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Asymmetric Synthesis of Tanshindiol A

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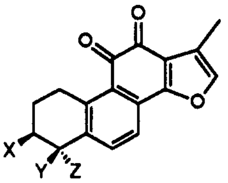
The ultrasound-promoted Diels–Alder reaction of 3-methyl-4,5-benzofurandione (**10**) with appropriately substituted vinylcyclohexenes has led to the synthesis of tanshindiol A (**9**), a minor component of the Chinese traditional medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge. The regioselectivity of the cycloaddition was enhanced by the ultrasonication and was also strongly influenced by the solvent. The asymmetric synthesis of (+)-(4*R*)-tanshindiol A [(+)-(4*R*)-**9**], the naturally occurring enantiomer, proceeded from the optically enriched methyl 6-(benzoyloxy)-1-vinylcyclohexene-6-carboxylate [(−)-(*R*)-**15**] or 6-hydroxy-6-(hydroxymethyl)-1-vinylcyclohexene acetonide [(+)-(*R*)-**29**] (both 92% ee). Enantioselectivity in the preparation of these diene systems was accomplished by the benzoyl peroxide quench of the lithioenamine derived from methyl 1-oxocyclohexane-2-carboxylate and (*S*)-valine *tert*-butyl ester. This procedure, adapted from Koga's asymmetric alkylation of α-alkyl β-keto esters, proved highly effective in preparing the necessary tertiary alcohol in protected form and with high optical purity.

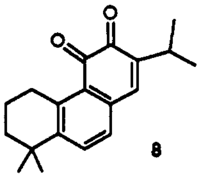
Introduction

The roots of the Chinese sage, *Salvia miltiorrhiza* Bunge (Labiateae) are used to prepare an important traditional medicine in the Chinese pharmacoepia,[1] Dan Shen. Indeed, related members of this genus are common traditional medicines throughout the world,[2] making *Salvia* species the targets of intense phytochemical scrutiny.[3] The active constituents of *S. miltiorrhiza* have long been reported to be several abietanoid diterpenes known as the tanshinones, which often bear an *o*-quinone moiety.[4] Bioassay-guided isolation schemes applied to *S. miltiorrhiza* roots, as well as those of related species, often lead to compounds of this class. Though most bioassay-guided isolations have employed some form of cytotoxicity assay,[5] reports on the isolation of compounds of this class using other bioassays such as platelet aggregation inhibition and benzodiazepine receptor blocking have also appeared.[6] It has been noted that the activity of the crude drug (Dan Shen) may exceed the activity of the purified natural products.[7] This has led to more intensive searches for minor metabolites which are active constituents.

We have been interested in the synthesis of the component abietanoid *o*-quinone diterpenes including several minor secondary metabolites and have reported the synthesis of seven (**1–7**) of these tanshinones,[8] four (**4–7**) asymmetrically,[9] utilizing a cycloaddition strategy employing 3-methylbenzofuran-4,5-dione (**10**) as a dienophile.[10] Furthermore, we have found that the cycloaddition could be promoted using ultrasonication. Similarly, 3-isopropyl-1,2-benzoquinone was successfully used as a dienophile in an ultrasound-promoted synthesis of miltirone (**8**) and related derivatives.[11] We now report the synthesis of the last of our *S. miltiorrhiza* abietanoid *o*-quinone targets, tanshindiol A (**9**),[12] utilizing a similar strategy (Scheme I). Key to this approach was the enantioselective generation of the tertiary alcohol function-



1: X = Y = H; Z = CH_3
2: X = H; Y,Z = (O)
3: X = H; Y = Z = CH_3
4: X = H; Y = CH_2OH; Z = CH_3
5: X = H; Y = CO_2CH_3; Z = CH_3
6: X = Y = OH; Z = CH_3
7: X = OH; Y = Z = CH_3



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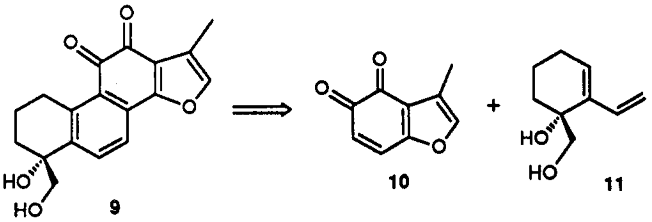
Scheme I



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(1) (a) In *Zhong Cao Yao Xue*; Nanjing Yao Xue Yuan, 'Zhong Cao Yao Xue' Bian Xie Zu, Jiangsu Ren Min Chu Ban She: Nanjing, 1976: Vol. 3, p 947. In *Pharmacology and Applications of Chinese Materia Medica*; Chang, H. M., But, P. P.-H., Eds; World Scientific: Singapore, 1986; Vol. 1, p 255–268. (c) In *Zhong Yao Da Ci*; Jiangsu Xin Yi Xue Yuan (Bian), Shanghai Ke Xue Ji Shu Chu Ban She: Shanghai, 1977; Vol. 1, p 478, no. 0977.

(2) (a) Grieve, M. In *A Modern Herbal*; Dover: New York, 1971; Vol. II, pp 700–707. (b) Morton, J. F. In *Atlas of Medicinal Plants of Middle America*; Charles, C. Thomas, Publisher: Springfield, IL., 1981; p 780–784. (c) Duke, J. A. In *Handbook of Medicinal Plants*; CRC Press, Inc.: Boca Raton, FL, 1985; pp 118, 419–422.

(3) This is particularly true of *Salvia* diterpenes, for example: (a) Hanson, J. R. *Nat. Prod. Rep.* **1988**, *5*, 211. (b) Hanson, J. R. *Nat. Prod. Rep.* **1989**, *6*, 347. (c) Rodriguez-Hahn, L.; Esquivel, B.; Adela Sanchez, A.; Sanchez, C.; Cardenas, J.; Ramamoorthy, T. P. *Rev. Latinoam. Quim.* **1989**, *20*, 110. (d) Hanson, J. R. *Nat. Prod. Rep.* **1990**, *7*, 149. (e) Hanson, J. R. *Nat. Prod. Rep.* **1991**, *8*, 1.

(4) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537 and references therein.

(5) For example: (a) Gao, Y. G.; Song, Y. M.; Yang, Y, Y.; Liu, W. F.; Tang, J. X. *Acta Pharm. Sin.* **1979**, *14*, 75. (b) Lee, A.-R.; Wu, W.-L.; Chang, W.-L.; Lin, H.-C.; King, M.-L. *J. Nat. Prod.* **1987**, *50*, 157. (c) Ginda, H.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H.; Zhao, W.; Chen, J.; Guo, Y. T. *Tetrahedron Lett.* **1988**, *29*, 4603. (d) Haro, G.; Kakisawa, H. *Chem. Lett.* **1990**, 1599.

(6) An excellent listing of natural products isolated from *S. miltiorrhiza* with any reported bioactivities is given in the introduction to ref 4.

(7) (a) Wu, W.-L.; Chang, W.-L.; Lee, A.-R.; Lin, H.-C.; King, M.-L. *J. Med. Sci.* **1985**, *6*, 159. (b) Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670.

(8) (a) Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522. (b) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995.

(9) Haiza, M.; Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5008.

(10) Lee, J.; Tang, J.; Snyder, J. K. *Tetrahedron Lett.* **1987**, *28*, 3427.

(11) Lee, J.; Mei, H. S.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 5013.

(12) Isolation and structure determination: Luo, H.-W.; Wu, B.-J.; Wu, M.-Y.; Yong, Z.-G.; Niwa, M.; Hirata, Y. *Phytochemistry* **1985**, *24*, 815.

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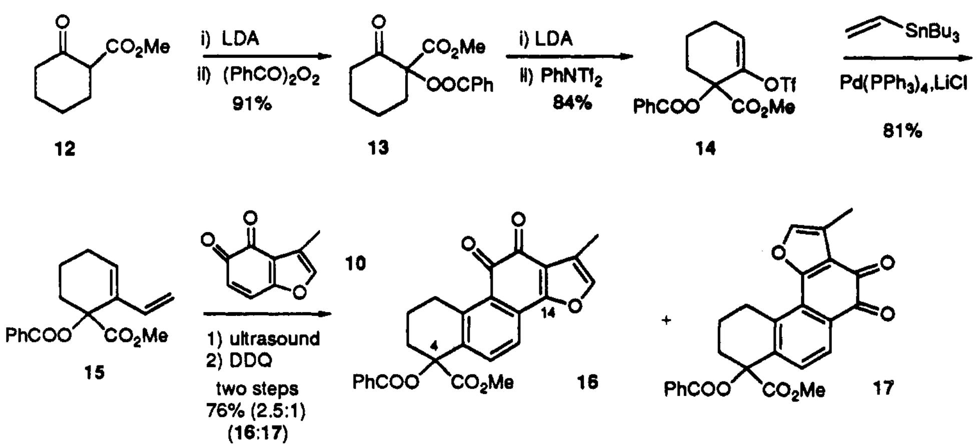
Scheme II



ality in protected form, as well as an advantageous solvent effect which enhanced the regioselectivity of the ultrasound promoted cycloaddition.

Results and Discussion

Synthesis of (±)-Tanshindiol A (9). With the established success of the ultrasound-promoted cycloaddition strategy in the syntheses of 1–8,[8,9,11] the problem to complete the synthesis of tanshindiol A was the preparation of the diol diene 11 or its equivalent. Following our previous approach, we sought to prepare this vinylcyclohexene derivative from the palladium-catalyzed vinyl coupling[13] of a suitable vinyl triflate derived from a substituted cyclohexanone. Our initial synthesis of racemic 9 proceeded through vinylcyclohexene 15, prepared as outlined in Scheme II.

The reaction of the enolate of methyl 1-oxocyclohexane-2-carboxylate (12) with benzoyl peroxide at room temperature generated the necessary tertiary alcohol functionality in protected form (13) in good yield. Conversion of 13 to vinylcyclohexene 15 via vinyl triflate 14 according to standard procedures[14] proceeded in 62% overall yield beginning with 12. The ultrasound-promoted cycloaddition of excess 15 with freshly prepared 10,[8b,10] in the absence of solvent, led to a mixture of regioisomers 16 and 17 after DDQ aromatization of the cycloadduct mixture in 76% combined yield under conditions optimized for the production of 16. Regioisomers 16 and 17 were separated with some difficulty in small amounts by centrifugal TLC, and the structure of the dominant regioisomer was assigned to the natural skeleton 16 (2.5:1, 16:17) by selective INEPT studies.[15] Thus, saturation of the high-field aromatic doublet (δ 7.68) led to an enhancement via three-bond polarization transfer of the nonprotonated aromatic carbon resonance assignable to the oxygenated furan carbon, C-14 (δ 160.6).[8b] Saturation of the low-field aromatic doublet (δ 8.15) led to an enhancement of the C-4 signal (δ 80.2). This assignment of 16 as the natural regioisomer was ultimately confirmed by conversion to 9. (The numbering used in the text is the traditional terpenoid numbering system.)

In earlier work, we had noted a dramatic solvent effect upon the regioselectivity of the thermal- and ultrasound-promoted cycloadditions using 10 as the dienophile.[8] Examination of the cycloaddition of 10 and 15 using small amounts of different solvents (Table I) revealed that the presence of methanol favored the natural regioisomer, though the regioselectivity could be reversed to favor the unnatural regioisomer using an aprotic solvent. Thus, in the presence of methanol, a 60% yield of cycloadducts (after DDQ aromatization) could be isolated with a regioselectivity of 3.5:1 in favor of 16 (item 16), while in the presence of dioxane, the cycloaddition gave an optimized 37% yield of regioisomers in favor of the 17 by a 1:2.6 ratio (16:17, item 13). Furthermore, in the absence of solvent, the slight regioselectivity in favor of the natural regioisomer at a low 10:15 ratio was lost with an increasing amount of 15, presumably as the diene serves the role of an aprotic solvent (items 1–3). A significant temperature effect upon the regioselectivity was also noted (compare item 1 with 6, items 2 and 7 with 8, and item 16 with 17). Thus, lowering the temperature improved the regioselectivity in favor of the natural regioisomer, presumably as the contribution from the thermal reaction was reduced. Indeed, without ultrasonication, little regioselectivity was observed in the absence of methanol (items 19–23), and the cycloaddition observed in items 2 and 3 were most likely thermally promoted.

In summary, ultrasonication enhanced both the yield and the regioselectivity of the cycloaddition. The natural regioisomer was favored in the absence of solvent (compare the regioselectivity in items 7 and 8 with those in items 20 and 21), as well as in the presence of methanol (compare item 16 with 23), while the unnatural regioisomer was favored in the presence of dioxane (compare item 13 with 22). Both lower temperature and the presence of methanol also improved the regioselectivity in favor of the natural regioisomer, but at the expense of the overall yield. Though the best regioselectivity was obtained at 0 °C in the presence of methanol (50% yield, 5.5:1 regioselectivity in favor of 16, item 18), the best yield of 16 was obtained under neat conditions at low temperature (76% yield, 2.5:1 regioselectivity at 8 °C, item 8). Longer periods of ultrasonication led to decomposition of both the initially formed cycloadducts as well as the excess diene (compare items 3–5). By using reaction times of 4 h or less most of the excess diene could be recovered.

Given the relative difficulty in separating 16 and 17, the mixture of regioisomers was carried through to tanshindiol A (9) and its regioisomer 20. Reductive acetylation yielded the diacetates 18 and 19 with subsequent DIBAL-H reduction giving 9 and 20 after air oxidation (Scheme III).

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[13] (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.

[14] Enol triflate formation: (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (b) Crisp, G. T.; Scott, W. J. *Synthesis* **1985**, 335. Procedure for palladium coupling of the vinyl triflate with tri-*n*-butylstannane, see ref 13a.

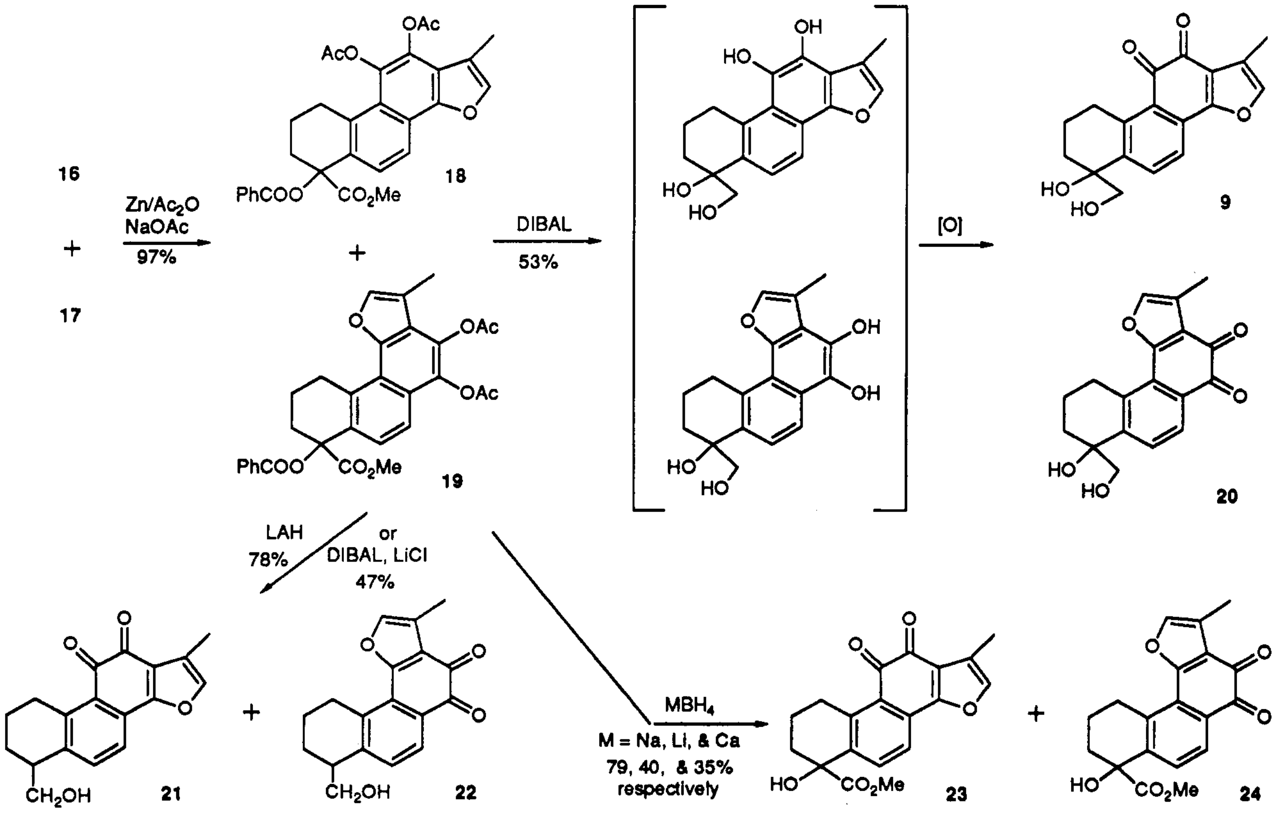
[15] (a) Bax, A. *J. Magn. Reson.* **1984**, *57*, 314. (b) Jakobsen, H. J.; Bildsoe, H.; Donstrup, S.; Sorensen, O. W. *J. Magn. Reson.* **1984**, *57*, 324. (c) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. M. *J. Org. Chem.* **1985**, *50*, 3029.

Table I. Cycloadditions of 10 and 15

item	10:15[a]	solvent	time (h)	temp (°C)	yield[b] (%)	16:17	recd 15 (%)
With Ultrasonication							
1[c]	1:1.5	neat	4	45	45	1.3:1	95
2[c]	1:3	neat	4	45	54	1:1	100
3	1:5	neat	4	45	56	1:1	90
4	1:5	neat	6	45	52	1:1	80
5	1:5	neat	24	45	0		0
6	1:1.5	neat	5	0	40	3:1	90
7	1:3	neat	4	25	43	1.5:1	90
8[c]	1:3	neat	6.5	8	76	2.5:1	98
9	1:1.5	dioxane (0.1 mL)	4	45	16	1:1	98
10	1:1.5	dioxane (0.1 mL)	8	45	25	1:1	90
11	1:1.5	dioxane (0.5 mL)	4	45	26	1:1.5	94
12	1:1.5	dioxane (1.2 mL)	4	45	22	1:2	94
13[c]	1:5	dioxane (0.5 mL)	4	45	37	1:2.6	99+
14	1:1.5	toluene (0.5 mL)	4	45	26	1:1	88
15	1:1.5	MeOH (0.4 mL)	4	45	50	3:1	90
16[c]	1:5	MeOH (0.5 mL)	4	45	60	3.5:1	90
17	1:5	MeOH (0.5 mL)	4	0	54	5.3:1	90
18	1:5	MeOH (0.5 mL)	8	0	50	5.5:1	95
Without Ultrasonication							
19	1:1.5	neat	3	45	45	1:1	90
20	1:3	neat	7	45	57	1:1	90
21	1:3	neat	24	0	20	1:1	99+
22	1:5	dioxane (0.5 mL)	4	45	10	1:1.2	90
23	1:5	MeOH (0.5 mL)	4	45	35	1.9:1	90

[a] All reactions employed 50 mg of 10. [b] Isolated yield of 16:17 mixture after DDQ oxidation. [c] Compare to results without ultrasonication, items 19–23.

Scheme III



All attempts to reduce **16** and **17** directly without protection of the *o*-quinone functionality not surprisingly[8b] met with failure. Furthermore use of LAH in the reduction of **18** and **19**, with subsequent air oxidation, led only to the mixture of isomeric alcohols **21** and **22** which also proved difficult to separate. Formation of the primary monoalcohols was indicated by the obvious loss of the benzoate group in the ^1H NMR spectrum, as well as the ^{13}C NMR spectra of the products. Thus, the loss of the signal for a quaternary oxygenated carbon in the starting diesters (δ 80.2 in **16**, 80.3 in **17**) with the appearance of a new methine carbon (δ 41.2 in **21** and 41.7 in **22**), in addition to the appearance of an oxygenated methylene carbon (δ 66.9 in **21**, 66.7 in **22**), was further confirmation for the reduced alcohols **21** and **22**.

Direct reduction of the benzylic position to yield the monoalcohols is apparently facilitated by the presence of the lithium cation. Thus, addition of lithium chloride to

Scheme IV

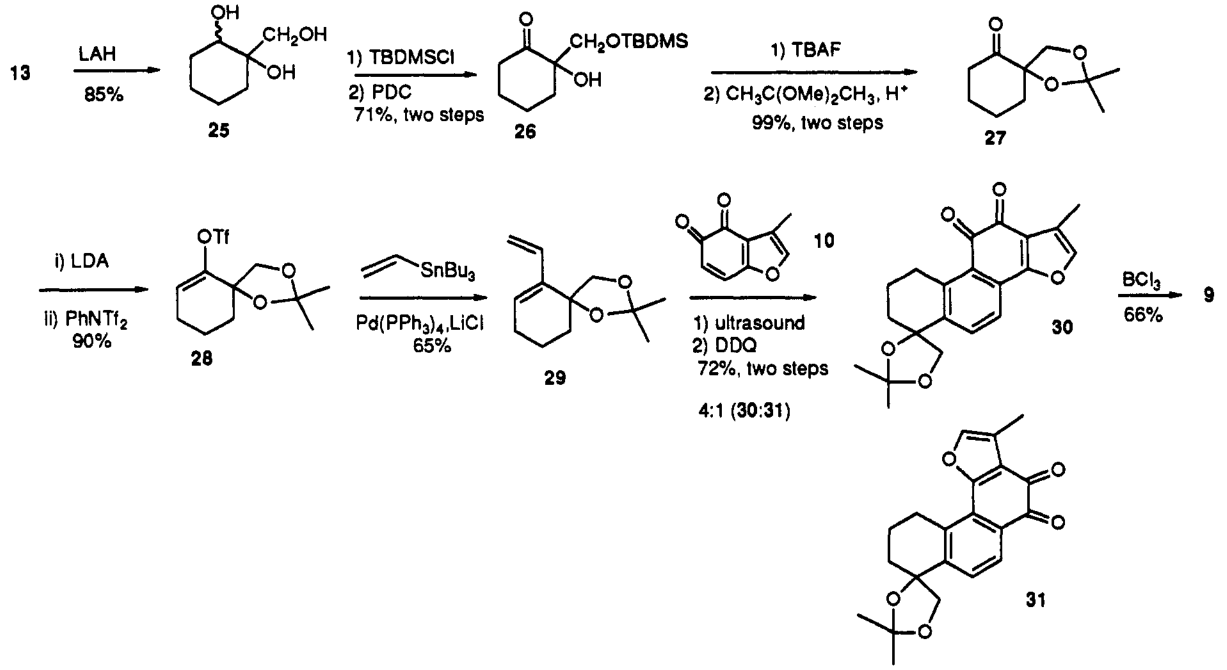


Table II. Ultrasound-Promoted Cycloaddition of 10 and 29

item	10:29[a]	solvent	time (h)	temp (°C)	yield[b] (%)	30:31
1	1:3	neat	2.5	25	66	3:1
2	1:4	neat	2.5	25	72	4:1
3	1:3	MeOH (0.2 mL)	3	25	48	10:1
4	1:2	MeOH (0.2 mL)	3	25	59	10:1
5	1:3	dioxane (0.2 mL)	3	25	54	10:1

[a] All reactions employed 50 mg of **10**. [b] Isolated yield of **30**:**31** mixture after DDQ oxidation.

the DIBAL-H reduction of **18** and **19** also gave alcohols **21** and **22** as the main products (44% combined yield) with only a lesser amount of the desired diols **9** and **20** (24% combined yield). Reductions of **18** and **19** using borohydrides under conditions reported to reduce esters ($LiBH_4$,[16] $NaBH_4$,[17] and $Ca(BH_4)_2$[18]) proved effective in selectively removing the benzoyl group, leading to the α-hydroxy esters **23** and **24**. The structures of **23** and **24** were readily apparent from both the ^1H and ^{13}C NMR spectra as these were simple debenzoylated products. Assignments of **21** and **23** as the natural regioisomers were based upon the conversion of purified **16** to **21** and also to **23**, while purified **17** produced **22** and **24** upon LAH and borohydride reduction, respectively.

Due to the moderate regioselectivity, and thus the modest overall yield of **9**, in the cycloaddition of **15** with **10** even under optimized conditions, we sought to incorporate the diol functionality in the vinylcyclohexene prior to the cycloaddition. In diene **15**, both faces of the diene system bear a relatively bulky group, the benzoyl and the methoxycarbonyl substituents which can rapidly interconvert between the pseudoaxial and pseudoequatorial positions. (Calculations using the QUANTA/CHARMm program predict only a 0.2 kcal/mol difference in the energies of these two conformations of **15**.) Molecular modeling studies clearly indicated a steric interaction between the methyl group on the dienophile **10** and the pseudoaxial substituent at the C-6 position of **15** in the endo transition state[19] leading to the natural regioisomer **16**. In the endo transition state leading to the unnatural regioisomer **17**, the methyl group on **10** is positioned above the cyclohexene ring with steric interactions with the pseudoaxial hydrogens (Figure 1). Thus, the regioselectivity in the cycloaddition of **15** with **10** is only poor to modest.

In the protected diol of vinylcyclohexene, **29**, however, the cyclic acetonide structure has the effect of retaining the C-6 substituents away from the face of the diene system. Molecular mechanics calculations again predicted only a subtle difference in the energies (0.8 kcal/mol) of the two possible conformations with the methylene group in the pseudoequatorial position, or with the C-6 oxygen occupying the pseudoequatorial position. Consequently, one face of **29** remains fairly flat with no impediment to the endo approach of the dienophile **10** (Figure 1C). We therefore anticipated that cycloadditions employing diene **29** would give an improved regioselectivity in favor of the natural skeleton.

Vinylcyclohexene **29** was prepared in a routine fashion

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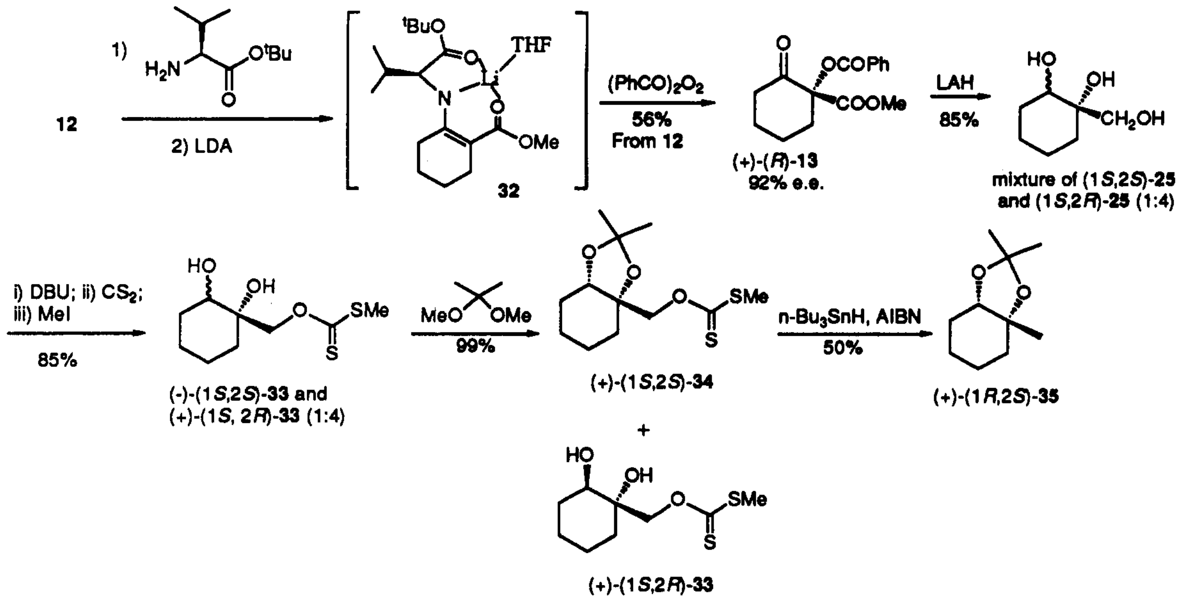
[16] Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.

[17] Brown, M. S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261.

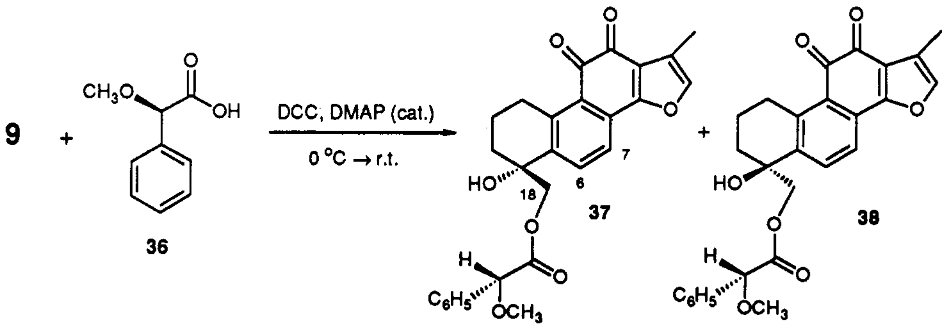
[18] Dvorken, J. V.; Smyth, R. B.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 486. Also, see ref 16.

[19] We have previously noted our reasons for believing that these cycloadditions using **10** as the dienophile proceed through the endo transition state in ref 8b. These reasons include the isolation of the nonaromatized adduct with cyclopentadiene which was established as the endo adduct, as well as the observed regioselectivity of the cycloaddition as a consequence of varying substituents on the vinylcyclohexenes. For a related experimental and theoretical study of the reaction of *o*-quinone dienophiles with vinylcyclohexene, see: Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mugnoli, A.; Abbondanti, E. *J. Org. Chem.* **1985**, *50*, 1853.

Scheme V



Scheme VI



beginning with 13 (Scheme IV). Reduction of 13 gave a mixture of syn- and anti-triols 25 in a 1:4 ratio (syn:anti) which were not separated. Subsequent protection of the primary alcohol group and PDC oxidation of the secondary alcohol gave cyclohexanone 26. Deprotection of the primary alcohol and subsequent protection of the product diol as the acetonide gave 27 which was then converted to 29 via the enol triflate 28 employing the Stille palladium-catalyzed vinyl coupling reaction.[13]

From the results in Table I, we had anticipated that the ultrasound-promoted cycloaddition between 29 and 10 in the presence of a small amount of methanol at low temperature would produce the best regioselectivity in favor of the natural skeleton. Our expectations were confirmed: a mixture of regioisomers 30 and 31 was obtained in 59% yield after DDQ aromatization in favor of the natural skeleton 30 (10:1, 54% yield of 30) under conditions which gave the best regioselectivity (Table II). The best yield of 30, however, was produced without solvent giving a 72% yield of cycloadducts after DDQ aromatization, though with a regioselectivity of only 4:1 in favor of the natural skeleton (a 58% yield of 30). The regioisomers were easily separated by recrystallization to give pure 30, which was subsequently deprotected with BCl_3 to give racemic tanshindiol A (9).[20,21] Synthetic 9 produced by both cycloaddition pathways (Schemes II–IV) was identical in all respects to authentic sample.

Asymmetric Synthesis of Tanshindiol A. According to either route, the asymmetric preparation of tanshindiol A requires the enantioselective preparation of cyclohexanone 13. Since the chirality is generated in 13 by the benzoyl peroxide quench of the enolate of 12, this step had to be accomplished with high optical yield. Koga[22] has reported the enantioselective alkylation of lithioenamine 32 derived from 12 and (*S*)-valine *tert*-butyl ester. As

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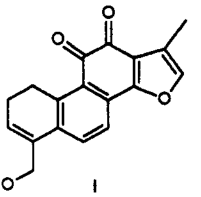
[20] (a) Bonner, T. G.; Saville, N. M. *J. Chem. Soc.* **1960**, 2851. Procedure followed: (b) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090.

[21] The use of protio acids for the deprotection, including Dowex 50-W resin (H^+) used previously to deprotect a similar acetonide in the synthesis of tanshindiol B (ref 8b) invariably led to loss of considerable material. The main byproduct was tentatively assigned as the elimination product i.



i

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J_{AB} = 8.0 Hz, 1 H), 7.62 (d, J_{AB} = 8.0 Hz, 1 H), 7.24 (q, J = 1.4 Hz, 1 H), 6.32 (t, J = 4.7 Hz, 1 H), 4.54 (d, J = 5.9 Hz, 2 H), 3.38 (t, J = 8.1 Hz, 2 H), 2.34 (dt, J = 8.1, 4.7 Hz, 2 H), 2.29 (br s, 3 H), 1.48 (t, J = 5.9 Hz, OH). Insufficient sample was in hand for a ^{13}C NMR spectrum.

[22] Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718.

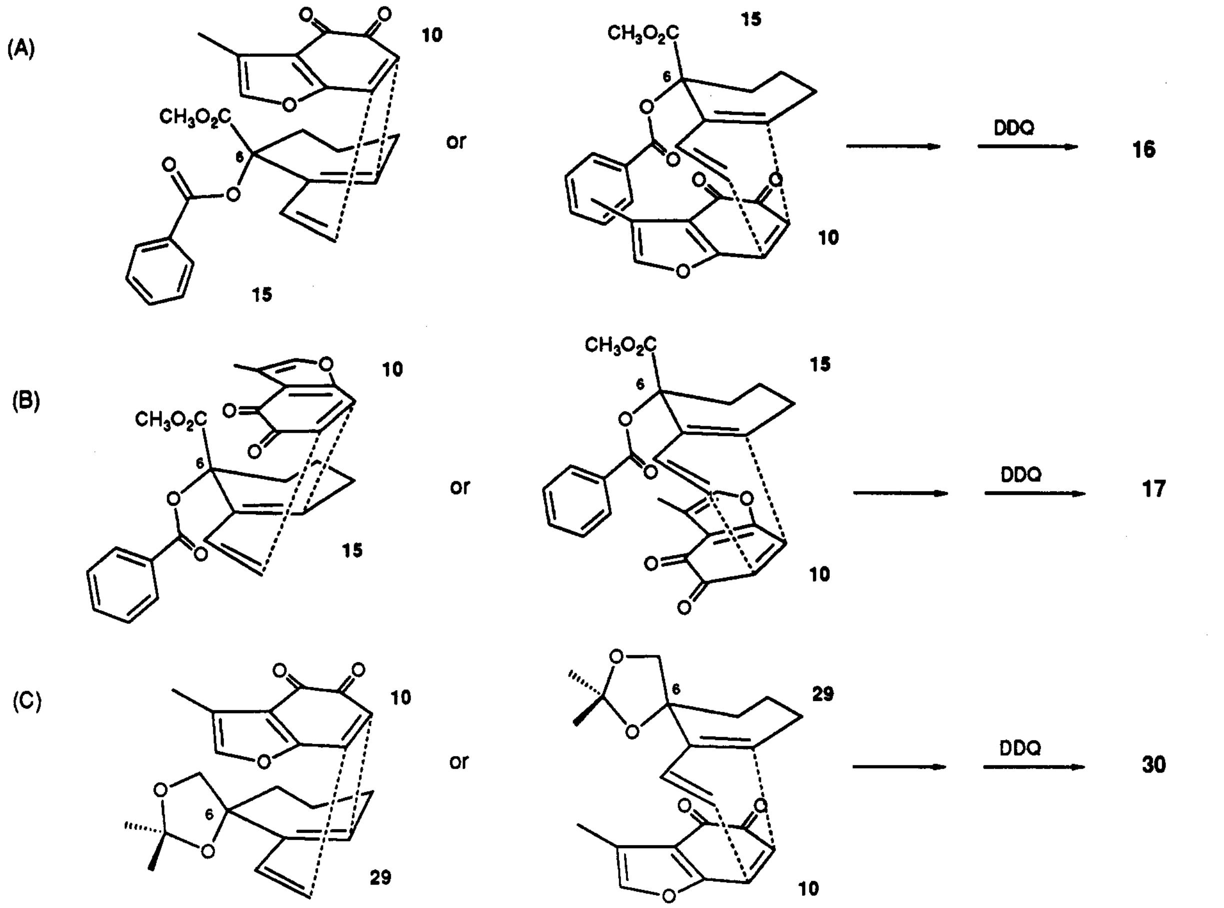


Figure 1. Endo transitions states leading to cycloadducts: (A) Cycloaddition between **10** and **15** from either top or bottom face to produce natural skeleton **16**. (B) Cycloaddition between **10** and **15** from either top or bottom face to produce unnatural skeleton **17**. (C) Cycloaddition between **10** and **29** from either top or bottom face to produce natural skeleton **30**.

recently reported,[23] adapting this procedure (Scheme V), (+)-(*R*)-**13** was prepared in 69% yield and 92% enantiomeric excess, as determined using the chiral shift reagent Eu(hfbc)$_3$.[24] Thus the chiral tertiary alcohol functionality was generated in excellent yield with excellent enantioselectivity.

The absolute stereochemistry of **13** was assigned by conversion to the known methylcyclohexanediol acetonide (+)-(1*R*,2*S*)-**35**[9] (Scheme V). Reduction of (+)-(*R*)-**13** was followed by treatment of the resultant *syn*- and *anti*-triol mixture with DBU, followed by carbon disulfide with a methyl iodide quench of the resultant dithiocarbonate anion, producing a mixture of methyl dithiocarbonates **33**. Attempted tri-*n*-butyltin hydride reduction of this mixture gave only an intractable mess. Upon treatment of the mixture **33** with 2,2-dimethoxypropane, only the minor, syn-diol formed an acetonide, yielding the dithiocarbonate (+)-(1*S*,2*S*)-**34** and enabling recovery of the unprotected diol (+)-(1*S*,2*R*)-**33**. Subsequent tri-*n*-butyltin hydride reduction of (+)-(1*S*,2*S*)-**34** gave the known (+)-(1*R*,2*S*)-**35**.

Following the strategy outlined in Schemes II–IV, (+)-(*R*)-**13** was carried through vinylcyclohexene (−)-(*R*)-**29** to (+)-(*R*)-tanshindiol A (**9**). Comparison of the optical rotation of the synthetic (+)-(*R*)-**9** with the authentic natural product enabled assignment of the absolute stereochemistry of the natural product as the (+)-4*R* isomer. Esterification of synthetic (+)-(*R*)-**9** prepared by the two routes by DCC coupling with (−)-(*R*)-2-*O*-methylmandelic acid (**36**) to produce the mandelate ester enabled measurement of the enantiomeric excess (Scheve VI).[25] Tanshindiol A produced asymmetrically following the strategy in Scheme IV showed only 30% ee. Examination of acetonide **30** using the chiral shift reagent Eu(hfbc)$_3$ indicated that this penultimate product retained the 92% enantiomeric excess achieved in the initial peroxide quench of **32** (Scheme V). Thus, racemization must have occurred during deprotection. Tanshindiol A (92% ee) produced asymmetrically following the strategy in Schemes II and III did not show any racemization.

The nonequivalence in the ^1H NMR spectrum of diastereomeric (−)-(*R*)-2-*O*-methylmandelate esters formed in the esterification of (±)-**9** are quite dramatic particularly for the H-18 protons, and deserve comment (Figure 2). The H-18 protons of the (4*R*)-diastereomer **37** are magnetically equivalent and give a singlet at δ 4.261. In contrast, the H-18 protons of the (4*S*)-diastereomer **38** are two well-separated doublets at δ 4.509 and 4.048 ($J = 11.6$ Hz), giving a diastereomeric nonequivalence ($\Delta\delta$) for the low-field doublet of 0.248 ppm and 0.213 ppm for the high-field doublet. These chemical shifts can be rationalized in terms of the extended Newman projections originally proposed by Dale and Mosher to interpret the diastereomeric nonequivalence of mandelate esters,[26] and more recently an-

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[23] Lee, J.; Oya, S.; Snyder, J. K. *Tetrahedron. Lett.* **1991**, *32*, 5899.

[24] For reviews: (a) Sullivan, G. R. *Top. Stereochem.* **1977**, *10*, 287. (b) Fraser, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 173.

[25] (a) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199. (b) Yamaguchi, S. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 127.

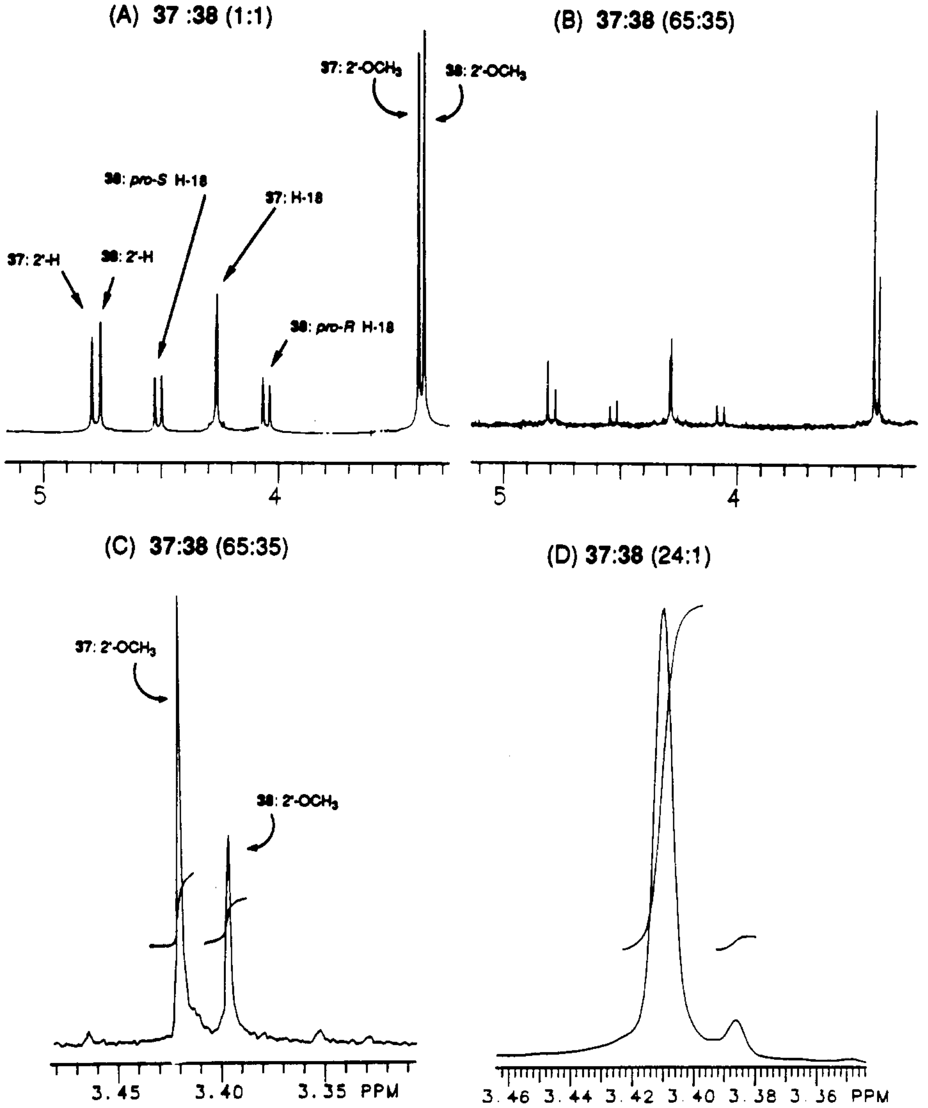

Figure 2. ^{1}H NMR spectra of (*R*)-2-*O*-methylmandelate esters of **37** and **38**: (A) Esters producd from racemic **9** (**37**:**38**, 1:1). (B) Esters produced from enriched (+)-(*R*)-**9** (30% ee, yielding **37**:**38**, 65:35). (C) Methoxyl singlets of esters produced from enriched (+)-(*R*)-**9** (30% ee, yielding **37**:**38**, 65:35). (D) Methoxyl singlets of esters produced from enriched (+)-(*R*)-**9** (92% ee, yielding **37**:**38**, 24:1).

alyzed by Trost for 2-*O*-methylmandelate esters.[27] In this latter work, sound evidence was provided which supports the proposed dominant conformation of the mandelate group with the C-2′ methoxyl group eclipsing the mandelate carbonyl.[28] In the diastereomeric 2-*O*-methylmandelate esters, hydrogen bonding to the C-4 hydroxyl group leads to a dominant conformation about the ester linkage for each. In the (4*S*)-diastereomer **38**, this places the *pro-R* H-18 in the shielding cones of both the mandelate aromatic ring and to a lesser extent, the aromatic B ring of the diterpene, resulting in the upfield doublet, while the *pro-S* proton "sees" neither shielding cone and can be assigned to the downfield doublet. In contrast, for the (4*R*)-diastereomer **37**, the *pro-R* H-18 proton is shielded by the aromatic ring of the mandelate unit while the *pro-S* proton is shielded by the diterpene aromatic B ring and are magnetically equivalent (Figure 3). (This equivalence of the methylene protons for one diastereomeric 2-*O*-methylmandelate ester was also observed in several related tetralone-derived diols, but not in other mandelate monoesters of vicinal diols without a second aromatic ring capable of counteracting the differential shielding of the mandelate phenyl ring. Details of these other model studies will be reported at a later date.)

This model is further supported by the diastereomeric nonequivalence of the aromatic H-6 ($\Delta\delta$ = 0.031 ppm) and H-7 ($\Delta\delta$ = 0.020 ppm) protons. For both of these resonances, those belonging to the (4*S*)-diastereomer **38** are upfield, which can be explained by the shielding cone of the mandelate aromatic ring extending to these protons. This model was further confirmed by an NOE from the high field H-18 doublet of the (4*S*)-diastereomer **38** to the low field aromatic doublet, confirming this assignment as the H-18 *pro-R* proton. In addition to these diastereomeric nonequivalences, the mandelate methoxyl singlets ($\Delta\delta$ = 0.024 ppm) and H-2′ protons ($\Delta\delta$ = 0.035 ppm) were also distinct for the two diastereomers.[29] While diastereomeric

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(26) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(27) (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370. A similar approach to assign the absolute stereochemistry of secondary alcohols using esters prepared from Mosher's acid has also been reported: (b) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147. Furthermore, this nonequivalence must be systematic: (c) Inouye, Y.; Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *Chem. Lett.* **1990**, 2073. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Org. Chem.* **1991**, *56*, 1296. (e) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(28) For further evidence on the conformation of 2-*O*-methylmandelate esters, see: Adamczeski, M.; Quinoa, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240.

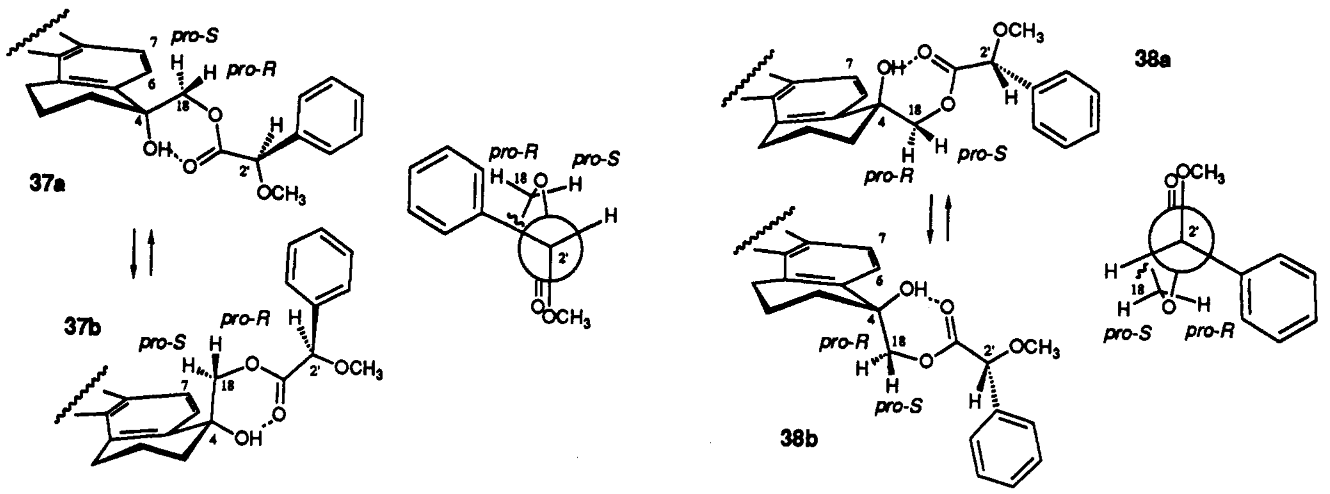

Figure 3. Analysis of the diastereomeric nonequivalence observed in the (*R*)-2-*O*-methylmandelate esters 37 and 38. In 37, shielding of the *pro-R* H-18 by the mandelate aromatic ring is balanced by shielding of the *pro-S* H-18 by the terpenoid aromatic B ring and the H-18 methylene protons are magnetically equivalent. In 38, the *pro–R* H-18 is shielded by both the mandelate and terpenoid aromatic rings and is shifted upfield.

nonequivalence most likely also exists in several of the A-ring methylene protons, overlap made the unambiguous assignment of these nonequivalences impossible. The nonequivalent methoxyl singlets were most appropriate for integration to establish optical purity in highly enriched samples due to the optimal height of the signal of the minor diastereomer relative to noise.

Conclusions

The ultrasound-promoted Diels–Alder reactions of 3-methyl-4,5-benzofurandione with vinylcyclohexene **15** or **29** has led to the synthesis of tanshindiol A (**9**). Following the strategy outlined in Schemes II and III, **9** was prepared in 11 steps with 14% overall yield, the route detailed in Scheme IV led to **9** in 14 steps in only 11% overall yield.[30] The main drawback of this latter route was the number of steps necessary in protecting group manipulation, though the regioselectivity of the ultrasound-promoted cycloaddition using diene **29** was improved in comparison with diene **15**. The nonquantitative deprotection of acetonide **30** was also disappointing. The asymmetric synthesis of tanshindiol A proceeded from the optically enriched (+)-(*R*)-**13** (92% ee). Again, the route detailed in Schemes II and III proved superior to that outlined in Scheme IV due to the racemization of **9** that occurred during deprotection of **30**. Enantioselectivity in the preparation of the diene systems for either route was achieved by the benzoyl peroxide quench of the lithioenamine derived from methyl 1-oxocyclohexane-2-carboxylate and (*S*)-valine *tert*-butyl ester. This procedure proved effective in preparing the necessary tertiary alcohol in protected form and with high optical purity. As a result of this work, the absolute stereochemistry of natural **9** was assigned as the (+)-(4*R*)-enantiomer. Current work in our labs has shown that this method is general for the formation of tertiary alcohols protected as the benzoate esters from β-keto esters.[23]

Experimental Section

General. The NMR spectra were recorded at 93.94 kG (400 MHz for ^{1}H, 100 MHz for ^{13}C) or 63.41 kG (270 MHz for ^{1}H, 67.5 MHz for ^{13}C) in $CDCl_3$ unless otherwise noted. Residual $CHCl_3$ (δ 7.24 ppm) and the center line of the $^{13}CDCl_3$ triplet (δ 77.0 ppm) were used as internal references for ^{1}H and ^{13}C, respectively. Hydroxyl proton assignments were confirmed by D_2O exchange. All compounds were shown to be >98% pure by ^{1}H NMR. All solvents were purified and dried prior to use.[31] "Pet ether" refers to petroleum ether, bp 35–60 °C. A "silica gel plug" refers to either a disposable Pasteur pipet or a 10-mm-i.d. flash column filled with approximately 5 cm of flash silica gel. All flash chromatography was run using standard flash silica gel-60 as adsorbent. Centrifugal TLC used preparative TLC grade silica gel as adsorbent. Experimental procedures for optically enriched and racemic compounds as well as spectroscopic data other than optical rotations are identical. Concentrations for the optical rotation measurements are reported in grams per 100 mL. Molecular modeling utilized the QUANTA/CHARMm program on a Silicon Graphics workstation. Sonication was performed with an ultrasound cleaner (55 kHz).

Starting Materials. *o*-Quinone **10** was prepared immediately before use as previously described.[8b] Methyl 1-oxocyclohexane-2-carboxylate (**12**),[32] (*S*)-valine *tert*-butyl ester,[33] tri-*n*-butylvinylstannane,[34] and (–)-(*R*)-2-*O*-methylmandelic acid (**36**)[35] were prepared according to known procedures.

General Procedure A. Preparation of Enol Triflates 14 and 28.[14a] Freshly prepared LDA solution in THF (0.15 M, 1 equiv) was cooled to –78 °C, and the ketone (1 equiv) in anhydrous THF (3 mL/mmol ketone) was added dropwise with stirring via syringe. The reaction was stirred for 30 min at –78 °C, and solid *N*-phenyltriflimide (1.5 equiv) was added.[14b] The reaction mixture was stirred for 2 h at –78 °C and then warmed to room temperature and stirred for 12 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/pet ether, 2:1).

General Procedure B. Palladium-Catalyzed Couplings of Enol Triflates with Tri-*n*-butylvinylstannane (15 and 29).[13a] To a slurry of LiCl (3 equiv) and $Pd(PPh_3)_4$ (0.03 equiv) in anhydrous THF (20 mL/mmol triflate) was added a solution of enol triflate (1 equiv) and tri-*n*-butylvinylstannane (1 equiv) in anhydrous THF (5 mL). The solution was refluxed overnight (12–15 h), cooled to room temperature, and diluted with pet ether (30 mL). The resultant solution was washed with 10% NH_4OH solution, water, and saturated brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the vinylcyclo-

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(29) Mislow also reported that the methoxyl and methine singlets of the mandelate unit of these esters exhibit diastereomeric nonequivalence. For example: Jacobus, J.; Raban, M.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 1142.

(30) This overall yield calculation includes three steps to prepare **10** in 96% yield beginning with *p*-benzoquinone (ref 8), and the preparation of **12** in 95% yield from cyclohexanone (ref 32 and 8).

(31) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, 1980.

(32) Ruest, L.; Blouin, G.; Deslongchamps, P. *Synth. Commun.* **1976**, *6*, 169.

(33) Roeske, R. W. *Chem. Ind.* **1959**, 1121.

(34) Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515.

(35) Reeve, W.; Christoffel, I. *J. Am. Chem. Soc.* **1950**, *72*, 1480.

hexene purified by flash chromatography (CH_2Cl_2/pet ether, 2:1).

(±)-Methyl 1-(Benzoyloxy)-2-oxocyclohexane-1-carboxylate [(±)-13]. An LDA solution prepared from *n*-butyllithium (2.0 mL of a 2.05 M solution in hexanes) and diisopropylamine (0.58 mL, 4.1 mmol) in anhydrous toluene (10 mL) was cooled to −78 °C, and a solution of 12 (0.624 g, 4.0 mmol) in anhydrous toluene (5 mL) was slowly added with stirring. The yellow color of the enolate was observed. The mixture was stirred at −78 °C for 1 h, and a solution of benzoyl peroxide (2.0 g, 8.3 mmol) in anhydrous toluene (5 mL) was added dropwise. The temperature was allowed to rise to 0 °C, and stirring was continued for 2 h. The cold bath was removed, and the reaction mixture stirred at room temperature for 19 h. The reaction was quenched by the dropwise addition of 2 N HCl (20 mL) at 0 °C, and the reaction mixture was extracted with diethyl ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution, water, and saturated brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography (CH_2Cl_2) to give pure (±)-13 (1.01 g, 91% yield) as a colorless oil which slowly crystallized after standing: mp 64–65 °C; IR (KBr) 2953, 2869, 1734, 1654, 1602, 1585, 1492, 1451, 1278, 1111, 1026, 1006, 958, 911, 879, 843, 803, 781, 710, 631 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, J = 7.8 Hz, 2 H), 7.57 (t, J = 7.3 Hz, 1 H), 7.44 (dd, J = 7.8, 7.3 Hz, 2 H), 3.79 (s, 3 H), 2.93 (m, 1 H), 2.69 (m, 1 H), 2.54 (m, 1 H), 2.34 (m, 1 H), 1.99 (m, 1 H), 1.91–1.76 (overlapped m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3, 168.5, 165.0, 133.5, 129.9 (2 C), 128.9, 128.4 (2 C), 85.7, 52.8, 40.2, 36.3, 27.3, 21.0; HRMS (EI, 40 eV) m/z 276.1000 (M^+, calcd for $C_{15}H_{16}O_5$ 276.0998). (Unreacted benzoyl peroxide was also recovered in the chromatography.)

(+)-(*R*)-Methyl 1-(Benzoyloxy)-2-oxocyclohexane-1-carboxylate [(+)-(*R*)-13]. A mixture of 12 (1.5 g, 10.2 mmol) and (*S*)-valine *tert*-butyl ester (1.73 g, 10.0 mmol) in anhydrous benzene (100 mL) was heated to reflux using a condenser equipped with a Dean–Stark water separator for 12 h. The solvent was removed in vacuo, and the residual oil was subjected to vacuum distillation to provide the enamine (3.0 g, 90% yield) which was used in the next step without further purification: $[\alpha]^{25}{}_D$ +47.2° (c 1.0, $CHCl_3$); bp 150 °C (0.5 mmHg); ^1H NMR ($CDCl_3$, 270 MHz) δ 9.18 (br d, J = 9.2 Hz, NH), 3.76 (dd, J = 9.2, 5.4 Hz, 1 H), 3.65 (s, 3 H), 2.2–2.0 (overlapped m, 5 H), 1.66–1.48 (overlapped m, 4 H), 1.43 (s, 9 H), 0.98 (d, J = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 171.3, 170.6, 158.0, 91.1, 80.9, 60.9, 50.0, 31.3, 27.6 (3 C), 26.1, 23.5, 22.9, 21.9, 18.9, 17.6. The appearance of the two sp^2-hybridized carbons at δ 158.0 and 91.1 confirmed the enamine structure rather than the tautomeric imine.

To a solution of LDA (11.0 mmol) in anhydrous THF (10 mL) cooled to −78 °C was slowly added with stirring a solution of the enamine (3.28 g, 10.5 mmol) in anhydrous THF (10 mL), producing the red color of the lithioenamine 32. The mixture was stirred at −78 °C for 1 h, and then a solution of benzoyl peroxide (5.57 g, 23 mmol) in THF (10 mL) was added. The solution was stirred for 72 h at −78 °C, the temperature was allowed to rise to 0 °C, and the reaction was quenched by slowly adding 2 N HCl (50 mL). Stirring was continued at 0 °C for 1 h, and the reaction mixture was thoroughly extracted with diethyl ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution, water, and saturated brine solution and then dried over Na_2SO_4 and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography (CH_2Cl_2) to give (+)-(*R*)-13 (2.0 g, 69% yield): $[\alpha]_D$ + 54.7° (c = 0.075, THF, 92% ee). (See procedure for (±)-13 for other spectral data.) The enantiomeric excess (92% ee) was determined by the use of $Eu(hfbc)_3$ chiral shift reagent. Nonequivalence was observed in the methoxyl singlet of the methyl ester (δ 3.79 before adding shift reagent, $\Delta\delta$ = 0.029 ppm with 0.5 eq of $Eu(hfbc)_3$). (*S*)-Valine *tert*-butyl ester was also recovered from the chromatography (1.65 g, 90% recovery).

(±)-6-(Benzoyloxy)-6-(methoxycarbonyl)cyclohex-1-enyl Trifluoromethanesulfonate [(±)-14]. Conversion of (±)-13 (0.745 g, 2.7 mmol) to (±)-14 (colorless oil, 0.92 g, 84% yield) followed the method of McMurry[14] as described in general procedure A: IR (NaCl) 2956, 2362, 1751, 1727, 1601, 1452, 1420, 1284, 1248, 1211, 1174, 1144, 1064, 913, 851, 811, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 7.5 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 2 H), 6.28 (t, J = 4.2 Hz, 1 H), 3.81 (s, 3 H), 2.80 (m, 1 H), 2.55 (m, 1 H), 2.39 (overlapped m, 2 H), 1.96 (m, 1 H), 1.77 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 164.9, 142.6, 133.4, 129.8 (2 C), 129.0, 128.3 (2 C), 127.4, 118.5 (q, $J_{^{13}C,^{19}F}$ = 317 Hz), 78.7, 52.9, 31.2, 24.1, 17.6; HRMS (EI, 40 eV) m/z 408.0505 (M^+, calcd for $C_{16}F_3H_{15}O_7S$ 408.0491). **(−)-(*R*)-6-(Benzyloxy)-6-(methoxycarbonyl)cyclohex-1-enyl trifluoromethanesulfonate [(−)-(*R*)-14)].** Prepared in identical procedure: $[\alpha]^{25}{}_D$ −50.0° (c 0.1, $CHCl_3$).

(±)-Methyl 6-(Benzoyloxy)-1-vinylcyclohex-1-ene-6-carboxylate [(±)-15]. Vinyl triflate (±)-14 (0.750 g, 1.84 mmol) was converted to (±)-15 (colorless oil, 0.425 g, 81% yield) via the procedure of Stille[13a] as described in general procedure B: IR (NaCl) 2952, 1746, 1718, 1451, 1435, 1315, 1282, 1165, 1108, 1070, 1027, 992, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 7.4 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.4 Hz, 2 H) 6.50 (dd, J = 17.5, 11.1 Hz, 1 H), 6.36 (t, J = 4.1 Hz, 1 H), 5.42 (d, J = 17.5 Hz, 1 H), 5.04 (d, J = 11.1 Hz, 1 H), 3.78 (s, 3 H), 2.73 (ddd, J = 13.8, 7.8, 3.2 Hz, 1 H), 2.4–2.2 (overlapped m, 3 H), 2.03 (m, 1 H), 1.80 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 165.1, 134.8, 133.5, 133.0, 132.4, 130.3, 129.7 (2 C), 128.3 (2 C), 113.9, 80.5, 52.4, 31.1, 25.1, 18.8; HRMS (EI, 70 eV) m/z 286.1224 (M^+, calcd for $C_{17}H_{18}O_4$ 286.1205). **(−)-(*R*)-Methyl 6-(Benzoyloxy)-1-vinylcyclohexene-6-carboxylate [(−)-(*R*)-(15)].** Prepared in identical procedure: $[\alpha]^{25}{}_D$ −90.7° (c 0.85, $CHCl_3$).

Cycloaddition of 10 and (±)-15. 6-(Benzoyloxy)-6-(methoxycarbonyl)-1-methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione (16) and 8-(Benzoyloxy)-8-(methoxycarbonyl)-3-methyl-8,9,10,11-tetrahydrophenanthro[4,3-*b*]furan-4,5-dione (17). Freshly prepared 10 (0.112 g, 0.69 mmol) and (±)-15 (0.593 g, 2.07 mmol) were sealed in a screw-cap vial and purged with nitrogen. The mixture was then subjected to ultrasonication for 6.5 h, maintaining the temperature of the sonication bath at 8 °C by the constant addition of ice. (For other reaction conditions, see Table I.) The mixture was then diluted with CH_2Cl_2 (5 mL) and passed through a silica gel plug, eluting initially with pet ether (50 mL) to recover unreacted 15 (0.435 g, 98% recovery) and then with CH_2Cl_2/ethyl acetate (10:1) to recover all cycloadducts. The solvent was removed in vacuo, and the dark red residue (0.240 g) was dissolved in anhydrous benzene, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 100 mg, 0.44 mmol) was added. The reaction mixture was refluxed for 12 h, the solvent was removed in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2) to give a mixture of 16 and 17 (2.5:1, **16**:**17**, 0.234 g, 76% yield) which was used in the next step without further purification. A small portion of this mixture was separated by repeated chromatography on centrifugal TLC (pet ether/CH_2Cl_2, 4:1) to give pure 16 and 17. Natural regioisomer 16 is a red solid: mp 129–131 °C; IR (KBr) 2957, 2926, 1734, 1718, 1696, 1684, 1473, 1275, 1096, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, J = 8.3 Hz, 1 H), 7.99 (d, J = 8.0 = Hz, 2 H), 7.67 (d, J = 8.3 Hz, 1 H), 7.56 (t, J = 7.1 Hz, 1 H), 7.42 (dd, J = 8.0, 7.1 Hz, 2 H), 7.28 (br s, 1 H), 3.79 (s, 3 H), 3.31 (m, AB system, 2 H), 2.87 (m, 1 H), 2.38 (m, 1 H), 2.27 (br s, 3 H), 2.15 (m, 1 H), 1.97 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.0, 175.3, 170.8, 165.3, 160.6, 146.2, 142.1, 136.0, 133.4, 130.3, 129.79 (2 C), 129.72, 129.69, 128.5 (2 C), 126.3, 121.4, 120.9, 120.5, 80.2, 53.0, 30.5, 28.3, 18.8, 8.8; HRMS (CI, ammonia) m/z 445.1263 ($[M + H]^+$, calcd for $C_{26}H_{21}O_7$ 445.1287). Unnatural regioisomer 17 is a red solid: mp 105–108 °C; IR (KBr) 2926, 1743, 1718, 1696, 1675, 1653, 1451, 1274, 1167, 1096, 1070, 1026, 801, 713 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98 (overlapped 2 d, J = 8.3, 1 H; J = 7.7, 2 H), 7.90 (d, J = 8.3 Hz, 1 H), 7.58 (t, J = 7.1 Hz, 1 H), 7.44 (dd, J = 7.7, 7.1 Hz, 2 H), 7.32 (br s, 1 H), 3.78 (s, 3 H), 3.40–3.20 (m, 2 H), 2.95 (m, 1 H), 2.40 (m, 1 H), 2.30 (br s, 3 H), 2.28 (m, 1 H), 2.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.0, 175.7, 170.4, 165.2, 161.6, 141.5, 141.1, 136.4, 133.5, 130.3, 129.8 (2 C), 129.7, 129.6, 128.5 (2 C), 127.3, 122.1, 121.5, 80.3, 53.1, 30.3, 27.4, 18.8, 8.9, (one aromatic carbon was not observed and is believed to be overlapped); HRMS (CI, ammonia) m/z 445.1274 ($[M + H]^+$, calcd for $C_{26}H_{21}O_7$ 445.1287).

Reductive Acetylation of (±)-16 and (±)-17 Mixture. (±)-6-(Benzoyloxy)-10,11-diacetoxy-6-(methoxycarbonyl)-1-methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan [(±)-18] and (±)-8-(Benzoyloxy)-4,5-diacetoxy-8-(methoxycarbonyl)-3-methyl-8,9,10,11-tetrahydrophenanthro[4,3-*b*]-

furan [(±)-19]. A mixture of the cycloadduct regioisomers 16 and 17 (16:17, 1:1, 0.180 g, 0.41 mmol) was dissolved in freshly distilled acetic anhydride (90 mL). Zinc dust (2.1 g) and sodium acetate (0.45 g, 5.5 mmol) were added, and the mixture was refluxed for 1 h. The mixture was filtered and the solvent removed in vacuo. Flash chromatography ($\mathrm{CH_2Cl_2}$/pet ether, 1:1) gave a mixture of diacetates 18 and 19 (0.206 g, 97% yield) which were used in the subsequent reactions without further separation. Acetate resonances from ^{1}H NMR spectrum of mixture ($\mathrm{CDCl_3}$, 400 MHz) δ 2.45, 2.35, 2.25, 2.20.

DIBAL-H Reduction of (±)-18 and (±)-19. (±)-Tanshindiol A: 6-Hydroxy-6-(hydroxymethyl)-1-methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione [(±)-9]. A mixture (1:1) of (±)-18 and (±)-19 (0.084 g, 0.159 mmol) in anhydrous THF (8.0 mL) under nitrogen was cooled to 0 °C, and a solution of diisobutylaluminum hydride (DIBAL-H, 1 N solution in THF, 2.5 mL) was slowly added with stirring. After the addition, the solution was warmed to 40 °C and maintained at this temperature for 9 h. The reaction mixture was then cooled to 0 °C, and the reaction was quenched with methanol (1 mL), followed by 50% aqueous methanol (1 mL), and filtered. Water (5 mL) was added to the filtrate, and the mixture was extracted three times with ether. The combined ether extracts were washed with water and saturated brine, dried over $\mathrm{Na_2SO_4}$, and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (ethyl acetate/$\mathrm{CH_2Cl_2}$, 2:1) to give a mixture of (±)-9 and (±)-20 (0.024 g, 53% yield). (±)-Tanshindiol A [(±)-9] isolated from the mixture by centrifugal TLC ($\mathrm{CH_2Cl_2}$) was identical to authentic sample. Spectral details for tanshindiol A are given below for the asymmetrically (30% ee) compound prepared from 10 and (+)-(*R*)-29.

Lithium Aluminum Hydride (LAH) Reduction of (+)-18 and (±)-19. 6-(Hydroxymethyl)-1-methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione (21) and 8-(Hydroxymethyl)-3-methyl-8,9,10,11-tetrahydrophenanthro[4,3-*b*]furan-4,5-dione (22). A slurry of LAH (0.0056 g, 0.015 mmol) in anhydrous THF was refluxed for 20 min and then cooled to 0 °C. A solution of (±)-18 and (±)-19 (0.019 g, 0.0036 mmol, 2.5:1, 18:19) in anhydrous THF (3 mL) was added with stirring, the solution was refluxed for 1 h under nitrogen and then cooled to 0 °C, and the reaction was quenched by the addition of 0.1 N KOH solution (0.5 mL). (The reaction mixture turned red upon exposure to air.) The mixture was refluxed for 15 min and filtered and the precipitate washed with ether until the red color was completely washed out. Water (10 mL) was added to the filtrate and the resultant solution extracted thoroughly with diethyl ether. The combined ether extracts were washed with water and saturated brine, dried over $\mathrm{Na_2SO_4}$, and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography ($\mathrm{CH_2Cl_2}$/ethyl acetate, 1:1) to give a mixture of 21 and 22 (21:22, 2.5:1, 0.0092 g, 78% yield), which were separated by centrifugal TLC ($\mathrm{CH_2Cl_2}$) to give pure 21 as a red solid: mp 179–182 °C; IR (KBr) 3500, 2925, 1734, 1669, 1539, 1457, 1175, 1097, 1045, 789 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz) δ 7.51 (s, 2 H), 7.20 (q, *J* = 1.3 Hz, 1 H), 3.80 (m, 2 H), 3.28 (ddd, *J* = 19.5, 5.3, 5.3 Hz, 1 H), 3.15–2.95 (overlapped m, 2 H), 2.24 (d, *J* = 1.3 Hz, 3 H), 1.95–1.75 (overlapped m, 3 H + OH), 1.55 (m, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$, 100 MHz) δ 183.4, 175.5 161.5, 146.0, 141.4, 141.3, 135.9, 128.2, 126.5, 121.2, 120.0, 116.8, 66.9, 41.2, 28.8, 23.8, 19.1, 8.8; HRMS (CI, ammonia) *m*/*z* 297.1110 ([M + H]$^+$, calcd for $\mathrm{C_{18}H_{17}O_4}$ 297.1127). Unnatural regioisomer 22 is a red solid: mp 212–213 °C; IR (KBr) 3500, 2924, 1730, 1660, 1563, 1530, 1467, 1439, 1253, 1130, 1049, 929 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz) δ 7.87 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.27 (q, *J* = 1.3 Hz, 1 H), 3.83 (br d, *J* = 6.0 Hz, 2 H), 3.25 (ddd, *J* = 18.3, 5.3, 5.3 Hz, 1 H), 3.12–3.00 (overlapped m, 2 H), 2.27 (br s, 3 H), 2.0–1.8 (overlapped m, 4 H + OH); ^{13}C NMR ($\mathrm{CDCl_3}$, 100 MHz) δ 181.0, 176.1, 162.2, 146.9, 141.2, 136.0, 130.9, 130.8, 128.2, 128.1, 127.0, 121.3, 66.7, 41.7, 27.9, 23.7, 19.1, 8.9; HRMS (CI, ammonia) *m*/*z* 297.1103 ([M + H]$^+$, calcd for $\mathrm{C_{18}H_{17}O_4}$ 297.1127).

The reduction of a mixture of (±)-18 and (±)-19 (0.014 g, 0.026 mmol) using DIBAL-H (1 N solution in THF, 0.4 mL) in anhydrous THF (10 mL) in the presence of LiCl (0.003 g, 0.07 mmol) under nitrogen was worked up as described above to give a mixture of (±)-21 and (±)-22 in 47% yield, along with a mixture of (±)-9 and (±)-20 in 24% yield.

Sodium Borohydride Reduction of (±)-18 and (±)-19. 6-Hydroxy-6-(methoxycarbonyl)-1-methyl-6,7,8,9-tetrahydrophenanthro[1,2-*b*]furan-10,11-dione [(±)-23] and 8-Hydroxy-8-(methoxycarbonyl)-3-methyl-8,9,10,11-tetrahydrophenanthro[4,3-*b*]furan-4,5-dione [(±)-24].[17] To a solution of a mixture of (±)-18 and (±)-19 (0.015 g, 0.026 mmol) in anhydrous methanol (10 mL) cooled to 0 °C was added with stirring $\mathrm{NaBH_4}$ (0.010 g, 0.026 mmol). The solution was refluxed for 20 h under nitrogen and then cooled to 0 °C and the reaction quenched by the addition of water (5 mL). The resultant solution was extracted thoroughly with diethyl ether, and the combined ether extracts were washed with water and saturated brine, dried over $\mathrm{Na_2SO_4}$, and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography ($\mathrm{CH_2Cl_2}$/ethyl acetate, 1:1) to give a mixture of 23 and 24 (23:24, 2.5:1, 0.0081 g, 79% yield), which were separated by centrifugal TLC ($\mathrm{CH_2Cl_2}$) to give 23 as an unstable red solid which could not be further purified: IR (KBr) 3480, 2925, 1734, 1669, 1539, 1457, 1157, 1175, 1097, 1045, 789 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz) δ 7.60 (d, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.18 (br s, 1 H), 3.90 (s, OH), 3.78 (s, 3 H), 3.37 (ddd, *J* = 19.0, 5.0, 5.0 Hz, 1 H), 3.10 (ddd, *J* = 19.0, 9.2, 5.2 Hz, 1 H), 2.22 (br s, 3 H), 2.10 (m, 1 H), 1.90 (overlapped m, 3 H); insufficient sample was available for ^{13}C due to instability of 23; HRMS (CI, ammonia) *m*/*z* 341.1004 ([M + H]$^+$, calcd for $\mathrm{C_{19}H_{17}O_6}$ 341.1025). Unnatural regioisomer 24 is a red solid: mp 170–172 °C; IR (KBr) 3480, 2924, 1730, 1687, 1660, 1563, 1530, 1467, 1439, 1253, 1136, 1049, 929 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz) δ 7.93 (d, *J* = 8.0 Hz, 1 H), 7.31 (br s, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 3.95 (s, OH), 3.75 (s, 3 H), 3.38 (ddd, *J* = 18.6, 5.0, 5.0 Hz, 1 H), 3.15 (m, 1 H), 2.28 (br s, 3 H), 2.15 (m, 1 H), 2.05 (overlapped m, 3 H); ^{13}C NMR ($\mathrm{CDCl_3}$, 100 MHz) δ 180.9, 176.5, 161.7, 144.6, 141.5, 141.4, 135.2, 129.4, 129.2, 129.1, 128.8, 127.4, 121.5, 74.3, 53.6, 29.7, 27.7, 18.2, 8.9; HRMS (CI, ammonia) *m*/*z* 341.1026 ([M + H]$^+$, calcd for $\mathrm{C_{19}H_{17}O_6}$ 341.1025).

The reduction of a mixture of (±)-18 and (±)-19 (0.020 g, 0.037 mmol) using $\mathrm{Ca(BH_4)_2}$ (0.050 g, 0.72 mmol) in 50% aqueous ethanol (10 mL)[18] was worked up as described above to give a mixture of 23 and 24 in 40% yield. The reduction of a mixture of (±)-18 and (±)-19 (0.020 g, 0.037 mmol) using $\mathrm{LiBH_4}$ (0.008 g, 0.36 mmol) in anhydrous THF/toluene (1:1, 10 mL)[16] was worked up as described above to give a mixture of 23 and 24 in 35% yield.

Reduction of (+)-(*R*)-13. Mixture of (1*S*,2*S*)-1-(Hydroxymethyl)cyclohexane-1,2-diol [(1*S*,2*S*)-25] and (1*S*,2*R*)-1-(Hydroxymethyl)cyclohexane-1,2-diol [(1*S*,2*R*)-25]. In a three-necked round-bottom flask (500 mL) were placed $\mathrm{LiAlH_4}$ (0.68 g, 17.8 mmol) and anhydrous THF (150 mL), and the suspension was heated to reflux for 15 min and then cooled to room temperature. A solution of (+)-(*R*)-13 (1.4 g, 5.07 mmol) in anhydrous THF (100 mL) was added via dropping funnel under nitrogen with stirring at such a rate as to a maintain gentle reflux. After the addition was complete, the mixture was refluxed for 1 h and then cooled to room temperature. Unreacted $\mathrm{LiAlH_4}$ was quenched by the careful addition of aqueous KOH solution (50 mg in 50 mL).[36] The mixture was refluxed for 15 min, the hot solution was suction filtered, and the precipitate was refluxed with aqueous THF (80 mL THF, 2 mL water) for 30 min and then suction filtered. The combined filtrates were concentrated in vacuo, and the residue was purified by flash chromatography (ethyl acetate/methanol, 10:1) to give a mixture of triols [(1*S*,2*S*)-25/(1*S*,2*R*)-25, (1:4)] as a colorless oil (0.621 g, 85% yield). The triols were not separated, but used without further purification. Identification of the syn isomer (1*S*,2*S*)-25 as the minor reduction product follows ultimately from the formation of the dithiocarbonate acetonide 34 from this triol (see below). The ^{13}C NMR ($\mathrm{CDCl_3}$, 67.5 MHz) on the triol mixture showed peaks for the major product: *anti*-(1*S*,2*R*)-25 δ 74.7, 72.2, 71.1, 32.1, 30.0, 23.5, 20.3; and the minor product *syn*-(1*S*,2*S*)-25 δ 76.1, 73.7, 65.5, 33.3, 30.9, 23.2, 22.2.

(+)-(*S*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-hydroxycyclohexanone [(+)-(*S*)-26]. To a solution of the (1*S*,2*S*)-25 (1*S*,2*R*)-25 mixture [(1:4), 0.388 g, 2.66 mmol)], triethylamine (0.296 g, 2.9 mmol) and 4-(dimethylamino)pyridine

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(36) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 584.

(DMAP, 0.011 g, 0.09 mmol) in anhydrous CH_2Cl_2 (20 mL), cooled to 0 °C, was added *tert*-butyldimethylsilyl chloride (0.421 g, 2.79 mmol). The resulting mixture was warmed to room temperature and stirred overnight (12 h). After removal of the solvent in vacuo, the residue was purified by flash chromatography (CH_2Cl_2/ethyl acetae, 9:1) to give a mixture of cis- and trans-diols (1:4) as a colorless oil (0.658, 95% yield). The diol mixture was used in the subsequent step without further purification. A small portion of the racemic cis- and trans-diols were separated for analytical purposes by careful flash chromatography (CH_2Cl_2/ethyl acetate, 9:1). The cis diol was less polar. 1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]cyclohexane-*cis*-1,2-diol: white solid, mp 53–55 °C; IR (KBr) 3338, 2936, 2858, 1472, 1449, 1384, 1257, 1094, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.65 (d, J_{AB} = 10.0 Hz, 1 H), 3.61 (ddd, J = 11.2, 4.6, 2.8 Hz, 1 H), 3.50 (d, J_{AB} = 10.0 Hz, 1 H), 3.39 (d, J = 2.8 Hz, OH), 2.69 (s, OH), 1.8–1.7 (overlapped m, 3 H), 1.58 (m, 2 H), 1.45 (m, 1 H), 1.3–1.1 (m, 2 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 73.8, 71.9, 71.7, 31.8, 29.5, 25.8 (3 C), 23.5, 20.3, 18.2, –5.55, –5.61; HRMS (CI, ammonia) m/z 261.1888 ($[M + H]^+$, calcd for $C_{13}H_{29}O_3Si$ 261.1886). 1–[[(*tert*-Butyldimethylsilyl)oxy]methyl]cyclohexane-*trans*-1,2-diol: colorless oil; IR (KBr) 3447, 2934, 2859, 1472, 1464, 1254, 1086, 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (d, J_{AB} = 10.0 Hz, 1 H), 3.65 (ddd, J = 8.6, 4.2, 3.8 Hz, 1 H), 3.57 (d, J_{AB} = 10.0 Hz, 1 H), 2.89 (s, OH), 2.75 (d, J = 4.2 Hz, OH), 1.90 (m, 1 H), 1.74 (m, 1 H), 1.61 (m, 2 H), 1.4–1.25 (overlapped m, 4 H), 0.91 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 74.7, 73.6, 65.9, 32.5, 30.4, 26.1 (3 C), 22.9, 22.5, 18.75, –5.22 (2 C). HRMS (CI, ammonia) m/z 261.1887 ($[M + H]^+$, calcd for $C_{13}H_{29}O_3Si$ 261.1886).

A solution of the cis-and trans-diols (0.521 g, 2.0 mmol) in anhydrous CH_2Cl_2 (50 mL) was added to a solution of pyridinium dichromate (PDC, 1.5 g, 4.0 mmol), also in anhydrous CH_2Cl_2 (100 mL) at room temperature. The mixture was stirred for 20 h and then passed through a pad of Florisil. The solvent was removed in vacuo and the residue purified by flash chromatography (CH_2Cl_2) to give pure (+)-(*S*)-**26** (0.387 g, 75% yield) as a white solid: mp 35–37 °C; $[\alpha]^{25}_{D}$ +66.7° (*c* 1.05, $CHCl_3$, 92% ee); IR (KBr) 3488, 2936, 2859, 1721, 1473, 1362, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (d, J = 10.3 Hz, 1 H), 3.97 (s, OH), 3.58 (d, J = 10.3 Hz, 1 H), 2.50 (m, 2 H), 2.05 (m, 2 H), 1.8–1.6 (overlapped m, 4 H), 0.82 (s, 9 H), 0.018 (s, 3 H), 0.013 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 211.7, 79.7, 68.2, 38.7, 37.4, 27.5, 25.7 (3 C), 22.8, 18.2, –5.4, –5.6. HRMS (CI, ammonia) m/z 258.1639 ($[M]^+$, calcd for $C_{13}H_{26}SiO_3$ 258.1627).

(+)-(*S*)-2-(Hydroxymethyl)-2-hydroxycyclohexanone Acetonide [(+)-(*S*)-27]. To a solution of (+)-(*S*)-**26** (0.378 g, 1.47 mmol) in anhydrous THF (50 mL) cooled to 0 °C was added tetrabutylammonium fluoride (TBAF, 1.0 M solution in THF, 1.7 mL, 1.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 min. After removal of the solvent in vacuo, the residue was purified by flash chromatography (initial elution with CH_2Cl_2 removed the silicon-containing byproducts, subsequent elution with ethyl acetate/CH_2Cl_2, 7:3) to give (+)-(*S*)-2-(hydroxymethyl)-2-hydroxycyclohexanone (0.209 g, 99% yield) as a colorless oil: $[\alpha]^{25}_{D}$ +42.5° (*c* 1.0, $CHCl_3$, 92% ee); IR (NaCl) 3420, 2941, 2867, 1715, 1456, 1338, 1169 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.15 (br s, OH), 3.96 (dd, J = 11.4, 8.6 Hz, 1 H; collapsed to d, J_{AB} = 11.4 Hz after D_2O exchange), 3.67 (dd, J = 11.4, 5.2 Hz, 1 H; collapsed to d, J_{AB} = 11.4 Hz after D_2O exchange), 2.59 (m, 2 H), 2.20 (m, 1 H), 2.11 (m, 2 H), 1.83 (m, 1 H), 1.70–1.6 (m, 2 H + OH); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 212.6, 79.9, 66.8, 38.3, 37.5, 27.7, 22.4.

A solution of (+)-(*S*)-2-(hydroxymethyl)-2-hydroxycyclohexanone (0.209 g, 1.45 mmol), (+)-(1*S*)-10-camphorsulfonic acid (0.001 g, 0.004 mmol), and 2,2-dimethoxypropane (3 mL) was stirred at room temperature for 12 h. Excess 2,2-dimethoxypropane was removed in vacuo, the residue dissolved in CH_2Cl_2 (2 mL) and passed through a plug of silica gel eluting with CH_2Cl_2, and the solvent was carefully removed in vacuo without heating to give (+)-(*S*)-**27** (0.267 g, 99+1% yield) as a colorless oil: $[\alpha]^{25}_{D}$ +4.8° (*c* 1.1, $CHCl_3$, 92% ee); IR (NaCl) 2988, 2939, 2866, 1726, 1382, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.41 (d, J = 8.6 Hz, 1 H), 3.64 (d, J = 8.6 Hz, 1 H), 2.76 (ddd, J = 13.2, 9.8, 5.5 Hz, 1 H), 2.30 (ddd, J = 13.2, 6.8, 6.0 Hz, 1 H), 1.97 (overlapped m, 3 H), 1.76 (m, 2 H), 1.73 (m, 1 H), 1.40 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 208.9, 110.4, 85.5, 69.2, 39.6, 38.4, 27.3, 26.8, 26.0, 22.2; LRMS (FAB, *p*-nitrobenzyl alcohol matrix) m/z (relative intensity) 185 ($[M + H]^+$, 100), 169 (27), 155 (10), 141 (56), 127 (54), 19 (19), 81 (49).

(+)-(*S*)-6-Hydroxy-6-(hydroxymethyl)cyclohex-1-enyl Trifluoromethanesulfonate Acetonide [(+)-(*S*)-28]. Conversion of (+)-(*S*)-**27** (0.245 g, 1.33 mmol) to (+)-(*S*)-**28** (colorless oil, 0.340 g, 90% yield) followed the method of McMurry[14] as described in general procedure A: $[\alpha]^{25}_{D}$ + 5.0° (*c* 2.0, $CHCl_3$, 92% ee); IR (NaCl) 2991, 2941, 2878, 1419, 1396, 1246, 1211 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.97 (dd, J = 4.2, 4.2 Hz, 1 H), 4.03 (d, J = 8.8 Hz, 1 H), 3.84 (d, J = 8.8 Hz, 1 H), 2.24 (m, 1 H), 2.16 (m, 1 H), 1.93 (m, 2 H), 1.81 (m, 1 H), 1.60 (m, 1 H), 1.434 (s, 3 H), 1.427 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 146.8, 123.0, 118.3 (q, $J_{^{13}C,^{19}F}$ = 317 Hz), 110.8, 78.8, 70.4, 35.8, 27.4, 25.7, 24.0, 19.5. We were unable to obtain a satisfactory MS of this compound.

(–)-(*R*)-6-Hydroxy-6-(hydroxymethyl)-1-vinylcyclohexene Acetonide [(–)-(*R*)-29]. Vinyl triflate (+)-(*S*)-**28** (0.235 g, 1.18 mmol) was converted to (–)-(*R*)-**29** (0.149 g, 65% yield) via the procedure of Stille[13a] as described in general procedure B: $[\alpha]^{25}_{D}$ –28.2° (*c* 1.1, $CHCl_3$, 92% ee); IR (NaCl) 2990, 2941, 2871, 1420, 1217, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.44 (ddd, J = 17.3, 10.9, 1.0 Hz, 1 H), 6.09 (dd, J = 4.1, 4.0 Hz, 1 H), 5.39 (dd, J = 17.3, 1.8 Hz, 1 H) 5.02 (dd, J = 10.9, 1.8 Hz, 1 H), 3.86 (dd, J_{AB} = 8.6 Hz, ^4J = 1.0 Hz, 1 H), 3.81 (d, J_{AB} = 8.6 Hz, 1 H), 2.13 (m, 1 H), 2.05 (m, 1 H), 1.88 (m, 1 H), 1.86 (m, 2 H), 1.54 (m, 1 H), 1.45 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 137.3, 134.8, 127.8, 114.0, 109.4, 80.6, 72.3, 35.3, 27.6, 26.5, 25.3, 20.3; LRMS (FAB, *p*-nitrobenzyl alcohol matrix) m/z (relative intensity) 195 ($[M + H]^+$, 19), 194 (30), 179 (35), 137 (83), 136 (100), 119 (64), 91 (40), 73 (33).

Cycloaddition of (–)-(*R*)-29 and 10. (+)-(*R*)-Tanshindiol A Acetonide [(+)-(*R*)-30]. A mixture of **10** (0.033 g, 0.2 mmol) and (–)-(*R*)-**29** was subjected to ultrasonication under the conditions shown in Table II. Unreacted (–)-(*R*)-**29** (> 95% recovery) and the mixture of cycloadducts were isolated, and the cycloadduct mixture was subjected to DDQ oxidation as described above for the cycloadducts from **10** and (±)-**15**. The mixture of (+)-(*R*)-**30** and its regioisomer (–)-(*R*)-**31** (see Table II for regioselectivity) was isolated by flash chromatography (CH_2Cl_2/ethyl acetate, 8:1). Pure (+)-(*R*)-**30** was isolated by recrystallization from ethyl acetate as red needles: mp 184–186 °C; $[\alpha]^{25}_{D}$ +3.8° (*c* 1.2, $CHCl_3$, 92% ee); IR (KBr) 3134, 2989, 2958, 2889, 1696, 1680, 1384 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, J = 8.2 Hz, 1 H), 7.64 (d, J = 8.2 Hz, 1 H), 7.26 (q, J = 1.2 Hz, 1 H), 4.14 (d, J = 9.0 Hz, 1 H), 3.90 (d, J = 9.0 Hz, 1 H), 3.35 (ddd, J = 19.6, 4.9, 4.8 Hz, 1 H), 3.18 (ddd, J = 19.6, 9.2, 5.9 Hz, 1 H), 2.27 (d, J = 1.2 Hz, 3 H), 2.10 (m, 1 H), 2.02 (m, 1 H), 1.83 (ddd, J = 11.3, 11.3, 0.9 Hz, 1 H), 1.65 (m, 1 H), 1.62 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 183.2, 175.3, 161.0, 145.1, 142.7, 141.7, 134.1, 129.2, 125.8, 121.3, 120.7, 120.4, 110.2, 81.3, 76.3, 33.9, 28.4, 27.4, 26.6, 20.3, 8.8; LRMS (FAB, *p*-nitrobenzyl alcohol) m/z (relative intensity) 353 ($[M + H]^+$, 46), 307 (19), 154 (100), 136 (73); HRMS (EI, 70 eV) m/z 352.1318 (M^+, calcd for $C_{21}H_{20}O_5$ 352.1311). The optical purity of (+)-(*R*)-**30** was determined using the chiral shift reagent $Eu(hfbc)_3$. The best nonequivalence was observed in signals for the lower field oxygenated methylene hydrogen (H-18, δ 4.14, d, J = 9.0 Hz in the absence of shift reagent: $\Delta\delta$ = 0.041 ppm), and for both acetonide methyl singlets (δ 1.62 in absence of shift reagent: $\Delta\delta$ = 0.026 ppm; δ 1.54 in absence of shift reagent: $\Delta\delta$ = 0.017) using excess shift reagent.

A small amount of impure unnatural regioisomer (–)-(*R*)-**31** was recovered from the mother liquors upon removal of the solvent in vacuo. Centrifugal TLC of the residue beginning with pet ether/CH_2Cl_2 (8:1) to load the sample and then using pet ether/CH_2Cl_2 (1:1) was stopped after the bands for **30** and **31** could be distinguished. The bands were carefully cut from the TLC plate and loaded on top of a flash column. Elution (CH_2Cl_2/ethyl acetate, 4:1) of the column containing the slower band gave (–)-(*R*)-**31** (1.5 mg) which was not further purified due to the limited amount: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.2 Hz, 1 H), 7.70 (d, J = 8.2 Hz, 1 H), 7.28 (q, J = 1.3 Hz, 1 H), 4.13 (d, J = 8.8 Hz, 1 H), 3.90 (dd, J = 8.8, 1.1 Hz, 1 H), 3.27 (br ddd, J = 18.3, 5.1, 5.0 Hz, 1 H), 3.11 (ddd, J = 18.3, 9.5, 5.5 Hz, 1 H), 2.28 (d, J = 1.3 Hz, 3 h), 2.15–2.08 (overlapped m, 2 H), 1.91 (m, 1 H), 1.76 (m, 1 H), 1.59 (s, 3 H), 1.52 (s, 3 H); HRMS (CI, ammonia) *m/z* 352.1320 (M^+, calcd for $C_{21}H_{20}O_5$ 352.1311). Insufficient sample was obtained for a ^{13}C NMR spectrum.

(+)-(*R*)-Tanshindiol A [(+)-(*R*)-9]. To a solution of (+)-(*R*)-**30** (0.018 g, 0.051 mmol) in anhydrous CH_2Cl_2 (8 mL) cooled to −20 °C was added BCl_3 (0.25 mL of a 1 M solution in anhydrous CH_2Cl_2).[20] The reaction mixture was stirred at −20 °C for 3 min, and then water was added (2 mL) with vigorous stirring. The organic phase was separated and washed with cold water (2 mL) and then saturated brine (5 mL). The organic layer was separated and dried with $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography to give (+)-(*R*)-**9** (0.015 g, 66% yield) as red crystals: mp 180–182 °C; $[\alpha]^{25}{}_D$ +11.4° (*c* 0.22, pyridine, 30% ee);[37] IR (KBr) 3531, 3494, 2936, 1659, 1576, 1539, 1384, 1157 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.90 (d, J = 8.2 Hz, 1 H), 7.73 (q, J = 1.3 Hz, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 5.06 (br s, OH), 4.79 (br s, OH), 3.45 (m, 2 H), 3.08 (m, 2 H), 2.17 (d, J = 1.3 Hz, 3 H), 2.14 (m, 1 H), 1.80 (m, 2 H), 1.62 (m, 1 H); ^{13}C NMR (DMSO-d_6, 67.5 MHz) δ 182.4, 175.0, 160.4, 145.3, 143.8, 142.4, 134.0, 127.7, 125.9, 120.1, 119.73, 119.66, 71.7, 68.4, 31.7, 28.7, 18.9, 8.5; LRMS (EI, 70 eV) *m/z* (relative intensity) 312 (M^+, 5), 294 (11), 281 (100), 265 (13); HRMS (EI, 70 eV) *m/z* 312.0994 (M^+, calcd for $C_{18}H_{16}O_5$ 312.0997).

(−)-(1*S*,2*S*)-1-[[[(Methylthio)(thiocarbonyl)]oxy]methyl]cyclohexane-*cis*-1,2-diol [(−)-(1*S*,2*S*)-33] and (+)-(1*S*,2*R*)-1-[[[(Methylthio)(thiocarbonyl)]oxy]methyl]cyclohexane-*trans*-1,2-diol [(+)-(1*S*,2*R*)-33].[38] To a mixture of triols (1*S*,2*S*)-**25** and (1*S*,2*R*)-**25** [1:4 mixture, (1*S*,2*S*):(1*S*,2*R*), 0.290 g, 1.98 mmol] in anhydrous DMF (2 mL) at room temperature was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.305, 2.0 mmol). The mixture was stirred for 10 min, after which carbon disulfide (1.0 mL) was slowly added, and stirring continued for 1.5 h. Methyl iodide (3.42 g, 1.5 mL, 12-fold excess) was added and the dark red mixture was stirred for 15 min, after which the solution was poured onto a watch glass and the solvent allowed to evaporate. The residue was dissolved in ethyl acetate (20 mL), washed with water (10 mL) and saturated brine (10 mL), and then dried over $MgSO_4$. The solution was filtered and the solvent removed in vacuo to give the mixture of dithiocarbonates (0.397 g, 85%). It was unnecessary to separate these epimers prior to the next step. The dithiocarbonates could be separated by careful flash chromatography (CH_2Cl_2/ethyl acetate, 4:1) to give the less polar syn-diol (−)-(1*S*,2*S*)-**33** and the more polar anti-diol (+)-(1*S*,2*R*)-**33**. (−)-(1*S*,2*S*)-**33**: mp 102–104 °C; $[\alpha]^{25}{}_D$ −36.3° (*c* 1.5, $CHCl_3$, 92% ee); IR (KBr) 3390, 3285, 2941, 2861, 1225, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.79 (d, J = 11.0 Hz, 1 H), 4.39 (d, J = 11.0 Hz, 1 H), 3.54 (ddd, J = 10.5, 4.9, 4.4 Hz, 1 H; collapses to dd, J = 10.5, 4.4 Hz upon D_2O exchange), 2.57 (s, 3 H), 2.41 (br s, OH), 2.31 (d, J = 4.9 Hz, OH), 1.83 (m, 1 H), 1.72 (m, 2 H), 1.65–1.55 (overlapped m, 3 H), 1.5–1.4 (overlapped m, 2 H), 1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.5, 77.1, 72.5, 70.4, 32.5, 29.5, 23.6, 20.2, 19.2; LRMS (EI, 70 eV) *m/z* (relative intensity) 236 (M^+, 8), 202 (19), 188 (30), 128 (32), 110 (100), 90 (23), 66 (24), 53 (64); HRMS (CI, ammonia) *m/z* 237.0630 ($[M + H]^+$, calcd for $C_9H_{17}O_3S_2$, 237.0620). (+)-(1*S*,2*R*)-**33**: mp 104–106 °C; $[\alpha]^{25}{}_D$ +3.8° (c = 0.8, $CHCl_3$, 92% ee); IR (KBr) 3360, 2938, 2862, 1217, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.84 (d, J_{AB} = 11.5 Hz, 1 H), 4.71 (d, J_{AB} = 11.5 Hz, 1 H), 3.73 (ddd, J = 8.0, 3.9, 3.6 Hz, 1 H, collapses to dd, J = 8.0, 3.6 Hz after D_2O exchange), 2.60 (s, 3 H), 2.34 (br s, OH), 2.20 (d, J = 3.9 Hz, OH), 1.90 (m, 2 H), 1.65 (m, 2 H), 1.52 (m, 1 H), 1.4 (overlapped m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.6, 75.7, 74.0, 73.2, 31.6, 29.6, 21.9, 21.6, 19.4; HRMS (CI, ammonia) *m/z* 237.0641 ($[M + H]^+$, calcd for $C_9H_{17}O_3S_2$ 237.0620).

(+)-(1*S*,2*S*)-1-[[(Methylthio)(thiocarbonyl)]oxy]methyl]cyclohexane-*cis*-1,2-diol Acetonide [(+)-(1*S*,2*S*)-34]. A solution containing the (−)-(1*S*,2*S*)-**33**/(+)-(1*S*,2*R*)-**33** (1:4, 0.397 g, 1.69 mmol) mixture, prepared in the previous step, and (1*S*)-(+)-10-camphorsulfonic acid (0.001 g, 0.0043 mmol) in 2,2-dimethoxypropane (3 mL) was stirred at room temperature for 12 h. Excess 2,2-dimethoxypropane was carefully removed in vacuo, and the residue was passed through a plug of flash silica gel eluting with pet ether/CH_2Cl_2 to give (+)-(1*S*,2*S*)-**34** [0.094 g, 100% from (−)-(1*S*,2*S*)-**33**] as a colorless oil: $[\alpha]^{25}{}_D$ +21.6° (*c* 0.9, $CHCl_3$, 92% ee); IR (NaCl) 2990, 2910, 2850, 1210, 1190, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.68 (d, $J_{A\beta}$ = 11.8 Hz, 1 H), 4.65 (d, J_{AB} = 11.8 Hz, 1 H), 4.14 (t, J = 3.0 Hz, 1 H), 2.59 (s, 3 H), 2.12 (br d, J = 10.3 Hz, 1 H), 1.76 (m, 1 H), 1.70–1.59 (overlapped m, 5 H), 1.51 (s, 3 H), 1.39 (s, 3 H), 1.23 (m, 1 H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 216.2, 107.8, 79.1, 74.2, 73.8, 32.1, 28.3, 26.6, 26.3, 22.3, 19.4, 19.2; HRMS (CI, ammonia) *m/z* 277.0932 ($[M + H]^+$, calcd for $C_{12}H_{21}O_3S_2$ 277.0932). Eluting the silica gel plug with CH_2Cl_2/ethyl acetate (3:1) enabled recovery of the unreacted (+)-(1*S*,2*R*)-**33**.

(+)-(1*R*,2*S*)-1-Methylcyclohexane-1,2-diol Acetonide [(+)-(1*S*,2*R*)-35].[39] To a solution of tri-*n*-butyltin hydride (0.124 g, 0.42 mmol) in toluene (5 mL) under mild reflux was slowly added (+)-(1*S*,2*S*)-**34** (0.058 g, 0.21 mmol) and azobisisobutyronitrile (AIBN, 0.032 g, 0.02 mmol). Reflux was continued for 30 min, and then the mixture was allowed to cool to room temperature and directly loaded onto a column packed with flash silica gel. Elution with CH_2Cl_2/ethyl acetate (9:1) gave (+)-(1*R*,2*S*)-**35** [0.085 g, 50% yield, $[\alpha]^{25}{}_D$ +18.7° (*c* 0.15, $CHCl_3$)] as a colorless oil identical in all respects to authentic compound.

General Procedure for Esterification of Tanshindiol A (9) with (−)-(*R*)-2-*O*-Methylmandelic Acid (36).[40] To a suspension of tanshindiol A (**9**) (0.015 g, 0.048 mmol), dicyclohexylcarbodiimide (DCC, 0.030 g, 0.14 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.001 g, 0.01 mmol) in anhydrous CH_2Cl_2 (25 mL) was added a solution of (−)-(*R*)-2-*O*-methylmandelic acid (**36**) (0.024 g, 0.05 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C. The solution was stirred at 0 °C for 10 min and then warmed to room temperature, producing a clear orange solution, and the stirring was continued for 0.5 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 2:1) to afford a quantitative yield of diastereomeric mandelate esters **37** and **38**. Identical procedures were done to esterify the racemic and optically enriched (+)-(*R*)-**9** samples obtained by the two routes (Scheme III and IV). ^1H NMR of **37**:**38** (1:1, $CDCl_3$, 400 MHz) δ 7.78 (d, J = 8.1 Hz, 1 H, H-6: **37**), 7.75 (d, J = 8.1 Hz, 1 H, H-6: **38**), 7.53 (d, J = 8.1 Hz, 1 H, H-7: **37**), 7.51 (d, J = 8.1 Hz, 1 H, H-7: **38**), 7.4–7.2 (overlapped m, 12 H), 4.79 (s, 1 H, H-2′: **37**), 4.76 (s, 1 H, H-2′: **38**), 4.51 (d, J = 11.5 Hz, 1 H, *pro–S* H-18: **38**), 4.26 (s, 2 H, H-18: **37**), 4.05 (d, J = 11.5 Hz, 1 H, *pro–R* H-18: **38**), 3.40 (s, 3 H, OCH_3: **37**), 3.38 (s, 3 H, OCH_3: **38**), 3.2–3.1 (overlapped m, 4 H), 2.28 (bs, 6 H), 1.95–1.45 (overlapped m, 8 H). Diastereomeric nonequivalences: H-6 ($\Delta\delta$ = 0.031 ppm); H-7 ($\Delta\delta$ = 0.020 ppm); H-2′ ($\Delta\delta$ = 0.035 ppm); *pro-S* H-18 ($\Delta\delta$ = 0.248 ppm); *pro-R* ($\Delta\delta$ = 0.213 ppm); 2′-OCH_3 ($\Delta\delta$ = 0.024 ppm).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for all new compounds (**9**, **13–17**, **21–31**, **33–35**, **37** + **38**, **i**, 1-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclohexane-*cis*-1,2-diol, 1-[[(*tert*-butyldimethylsilyl)oxy]methyl]cyclohexane-*trans*-1,2-diol, and (+)-(*S*)-2-(hydroxymethyl)-2-hydroxycyclohexanone) with the exceptions of **23**, **31**, **37** + **38**, and **i**, for which only ^1H NMR spectra could be obtained (48 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(37) Optical rotation for authentic tanshindiol A: $[\alpha]_D$ +18.7° (*c* 0.08, pyridine).

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

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