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]

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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.

(2) (a) Lee, J.; Snyder, J. K. *J. Org. Chem.*, preceeding paper in this issue. Preliminary accounts: (b) Lee, J.; Tang, J.; Snyder, J. K. *Tetrahedron Lett.* **1987**, *28*, 3427. (c) Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522.

(3) (a) Kakisawa, H.; Hayashi, T.; Okazaki, I.; Ohashi, M. *Tetrahedron Lett.* **1968**, 3231. (b) Chien, M. K.; Young, P. T.; Ku, W. H.; Chen, Z. X.; Chen, H. T.; Yeh, C. T. *Acta Chim. Sin.* **1978**, *36*, 35.

(4) Luo, H.-W.; Wu, B.-J.; Wu, M.-Y.; Yong, Z.-C.; Niwa, M.; Hirata, Y. *Phytochemistry* **1985**, *24*, 815.

(5) Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 48.

(6) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718.

(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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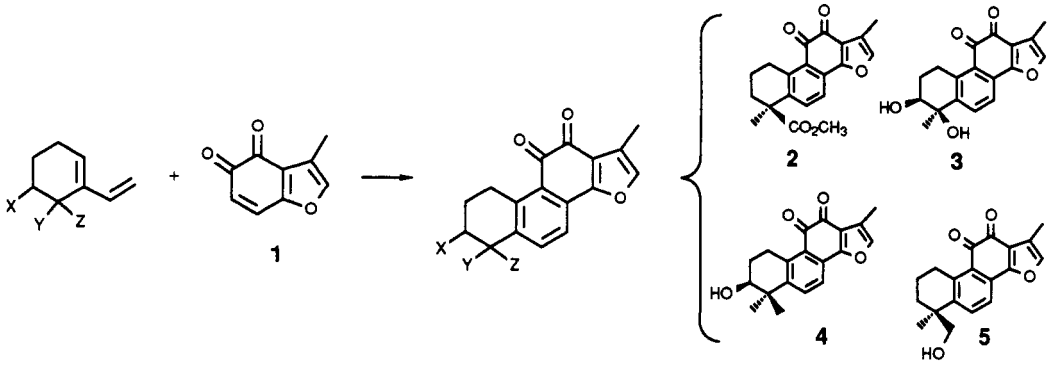
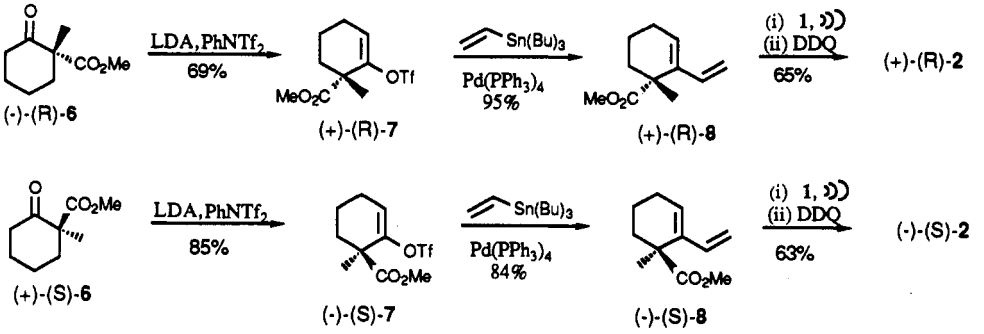
Scheme I



Scheme II

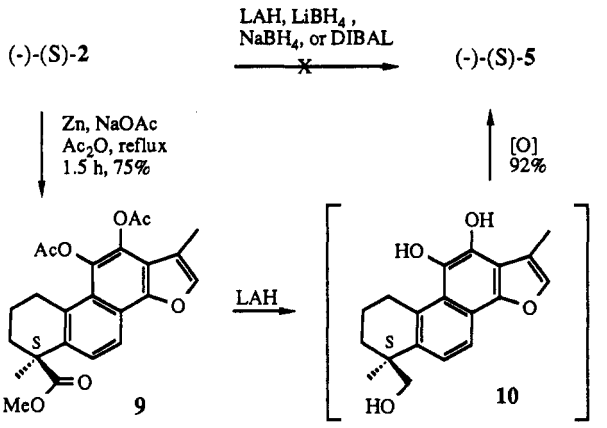


(+)-(*R*)-7 and (−)-(*S*)-7 using Stille's palladium-catalyzed vinyl coupling reaction[8] as previously described for the racemate.[2a]

The ultrasound-promoted cycloaddition of (+)-(*R*)-8 and (−)-(*S*)-8 with 1 in the presence of a small amount of anhydrous methanol (to solubilize 1 in the diene) proceeded with high regioselectivity to give the cycloadducts which were aromatized with DDQ to give (+)-(*R*)-2 (65% yield) and (−)-(*S*)-2 (63% yield), respectively. The natural regioisomers were purified by recrystallization and were identical in their IR and ^1H and ^{13}C NMR spectra with the racemate previously prepared. Comparison of the sign of optical rotation reported for the natural product[3b] [$[\alpha]_D$ = −139° (*c* 0.25, $CHCl_3$)] with those found for the synthetic products (+)-(*R*)-2 [$[\alpha]_D$ = +111° (95% ee, *c* 0.35, $CHCl_3$)] and (−)-(*S*)-2 [$[\alpha]_D$ = −100° (59% ee, *c* 0.2, $CHCl_3$)] enables assignment of the absolute stereochemistry of natural 2 as (−)-(*S*)-methyl tanshinonate.[9]

Conversion of (−)-(*S*)-2 to (−)-(*S*)-5. In the previous paper the synthesis of (±)-5 was described which also utilized the methylated β-keto ester 6 to prepare the appropriate diene.[2a] Consequently the enantioselective preparation of both enantiomers of 6 could also be employed for the asymmetric synthesis of 5 following this route. Alternatively, we sought to convert (−)-(*S*)-2 to (*S*)-5 by reduction of the ester funtionality. All attempts to carry out this approach directly failed due to interfering reduction of the *o*-quinone functionality. Protection of the

Scheme III



o-quinone carbonyl groups by reductive acetylation to form the diacetate 9, followed by LAH reduction with subsequent air oxidation of the catechol 10, gave (−)-(*S*)-5 in 69% overall yield (Scheme III) with IR and ^1H and ^{13}C NMR spectra identical with those of the racemate previously prepared.[2a] Comparison of the sign of optical rotation reported for the natural product[5] [$[\alpha]_D$ = −48.4° (*c* 0.248, acetone)] with that recorded for the synthetic product, (−)-(*S*)-5 [$[\alpha]_D$ = −35.7° (59% ee, *c* 0.084, acetone)] establishes the *S* configuration at C-4 in the natural product.[9] The optical purity of (−)-(*S*)-5 and (+)-(*R*)-5 were determined by NMR using (+)-(*S*)-*O*-nitromandelic acid as a chiral solvating agent.[10] Nonequivalence suitable for integration was observed in the carbinol resonances.

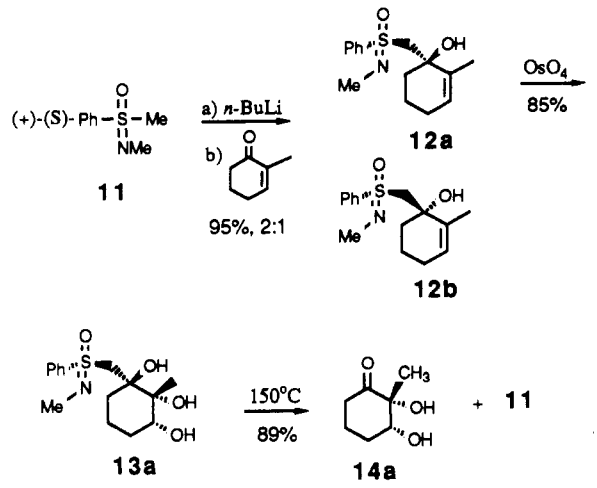
Tanshindiol B (3). The two stereocenters in 3 are vicinal and both bear hydroxyl groups. In the synthesis of racemic 3, this vicinal diol functionality was incorporated by an osmium tetraoxide hydroxylation of 2-

(8) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(9) We assume the variation in specific rotation between literature values and those reported in this work (after correction for ee) are a consequence of different concentrations used in the measurements. In support of this assumption, we measured the specific rotation of (+)-2 at various concentrations and found $[\alpha]_D$ to vary considerably with concentration. (+)-2 (95% ee): $[\alpha]_D$ +93° (*c* 0.1, $CHCl_3$), +111° (*c* 0.35, $CHCl_3$). Specific rotations are well known to vary significantly with concentration: (a) Horn, D. H. S.; Pretorius, Y. Y. *J. Chem. Soc.* **1954**, 1460. (b) Horeau, A. *Tetrahedron Lett.* **1969**, 3121. (c) Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3920. (d) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(10) Haiza, M.; Snyder, J. K., unpublished results. Full details of the preparation and applications of *O*-nitromandelic acid as a chiral solvating agent for the NMR determination of optical purity will be presented in a later manuscript.

Scheme IV



methylcyclohexenone. Johnson was shown that this hydroxylation can be performed diastereoselectively using optically pure sulfoximine **11** as a chiral auxiliary.[11] Via the procedure of Johnson, both enantiomers of 2,3-dihydroxy-2-methylcyclohexanone (**14**) were prepared in optically pure form (Scheme IV). Chelation control by the imino nitrogen provides excellent diastereofacial selectivity using catalytic osmylation to give triols **13a** and **13b**. Since the facial selectivity in the sulfoximine anion addition to cyclohexanone produced cyclohexenol adducts in a ratio of 2:1 (**12a**:**12b**, 95% combined yield), the main diol ultimately produced upon regeneration of the cyclohexanone was (+)-**14a**, and only this diol was carried through to tanshindiol B.[12]

The absolute stereochemistry of (+)-**14a** was established as 2*R*,3*R* by conversion to (−)-(1*S*,2*R*)-1-methylcyclohexane-1,2-diol acetonide (**18**) utilizing Barton's tri-*n*-butyltin hydride reduction of methyl dithiocarbonates (Scheme V).[13] Thus, acetonide **15** produced a diastereomeric mixture of alcohols upon borohydride reduction (99+%, 3:1, **16**), easily separated by flash chromatography. It proved beneficial to remove the minor cis,trans alcohol since the methyl dithiocarbonate derived from this diastereomer did not undergo smooth stannane reduction but led to very messy reaction mixtures. Formation of the methyl dithiocarbonate from the axial cis,cis alcohol proceeded readily to give **17** in 89% yield,[14] and **17** was subsequently reduced by tri-*n*-butyltin hydride to the acetonide **18**. The absolute stereochemistry of **18** was previously assigned[12b] by oxidation of the precursor (+)-diol to the known (−)-(*S*)-2-methyl-2-hydroxycyclohexanone.[15]

Conversion of (+)-(2*R*,3*R*)-**15** to the vinylcyclohexene enantiomer (−)-(5*R*,6*S*)-**20** then followed the same pathway as described in the synthesis of the racemate (Scheme VI). (−)-Tanshindiol B was prepared optically pure by the high pressure promoted cycloaddition[16] of (−)-(5*R*,6*S*)-**20** with **1** with subsequent DDQ aromatization (64%, **21**) and deprotection of **21**. The IR and ^{1}H and ^{13}C NMR spectra were identical with those of the racemate previously prepared.[2a] Comparison of the optical rotation authentic natural product[17] [$[\alpha]_D$ = −30.0° (*c* 0.01, $CHCl_3$)] with that recorded for the synthetic product, (3*R*,4*S*)-**3** [$[\alpha]_D$ = +48° (*c* 0.05, $CHCl_3$)], established the absolute stereochemistry of natural **3** as the (−)-3*S*,4*R* enantiomer.

3-Hydroxytanshinone (4). 3-Hydroxytanshinone, which has the carbinol carbon as the sole stereocenter, was not previously prepared as a racemate. Via the cycloaddition strategy, the asymmetric synthesis of **4** requires protected 6,6-dimethyl-1-vinylcyclohexen-5-ol (**27**) as the diene component for the Diels–Alder reaction with **1**. Enantioselective reduction of 2,2-dimethylcyclohexan-1,3-dione (**23**) with Baker's yeast gave (+)-(*S*)-**24** in 70% yield (100% ee.)[18] Protection of the hydroxyl group (**25**) followed by conversion to triflate (−)-(*S*)-**26** and palladium-catalyzed vinyl coupling afforded diene (−)-(*S*)-**27** (Scheme VII). The ultrasound-promoted cycloaddition of (−)-(*S*)-**27** with **1**, which required a minimum amount of anhydrous methanol to improve solubility, proved to be highly regioselective. Following DDQ aromatization, a mixture of cycloadducts **28** and **29** was obtained in 73% yield with the natural regioisomer dominating (30:1). When anhydrous dioxane was used instead of methanol, the regioselectivity decreased to 10:1. The regioisomers were separated by recrystallization. Deprotection of **28** gave (+)-(*S*)-**4** in 32% overall yield beginning with 2-methylcyclohexane-1,3-dione and *p*-benzoquinone (for the preparation of **1**). The IR and ^{1}H and ^{13}C NMR spectra were identical with those reported in the literature for **4**. Comparison of the sign of optical rotation for the authentic natural product[4,17] [$[\alpha]_D$ = +20° (*c* 0.03, $CHCl_3$)] with that recorded for the synthetic product, (*S*)-**4** [$[\alpha]_D$ = +22.2° (*c* 0.01, $CHCl_3$)], establishes the *S* configuration at C-3 in the natural product, the same natural chirality determined for the C-3 stereocenter in tanshindiol B, **3**.

Conclusions

By employing the ultrasound- or pressure-promoted Diels–Alder strategy, using *o*-quinone **1** as a dienophile with appropriately substituted vinylcyclohexene derivatives, the asymmetric synthesis of four components of the Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge, has been accomplished. 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.

Experimental Section

General. The NMR spectra were recorded on a Varian XL-400 (93.93 kG, 400 MHz for ^{1}H, 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 ^{1}H and ^{13}C, respectively. Assignments of "OH" protons were confirmed by D_2O exchange. All compounds were shown to be >98% pure by ^{1}H NMR spectroscopy. 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

(11) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459.

(12) All attempts to obtain optically pure or optically enriched 2,3-dihydroxy-2-methylcyclohexanone from the asymmetric osmium tetraoxide hydroxylation of 2-methylcyclohex-2-enone using many of the chiral osmium ligands reported to induce asymmetry in the osmylation reaction failed with this substrate under both stoichiometric and catalytic conditions (e.e. <20%). (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (b) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. (c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (d) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perk. Trans. 1* **1975**, 1574.

(14) (a) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367. (b) Iacono, S.; Rasmussen, J. R. *Org. Synth.* **1984**, *64*, 57.

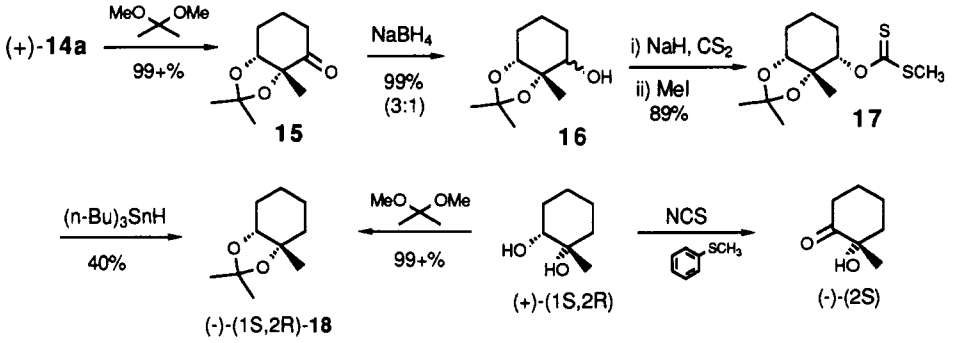
(15) Fujisawa, T.; Watanabe, M.; Sato, T. *Chem. Lett.* **1984**, 2055.

(16) In the synthesis of the racemate of **3**, ultrasound promotion of the Diels–Alder reaction proceeded in 66% yield with a 5:1 mixture of regioisomers in favor of the natural skeleton.

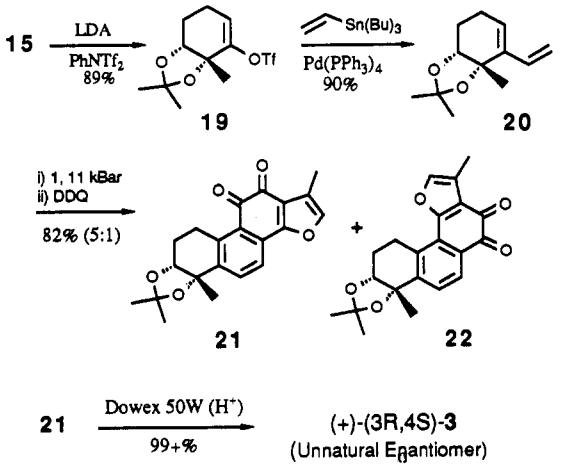
(17) An authentic sample was kindly provided by Professor Houwei Luo of the Nanjing College of Pharmacy.

(18) (a) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273. (b) Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820.

Scheme V



Scheme VI



IR spectrometer, and optical rotations were recorded on a Rudolph Autopol III with concentrations reported in grams per 100 milliliters. Melting points are uncorrected. All solvents were purified and dried prior to use according to standard procedures.[19] "Petroleum ether" refers to petroleum ether bp 35–60 °C; "ether" refers to diethyl ether. *o*-Quinone **1** was freshly prepared immediately before use as previously described.[2a] 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.

Starting Materials. (*S*)-Valine *tert*-butyl ester,[20] methyl (-)-(*R*)-2-methyl-1-oxocyclohexane-2-carboxylate, (-)-(*R*)-**6**,[7] methyl (+)-(*S*)-2-methyl-1-oxocyclohexane-2-carboxylate, (+)-(*S*)-**6**,[7] (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine, (+)-(*S*)-(**11**),[21] (+)-(2*R*,3*R*)-2,3-dihydroxy-2-methylcyclohexanone, (+)-(2*R*,3*R*)-**14a**,[11] and (*S*)-(+)-3-hydroxy-2,2-dimethylcyclohexanone, (+)-(*S*)-**24**,[18] were prepared according to known procedures.

General Procedure for Ultrasound-Promoted Cycloadditions. Freshly prepared **1** (typically 100 mg, 0.62 mmol) was placed in a conical reaction vial with the diene (3–7 equiv), and the vial was sealed, placed in an ultrasound cleaner (Cole-Parmer 8851, 50/60 kHz, 125 W), and subjected to ultrasonication. 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 yielded the mixture of cycloadducts as the tetrahydro, dihydro, and aromatized products. Without further purification this mixture was subjected to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation in refluxing benzene or toluene to yield the aromatized cycloadducts.

(+)-(*R*)-6-Carbomethoxy-1-hydroxy-6-methylcyclohexene 1-Triflate [(+)-(*R*)-7] and (-)-(*S*)-6-Carbomethoxy-1-hydroxy-6-methylcyclohexene 1-Triflate [(-)-(*S*)-7]. Beginning with (-)-(*R*)-**6** and (+)-(*S*)-**6**, respectively, (+)-(*R*)-**7** and (-)-(*S*)-**7** were prepared as previously reported for the racemates.[2a] (+)-(*R*)-**7** (69% yield, 95% ee): $[\alpha]_D$ +34.0° (*c* 1.0, $CHCl_3$). (-)-(*S*)-**7** (85% yield, 59% ee): $[\alpha]_D$ -28.7° (*c* 0.9, $CHCl_3$).

(+)-(*R*)-6-Carbomethoxy-6-methyl-1-vinylcyclohexene [(+)-(*R*)-8] and (-)-(*S*)-6-Carbomethoxy-6-methyl-1-vinylcyclohexene [(-)-(*S*)-8]. Beginning with (+)-(*R*)-**7** and (-)-(*S*)-**7**, respectively, (+)-(*R*)-**8** and (-)-(*S*)-**8** were prepared as previously reported for the racemates.[2a] (+)-(*R*)-**8** (95% yield, 95% ee): $[\alpha]_D$ +20.8° (*c* 1.05, $CHCl_3$). (-)-(*S*)-**8** (84% yield, 59% ee): $[\alpha]_D$ -16.4° (*c* 0.9, $CHCl_3$).

Cycloaddition of 1 with (+)-(*R*)-8: Methyl (+)-(*R*)-Tanshinonate [(+)-(*R*)-2]. A mixture of **1** (100 mg, 0.62 mmol), (+)-(*R*)-**8** (200 mg, 1.09 mmol), and anhydrous methanol (0.25 mL) was subjected to ultrasonication for 1 h; workup, DDQ (150 mg, 0.67 mmol) oxidation, and purification of the natural regioisomers proceeded as previously reported for the racemate.[2a] Methyl (+)-(*R*)-tanshinonate, (+)-(*R*)-**2** (136 mg, 65% yield, 95% ee): $[\alpha]_D$ +111° (*c* 0.35, $CHCl_3$).

Cycloaddition of 1 with (-)-(*S*)-8: Methyl (-)-(*S*)-Tanshinonate [(-)-(*S*)-2]. A mixture of **1** (105 mg, 0.65 mmol), (-)-(*S*)-**8** (180 mg, 1.0 mmol), and anhydrous methanol (0.25 mL) was subjected to ultrasonication for 1 h; workup, DDQ (150 mg, 0.67 mmol) oxidation, and purification of the natural regioisomers proceeded as previously reported for the racemate.[2a] Methyl (-)-(*S*)-tanshinonate, (-)-(*S*)-**2** (138 mg, 63% yield, 59% ee): $[\alpha]_D$ -100° (*c* 0.2, $CHCl_3$).

Methyl (*S*)-Dihydrotanshinonate Diacetate (9). A mixture of (-)-(*S*)-**2** (35 mg, 0.09 mmol, 82% ee), zinc dust (600 mg), sodium acetate (800 mg), and anhydrous acetic anhydride (4 mL) was refluxed for 1.5 h. After cooling to room temperature, the reaction mixture was filtered through Celite, washing the residue with ethyl acetate. The filtrate was collected, the solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/CH_2Cl_2, 1:2) to give **9** (33 mg, 75% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 8.8 Hz, 1 H), 7.48 (q, *J* = 1.0 Hz, 1 H), 7.34 (d, *J* = 8.8 Hz, 1 H), 3.63 (s, 3 H), 3.61 (m, 2 H), 2.41 (s, 3 H), 2.40 (s, 3 H), 2.22 (d, *J* = 1.0 Hz, 3 H), 1.71–1.96 (m, 4 H), 1.62 (s, 3 H). This diacetate was used in the next step without further purification.

(-)-(*S*)-Tanshinone IIB (5). The diacetate **9** (33 mg, 0.08 mmol) was dissolved in anhydrous ether containing $LiAlH_4$ (250 mg, 6.6 mmol), and the mixture was refluxed for 2 h. After cooling to room temperature, ethyl acetate (30 mL) followed by a saturated solution of potassium sodium tartrate (5 mL) was added. The red organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with water (15 mL), and saturated brine (15 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, 5:1) to give pure (-)-(*S*)-**5** (22 mg, 92% yield) as red crystals. The IR and ^1H NMR spectra were identical with those of (±)-**5** as previously reported.[2a] (-)-(*S*)-**5** (59% ee): $[\alpha]_D$ -35.7° (*c* 0.084, acetone).

(+)-(2*R*,3*R*)-2,3-Dihydroxy-2-methylcyclohexanone 2,3-Acetonide (15). Beginning with (+)-(2*R*,3*R*)-**14a**, **15** was prepared as previously reported for the racemate.[2a] **15** (98% yield): $[\alpha]_D$ +1.0° (*c* °1.05, $CHCl_3$).

(-)-(5*R*,6*R*)-1,5,6-Trihydroxy-6-methylcyclohexene 5,6-Acetonide 1-Triflate (19). Beginning with **15**, **19** was prepared

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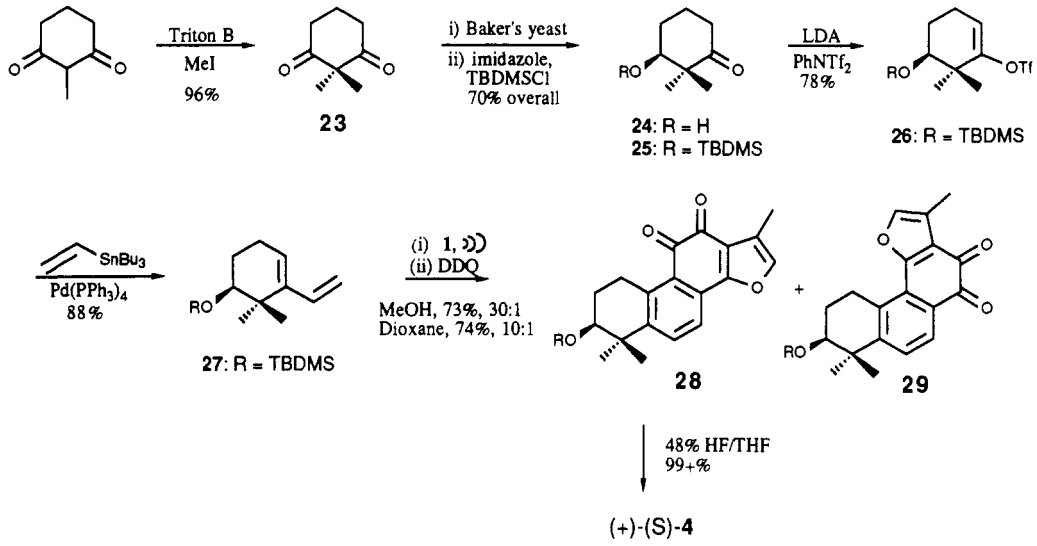
Scheme VII



as previously reported for the racemate.[1a] **19** (89% yield): $[\alpha]_D$ −41° (*c* 1.0, $CHCl_3$).

(−)-(5*R*,6*S*)-5,6-Dihydroxy-6-methyl-1-vinylcyclohexene 5,6-Acetonide (20). Beginning with **19**, **20** was prepared as previously reported for the racemate.[1a] **20** (90% yield): $[\alpha]_D$ −85.6° (*c* 3.12, $CHCl_3$).

Cycloaddition 1 with 20: (+)-(3*R*,4*S*)-Tanshindiol B [(+)-(3*R*,4*S*)-3]. A mixture of **1** (106 mg, 0.65 mmol) and **20** (150 mg, 0.78 mmol) in anhydrous toluene (5 mL) was placed into a 10-mL compressible syringe and subjected to 160000 psi (11 kBar) at room temperature for 1 h. The solvent was removed in vacuo, and workup proceeded as described for the racemate[1a] to yield unreacted **20** and the cycloadduct mixture, which was subsequently oxidized with DDQ, deprotected, and purified. Yield of aromatized cycloadducts: 167 mg, 73%, 7:1 **21**:**22** by ^1H NMR. Deprotection of **21** (10 mg, 0.03 mmol) using Dowex 50-W resin proceeded as previously described to yield (+)-(3*R*,4*S*)-tanshindiol B, (+)-(3*R*,4*S*)-**3** (8 mg, 91% yield): $[\alpha]_D$ +48° (*c* 0.05, $CHCl_3$).

Borohydride Reduction of 15: *cis*,*cis*- and *cis*,*trans*-2-Methylcyclohexane-1,2,3-triol (16). To a solution of **15** (120 mg, 0.66 mmol) in anhydrous methanol (10 mL) was added solid sodium borohydride (50 mg, 1.32 mmol), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was filtered, the solvent was removed in vacuo, and the residue (121 mg, 99%+ yield, diastereomeric mixture, 3:1) was purified by flash chromatography on silica gel (CH_2Cl_2/ethyl acetate, 9:1) to afford the major diastereomer, *cis*,*cis*-**16**, as a colorless oil (91 mg, 75%): $[\alpha]_D$ −24.1° (*c* 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.09 (dd, *J* = 3.4, 3.2 Hz, 1 H), 3.45 (m, 1 H), 2.36 (d, *J* = 5.6 Hz, OH), 2.01 (br d, J_{AB} = 14.8 Hz, 1 H), 1.87–1.78 (m, 2 H), 1.6–1.4 (m, 3 H), 1.52 (s, 3 H), 1.43 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 107.8, 79.8, 79.3, 71.6, 27.2, 26.7, 26.0, 24.2, 23.8, 14.4. *trans*,*cis*-**16**: white solid (30 mg, 25%); mp 68–70 °C; $[\alpha]_D$ −38.7° (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.98 (br s, 1 H), 3.82 (dd, *J* = 12, 4.2 Hz, 1 H), 2.22 (br s, OH), 2.05 (br dd, *J* = 12, 2.0 Hz, 1 H), 1.78 (m, 2 H), 1.59 (m, 3 H), 1.47 (s, 3 H), 1.34 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 107.6, 83.1, 80.3, 74.8, 30.5, 28.6, 27.1, 25.0, 19.8, 15.8.

***cis*,*cis*-2-Methylcyclohexane-1,2,3-triol 2,3-Acetonide 1-(Methyl dithiocarbonate) (17).**[14] To a solution of sodium hydride (39 mg, 60% dispersion in mineral oil, 0.98 mmol) in anhydrous THF (2 mL) were added a solution of *cis*,*cis*-**16** (91 mg, 0.49 mmol) in anhydrous THF (1.5 mL) and 10 mg of imidazole. The reaction mixture was refluxed for 2 h, carbon disulfide (0.5 mL, 8.3 mmol) was added, and refluxing was continued for an additional 30 min. Methyl iodide (0.5 mL, 5.4 mmol) was added, refluxing was continued for 30 additional min, and the reaction mixture allowed to cool to room temperature. Water (25 mL) was added, the solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) to afford **17** (121 mg, 89%) as a colorless oil: $[\alpha]_D$ −18.2° (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.64 (dd, *J* = 6.8, 3.3 Hz, 1 H), 4.01 (m, 1 H), 2.57 (s, 3 H), 2.1–2.0 (m, 2 H), 1.81 (m, 1 H), 1.7 (m, 1 H), 1.6 (m, 1 H), 1.54 (s, 3 H), 1.5 (m, 1 H), 1.40 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.2, 108.3, 83.0, 79.1, 78.6, 26.6, 26.3, 24.6, 24.4, 24.3, 19.1, 14.9; HRMS (EI, 70 eV) *m*/*z* 276.0852 (M^+, calcd for $C_{12}H_{20}O_3S_2$ 276.0854).

(−)-(1*S*,2*R*)-1-Methylcyclohexane-1,2-diol 1,2-Acetonide (18).[13] A solution of **17** (52 mg, 0.19 mmol) and tri-*n*-butyltin hydride (118 mg, 0.40 mmol) in anhydrous toluene (5 mL) was refluxed under argon for 3 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 95:5) to afford **18** (13 mg, 40%, **18** is quite volatile) as a colorless oil: $[\alpha]_D$ −13.2° (*c* 1.82, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.74 (br s, 1 H), 2.01 (br dd, *J* = 12.4, 1.4 Hz, 1 H), 1.7–1.4 (m, 6 H), 1.41 (s, 3 H), 1.26 (s, 3 H), 1.18 (s, 3 H), 1.07 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 106.5, 78.6, 78.2, 35.7, 28.3, 27.0, 26.2, 23.0, 22.8, 19.9; HRMS (EI, 70 eV) *m*/*z* 170.1310 (M^+, calcd for $C_{10}H_{18}O_2$ 170.1307).

(+)-(*S*)-3-(*tert*-Butyldimethylsiloxy)-2,2-dimethylcyclohexanone (25). To a solution of **24**[18] (620 mg, 4.4 mmol) and imidazole (750 mg, 11 mmol) in anhydrous DMF (6 mL) was added a solution of *tert*-butyldimethylsilyl chloride (720 mg, 4.8 mmol) in anhydrous DMF (8 mL). The resulting solution was stirred at room temperature for 18 h. Sodium bicarbonate solution (5%, 25 mL) and ether (30 mL) were added, and the aqueous layer was separated and extracted with additional ether (3 × 30 mL). The combined ether extracts were washed with water (30 mL) and saturated brine (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) to afford **25** as a colorless oil (1.05 g, 93%): $[\alpha]_D$ +22.3° (*c* 1.27, $CHCl_3$); IR (NaCl) 2954, 2858, 1712, 1473, 1256, 1121, 1082, 1062, 1002, 869, 834, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.64 (dd, *J* = 7.0, 2.3 Hz, 1 H), 2.35 (dd, *J* = 6.9, 6.7 Hz, 2 H), 1.97 (m, 2 H), 1.71 (m, 1 H), 1.61 (m, 1 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.0, 78.3, 51.6, 37.3, 29.3, 25.8 (3 C), 25.7, 23.2, 20.5, 18.0, −4.3, −5.0.

(+)-(*S*)-5-(*tert*-Butyldimethylsiloxy)-1-hydroxy-6,6-dimethylcyclohexene 1-Triflate (26). The general procedure of McMurry[22] was followed: Freshly generated LDA solution (2.6 mmol in THF, 1.4 mL) was cooled to −78 °C, and the cyclohexanone **25** (550 mg, 2.15 mmol) in THF (40 mL) was added dropwise via syringe. The reaction was stirred at −78 °C for 1.5 h, and solid *N*-phenyltriflimide[23] (1.15 g, 3.24 mmol) was added. The solution was stirred at −78 °C for 1.5 h and then at room temperature overnight (14 h). After the solvent was removed in

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vacuo, the enol triflate was purified by flash chromatography on silica gel (petroleum ether) to give **26** (650 mg, 78% yield) as a colorless oil: $[\alpha]_D$ -2.47° (*c* 1.33, $CHCl_3$); IR (NaCl) 2965, 2860, 1682, 1473, 1415, 1252, 1212, 1145, 1024, 993, 876, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.67 (dd, *J* = 4.0, 4.0 Hz, 1 H), 3.66 (dd, *J* = 8.8, 3.2 Hz, 1 H), 2.26 (m, 1 H), 2.18 (m, 1 H), 1.74 (m, 2 H), 1.17 (s, 3 H), 1.12 (s, 3 H), 0.93 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 118.4 (q, $J_{^{13}C,^{19}F}$ = 319.6 Hz), 115.3, 75.5, 41.0, 26.4, 25.8 (3 C), 24.5, 20.9, 20.5, 18.1, -4.2, -5.0.

(-)-(*S*)-5-(*tert*-Butyldimethylsiloxy)-6,6-dimethyl-1-vinylcyclohexene (27). The general procedure of Stille was followed.[8] To a slurry of LiCl (320 mg, 6.5 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) in anhydrous THF (25 mL) were added triflate **26** (500 mg, 1.3 mmol) in THF (5 mL) and tri-*n*-butylvinylstannane (410 mg, 1.3 mmol). The solution was refluxed for 18 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 (petroleum ether) to give **27** (304 mg, 88% yield) as a colorless oil: $[\alpha]_D$ -15.0° (*c* 1.03, $CHCl_3$); IR (NaCl) 2957, 2931, 2886, 2858, 1616, 1472, 1361, 1256, 1122, 1092, 1044, 907, 889, 864, 836, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.34 (dd, *J* = 17.1, 10.8 Hz, 1 H), 5.73 (dd, *J* = 3.7, 3.7 Hz, 1 H), 5.30 (dd, *J* = 17.1, 2.1 Hz, 1 H), 4.96 (dd, *J* = 10.8, 2.1 Hz, 1 H), 3.56 (dd, *J* = 6.7, 6.7 Hz, 1 H), 2.18 (m, 2 H), 1.70 (m, 2 H), 1.08 (s, 3 H), 1.04 (s, 3 H), 0.96 (s, 9 H), 0.10 (s, 3 H) 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 136.8, 121.4, 113.2, 76.3, 39.1, 27.2, 25.9, 25.8 (3 C), 24.1, 21.7, 18.1, -4.0, -4.9; HRMS (EI, 70 eV) *m/z* 266.2030 (M^+, calcd for $C_{16}H_{30}OSi$ 266.2065).

Cycloaddition 1 with 27: (+)-(3*S*)-3-Hydroxytanshinone IIA *tert*-Butyldimethylsilyl Ether (28). A mixture of **1** (100 mg, 0.62 mmol), **27** (304 mg, 1.14 mmol), and anhydrous methanol (0.25 mL) was subjected to ultrasonication at 35 °C for 1 h. Excess diene **27** was recovered (162 mg, 88% recovery), and the crude cycloadducts were isolated and oxidized with DDQ (180 mg, 0.80 mmol) in refluxing benzene (35 mL, 12 h). After removal of the solvent in vacuo, flash chromatography on silica gel (CH_2Cl_2) gave a mixture of adducts **28** and **29** (191 mg, 73% yield, 30:1 **28**:**29** by ^1H NMR). Purification by recrystallization from petroleum ether and benzene yielded pure **28** as colorless crystals (165 mg, 65% yield): mp 185-186 °C; $[\alpha]_D$ +23.4° (*c* 0.05, $CHCl_3$); IR 3159, 2957, 2858, 1690, 1671, 1580, 1536, 1471, 1384, 1255, 1082, 891, 849, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 8.3 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 7.23 (br s, 1 H), 3.70 (dd, *J* = 8.8, 2.3 Hz, 1 H), 3.34 (m, 1 H), 3.23 (m, 1 H), 2.26 (br s, 3 H), 1.90 (m, 2 H), 1.29 (s, 3 H), 1.26 (s, 3 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.5, 175.6, 161.7, 149.8, 143.3, 141.3, 133.7, 127.5, 125.8, 121.1, 120.5, 119.9, 74.6, 40.5, 29.5, 26.7, 26.6, 25.8 (3 C), 25.7, 18.1, 8.8, -4.0, -4.9; HRMS (EI, 70 eV) *m/z* 424.2068 (M^+, calcd for $C_{25}H_{32}O_4Si$ 424.2069).

(+)-(3*S*)-3-Hydroxytanshinone IIA (4).[3] Silyl ether **28** (30 mg, 0.07 mmol) was dissolved in a solution of 48% aqueous HF/THF (20 mL, 1:1, v/v) and stirred at room temperature for 2.5 h. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and water (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, 5:1). Recrystallization from $CHCl_3$/methanol yielded pure **4** as red crystals: mp 205-206 °C; $[\alpha]_D$ +22.2° (*c* 0.01, $CHCl_3$); IR (KBr) 3503, 3129, 2951, 2905, 1666, 1580, 1536, 1462, 1398, 1384, 1065, 995, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, *J* = 8.3 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.23 (q, *J* = 1.2 Hz, 1 H), 3.78 (dd, *J* = 8.0, 2.7 Hz, 1 H), 3.42 (ddd, *J* = 19.5, 6.5, 6.5 Hz, 1 H), 3.26 (ddd, *J* = 19.5, 7.0, 7.0 Hz, 1 H), 2.26 (d, *J* = 1.2 Hz, 3 H), 2.05 (m, 1 H), 1.94 (m, 1 H), 1.35 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.4, 175.4, 161.5, 148.7, 142.8, 141.4, 133.7, 127.8, 125.9, 121.2, 120.7, 120.0, 74.0, 39.8, 29.3, 26.3, 26.1, 25.2, 8.8; HRMS (EI, 70 eV) *m/z* 310.1216 (M^+, calcd for $C_{19}H_{18}O_4$ 310.1205).

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Registry No. **1**, 113297-21-5; (+)-(*R*)-**2**, 127758-15-0; (-)-(*S*)-**2**, 18887-19-9; (+)-(3*R*,4*S*)-**3**, 96894-91-6; (-)-(3*S*,4*R*)-**3**, 97465-70-8; **4**, 127665-82-1; (+)-(*R*)-**5**, 127851-84-7; (-)-(*S*)-**5**, 17397-93-2; (-)-(*R*)-**6**, 89656-82-6; (+)-(*S*)-**6**, 89656-83-7; (+)-(*R*)-**7**, 127665-83-2; (-)-(*S*)-**7**, 127665-84-3; (+)-(*R*)-**8**, 127758-16-1; (-)-(*S*)-**8**, 127758-17-2; **9**, 127685-49-8; **10**, 127685-50-1; **11**, 33993-53-2; **12a**, 127759-63-1; **12b**, 127665-85-4; **13a**, 127758-18-3; **13b**, 127758-19-4; **14a**, 89576-08-9; **15**, 127851-85-8; *cis,cis*-**16**, 127665-86-5; *trans,cis*-**16**, 127665-87-6; **17**, 127665-88-7; **18**, 127665-89-8; **18** diol, 108392-44-5; **19**, 127758-20-7; **20**, 127758-21-8; **21**, 127758-22-9; **22**, 127758-23-0; **23**, 562-13-0; **24**, 87655-21-8; **25**, 106540-31-2; **26**, 127665-90-1; **27**, 127665-91-2; **28**, 127665-92-3; **29**, 127665-93-4; 2-methyl-1,3-cyclohexanedione, 1193-55-1.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for new compounds described in this paper (17 pages). Ordering information is given on any current masthead page.

Synthesis of Miltirone by an Ultrasound-Promoted Cycloaddition

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The ultrasound-promoted cycloaddition of 3-isopropyl-*o*-benzoquinone, generated by the in situ silver oxide oxidation of the corresponding catechol, with 6,6-dimethyl-1-vinylcyclohexene has led to the synthesis of miltirone.

Introduction

The Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza*, has proven to be a rich source of abietane *o*-quinone diterpenoids. The synthesis of several of these natural products bearing the benzofuran-3,4-dione moiety was described in the preceding papers.[1] The Chinese species of sage, *S. miltiorrhiza*,[2] *S. przewalskii*,[3] and *S. trijuga*[4] are the best known

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