butylsilyl)oxy]methyl]-1-hydroxy-6-methylcyclohexene 1-Triflate (50). From **49** (640 mg, 2.5 mmol), general procedure A, as a colorless oil (705 mg, 85% yield): IR (NaCl) 2920, 2840, 1670, 1460, 1400, 1210, 1140, 1095, 885, 845, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.79 (dd, J = 4.0, 4.0 Hz, 1 H), 3.61 (d, J = 9.7 Hz, 1 H), 3.33 (d, J = 9.7 Hz, 1 H), 2.17 (m, 2 H), 2.02 (m, 1 H), 1.69 (m, 1 H), 1.61 (m, 1 H), 1.44 (m, 1 H), 1.07 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.2, 118.6, 118.5 (q, $J_{^{13}C^{19}F}$ = 319 Hz), 67.2, 40.8, 33.4, 25.8 (3 C), 24.8, 21.0, 18.3, 18.2, -5.7, -5.8; LRMS (CI, isobutane) m/z (relative intensity) 331 ([M + 1]$^+$, 100).

6-[[(Dimethyl-*tert*-butylsilyl)oxy]methyl]-6-methyl-1-vinylcyclohexene (51). General procedure A[20a] using **50** (560 mg, 1.44 mmol), tri-*n*-butylvinylstannane (480 mg, 1.52 mmol), LiCl (360 mg, 7.2 mmol), and $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) in anhydrous THF (35 mL), as a colorless oil (341 mg, 89% yield): IR (NaCl) 2930, 2855, 1620, 1465, 1255, 998, 840, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.33 (dd, J = 17.1, 10.8 Hz, 1 H), 5.91 (dd, J = 4.1, 4.1 Hz, 1 H), 5.26 (d, J = 17.1 Hz, 1 H), 4.90 (d, J = 10.8 Hz, 1 H), 3.49 (d, J_{AB} = 9.6 Hz, 1 H), 3.41 (d, J_{AB} = 9.6 Hz, 1 H), 2.07 (m, 2 H), 1.80 (m, 1 H), 1.61 (m, 2 H), 1.32 (m, 1 H), 1.04 (s, 3 H), 0.91 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9, 137.2, 125.2, 112.7, 69.1, 38.6, 33.1, 26.1, 25.9 (3 C), 23.0, 18.7, 18.3, -5.49, -5.52; LRMS (CI, isobutane) m/z (relative intensity) 267 ([M + 1]$^+$, 100).

1-Hydroxy-6-methylcyclohexene 1-Triflate (52). 2-Methylcyclohexanone (500 mg, 4.46 mmol) was converted to **52** (880 mg, 81% yield) according to the method of McMurry:[23] ^1H NMR ($CDCl_3$, 400 MHz) δ 5.70 (dd, J = 4.0, 4.0 Hz, 1 H), 2.51 (m, 1 H), 2.14 (m, 2 H), 1.91 (m, 1 H), 1.42–1.63 (m, 4 H), 1.11 (d, J = 6.9 Hz, 3 H).

6-Methyl-1-vinylcyclohexene (53). General procedure A[20a] using **52** (350 mg, 1.5 mmol), tri-*n*-butylvinylstannane (510 mg, 1.6 mmol), LiCl (237 mg, 4.8 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in anhydrous THF (35 mL), as a colorless oil (163 mg, 97% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 6.25 (dd, J = 17.5, 11.0 Hz, 1 H), 5.71 (dd, J = 3.9, 3.9 Hz, 1 H), 5.14 (d, J = 17.5 Hz, 1 H), 4.94 (d, J = 11.0 Hz, 1 H), 2.59 (m, 1 H), 2.14 (m, 2 H), 1.57–1.73 (m, 4 H), 1.13 (d, J = 7.0 Hz, 3 H).

Cycloaddition of 4 and 43: Tanshindiol B Acetonide (54) and Regioisomer 55. Method A. A solution of **43** (161 mg, 0.83 mmol) and **4** (130 mg, 0.80 mmol) was refluxed in anhydrous benzene (80 mL) for 8 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with petroleum ether to recover unreacted **43** and then with CH_2Cl_2 to give a mixture of aromatized and dihydro adducts. This mixture was fully aromatized by refluxing overnight (12 h) in benzene (15 mL) with DDQ (150 mg, 0.66 mmol) to give a mixture of **54** and **55** (34 mg, 15% yield, **54**:**55**, 1:1, from ^1H NMR). Pure **54** was purified by flash chromatography on silica gel (CH_2Cl_2/ether, 20:1) to afford a red solid: mp 122–123 °C; IR (KBr) 2981, 2929, 1692, 1672, 1580, 1537, 1481, 1416, 1384, 1369, 1343, 1317, 1260, 1102, 1069, 1001, 962, 920, 851, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J = 8.2 Hz, 1 H), 7.63 (d, J = 8.2 Hz, 1 H), 7.23 (q, J = 1.3 Hz, 1 H), 4.14 (dd, J = 4.3, 2.3 Hz, 1 H), 3.37 (ddd, J = 19, 5.7, 2.7 Hz, 1 H), 3.20 (m, 1 H), 2.28 (m, 1 H), 2.25 (d, J = 1.3 Hz, 3 H), 1.87 (m, 1 H), 1.56 (s, 3 H), 1.40 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.4, 175.5, 161.1, 144.6, 142.2, 141.6, 135.0, 128.8, 128.3, 125.3, 121.3, 120.8, 120.2, 108.5, 78.7, 77.6, 27.3, 26.8, 23.0, 22.3, 8.7; LRMS (EI, 70 eV) m/z (relative intensity) 352 (M$^+$, 10), 310 (18), 298 (34), 266 (68), 244 (21), 194 (29), 167 (38), 128 (15), 84 (30), 43 (100); HRMS (EI, 70 eV) m/z

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352.1313 (M^+, calcd for $C_{21}H_{20}O_5$ 352.1311). Pure **55** was obtained by two additional flash columns on silica gel (CH_2Cl_2/ether, 20:1) as a red solid: mp 169–170 °C; IR (KBr) 3142, 2961, 2925, 2854, 1693, 1673, 1568, 1529, 1382, 1259, 1093, 1062, 1020, 931, 869, 798 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.1 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 1 H), 7.32 (s, 1 H), 4.17 (br d, J = 4.1 Hz, 1 H), 3.42 (m, 1 H), 3.24 (m, 1 H), 2.38 (m, 1 H), 2.29 (s, 3 H), 1.98 (m, 1 H), 1.59 (s, 3 H), 1.42 (s, 3 H), 0.98 (s, 3 H); LRMS (EI, 70 eV) m/z (relative intensity) 352 (M^+, 16), 295 (36), 139 (7), 167 (12), 165 (10), 149 (39), 111 (25), 97 (39), 71 (71), 57 (100); HRMS (EI, 70 eV) m/z 352.1307 (M^+, calcd for $C_{21}H_{20}O_5$ 352.1311). Insufficient material was obtained for a ^{13}C NMR spectrum.

Method B. A mixture of **4** (100 mg, 0.62 mmol) and **43** (350 mg, 1.8 mmol) was subjected to ultrasonication for 1 h, and unreacted **43** (215 mg, 94% recovery) and the mixture of cycloadducts were isolated. Oxidation with DDQ (150 mg, 0.67 mmol, method A) gave a mixture of **54** and **55** (143 mg, 66% yield, **54**:**55**, 5:1, by ^1H NMR). The cycloadducts were purified as described in method A.

Deprotection of 54: Tanshindiol B (3). A solution of **54** (50 mg, 0.14 mmol) was dissolved in THF/H_2O (25 mL, 1:1, v/v) containing Dowex 50-W resin (H^+, 1.0 g).[45] The resulting mixture was stirred at 65 °C until **54** disappeared (4 h). The reaction mixture was filtered and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with water (20 mL) and saturated NaCl (20 mL), dried (Na_2SO_4), and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/ethyl acetate/MeOH, 15:5:1) to afford **3** (25 mg, 64%) as red crystals: mp 216–217 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, J = 8 Hz, 1 H), 7.67 (d, J = 8 Hz, 1 H), 7.26 (q, J = 1.2 Hz, 1 H), 3.99 (d, J = 3.4 Hz, 1 H), 3.36 (m, 2 H), 2.27 (d, J = 1.2 Hz, 3 H), 2.20 (m, 1 H), 2.07 (m, 1 H), 1.52 (s, 3 H); ^{13}C NMR (CD_3OD + 1 drop $CDCl_3$, only very slightly soluble 100 MHz) δ 176.6, 163.0, 147.5, 144.4, 143.3, 135.4, 129.8, 126.4, 122.1, 121.7, 77.8, 72.9, 29.4, 26.9, 25.4, 8.8 (one carbonyl carbon and one aromatic carbon not observed); HRMS (EI, 70 eV) m/z 312.1006 (M^+, calcd for $C_{18}H_{16}O_5$ 312.0998).

Cycloaddition of 4 and 46: Methyl Tanshinonate (6) and Regioisomer 56. A mixture of **4** (100 mg, 0.62 mmol), **46** (195 mg, 1.1 mmol), and anhydrous methanol (0.25 mL) was subjected to ultrasonication for 1 h, and unreacted **46** (76 mg, 90% recovery, CH_2Cl_2 elution) and the mixture of cycloadducts (CH_2Cl_2/ethyl acetate, 5:1, elution) were isolated. Oxidation with DDQ (150 mg, 0.67 mmol) in refluxing benzene (30 mL) overnight (12 h) afforded the aromatized cycloadducts **6** and **56** (138 mg, 66% yield, **6**:**56**, 8:1, by ^1H NMR). Pure **6** was obtained by recrystallization (petroleum ether/ethyl acetate, 10:1.5) as red needles: mp 196–197 °C; IR (KBr) 3128, 2954, 1726, 1692, 1672, 1578, 1536, 1428, 1158, 912, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 8.1 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.23 (q, J = 1.2 Hz, 1 H), 3.67 (s, 3 H), 3.23 (m, 2 H), 2.26 (m, 1 H), 2.25 (br s, 3 H), 1.82 (m, 2 H), 1.76 (m, 1 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.3, 177.0, 175.5, 161.2, 144.4, 143.0, 141.6, 134.9, 128.5, 126.5, 121.2, 120.2 (2 C), 52.5, 47.2, 34.0, 29.0, 27.6, 19.1, 8.8; LRMS (EI, 70 eV) m/z (relative intensity) 338 (M^+, 68), 310 (18), 279 (82), 235 (39), 251 (100), 179 (27), 165 (41); HRMS (EI, 70 eV) m/z 338.1136 (M^+, calcd for $C_{20}H_{18}O_5$ 338.1154). Compound **56** recovered from the mother liquors was purified to 85% enrichment by flash chromatography on silica gel (CH_2Cl_2): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.2 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.27 (d, J = 1.3 Hz, 1 H), 3.68 (s, 3 H), 3.2 (m, 2 H), 2.29 (q, J = 1.3 Hz, 3 H), 1.92 (m, 2 H), 1.78 (m, 2 H), 1.60 (s, 3 H).

Cycloaddition of 4 and 51: Tanshinone IIB *tert*-Butyldimethylsilyl Ether (57). A mixture of **4** (110 mg, 0.68 mmol), **51** (340 mg, 1.28 mmol), and anhydrous methanol (0.25 mL) was subjected to ultrasonication for 1.5 h, and unreacted **51** and the mixture of cycloadducts were isolated. Oxidation with DDQ (180 mg, 0.79 mmol) in refluxing benzene (40 mL) overnight (12 h) afforded the aromatized cycloadducts **57** and **58** (204 mg, 71% yield, **57**:**58**, 10:1, by ^1H NMR). Pure **57** (182 mg, 63%) was obtained by recrystallization (petroleum ether/ethyl acetate, 12:1) as orange-red crystals: mp 126–127 °C; IR (KBr) 3129, 2955, 2929, 2857, 1693, 1670, 1537, 1472, 1256, 1090, 836, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 8.3 Hz, 1 H), 7.47 (d, J = 8.3 Hz, 1 H), 7.20 (br s, 1 H), 3.59 (d, J_{AB} = 9.8 Hz, 1 H), 3.51 (d, J_{AB} = 9.8 Hz), 3.15 (dd, J = 6.4, 6.4 Hz, 2 H), 2.23 (br s, 3 H), 1.92 (m, 1 H), 1.78 (m, 2 H), 1.49 (m, 1 H), 1.27 (s, 3 H), 0.84 (s, 9 H), –0.002 (s, 3 H), –0.003 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.3, 175.5, 161.5, 146.6, 145.6, 141.2, 134.1, 127.4, 126.6, 121.1, 119.8, 119.7, 71.1, 39.7, 32.2, 29.7, 26.4, 25.7 (3 C), 18.1, 16.7, 8.7, –5.6, –5.7; HRMS (EI, 70 eV) m/z 424.2075 (M^+, calcd for $C_{25}H_{32}O_4Si$ 424.2070). Insufficient **58** was recovered from the mother liquors for characterization.

Deprotection of 57: Tanshinone IIB (7). Silyl ether **57** (84 mg, 0.20 mmol) was dissolved in acetonitrile/48% aqueous HF solution (1:1, v/v) at room temperature. After deprotection was complete (2.5 h), CH_2Cl_2 (20 mL) and water (15 mL) were added and the organic layer was removed, washed with water (10 mL), dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to give a solid, which was purified by recrystallization from ether to give pure **7** (58 mg, 95%) as red-orange needles: mp 218–219 °C; IR (KBr) 3562, 3498, 2952, 2922, 2872, 1686, 1668, 1578, 1536, 1348, 914, 838, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 8.1 Hz, 1 H), 7.55 (d, J = 8.1 Hz, 1 H), 7.22 (q, J = 1.1 Hz, 1 H), 3.79 (br d, J = 10.6 Hz, 1 H), 3.60 (m, 1 H), 3.18 (m, 2 H), 2.26 (d, J = 1.1 Hz, 3 H), 1.98 (m, 1 H), 1.86 (m, 1 H), 1.76 (m, 1 H), 1.58 (m, 2 H), 1.29 (s, 3 H); ^{13}C NMR (pyridine-d_5, 100 MHz) δ 183.8, 176.3, 161.5, 147.4, 145.2, 142.1, 134.2, 127.4, 126.2, 121.0, 120.2 (2 C), 70.9, 40.4, 32.5, 30.3, 27.0, 19.3, 8.9; HRMS (EI, 70 eV) m/z 310.1129 (M^+, calcd for $C_{19}H_{18}O_4$ 310.1205).

Cycloaddition of 4 and 53: Methyltanshinquinone (8). Method A. A solution of **53** (90 mg, 0.8 mmol) and **4** (100 mg, 0.62 mmol) in anhydrous benzene (30 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was passed through a silica gel plug, eluting initially with petroleum ether to recover unreacted **53** (10 mg, 50% recovery), and then with CH_2Cl_2 to give a mixture of aromatized and dihydro adducts. This mixture was fully aromatized by refluxing overnight (12 h) in benzene (25 mL) with DDQ (80 mg, 0.35 mmol) to give a mixture of **8** and **59** (19 mg, 11% yield, **8**:**59**, 10:1, from ^1H NMR). Pure **8** was purified by flash chromatography on silica gel (CH_2Cl_2) to afford an orange-red solid: mp 169–170 °C; IR (KBr) 2954, 1726, 1692, 1672, 1578, 1482, 1240, 1158, 1112, 912, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 8.0 Hz, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.21 (q, J = 1.3 Hz, 1 H), 3.27 (dt, J = 9.5, 5.6 Hz, 1 H), 3.11 (dt, J = 9.5, 7.0 Hz, 1 H), 2.96 (m, 1 H), 2.26 (d, J = 1.3 Hz, 3 H), 1.86 (m, 2 H), 1.75 (m, 1 H), 1.59 (m, 1 H), 1.32 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.6, 175.7, 161.8, 146.5, 145.0, 141.2, 135.0, 127.6, 126.4, 121.2, 120.1, 119.8, 33.4, 29.8, 29.1, 23.1, 19.5, 8.8; LRMS (EI, 70 eV) m/z (relative intensity) 280 (M^+, 82), 247 (25), 237 (42), 44 (52), 39 (100); HRMS (EI, 70 eV) m/z 280.1076 (M^+, calcd for $C_{18}H_{16}O_3$ 280.1099). Insufficient **59** was recovered for characterization.

Method B. A mixture of **4** (80 mg, 0.49 mmol) and **53** (150 mg, 1.34 mmol) was subjected to ultrasonication for 1.5 h, and unreacted **53** (92 mg, 96% recovery) and the mixture of cycloadducts were isolated. Oxidation with DDQ (100 mg, 0.44 mmol, method A) gave a mixture of **8** and **59** (77 mg, 56% overall yield, **8**:**59**, 20:1, by ^1H NMR). The cycloadducts were purified as described in method A. Insufficient **59** was recovered for characterization.

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Registry No. **2**, 568-72-9; (±)-**3**, 119477-12-2; **4**, 113297-21-5; **5**, 97399-70-7; (±)-**6**, 127758-05-8; (±)-**7**, 127665-43-4; (±)-**8**, 127665-44-5; **12**, 127665-45-6; **13**, 7182-21-0; **14**, 127665-46-7; **15**,

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127665-47-8; (±)-16, 127758-06-9; (±)-17, 127665-48-9; 18, 52422-61-4; 19, 118949-98-7; 20, 118949-99-8; 21, 2622-21-1; 22, 113297-29-3; 23, 113297-30-6; 24, 113297-25-9; 25, 113297-27-1; 26, 113297-28-2; 27, 127665-49-0; 28, 127665-50-3; 29, 18238-29-4; 30, 118950-00-8; 31, 118949-96-5; 32, 127665-51-4; 33, 127665-66-1; 34, 70156-98-8; 35, 127665-65-0; 36, 118950-01-9; 37, 118950-02-0; 38, 127665-52-5; 39, 1121-18-2; (±)-40, 127758-07-0; (±)-41, 73511-09-8; (±)-42, 127665-53-6; (±)-43, 118949-97-6; (±)-44, 127758-08-1; (±)-45, 127759-60-8; (±)-46, 127665-54-7; (±)-*cis*-47, 99892-73-6; (±)-*trans*-47, 73372-55-1; (±)-*cis*-48, 127665-55-8; (±)-*trans*-48, 127665-67-2; (±)-49, 127665-56-9; (±)-50, 127665-57-0; (±)-51, 127665-58-1; (±)-52, 127665-59-2; (±)-53, 127665-60-5; (±)-54, 118950-03-1; (±)-55, 118950-04-2; (±)-56, 127665-61-6; (±)-57, 127665-62-7; (±)-58, 127665-63-8; (±)-59, 127665-64-9; (*E*)-CH_2=CHCH=CHOAc, 35694-20-3; (*E*)-CH_2=CHCH=CHOTMS, 63383-46-0; C_2H_5CHO, 123-38-6; CH_2=C(Br)TMS, 13683-41-5; cyclopentadiene, 542-92-7; isoprene, 78-79-5; butadiene, 106-99-0; (±)-2-methylcyclohexanone, 24965-84-2; 2-cyclohexen-1-one, 930-68-7; cyclohexane-1,2-dione ethylene glycol monoketal, 4746-96-7; (*E*)-1-morpholinopropene, 51043-49-3; morpholine, 110-91-8; *o*-phenylenediamine, 95-54-5; cyclohexanone, 108-94-1; 1-[α-(trimethylsilyl)vinyl]cyclohexan-1-ol, 51666-97-8; (±)-2-hydroxycyclohexanone ethylene glycol ketal, 127758-09-2; (±)-2-hydroxycyclohexanone dimethyl acetal, 118907-62-3.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for new compounds described in this paper (64 pages). Ordering information is given on any current masthead page.

Asymmetric Syntheses of *Salvia miltiorrhiza* Abietanoid *o*-Quinones: Methyl Tanshinonate, Tanshinone IIB, Tanshindiol B, and 3-Hydroxytanshinone[1]

Mohammed Haiza, Junning Lee, and John K. Snyder*

Department of Chemisty, Boston University, 590 Commonwealth Ave., Boston, Massachusetts 02215

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The Diels–Alder reaction of 3-methyl-4,5-benzofurandione with vinylcyclohexene derivatives using either high-pressure or ultrasound promotion has led to the asymmetric synthesis of methyl tanshinonate, tanshinone IIB, tanshindiol B, and 3-hydroxytanshinone. The abietanoid diterpenes are active constituents of the Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge. As a result, the absolute stereochemistry of these natural products has been assigned: (−)-(4*S*)-methyl tanshinonate, (−)-(4*S*)-tanshinone IIB, (−)-(3*S*,4*R*)-tanshindiol B, and (+)-(3*S*)-3-hydroxytanshinone.

Introduction

In the previous paper, a general strategy utilizing an ultrasound-promoted Diels–Alder reaction with *o*-quinone **1** as a dienophile was applied to the synthesis of six abietanoid diterpenes isolated from the Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge.[2] We now report the adaptation of this approach for the asymmetric synthesis of methyl tanshinonate[3] (**2**) and tanshindiol B[4] (**3**), as well as 3-hydroxytanshinone[4] (**4**) in order assign their absolute stereochemistries (Scheme I). Since the suitability of the cycloaddition of **1** with vinylcyclohexene derivatives using either high-pressure or ultrasound promotion was established, the asymmetric syntheses of **2**–**4** focused on the preparation of the optically pure vinylcyclohexene derivatives. Furthermore, optically pure methyl tanshinonate was converted to tanshinone IIB[5] (**5**), thus enabling the assignment of the absolute stereochemistry of this natural product as well.

Results and Discussion

Methyl Tanshinonate (2). The synthesis of racemic **2** was accomplished by the cycloaddition of **1** with methyl 1-vinyl-6-methylcyclohexene-6-carboxylate (**8**).[2a] The preparation of **8** began with the methylation of methyl cyclohexanone-2-carboxylate, thereby incorporating the only chiral center required for the synthesis of **2**. Koga et al. have shown that this methylation may be accomplished asymmetrically using the *tert*-butylvaline lithioenamine of this β-keto ester.[6] Diastereofacial selectivity in the methylation is achieved by the use of either HMPA as a lithium ligand, generating (−)-(*R*)-**6** (90% yield, 59% ee in our hands), or THF as the ligand to generate (+)-(*S*)-**6** (92% yield, 95% ee in our hands) after workup in accord with Koga's results. The optical purities of (−)-(*R*)-**6** and (+)-(*S*)-**6** were originally estimated by optical rotation and ultimately determined unambiguously after conversion to tanshinone IIB by induced nonequivalence in the NMR spectra using a chiral solvating agent.[7] The enantiomers of **6** were converted to vinylcyclohexene derivatives, (+)-(*R*)-**8** and (−)-(*S*)-**8** (Scheme II) via the vinyl triflates

(1) Taken in part from the PhD Dissertation of Junning Lee, Boston University, 1989.

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(7) The optical purity of (+)-(*R*)-**2** and (−)-(*S*)-**2**, as well as all synthetic intermediates, are based upon the optical purity of (+)-(*R*)-**5** and (−)-(*S*)-**5** as measured from induced nonequivalence in the ^1H NMR spectra upon addition of (+)-(*S*)-*O*-nitromandelic acid as a chiral solvating reagent. The validity of this optical purity determination for these compounds rests upon the assumption that no racemization had occurred in the transformations from (−)-(*R*)-**6** and (+)-(*S*)-**6** to (+)-(*R*)-**5** and (−)-(*S*)-**5**. Such an assumption seems quite reasonable since racemization would require cleavage and reformation of a carbon–carbon bond, a process which would be unlikely under the reaction conditions. An important corollary of this approach is that optical rotation measurements do NOT give accurate measurements of optical purity (see ref 9). The specific rotations given in this work simply record an observed measurement and have NOT been used for optical purity calculations, only for enantiomeric assignment. We were unable to induce nonequivalence in the ^1H NMR spectra of (±)-**2** or any synthetic intermediate with any chiral solvating reagent, nor were we able to achieve separation of the enantiomers of (±)-**2**, (±)-**5**, or any synthetic intermediate using a chiral HPLC column (Pirkle Covalent D-naphthylalanine, 5 μm, 4.6 × 250 mm, Regis).

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