Aromatic Annulation Strategy for the Synthesis of Angularly-Fused Diterpenoid Quinones. Total Synthesis of (+)-Neocryptotanshinone, (−)-Cryptotanshinone, Tanshinone IIA, and (±)-Royleanone

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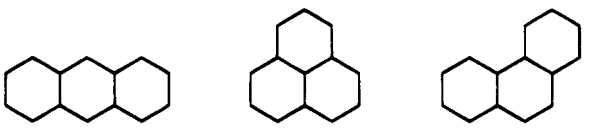
The application of a photochemical aromatic annulation strategy in highly efficient total syntheses of several diterpenoid quinones isolated from the traditional Chinese medicine Dan Shen is reported. The pivotal step in each synthesis involves the assembly of a key tricyclic intermediate via the application of a recently developed "second-generation" photochemical aromatic annulation method for the construction of highly substituted aromatic systems. In the total synthesis of neocryptotanshinone, the synthesis of the requisite diazo ketone annulation substrate **7** was achieved using palladium-mediated coupling reactions and an intramolecular Friedel–Crafts cyclization to form key carbon–carbon bonds. The pivotal aromatic annulation reaction was then accomplished by irradiating a solution of the diazo ketone **7** and the readily available siloxyalkyne **6** in benzene at room temperature. The desired tricyclic phenol **16** was produced in 58–65% yield and was then converted to (+)-neocryptotanshinone (**1**) by treatment with tetra-*n*-butylammonium fluoride in the presence of oxygen. Cyclization to generate (−)-cryptotanshinone (**2**) was accomplished in high yield by brief exposure of **1** to an ethanolic solution of concentrated sulfuric acid, and dehydrogenation of **2** with DDQ furnished tanshinone IIA (**3**). As a further demonstration of the utility of the photochemical aromatic annulation strategy in the construction of angularly-fused diterpenes, the total synthesis of (±)-royleanone (**4**) was also investigated. Irradiation of a solution of the diazo ketone **18** and siloxyalkyne **25** produced the tricyclic intermediate **26**, which was converted in two steps to royleanone by desilylation and oxidation.

Reported herein are concise and efficient total syntheses of the angularly-fused diterpenoid quinones (+)-neocryptotanshinone, (−)-cryptotanshinone, tanshinone IIA, and (±)-royleanone. This research was undertaken in connection with our program aimed at the development of efficient strategies for the synthesis of highly substituted aromatic systems. Highly substituted aromatic rings are common features incorporated in the structures of numerous biologically significant natural products and pharmaceutical compounds, and the development of improved methods for their construction constitutes an important goal for organic synthesis. Historically, the synthesis of substituted benzenoid compounds has most often been achieved by employing *linear substitution strategies* based on sequential electrophilic substitution and metalation–alkylation reactions. A more effective approach to highly substituted aromatic compounds, however, involves the application of *annulation methods*: convergent strategies in which the aromatic system is assembled from acyclic precursors in a single step, with all (or most) substituents already in place. Annulation strategies enjoy significant advantages over classical linear substitution strategies, especially when applied to the preparation of highly substituted target molecules. For example, annulation routes generally avoid the regiochemical ambiguities associated with aromatic substitution reactions, and their intrinsic convergent character facilitates the efficient assembly of highly substituted aromatics that would require long, multistep routes using classical substitution methodology.

We have previously shown that the addition of vinylketenes to acetylenes provides the basis for a very efficient annulation route to highly substituted aromatic systems.[1,2] In connection with our interest in defining the scope of this methodology as applied to *polycyclic* compounds, we have examined its application to the construction of each of the three possible tricyclic arrangements of fused six-membered rings shown below.



Recently we demonstrated the utility of this strategy by developing extremely direct synthetic routes to the linearly-fused aegyptinone diterpenes,[1g] several angularly-fused *Dan Shen* diterpenoid quinones,[1f] and the condensed tricyclic system of the phenalenone diterpene

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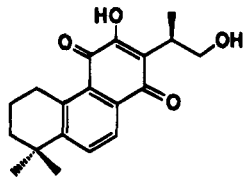
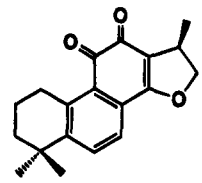
salvilenone.[1h] In this paper we now describe the application of our aromatic annulation strategy to the total synthesis of the *angularly-fused* diterpenes (+)-neocryptotanshinone, (−)-cryptotanshinone, tanshinone IIA, and (±)-royleanone.



1
(+)-Neocryptotanshinone



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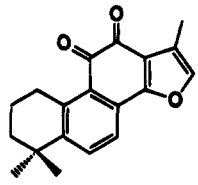
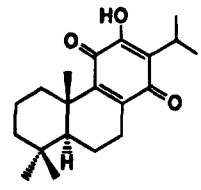
(-)-Cryptotanshinone



3
Tanshinone IIA



4
Royleanone

Dan Shen is regarded as one of the most important drugs in Chinese traditional medicine.[3] Obtained from the dried root of the Chinese red-rooted sage *Salvia miltiorrhiza*, today Dan Shen is used clinically for the treatment of heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis.[3b] Dan Shen also displays antipyretic, antineoplastic, antimicrobial, and anti-inflammatory properties and exhibits strong activity against collagen-induced platelet aggregation.[3b,4] Previously it has been shown that the broad spectrum biological activity of Dan Shen is due to a number of interesting abietane diterpenoid quinones.[3-5] Unfortunately, the identification of the most active individual components in *Salvia miltiorrhiza* has been frustrated by the extreme scarcity of some of these substances, and to date all of the medical properties of the crude drug have not been reproduced in the purified natural products.

The tanshinones were first isolated from Dan Shen by Nakao and Fukushima.[6] After some early confusion, the existence of four distinct compounds, tanshinones I, IIA, and IIB and cryptotanshinone, was established.[7] Extensive studies by Takiura,[7a,8] Kakisawa,[9] and von Wessely and his co-workers[10] ultimately resulted in structural assignments for tanshinones I[10] and IIA[7b,8] and cryptotanshinone.[7a,8] Neocryptotanshinone was first reported by Takiura in the course of his work on the structure determination of tanshinone IIA.[8a] It was not until recently, however, that neocryptotanshinone was isolated from Dan Shen.[11] To our knowledge, the absolute stereochemistries of neocryptotanshinone and cryptotanshinone have not previously been established, although optical rotations for these compounds have been reported.[11,12]

Baillie and Thomson reported the first successful total syntheses of racemic cryptotanshinone (**2**) and tanshinone IIA (**3**) in 1968 using a classical linear substitution strategy.[13,14] Kakisawa described a second synthesis of tanshinone IIA that same year, also employing a stepwise cyclization approach.[15] Kakisawa has reported syntheses of racemic cryptotanshinone and tanshinone IIA based on a Diels–Alder strategy,[16] and more recently Snyder and Lee have applied an ultrasound-promoted [4 + 2] cycloaddition in the most convergent and efficient route to tanshinone IIA reported to date.[17] The total synthesis of neocryptotanshinone has not been reported previously.

The pivotal step in our strategy for the synthesis of neocryptotanshinone involves the recently developed "second-generation" version of our aromatic annulation strategy[1d] which has expanded the scope of the method to include the synthesis of *polycyclic* compounds which were not readily accessible using the original cyclobutenone-based reaction. Prior experience gained in the synthesis of other Dan Shen diterpene quinones[1f,g] suggested that the tricyclic phenol **5** might serve as a suitable precursor to neocryptotanshinone. Our retrosynthetic plan for this key intermediate called for its assembly in one step via an annulation involving the previously synthesized siloxyalkyne **6**[1g] and the diazo ketone **7**. Scheme 1 outlines the mechanistic course of the proposed key annulation reaction. Irradiation of the α-diazo ketone **7** triggers a photochemical Wolff rearrangement producing the arylketene **8**, which combines with acetylene **6** in a regiospecific [2 + 2] cycloaddition to form **9**. Further irradiation then induces 4π electrocyclic opening of the cyclobutenone ring, thus generating the vinylketene **10** which undergoes rapid 6π electrocyclization to afford, after tautomerization, the desired tricyclic phenol.

Scheme 2 summarizes our plan for the preparation of the key diazo ketone intermediate **7**, which we anticipated would be readily available via a carbonylative Stille coupling reaction[18] involving the triflate derivative of **12**, followed by diazo transfer. Tetralol **12** appeared to be an extremely attractive intermediate, since Hart has

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(4) For additional references documenting the biological activity of Dan Shen, see the following: (a) Footnotes 3–5 in Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995. (b) References cited in 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.

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(7) (a) Takiura, K. *J. Pharm. Soc. Jpn.* **1941**, *61*, 475. (b) Takiura, K. *Chem. Pharm. Bull.* **1962**, *10*, 112.

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(9) (a) Okamura, Y.; Kakisawa, H.; Kato, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 895. (b) Okamura, Y.; Kakisawa, H.; Kato, M.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 2061.

(10) (a) von Wessely, F.; Wang, S. *Chem. Ber.* **1940**, *73*, 19. (b) von Wessely, F.; Bauer, A. *Chem. Ber.* **1942**, *75*, 617. (c) von Wessely, F.; Laterbach, T. *Chem. Ber.* **1942**, *75*, 958.

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(14) For reviews on the synthesis of the tanshinones and related diterpenoid quinones, see (a) Goldsmith, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 8, p 1. (b) Thomson, R. H. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 8, p 311.

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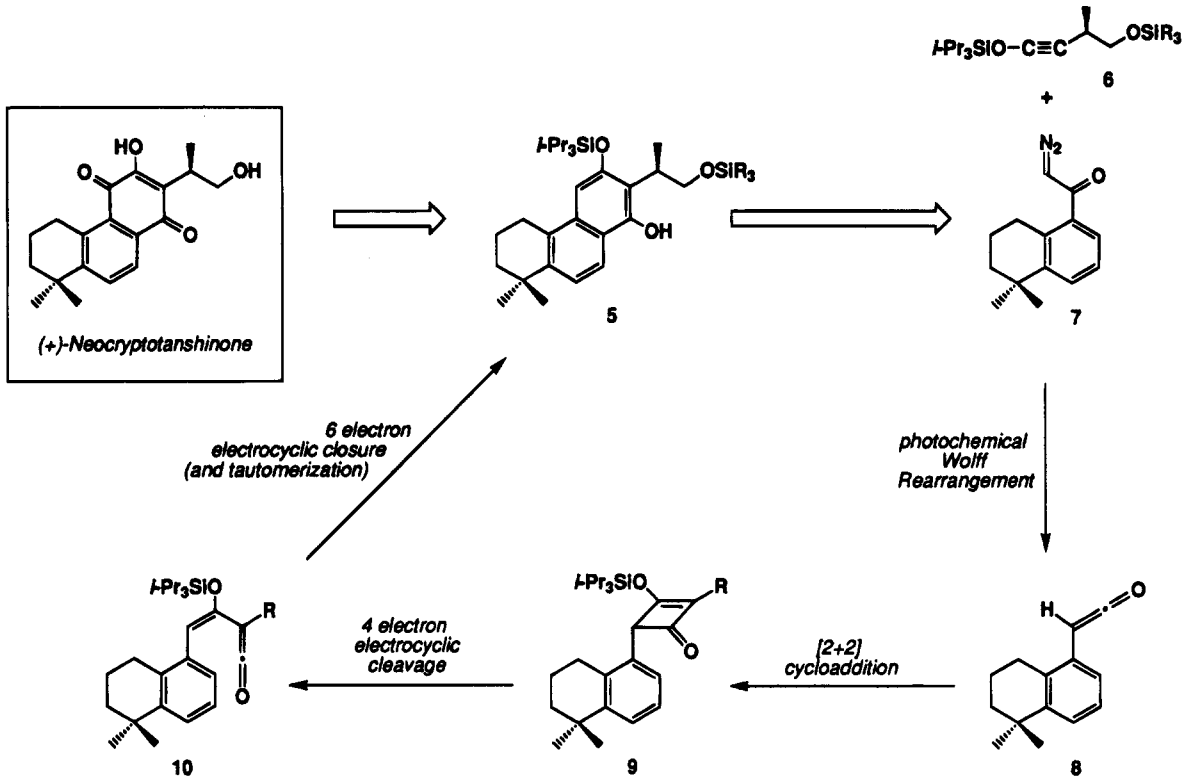
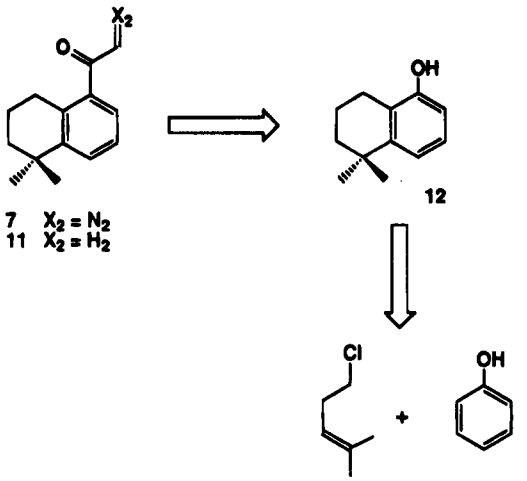
Scheme 1



Scheme 2

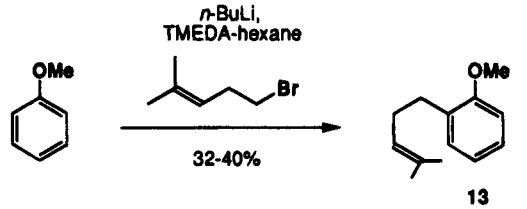


reported its preparation in one step by simply heating 1-chloro-4-methyl-3-pentene with 5 equiv of phenol at 150 °C for 24 h.[19] In principle, this route thus had the potential to provide access to (+)-neocryptotanshinone in as few as six steps.

Results and Discussion

Synthesis of Diazo Ketone 7. Attempts to develop a practical route to tetralol **12** based on the one-step Hart annulation did not prove fruitful, chiefly due to difficulties associated with the separation of the desired phenol from isomeric byproducts. Consequently, we turned our attention to an alternative stepwise strategy involving the coupling of phenol to a suitable homoallylic halide, followed by intramolecular Friedel–Crafts cyclization.[20]

Our initial efforts to prepare the proposed cyclization substrate **13** focused on the directed *ortho*-metalation of anisole[21] and alkylation of the resulting aryllithium compound with 1-bromo-4-methyl-3-pentene[22] or the corresponding iodide.[23] Best results were obtained by metalation of anisole with 1.1 equiv of *n*-butyllithium in hexane containing 1.1 equiv of TMEDA (0 °C; then 45 °C for 45 min), followed by alkylation with 1-bromo-4-methylpent-3-ene at 60 °C for 20 h (eq 1). In this fashion, the desired aryl ether **13** was obtained in 32–40% yield after purification. Metalation under other conditions (e.g., with *n*-BuLi in Et_2O or THF) or via halogen–metal exchange beginning with 2-bromoanisole did not lead to improved results.



(1)

Transition-metal-mediated coupling procedures were investigated next in an effort to develop a more efficient

(18) For reviews of the Stille coupling reaction, see (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.

(19) (a) Hart, H.; Corbin, J. L.; Wagner, C. R.; Wu, C.-Y. *J. Am. Chem. Soc.* **1963**, *85*, 3269. (b) Hart, H.; Corbin, J. L.; Wagner, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 1740.

(20) For a review, see: Olah, G. A.; Krishnamurti, R.; Surya, G. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293–339.

(21) For reviews on directed metalation reactions, see: (a) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 459–476. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (d) Narasimhan, N. S.; Mali, R. S. *Top. Curr. Chem.* **1987**, *138*, 63.

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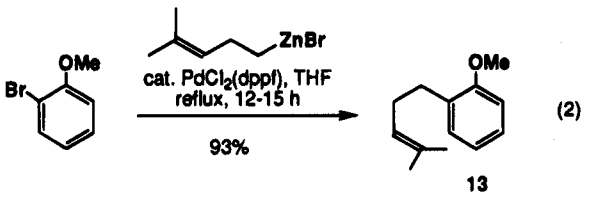
(23) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37 and references cited therein.

route to intermediate **13**. However, attempted coupling of the Grignard reagent derived from 2-bromoanisole with 1-bromo-4-methylpent-3-ene in the presence of Li_2CuCl_4[24] led to the formation of a complex mixture of products, and the higher-order cyanocuprate[25] derived from 2-lithioanisole reacted with the homoallylic bromide to produce the desired product contaminated with a large amount of the biphenyl homocoupling product. Dramatically improved yields were finally achieved through the application of palladium-mediated coupling chemistry. As outlined in eq 2, optimal results were obtained by the reaction of the indicated homoallylic organozinc compound[26,27] with 2-bromoanisole in the presence of 0.1 equiv of $PdCl_2$(dppf).[28] In this manner, the desired aryl ether was obtained in 93% yield after chromatographic purification.

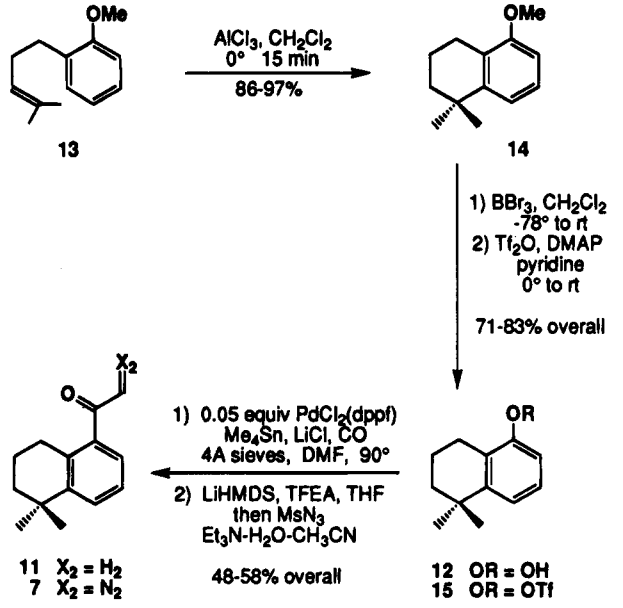


(2)

With the alkylated anisole **13** in hand, we next turned our attention to the elaboration of this intermediate to the key diazo ketone **7** (Scheme 3). Cyclization of **13** to methoxytetralin **14**[29] proceeded in excellent yield upon exposure to 1.0 equiv of aluminum chloride in CH_2Cl_2 at 0 °C for 15 min. Treatment of **14** with boron tribromide under standard conditions (CH_2Cl_2, −78 °C to rt, 4 h) provided the phenol **12** in 82−95% yield as colorless crystals with spectral characteristics identical to those previously reported by Hart.[19] Slow addition of 1.5 equiv of triflic anhydride to a solution of **12** and 1.0 equiv of DMAP in pyridine (0 °C to rt, 48 h) then furnished the triflate **15**[31] required for the Stille coupling step.

The key carbonylative Stille reaction[32] was accomplished by heating **15** and tetramethyltin in the presence of catalytic $PdCl_2$(dppf), LiCl, and 4 Å molecular sieves in DMF under 3 atm of carbon monoxide at 90 °C for 12−30 h. Chromatographic purification provided the methyl ketone **11** as cream-colored crystals (mp 30−31 °C) in 59−71% yield. Conversion of this ketone to the α-diazo derivative **7** was then achieved by employing the

Scheme 3



improved "detrifluoroacetylative" diazo transfer method recently developed in our laboratory.[33] The α-diazo ketone **7** was obtained as yellow crystals (mp 65−66 °C) in 82% yield in this fashion.

Photochemical Aromatic Annulation Step. The siloxyalkyne **6** was selected to serve as the acetylene component for the pivotal aromatic annulation step. This acetylene was conveniently prepared from commercially available (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate using the Kowalski reaction[34] as described by us previously.[1g]

Initially the key aromatic annulation reaction was attempted by irradiating a degassed solution of the diazo ketone **7** and a small excess of **6** in 1,2-dichloroethane at 254 nm in a Vycor tube at 20−25 °C using a standard Rayonet photochemical reactor. After 6 h, two products were found to be present: the desired tricyclic phenol **16** and a second compound believed to be the cyclobutenone intermediate corresponding to structure **9**. Heating the reaction mixture at 90 °C for 3 h led to the conversion of the second compound to the desired annulation product, which after chromatographic purification was isolated in 55−74% yield. In this case, as in several other annulations studied previously,[1d,f,h] the accumulation of colored polymers on the walls of the reaction vessel apparently impedes the complete photochemical conversion of the cyclobutenone intermediate to final product. Further investigation revealed, however, that complete conversion to **16** could be accomplished directly at room temperature, provided that benzene is employed as the reaction solvent. Thus, irradiation of diazo ketone **7** and 1.5 equiv of acetylene **6** in benzene (0.07−0.15 M) at 25 °C for 24 h provided the tricyclic phenol as off-white crystals [mp 145−147 °C; $[\alpha]^{25}_D = -10.2°$ ($CHCl_3$, $c = 1.34$)] in 58−65% yield after purification by column chromatography (eq 3).

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(26) For a review of transition-metal-catalyzed reactions of organozinc compounds, see: Erdick, E. *Tetrahedron* **1992**, *48*, 9577.

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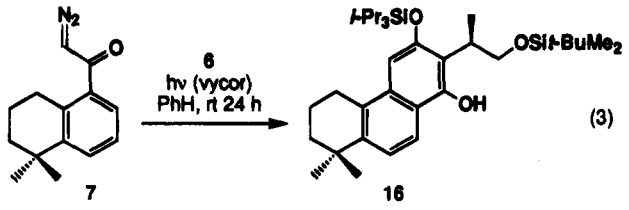
(34) (a) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. (b) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (c) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140. (d) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1991**, *57*, 7194. (e) Reddy, R. E.; Kowalski, C. J. *Org. Synth.* **1992**, *71*, 146.

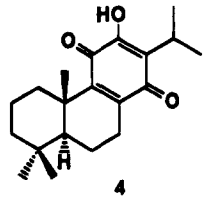


Conversion of 16 to (+)-Neocryptotanshinone, (−)-Cryptotanshinone, and Tanshinone IIA. Cleavage of the silyl ether protective groups and oxidation to produce (+)-neocryptotanshinone was achieved in a single operation by exposure of **16** to the action of tetra-*n*-butylammonium fluoride in THF (−78 °C to rt, 40 h) in the presence of oxygen (Scheme 4). Chromatographic purification furnished (+)-neocryptotanshinone as bright yellow needles, mp 163−165 °C (lit.[11] mp 165−167 °C) and $[\alpha]^{25}_D$ = +29.2° ($CHCl_3$, *c* = 0.91) [lit.[11] $[\alpha]^{25}_D$ = +29.8° ($CHCl_3$, *c* = 0.84)]. Overall, our aromatic annulation strategy provides access to (+)-neocryptotanshinone in only eight steps from 2-bromoanisole (five steps from the Hart tetralol **12**) and establishes the absolute stereochemistry of this diterpene for the first time.

Prior experience gained in the synthesis of other diterpene quinones[1fg,16,35] suggested that the *o*-quinone system of cryptotanshinone (**2**) could be easily generated by exposure of neocryptotanshinone to strong acid. In fact, brief treatment of **1** with an ethanolic solution of concentrated sulfuric acid afforded (−)-cryptotanshinone as orange-red needles in quantitative yield. Synthetic cryptotanshinone [mp 188−189 °C (lit.[12] mp 191−192 °C)] and $[\alpha]^{25}_D$ = −84.5° ($CHCl_3$, c = 1.72) [lit.[12] $[\alpha]^{25}_D$ = −79.9° ($CHCl_3$, c = 0.18)] was indistinguishable from an authentic sample[36] of the natural product by comparison of NMR, IR, TLC, and melting point characteristics.

Dehydrogenation of **2** to form tanshinone IIA in fair to good yield has previously been reported by Baillie and Thomson[13] and by Kakisawa and his co-workers.[16] We found that exposure of cryptotanshinone to 2.5 equiv of DDQ in benzene (rt, 24 h) affords tanshinone IIA in 91% yield as red crystals, mp 199−200 °C (lit.[12] mp 196−198 °C), identical in all respects with an authentic sample of the natural product.[37]

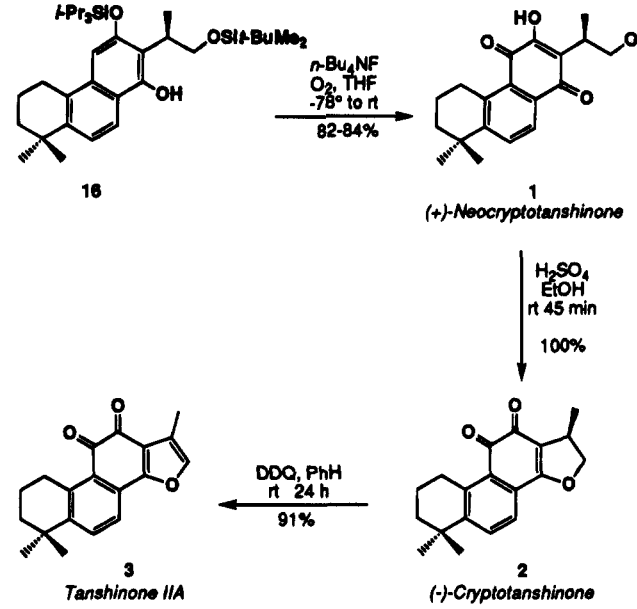
Royleanone. As a further demonstration of the utility of the photochemical aromatic annulation strategy in the construction of angularly-fused diterpenes, we have examined its application to the total synthesis of (±)-royleanone (**4**). Royleanone is a diterpenoid quinone



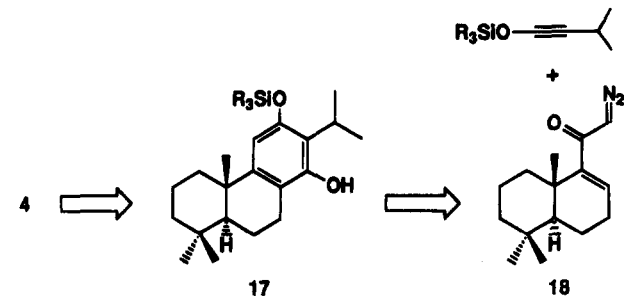
originally isolated by Edwards[38] from the roots of *Inula royleana*, a Himalayan herb used locally as an insecticide and disinfectant. Kupchan subsequently reported the presence of royleanone in the seeds of *Taxodium distichum* (swamp cypress) and found the diterpene to possess modest antitumor activity.[39] Royleanone and its derivatives have also been found to occur in a variety of other *Salvia* species. As outlined in Scheme 5, our strategy for the synthesis of royleanone[40] revolved around an aromatic annulation involving the diazo ketone **18** and a suitable alkoxy derivative of isopropylacetylene. This key step was expected to provide the tricyclic intermediate **17**, which would afford royleanone upon ether cleavage and oxidation.

Synthesis of Diazo Ketone 18. One attractive plan for the preparation of the key diazo ketone **18** involved the use of the known α,β-unsaturated ester **21** (Scheme 6) previously prepared by Eschenmoser via the keto ester **19**.[41] This well-known bicyclic β-keto ester is readily available through routes based on various cation-π cy-

Scheme 4



Scheme 5



(35) For a related cyclization involving the acid-catalyzed conversion of danshexinkun A to dihydrotanshinone I, see: Fang, C. N.; Chang, P.-L.; Hsu, T.-P. *Acta Chim. Sin.* **1976**, *34*, 197.

(36) We are grateful to Professor Henry C. Wong (Chinese University of Hong Kong) for providing us with an authentic sample of (−)-cryptotanshinone.

(37) We are grateful to Professor John Snyder (Boston University) for providing us with an authentic sample of tanshinone IIA.

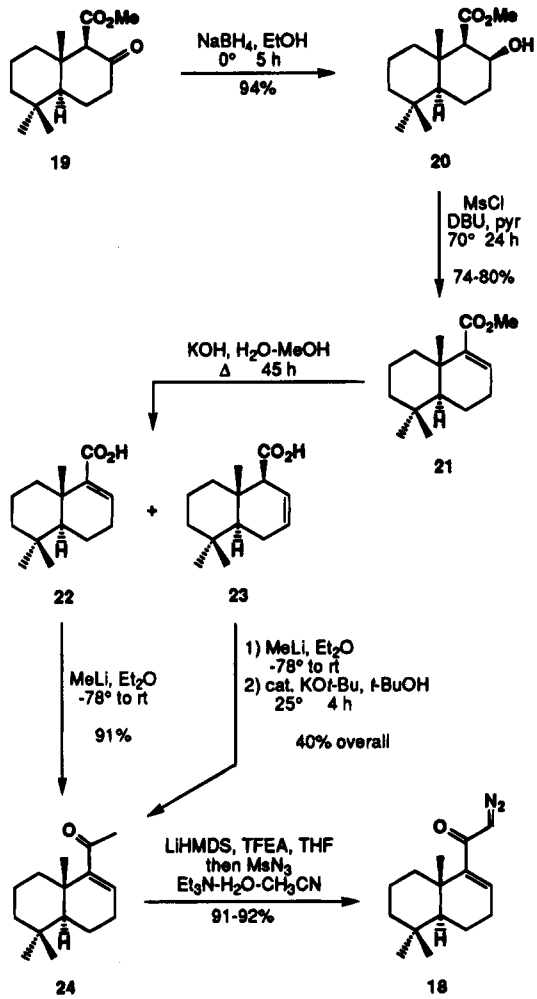
(38) Edwards, O. E.; Feniak, G.; Los, M. *Can. J. Chem.* **1962**, *40*, 1540.

(39) (a) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923. (b) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Org. Chem.* **1969**, *34*, 3912.

(40) For previous partial and total syntheses of royleanone, see: (a) Tachibana, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 298. (b) Matsui, T. *J. Sci. Hiroshima Univ., Ser. A* **1976**, *40*, 129. (c) Matsumoto, T.; Ohsuga, Y.; Harada, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 266. (d) Ohtsuka, Y.; Tahara, A. *Chem. Pharm. Bull.* **1978**, *26*, 2007. (e) Engler, T. A.; Sampath, U.; Naganathan, S.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712. (f) Liebeskind, L. S.; Chidabaram, R.; Nimkar, S.; Liotta, D. *Tetrahedron Lett.* **1990**, *26*, 3723.

(41) Stadtler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373.

Scheme 6

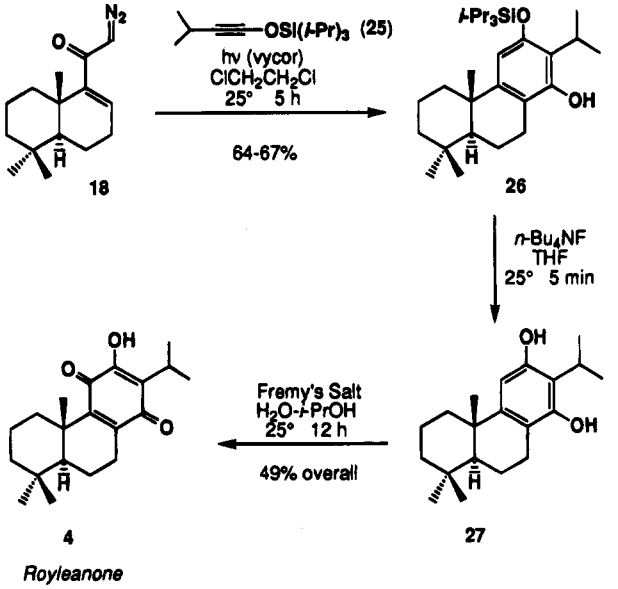


clizations[41,42] and also has served as an intermediate in the synthesis of the fragrance substance Ambrox.[43] We found that the conversion of **19** to **21** proceeded smoothly employing a modification of the approach previously used by Eschenmoser. Thus, reduction of **19** with excess sodium borohydride in absolute ethanol at 0 °C gave the expected axial alcohol in high yield. Elimination to produce the unsaturated ester **21** was achieved in one synthetic operation by exposure of the mesylate derivative of **20** (generated *in situ*) to the action of DBU in pyridine at 70 °C. Saponification with KOH in aqueous methanol then provided the known α,β-unsaturated acid **22**[41] (54%), as well as the previously unreported β,γ-isomer **23** (30%) which was separated by low-temperature crystallization. Treatment of either acid with excess methyllithium in ether furnished the corresponding methyl ketone; in the case of the β,γ-isomer, subsequent exposure to a catalytic amount of KO-*t*-Bu in *tert*-butyl alcohol produced the desired conjugated enone **24**. In preparative runs, the isomeric acids **22** and **23** were not separated, but were treated with methyllithium and then potassium *tert*-butoxide to afford enone **24**. Finally, diazo transfer according to our detrifluoroacetylative protocol[33] provided the key diazo ketone intermediate **18** in excellent yield.

(42) For other examples, see: (a) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939. (b) Harring, S. R.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1992**, 503 and references cited therein.

(43) We thank Professor George Büchi for a generous gift of keto ester **19**.

Scheme 7



Aromatic Annulation and Conversion to Royleanone. Scheme 7 outlines the completion of the synthesis of royleanone. The requisite siloxyalkyne **25**[1c,d,h] for the key aromatic annulation step is readily available in one step from ethyl isobutyrate using the Kowalski reaction.[34] Irradiation of a degassed 0.33 M solution of the diazo ketone **18** and 2–5 equiv of **25** in 1,2-dichloroethane at 254 nm at room temperature for 5 h furnished the desired tricyclic annulation product **26** in 64–67% yield after chromatographic purification. The majority of the unreacted siloxyacetylene was recovered and could be recycled.

Exposure of **26** to 1.1 equiv of TBAF in THF at room temperature for 5 min provided the diol **27**, which was best oxidized directly to royleanone without prior purification. For this oxidation, Fremy's salt (potassium nitrodisulfonate) was found to be superior to other reagent systems such as cerium ammonium nitrate and salcomine–oxygen. (±)-Royleanone was obtained as yellow crystals, mp 153–154 °C (lit.[40a] mp 153–154 °C), with spectroscopic characteristics consistent with those reported previously.[40a] The spectral properties of our synthetic royleanone were also fully in accord with those of an authentic sample prepared from (+)-taxoquinone (7β-hydroxyroyleanone) according to the procedure of Eugster.[44,45]

Experimental Section

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated. Organic extraction solutions were dried over anhydrous magnesium sulfate. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi rotary evaporator at ca. 20 mmHg. Column chromatography was performed on Baker silica gel (230–400 mesh). Melting points are uncorrected.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below.

(44) Hensch, M.; Ruedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1975**, *58*, 1421.

(45) We are grateful to Professor C. H. Eugster for providing us with a sample of (+)-taxoquinone.

Acetonitrile, anisole, 1,2-dichloroethane, dichloromethane, diisopropylamine, dimethylformamide, 1,1,1,3,3,3-hexamethyldisilazane, pyridine, triethylamine, 2,2,2-trifluoroethyl trifluoroacetate, and triisopropylsilyl chloride were distilled from calcium hydride. Tetrahydrofuran, ether, and benzene were distilled from sodium benzophenone ketyl or dianion. TMEDA was distilled from potassium hydroxide. Methanesulfonyl chloride was distilled at reduced pressure. Lithium chloride was dried at 140 °C (< 0.05 mmHg) for 24 h immediately prior to use. Molecular sieves were heated under vacuum with a Bunsen burner and then stored at 140 °C in an oven until use. 1-Bromo-4-methyl-3-pentene and $PdCl_2$(dppf) were prepared according to literature procedures (*vide infra*).

1-(1′-Methoxyphenyl)-4-methylpent-3-ene (13). Palladium-Mediated Coupling Method. A 25-mL, two-necked flask (A) equipped with a rubber septum, argon inlet adapter, and magnetic stir bar was charged with freshly cut lithium wire (0.072 g, 10.4 mmol), naphthalene (1.36 g, 10.6 mmol), and 5 mL of THF. The resulting mixture was stirred at 25 °C for 3 h (after 30 s, the solution changed from colorless to dark green). A solution of anhydrous $ZnCl_2$–dioxane complex (1.22 g, 5.44 mmol) in 5 mL of THF was then added dropwise to flask A via cannula over 10 min, and the resulting solution was stirred at 25 °C for 20 min. A solution of 1-bromo-4-methylpent-3-ene[22] (0.385 g, 2.36 mmol) in 1 mL of THF was then added over 1 min via cannula, and the resulting solution was stirred at 25 °C for 4.5 h. The unreacted zinc was then allowed to settle over 2 h. A 50-mL, two-necked flask (B) equipped with a rubber septum and a condenser fitted with an argon inlet adapter was charged with 2-bromoanisole (0.221 g, 1.18 mmol), $PdCl_2$(dppf)[28] (0.087 g, 0.12 mmol), and 5 mL of THF. The brown alkylzinc bromide solution in flask A was then transferred into flask B via cannula over 1 min. The residual unreacted zinc was washed with an additional 3 mL of THF. The reaction mixture was heated at reflux for 15 h, then cooled to room temperature, diluted with 20 mL of a 10% HCl solution, stirred for 15 min, and poured into 40 mL of ether and 20 mL of a 10% HCl solution. The aqueous phase was separated and extracted with two portions of ether, and the combined organic layers were washed with water and a saturated aqueous NaCl solution, dried, filtered, and concentrated to afford 1.421 g of an orange solid. Column chromatography on silica gel (gradient elution with 0–20% benzene in hexane) afforded 0.208 g (93%) of **13** as a colorless liquid: IR (film) 2960, 2920, 1600, 1590, 1490, 1440, 1240, and 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (m, 2 H), 6.87 (m, 2 H), 5.20 (t, J = 7 Hz, 1 H), 3.81 (s, 3 H), 2.61 (m, 2 H), 2.24 (m, 2 H), 1.67 (s, 3 H), and 1.56 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 131.7, 130.8, 129.8, 126.9, 124.3, 120.3, 110.1, 55.2, 30.5, 28.3, 25.6, and 17.5. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found C, 81.73; H, 9.79.

1-(1′-Methoxyphenyl)-4-methylpent-3-ene (13). Directed Metalation–Alkylation Method. A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, a reflux condenser fitted with an argon inlet adapter, and a pressure-equalizing addition funnel fitted with a rubber septum was charged with an *n*-butyllithium solution (2.50 M in hexanes, 24.3 mL, 0.061 mol) and cooled at 0 °C. TMEDA (7.05 g, 9.2 mL, 0.061 mol) and anisole (5.97 g, 6.0 mL, 0.055 mol) were added over 15 min, and the reaction mixture was warmed to room temperature (a yellow precipitate formed), heated at 45 °C for 30 min, and then cooled at 0 °C. A solution of 1-bromo-4-methylpent-3-ene (13.5 g, 0.083 mol) in 25 mL of THF was added over 45 min via the addition funnel, and the reaction mixture was heated at 55–60 °C for 20 h. The reaction mixture was then poured into 200 mL of a 10% HCl solution and 200 mL of ether. The aqueous layer was separated and extracted with two portions of ether, and the combined organic phases were washed with a 10% HCl solution, water, and a saturated aqueous NaCl solution, dried, filtered, and concentrated to afford 8.32 g of a pale yellow liquid. The unreacted alkyl bromide and anisole were removed by fractional distillation (54–60 °C) under aspirator pressure (ca. 14 mmHg). Column chromatography of the residue on 92 g of silica gel (gradient elution with 0–1% EtOAc–petroleum ether) afforded 3.38 g (32%) of **13** as a colorless liquid.

1,1-Dimethyl-5-methoxytetralin (14). A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a rubber septum was charged with a solution of 1-(1′-methoxyphenyl)-4-methylpent-3-ene (**13**) (8.66 g, 46 mmol) in 250 mL of CH_2Cl_2 and cooled at 0 °C while $AlCl_3$ (6.13 g, 46 mmol) was added in one portion. The resulting orange solution was stirred at 0 °C for 15 min and then poured into 300 mL of ice–water. The aqueous phase was separated and extracted with two portions of Et_2O, and the combined organic phases were washed with two portions of water, a saturated $NaHCO_3$ solution, and a saturated NaCl solution, dried, filtered, and concentrated to afford 10.46 g of a pale yellow oil. Column chromatography on silica gel (elution with pentane) furnished 8.38 g (97%) of **14** as a colorless oil, with spectral data consistent with that previously reported for this compound:[29] IR (film) 3080, 2940, 2880, 1580, 1460, 1440, and 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, J = 8 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 6.66 (d, J = 8 Hz, 1 H), 3.82 (s, 3 H), 2.66 (t, J = 6 Hz, 2 H), 1.76–1.82 (m, 2 H), and 1.30 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 147.4, 126.0, 125.4, 118.8, 106.5, 55.1, 38.6, 33.6, 31.5, 23.7, and 18.7.

1,1-Dimethyl-5-tetralol (12). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a pressure-equalizing dropping funnel was charged with a solution of 1,1-dimethyl-5-methoxytetralin (**14**) (8.45 g, 44.4 mmol) in 100 mL of CH_2Cl_2. The solution was cooled at −78 °C, and a solution of boron tribromide (1.0 M in CH_2Cl_2, 22.2 mL, 22.2 mmol) was added via the dropping funnel over ca. 10 min. The reaction mixture was allowed to warm to 25 °C over the course of 4 h. The resulting brown-red solution was then poured into 150 mL of water and 100 mL of ether. The organic phase was washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution, dried, filtered, and concentrated to afford 4.96 g of a brown oil. Recrystallization from 50 mL of petroleum ether provided 4.69 g of 1,1-dimethyl-5-tetralol (**12**) as white crystals. Concentration of the mother liquor and subsequent recrystallization afforded a total yield of 7.42 g (95%) of **12**, mp 111–112 °C (lit.[19] mp 112.5–113.5). Spectral data were consistent with those previously reported[19] for this compound: IR (CCl_4) 3400, 2960, 2940, 2860, 1575, 1450, and 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (t, J = 8 Hz, 1 H), 6.92 (d, J = 8 Hz, 1 H), 6.57 (d, J = 8 Hz, 1 H), 4.60 (br s, 1 H), 2.61 (t, J = 6 Hz, 2 H), 1.81 (m, 2 H), 1.62 (m, 2H), and 1.26 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 148.0, 126.3, 122.9, 119.2, 111.5, 38.5, 33.7, 31.5, 23.4, and 18.5.

1,1-Dimethyl-5-tetralyl Trifluoromethanesulfonate (15). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a pressure-equalizing addition funnel was charged with a solution of 1,1-dimethyl-5-tetralol (**12**) (4.70 g, 26.7 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (33.26 g, 26.7 mmol) in 100 mL of pyridine and then cooled at 0 °C. After 20 min, trifluoromethanesulfonic anhydride (11.29 g, 6.73 mL, 40.0 mmol) was added dropwise via the addition funnel over 5 min. The reaction mixture was allowed to warm to 25 °C over 1 h and then stirred at 25 °C for 48 h. The resulting mixture was partitioned between 150 mL of a 5% HCl solution and 150 mL of ether, and the aqueous phase was separated and extracted with three portions of ether. The combined organic layers were washed with water, six portions of a half-saturated aqueous $CuSO_4$ solution, and a saturated NaCl solution, dried, filtered, and concentrated to afford 7.18 g (87%) of the triflate **15** as a yellow oil, which was used in the next step without further purification: IR (CCl_4) 2970, 2935, 1610, 1565, 1470, 1450, 1420, 1250, 1210, 1140, 1110, and 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.03 (d, J = 8 Hz, 1 H), 2.77 (t, J = 8 Hz, 2 H), 1.81 (m, 2 H), 1.65 (m, 2 H), and 1.28 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 148.0, 129.5, 126.7, 120.7, 117.8, 116.5, 38.2, 34.1, 31.7, 24.5, and 18.5; HRMS *m*/*e* calcd for $C_{13}H_{15}F_3O_3S$ 308.0694, found 308.0692.

1-(5,5-Dimethyl-5,6,7,8-tetrahydro-1-naphthyl)ethan-1-one (11). A Fisher–Porter tube was charged with LiCl (0.800 g, 18.8 mmol) and 4 Å molecular sieves (0.400 g) and flame dried under vacuum. The tube was then charged via

cannula with a solution of the triflate **15** (1.870 g, 6.07 mmol), tetramethyltin (1.18 g, 0.92 mL, 6.56 mmol), and 2,6-di-*tert*-butylhydroxytoluene (ca. 10 mg) in 8 mL of DMF. A solution of [1,1'-bis(diphenylphosphino)ferrocenyl]palladium(II) chloride[28] (0.180 g, 0.240 mmol) in 20 mL of DMF was then added, and the tube was sealed and pressurized to 50 psi with carbon monoxide. The reaction mixture was vented, repressurized, and heated at 90 °C for 12 h. After cooling to room temperature, the tube was vented, and the reaction mixture was diluted with 100 mL of ether and 100 mL of water. The aqueous phase was separated and extracted with two portions of ether, and the combined organic layers were washed with three portions of water, a saturated $NaHCO_3$ solution, and a saturated NaCl solution, dried, filtered, and concentrated to afford 1.38 g of a red-brown oil. Column chromatography on silica gel (elution with 1% ethyl acetate–petroleum ether) furnished 0.872 g (71%) of ketone **11** as cream-colored crystals: mp 30–31 °C; IR (CCl_4) 3080, 2980, 2950, 2880, 1690, 1580, 1450, 1360, and 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 2.88 (t, J = 6 Hz, 2 H), 2.52 (s, 3 H), 1.59–1.76 (m, 4 H), and 1.27 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 147.4, 139.3, 135.5, 130.2, 125.8, 125.4, 38.4, 34.1, 31.9, 30.1, 28.7, 19.2. Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.82; H, 8.58.

2-Diazo-1-(5,5-dimethyl-5,6,7,8-tetrahydro-1-naphthyl)-1-ethanone (7). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.132 g, 1.48 mL, 7.01 mmol) in 20 mL of tetrahydrofuran and cooled at 0 °C while an *n*-butyllithium solution (2.50 M in hexane, 2.58 mL, 6.45 mmol) was added dropwise over ca. 2 min. The resultant solution of LiHMDS was stirred at 0 °C for 15 min and then was cooled at −78 °C while a solution of ketone **11** (1.18 g, 5.83 mmol) in 9 mL of THF was added dropwise over 15 min. The solution of the resulting enolate was stirred at −78 °C for 35 min, after which time 2,2,2-trifluoroethyl trifluoroacetate (1.376 g, 0.94 mL, 7.02 mmol) was added in one portion. The reaction mixture was stirred at −78 °C for 45 min and then poured into 50 mL of a 1 N HCl solution and 60 mL of ether. The aqueous phase was separated and extracted with ether, and the combined organic layers were washed with saturated NaCl solution, dried, filtered, and concentrated to afford a pale green oil, which was dissolved in 13 mL of acetonitrile and transferred to a one-necked flask equipped with a magnetic stir bar and a rubber septum. Water (0.11 g, 0.11 mL, 6.11 mmol), triethylamine (0.947 g, 1.22 mL, 8.75 mmol), and methanesulfonyl azide (1.407 g, 1.0 mL, 11.62 mmol) were added, and the resultant yellow solution was stirred at 25 °C for 6 h. The reaction mixture was concentrated, and the residual oil was partitioned between 60 mL of Et_2O and 40 mL of a 2 N NaOH solution. The organic phase was washed with three portions of a 2 N NaOH solution, three portions of water, and a saturated NaCl solution, dried, filtered, and concentrated to afford 1.63 g of a green oil. Column chromatography on silica gel (gradient elution with 2–4% EtOAc–hexane) provided 1.094 g (82%) of the α-diazo ketone **7** as a yellow solid: mp 65–66 °C; IR (CCl_4) 3080, 2960, 2940, 2870, 2100, 1620, 1585, 1450, 1350, and 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, J = 2, 8 Hz, 1 H), 7.11–7.19 (m, J = 6, 8, 2 H), 5.50 (br s, 1 H), 2.88 (t, J = 6 Hz, 2 H), 1.62–1.79 (m, 4 H), and 1.27 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 147.1, 138.1, 134.3, 129.4, 125.4, 124.0, 56.5, 38.6, 34.2, 32.0, 28.2, and 19.3. Anal. Calcd for $C_{14}H_{15}ON_2$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.90; H, 6.91; N, 11.99.

3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-propyl)-7,7-dimethyl-4-hydroxy-2-((triisopropylsilyl)oxy)-7,8,9,10-tetrahydrophenanthrene (16). A solution of the α-diazo ketone **7** (0.817 g, 3.58 mmol), siloxyacetylene **6** (2.00 g, 5.87 mmol), and 50 mL of benzene was distributed equally between four 20-cm Vycor tubes (15 mm i.d.) fitted with rubber septa. The reaction mixtures were degassed (three freeze–pump–thaw cycles at −196 °C, ca. 0.1 mmHg) and then irradiated with 254 nm light for 24 h in a Rayonet photoreactor. The contents of the tubes were then combined in a 100-mL pear-shaped flask and concentrated to afford 3.34 g of an orange oil. Column chromatography on silica gel (gradient elution with 0–5% CH_2Cl_2–hexane) furnished 1.31 g (64%) of **16** as off-white crystals: mp 145–147 °C; $[\alpha]^{25}_D$ = −10.2° ($CHCl_3$, c = 1.34); IR (CCl_4) 3220, 2950, 2880, 1630, 1595, 1500, 1470, 1410, 1255, and 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 8.07 (d, J = 9 Hz, 1 H), 7.29 (d, J = 9 Hz, 1 H), 6.85 (s, 1 H), 4.02 (br s, 2 H), 3.94 (m, 1 H), 2.92 (app t, J = 6 Hz, 2 H), 1.93 (m, 2 H), 1.71 (m, 2 H), 1.38 (d, J = 7 Hz, 3 H), 1.34, (s, 6 H), 1.15 (d, J = 7 Hz, 18 H), 0.99 (s, 9 H), 0.85–1.30 (m, 3 H), 0.18 (s, 3 H), and 0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 152.7, 143.1, 132.5, 128.3, 121.7, 120.7, 120.0, 117.3, 101.7, 69.3, 38.8, 33.9, 31.4, 31.2, 26.8, 25.7, 19.4, 18.2, 18.0, 14.8, 12.9, and −5.9; HRMS m/e calcd for $C_{34}H_{58}O_3Si_2$ 570.3925, found 570.3923.

7,7-Dimethyl-2-hydroxy-3-((*S*)-1-hydroxy-2-propyl)-7,8,9,10-tetrahydro-1,4-phenanthrenequinone (1, (+)-Neocryptotanshinone). A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of the phenol **16** (0.585 g, 1.03 mmol) in 15 mL of THF and cooled at −78 °C. A tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 2.25 mL, 2.25 mmol) was then added dropwise over 5 min, and oxygen was bubbled into the reaction mixture via a syringe needle. The cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C. The resulting dark red solution was stirred at 25 °C for 40 h (oxygen bubbling was continued) and then poured into 100 mL of a 10% aqueous HCl solution and 100 mL of CH_2Cl_2. The aqueous phase was separated and extracted with two portions of CH_2Cl_2, and the combined organic layers were washed with a 10% HCl solution, water, and a saturated NaCl solution, dried, filtered, and concentrated to afford 0.656 g of a red oil. Column chromatography on silica gel (gradient elution with 1–20% EtOAc in CH_2Cl_2) provided 0.270 g (84%) of (+)-neocryptotanshinone (**1**) as a bright yellow solid: mp 163–165 °C (lit.[11] 165–167 °C); $[\alpha]^{25}_D$ +29.2° ($CHCl_3$, c = 0.73); IR (CCl_4) 3330, 2970, 2940, 2870, 1770, 1660, 1570, and 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8 Hz, 1 H), 7.70 (d, J = 8 Hz, 1 H), 3.94 (dd, J = 8, 11 Hz, 2 H), 3.84 (dd, J = 5, 11 Hz, 1 H), 3.42 (m, 1 H), 3.20 (t, J = 6 Hz, 2 H), 1.77–1.81 (m, 2 H), 1.62–1.65 (m, 2 H), 1.27 (s, 6 H), and 1.23 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 183.3, 154.5, 153.2, 141.1, 133.6, 132.7, 126.6, 125.2, 123.1, 65.4, 37.5, 34.6, 32.7, 31.6, 29.7, 18.8, and 14.3. Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05 Found: C, 72.81; H, 7.24.

8,8-Dimethyl-3(*S*)-methyl-3,4,8,9,10,11-hexahydro[3,2-*c*]furophenanthrene-1,2-dione (2, (−)-Cryptotanshinone). A 25-mL, pear-shaped flask was charged with a solution of (+)-neocryptotanshinone (**1**) (0.126 g, 0.401 mmol) in 5 mL of ethanol. Concentrated H_2SO_4 (3 mL) was then added dropwise over 10 min (caution: exothermic reaction), and the resulting dark red solution was stirred for 45 min at 25 °C. The reaction mixture was then poured into 50 mL of water and 50 mL of ether. The aqueous phase was separated and extracted with two portions of ether, and the combined organic layers were washed with two portions of a 5% HCl solution, a saturated $NaHCO_3$ solution, and a saturated NaCl solution, dried, filtered, and concentrated to afford 0.214 g of an orange solid. Column chromatography on silica gel (gradient elution with 1–20% EtOAc in CH_2Cl_2) provided 0.118 g (100%) of (−)-cryptotanshinone (**2**) as orange-red crystals: mp 188–190 °C (lit.[12] mp 191–192 °C); $[\alpha]^{25}_D$ −84.5° ($CHCl_3$, c = 1.82); IR (CCl_4) 2870, 2840, 2780, 1660, 1625, 1560, and 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 4.89 (app t, J = 9 Hz, 1 H), 4.36 (dd, J = 6, 10 Hz, 1 H), 3.62 (ddq, J = 6, 7, 9 Hz, 1 H), 3.22 (t, J = 7 Hz, 2 H), 1.78–1.82 (m, 2 H), 1.64–1.68 (m, 2 H), 1.36 (d, J = 7 Hz, 3 H), and 1.31 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 176.0, 171.1, 152.6, 143.9, 132.7, 128.6, 126.4, 122.6, 118.4, 81.4, 37.6, 34.6, 34.4, 31.7, 29.5, 18.8, and 18.6. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.21; H, 6.78.

8,9,10,11-Tetrahydro-3,8,8-trimethyl[3,2-c]furophenanthrene-1,2-dione (3, Tanshinone IIA). A 25-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and a rubber septum was charged with DDQ (0.220 g, 0.971 mmol), (−)-cryptotanshinone (**2**) (0.115 g, 0.389 mmol),

and 10 mL of benzene. The reaction mixture was stirred at 25 °C for 42 h and then filtered and concentrated to afford 0.416 g of a dark brown-red solid. Column chromatography on silica gel (gradient elution with 0–75% $CHCl_3$ in benzene) furnished 0.104 g (91%) of tanshinone IIA (**3**) as red crystals: mp 199–200 °C (lit.[12] mp 196–198 °C); IR (CCl_4) 3140, 2960, 2840, 2780, 1690, 1670, 1640, 1585, 1540, and 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H), 7.19 (d, J = 1.3 Hz, 1 H), 3.15 (t, J = 6 Hz, 2 H), 2.23 (d, J = 1.3 Hz, 3 H), 1.70–1.75 (m, 2 H), 1.59–1.65 (m, 2 H), and 1.28 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 184.3, 176.5, 162.4, 150.8, 145.1, 141.9, 134.1, 128.0, 127.0, 121.7, 120.8, 120.4, 38.1, 34.9, 32.0, 30.1, 19.3, and 8.9. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.40 ; H, 6.19.

1β-Carbomethoxy-2β-hydroxy-5,5,8aβ-trimethyl-*trans*-decahydronaphthalene (20). A 500-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel fitted with a rubber septum, a glass stopper, and an argon inlet adapter was charged with the keto ester **19**[43] (10.0 g, 39.6 mmol) and 175 mL of absolute EtOH. The reaction mixture was cooled at 0 °C while a solution of sodium borohydride (3.06 g, 80.9 mmol) in 125 mL of absolute EtOH was added dropwise over 40 min. After 4 h, 10 mL of water was added, and the resulting solution was concentrated at reduced pressure. The residual oil was partitioned between 250 mL of ether and 250 mL of water, and the aqueous phase was separated and extracted with ether. The combined organic phases were washed with two portions of a 10% HCl solution and a saturated NaCl solution, dried, filtered, and concentrated to afford 10.54 g of a cream-colored solid. Filtration through 3 cm of silica gel with the aid of 1% EtOAc–petroleum ether and concentration afforded 9.52 g (94%) of the alcohol **20** as white crystals: mp 56–57 °C (lit.[41] mp 57 °C); IR (CCl_4) 3520, 2940, 2920, 2860, 2840, 1705, and 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (d, J = 3.1 Hz, 1 H), 3.99 (app d, J = 1.7 Hz, 1 H), 3.70 (s, 3 H), 2.15 (d, J = 1.7 Hz, 1 H), 1.94–2.00 (m, 1 H), 1.35–1.70 (m, 10 H), 1.17 (s, 3 H), 0.87 (s, 3 H), and 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 67.7, 59.0, 55.4, 51.3, 42.0, 40.5, 38.0, 33.6, 33.4, 33.3, 21.5, 18.2, 16.9, and 16.8.

1-Carbomethoxy-5,5,8a-trimethyl-*trans*-3,4,4a,5,6,7,8,-8a-octahydronaphthalene (21). A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and reflux condenser fitted with an argon inlet adapter was charged with the hydroxy ester **20** (9.02 g, 35.5 mmol) and 200 mL of pyridine, and the resultant solution was cooled at 0 °C in an ice bath while methanesulfonyl chloride (5.68 g, 3.84 mL, 49.6 mmol) was added dropwise via syringe over 4 min. 1,8-Diazabicyclo[5.4.0]undecene (7.55 g, 7.42 mL, 49.6 mmol) was added via syringe over 10 min, and the reaction mixture was heated at 70 °C for 12 h. The reaction mixture was then allowed to cool to 25 °C, and additional methanesulfonyl chloride (5.68 g, 3.84 mL, 49.6 mmol) was added dropwise via syringe. The reaction mixture was next heated at 70 °C for 12 h and then cooled to 25 °C and diluted with 300 mL of a 10% HCl solution. The aqueous phase was separated and extracted with two portions of ether, and the combined organic layers were washed with eight portions of a half-saturated aqueous $CuSO_4$ solution, two portions of a 10% HCl solution, and a saturated NaCl solution, dried, filtered through a 3-cm plug of silica gel with the aid of 5% EtOAc–petroleum ether, and concentrated to afford 6.31 g (75%) of the ester **21** as a pale yellow oil, with spectral properties consistent with those reported previously:[41] IR (CCl_4) 2970, 2940, 2880, 2860, 1725, 1640, and 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (t, J = 3.6, 1 H), 3.65 (s, 3 H), 2.15–2.28 (m, 2 H), 1.55–1.68 (m, 2 H), 1.38–1.47 (m, 3 H), 1.23 (s, 3 H), 1.10–1.21 (m, 4 H), 0.87 (s, 3 H), and 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 142.2, 137.0, 51.6, 51.0, 41.8, 37.4, 35.9, 33.5, 33.3, 27.5, 21.6, 20.4, 18.8, and 17.9.

5,5,8a-Trimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydro-1-naphthoic Acid (22) and 5,5,8aα-trimethyl-*trans*-1,4,-4a,5,6,7,8,8a-octahydro-1α-naphthoic Acid (23). A 500-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with the α,β-unsaturated ester **21** (6.31 g, 26.7 mmol), potassium hydroxide (20.0 g, 356 mmol), 200 mL of MeOH, and 40 mL of H_2O, and the resultant solution was heated at reflux for 48 h. The reaction mixture was diluted with 100 mL of water and then extracted with 100 mL of ether. The aqueous phase was acidified to pH 1.0 with concd HCl and extracted twice with ether. The combined organic phases were washed with three portions of a 10% HCl solution and a saturated NaCl solution, dried, filtered, and concentrated to afford 5.5 g of a cream-colored solid. Low-temperature crystallization from ca. 20 mL of 2:1 pentane–ether provided 3.18 g (54%) of the α,β-unsaturated acid **22**: mp 207–209 °C (lit.[27] mp 206 °C). Column chromatography of the mother liquor on silica gel (elution with 15% EtOAc–petroleum ether) afforded 1.78 g (30%) of the β,γ-unsaturated acid **23**: mp 197–198 °C. **For 22:** IR (CCl_4) 3400, 2960, 2920, 1685, and 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (t, J = 4 Hz, 1 H), 2.14–2.41 (m, 3 H), 1.40–1.78 (m, 5 H), 1.26 (s, 3 H), 1.00–1.22 (m, 3 H), 0.92 (s, 3 H), and 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 141.3, 140.5, 51.7, 41.8, 37.3, 35.8, 33.5, 33.2, 27.6, 21.8, 20.2, 18.8, and 17.8. **For 23:** IR (CCl_4) 3020, 3000, 2960, 2930, 1695, and 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79–5.83 (m, 1 H), 5.53 (dd, J = 2.2, 7.7 Hz, 1 H), 2.94 (br s, 1 H), 1.93–2.05 (m, 2 H), 1.19–1.52 (m, 7 H), 0.92(s, 3 H), 0.89 (s, 3 H), and 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 128.7, 123.6, 57.0, 53.6, 49.5, 42.1, 39.8, 36.1, 33.1, 23.3, 21.6, 18.5, and 14.6. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.52; H, 9.74.

1-(5,5,8a-Trimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydro-1-naphthyl)ethanone (24). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with the α,β-unsaturated acid **22** (3.00 g, 13.5 mmol) and 75 mL of ether and cooled at −78 °C with a dry ice–acetone bath while a methyllithium solution (2.04 M in Et_2O, 26.5 mL, 54.1 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to 25 °C over 18 h and then was transferred via cannula over 20 min into 100 mL of a 10% HCl solution. The aqueous phase was separated and extracted with two portions of ether, and the combined organic layers were washed with two portions of a 10% HCl solution and a saturated NaCl solution, dried, filtered, and concentrated to afford 3.00 g of an off-white solid. Column chromatography on silica gel (elution with 1% EtOAc–petroleum ether) furnished 2.70 g (91%) of the enone **24** as white crystals: mp 65 °C; IR (CCl_4) 2950, 2910, 2860, 2840, 1660, 1620, 1365, and 1245 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 6.51 (t, J = 3 Hz, 1 H), 2.15–2.42 (m, 2 H), 2.22 (s, 3 H), 1.37–1.70 (m, 7 H), 1.23 (s, 3 H), 0.90–1.20 (m, 2 H), 0.89 (s, 3 H), and 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 151.5, 138.2, 51.6, 41.8, 38.0, 35.7, 33.5, 33.3, 28.6, 27.5, 21.6, 20.2, 18.8, and 17.8. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.95; H, 10.96.

1-(5,5,8a-Trimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydro-1-naphthyl)ethanone (24) (from the β,γ-Unsaturated Acid 23). Treatment of the β,γ-unsaturated acid **23** (1.50 g, 6.75 mmol) with a methyllithium solution (2.04 M in Et_2O, 13.24 mL, 27.0 mmol) according to the preceding procedure afforded 1.4 g of a pale brown oil. Column chromatography on silica gel (elution with 1% EtOAc–petroleum ether) furnished 1.02 g (69%) of the enone **24** and its β,γ-isomer as a white solid. A 50-mL pear-shaped flask fitted with a rubber septum was charged with a solution of this solid in 15 mL of *tert*-butyl alcohol and was treated with potassium *tert*-butoxide (0.056 g, 0.5 mmol) at 25 °C for 4 h. The resulting mixture was partitioned between 100 mL of a 0.05 M $KHPO_4$ solution and 100 mL of ether, and the aqueous phase was separated and extracted twice with ether. The combined organic layers were washed with ten portions of a 0.05 M $KHPO_4$ solution and a saturated NaCl solution, dried, filtered, and concentrated to furnish 0.80 g of a white solid. Column chromatography on silica gel (elution with 1% EtOAc–petroleum ethers) gave 0.73 g (49% overall yield from **23**) of the enone **24** as white crystals: mp 64–65 °C.

2-Diazo-1-(5,5,8a-trimethyl-*trans*-3,4,4a,5,6,7,8,8a-octahydro-1-naphthyl)ethanone (18). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet

adapter, rubber septum, and glass stopper was charged with a solution of diisopropylamine (0.83 g, 1.15 mL, 8.2 mmol) in 70 mL of tetrahydrofuran and cooled at 0 °C while a solution of *n*-butyllithium (1.86 M in hexanes, 4.1 mL, 7.6 mmol) was added dropwise over 5 min. The straw-colored solution was stirred at 0 °C for 10 min and then cooled at −78 °C in a dry ice−acetone bath while a solution of the methyl ketone **24** (1.50 g, 6.8 mmol) in 30 mL of tetrahydrofuran was added by syringe over 15 min. The reaction mixture was stirred at −78 °C for 1 h, and then 2,2,2-trifluoroethyl trifluoroacetate (2.7 g, 1.8 mL, 13.6 mmol) was added in one portion by syringe. After 30 min, the reaction mixture was partitioned between 100 mL of a 5% HCl solution and 100 mL of ether. The organic phase was separated and washed with two portions of a saturated $NaHCO_3$ solution, water, and a saturated NaCl solution, dried, filtered, and concentrated to afford a green oil, which was dissolved in 25 mL of acetonitrile in a 100-mL Kjedahl flask fitted with a rubber septum. Water (0.12 g, 0.121 mL, 6.8 mmol), triethylamine (1.03 g, 1.42 mL, 10.2 mmol), and a solution of methanesulfonyl azide (1.24 g, 10.2 mmol) in 10 mL of acetonitrile were added, and the resulting orange solution was stirred for 4 h at 25 °C and then concentrated to afford 1.91 g of a yellow solid. Column chromatography on silica gel (elution with 1% EtOAc−petroleum ether) furnished 1.52 g (91%) of the α-diazo ketone **18** as pale yellow crystals: mp 96−97 °C; IR (CCl_4) 3120, 2940, 2860, 2100, 1615, and 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (t, J = 4 Hz, 1 H), 5.26 (s, 1 H), 2.10−2.24 (m, 2 H), 1.00−1.73 (m, 9 H), 1.29 (s, 3 H), 0.87 (s, 3 H), and 0.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 149.9, 131.7, 54.9, 51.3, 41.9, 38.2, 35.8, 33.4, 26.8, 21.6, 21.0, 18.7, and 17.9. Anal. Calcd for $C_{15}H_{22}NO$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.20; H, 9.12; N, 11.49.

14-Hydroxy-12-((triisopropylsilyl)oxy)abieta-8,11,13-triene (26). A Vycor tube (7 mm i.d.) fitted with a rubber septum was charged with a solution of the α-diazo ketone **18** (0.246 g, 1.0 mmol) and (silyloxy)acetylene **25**[1h] (1.25 g, 5.2 mmol) in 3.0 mL of 1,2-dichloroethane. A second septum (inverted) was secured with wire over the first to provide a good seal. The reaction mixture was degassed (three freeze−pump−thaw cycles at −196 °C, <0.5 mmHg) and then irradiated with 254 nm light in a Rayonet photoreactor for 5 h. The contents of the tube were transferred to a 25-mL pear flask and concentrated to afford 1.6 g of a yellow oil. Column chromatography on silica gel (gradient elution with hexanes and 0−1% EtOAc−petroleum ether) gave 0.940 g of unreacted (silyloxy)acetylene **25** and 0.294 g (64%) of the phenol **26** as a pale yellow oil: IR (CCl_4) 3625, 2950, 2870, 1620, 1580, 1475, 1425, and 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (s, 1 H), 4.61 (s, 1 H), 3.56 (sept, J = 7 Hz, 1 H), 2.35−2.75 (m, 3 H), 1.85−2.15 (m, 2 H), 1.10−1.75 (m, 9 H), 1.32 (d, J = 7 Hz, 3 H), 1.30 (d, J = 7 Hz, 3 H), 1.14 (s, 3 H), 1.11 (d, J = 7 Hz, 18 H), 0.93 (s, 3 H), and 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 152.9, 148.7, 120.4, 113.7, 107.0, 49.8, 41.6, 38.9, 37.4, 33.2, 33.0, 24.5, 24.3, 23.6, 21.4, 20.7, 20.6, 19.2, 18.3, 17.9, and 13.0.

11,14-Dioxo-12-hydroxyabieta-8,12-diene (4, (±)-Royleanone). A two-necked, 25-mL, pear-shaped flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of the phenol **26** (0.571 g, 1.24 mmol) in 20 mL of THF. A tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 1.4 mL, 1.4 mmol) was added dropwise over 3 min, and the resultant solution was stirred for 5 min at 25 °C and then partitioned between 100 mL of water and 100 mL of ether. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with a saturated NaCl solution, dried, filtered, and concentrated to afford 0.612 g of an orange oil. A solution of this material in 40 mL of 2-propanol was added in one portion to a rapidly stirred solution of potassium nitrosodisulfonate (3.41 g, 12.7 mmol) in 250 mL of 0.05 M potassium phosphate buffer and 210 mL of 2-propanol in a 1-L, three-necked flask fitted with a glass stopper, an argon inlet adapter, and a rubber septum. The reaction mixture was stirred for 12 h at 25 °C and then extracted with two portions of ether. The combined organic phases were washed with two portions of a 5% HCl solution and with a saturated NaCl solution, dried, filtered, and concentrated to afford 0.634 g of a foul-smelling brown oil. Column chromatography on silica gel (elution with 1% EtOAc−petroleum ether) afforded 0.193 g (49% overall from **26**; 56% corrected for 0.071 g of recovered phenol **26**) of (+)-royleanone (**4**) as a yellow solid, identical with the natural product by ^1H NMR, ^{13}C NMR, IR, and UV spectroscopic analyses. Recrystallization from acetic acid provided deep red plates while recrystallization from methanol gave yellow crystals: mp 153−154 °C (lit. mp 153−154 °C[40a] and 153−155 °C[40b]); IR (CCl_4) 3345, 2980, 2940, 2885, 1650, 1635, 1610, 1470, and 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 1 H), 3.15 (sept, J = 6.5 Hz, 1 H), 2.71 (m, 2 H), 2.30 (ddd, J = 21, 12, and 7 Hz, 1 H), 0.98−1.90 (m, 6 H), 0.80−0.94 (m, 2 H), 1.25 (s, 3 H), 1.20 (d, J = 6.5 Hz, 3 H), 1.19 (d, J = 6.5 Hz, 3 H), 0.93 (s,3 H), and 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 183.4, 150.6, 146.5, 146.0, 123.7, 51.7, 41.3, 38.4, 36.2, 33.5, 33.4, 26.7, 24.1, 21.8, 20.1, 20.0, 19.9, 18.9, and 17.4. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.56; H, 8.88.

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Supporting Information Available: ^1H NMR spectra of **15**, **16**, and **26** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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