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Unified Synthesis of Quinone Sesquiterpenes Based on a Radical Decarboxylation and Quinone Addition Reaction

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Abstract: A unified synthesis of several quinone sesquiterpenes is described herein. Essential to this strategy is a novel radical addition reaction that permits the attachment of a fully substituted bicyclic core **16** to a variably substituted quinone **10**. The addition product **15** can be further functionalized, giving access to natural products with a high degree of oxygenation at the quinone unit. The quinone addition reaction is characterized by excellent chemoselectivity, taking place only at conjugated and unsubstituted double bonds, and regioselectivity, being strongly influenced by the resonance effect of heteroatoms located on the quinone ring. These features were successfully applied to the synthesis of avarol (**1**), avarone (**2**), methoxyavarones (**4**, **5**), ilimaquinone (**6**), and smenospongidine (**7**), thereby demonstating the synthetic value of this new method.

Introduction

Marine natural products exhibit an impressive array of structural motifs, many of which are derived from biosynthetic pathways that are exclusive to marine organisms. In addition, some marine metabolites possess remarkable biological activities whose potential benefit extends beyond the marine ecosystem and embodies the development of new antifungal, anticancer, and/or antiviral agents.[1] Among the many marine compounds of biological and structural interest is a family of quinone sesquiterpenes best represented by avarol (**1**),[2] avarone (**2**),[2] nakijiquinone A (**3**),[3] methoxyavarones (**4**, **5**),[4] ilimaquinone (**6**),[5] and smenospongidine (**7**)[6] (Figure 1).

From a structural standpoint, all these marine metabolites are composed of a *trans*-decalin ring, varying only at the relative position of the double bond at the C4 carbon, and decorated at the C9 position with a variably hydroxylated, or heteroatom-substituted, benzoquinone substructure. Interestingly, this ubiquitous structural motif translates to a variety of biological properties that are often unique to each family member. For

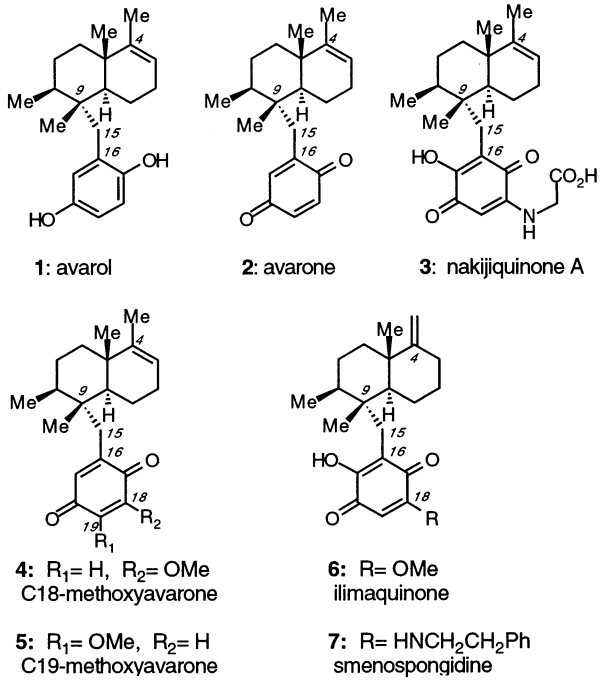

Figure 1. Selected members of the family of quinone sesquiterpenes.

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(1) For selected recent reports on this topic see (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48. (b) Biomedical Importance of Marine Organisms; Fautin, D. G., Ed.; *Memoirs Calif. Acad. Sci 13*. **1988**, 1−158. (c) Capon, R. J. *Eur. J. Org. Chem.* **2001**, 633−645. (d) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Grant Burgess, J.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347−9377. (e) Sennett, S. H. *Marine Chem. Ecol.* **2001**, 523−542. (f) *Drugs Discovery from Nature*; Grabley, Thiericke, R., Eds.; Springer-Verlag: New York, 2000.

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(5) (a) Luibrand, R. T.; Erdman, T. R.; Vollmer, J. J.; Scheuer, P. J.; Finer, J.; Clardy, J. C. *Tetrahedron* **1979**, *35*, 609−612. (b) Capon, R. J.; MacLeod, J. K. *J. Org. Chem.* **1987**, *52*, 5059−5060. (c) Carté, B.; Rose, C. B.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 2785−2787.

(6) (a) Kondracki, M.-L.; Guyot, M. *Tetrahedron Lett.* **1987**, *28*, 5815−5818. (b) Kondracki, M.-L.; Guyot, M. *Tetrahedron* **1989**, *45*, 1995−2004. (c) Rodriguez, J.; Quinoa, E.; Riguera, R.; Peters, B. M.; Abrell, L. M.; Crews, P. *Tetrahedron* **1992**, *48*, 6667−6680.

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example, avarol (**1**) and avarone (**2**) were shown to inhibit HIV-1 reverse transcriptase,[7] while their methoxylated relatives **4** and **5** are reported to have tyrosine kinase modulatory properties.[4c] On the other hand, the strong antiviral, antimitotic, and antiinflammatory activities of ilimaquinone (**6**)[8] may be connected to its ability to promote a reversible vesiculation of the Golgi apparatus and interfere with intracellular protein trafficking.[9] Furthermore, the most recently identified member of this family, nakijiquinone A (**3**), was reported to have excellent activity as an inhibitor of the *erbB*-2 protooncogene that is frequently implicated in the development of breast cancer.[10] Although the chemical origins of these biological properties remain obscure, the redox properties of the hydroquinone−quinone system present in all of these compounds may account for their diverse medicinal profiles.[11]

Intrigued with the interesting chemical structures and biological activities, we sought to design a "unified" synthetic approach to these quinone metabolites. Central to this strategy is a novel radical-based addition method that serves to connect the decalin fragment with the quinone unit. Herein we present the chemo- and regioselectivity of this reaction, expand upon its concept, and define its overall scope and limitations. Moreover, we demonstrate the synthetic value of this new method with enantioselective syntheses of avarol (**1**),[12] avarone (**2**),[12] methoxyavarones (**4**, **5**), ilimaquinone (**6**),[13] and smenospongidine (**7**).

Retrosynthetic Analysis and Strategic Bond Disconnections. The combination of a challenging structure and intriguing biological applications has prompted several research groups to investigate the synthesis of the quinone sesquiterpenes. In fact, the first synthetic entry to these compounds, a racemic synthesis of avarone (**1**), was reported in the literature in 1982,[14] and since then several syntheses of **1**,[15] **2**,[15] **3**,[16] and **6**[16] have been published. A common characteristic to all these synthetic strategies is the assembly of the entire backbone of the molecule by constructing the C9−C15 bond. This is achieved by a reductive alkylation (Li/NH_3) of a suitably functionalized enone with an appropriately substituted benzyl bromide. A consequence of this approach is that the quinone unit is attached on the decalin core relatively early during the synthesis, substantially restricting access to different natural products from a common intermediate. Moreover, due to functional group incompatibility issues, the quinone ring has to be introduced as an aromatic unit in which the phenolic groups are masked with robust protecting groups. Consequently, the final deprotection steps afford the natural product(s) in rather low yields.

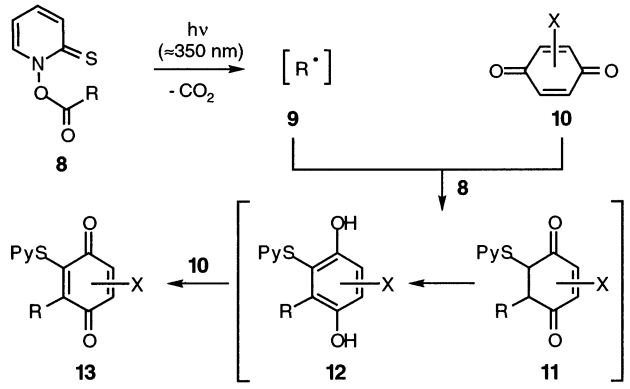

Figure 2. Radical decarboxylation and quinone addition reaction.

The above observations led us to consider an alternative disconnection centered around the formation of the C15−C16 bond. In principle, this connection could be accomplished by reacting a C15 carbon-centered radical with a quinone such as **10** (Figure 2). The concept of this method, herein referred to as the radical decarboxylation and quinone addition reaction, is based on generating radical **9** from thiopyridone derivative **8**[17] and trapping it with quinone **10** by a radical-chain process.[18] The newly formed semiquinone **11** was expected to undergo tautomerization to hydroquinone **12**, thus protecting the second double bond of the semiquinone from further attack by carbon radicals. A slow oxidation of **11** or **12** in the presence of excess **10** could then produce the desired quinone **13**.[19]

A general retrosynthetic scheme based on the above disconnection is shown in Figure 3. Photochemical decarboxylation of thiocarbonyl derivative **16** and trapping of the derived C15 radical with appropriately substituted quinone **10** could produce adduct **15**. It was expected that further functionalization (reductive desulfurization and/or addition−elimination) of the thiopyridyl group of **15** would allow access to all structures of

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(10) For an interesting account on the synthesis and biological investigation of this natural product, see (a) Stahl, P.; Waldmann, H. *Angew. Chem.* **1999**, *38*, 3710−3713. (b) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586−11593.

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(12) For a preliminary communication on the synthesis of **1** and **2**, see Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem.* **1999**, *38*, 3089−3091.

(13) For a preliminary communication on the synthesis of **6**, see Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819−822.

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(15) For other syntheses of avarol and avarone, see (a) Locke, E. P.; Hecht, S. M. *Chem. Commun.* **1996**, 2717−2718. (b) An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775−8779.

(16) For other syntheses of **6**, see (a) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114−1115. (b) Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823−2831. (c) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890−5894.

(17) For selected reviews on the photochemical decarboxylation of thiopyridone derivatives, see (a) Crich, D. *Aldrichim. Acta* **1987**, *20*, 35−49. (b) Barton, D. H. R. *Pure Appl. Chem.* **1994**, *66*, 1943−1954. (c) Barton, D. H. R. *Tetrahedron* **1992**, *48*, 2529−2544.

(18) (a) Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419−3430. (b) Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 5307−5314.

(19) This oxidation can be mechanistically explained if we consider that alkyl-substituted quinones are known to have lower oxidation potentials than the nonsubstituted counterparts. For recent reviews on this topic see (a) *The Chemistry of the Quinonoid Compounds, Volumes 1 and 2*; Patai, S., Rappoport Z., Eds.; Wiley: New York, 1988. (b) *Naturally Occurring Quinones IV: Recent Advances*, 4th ed.; Thomson, R. H., Eds.; Blackie Academic & Professional: London, 1997.

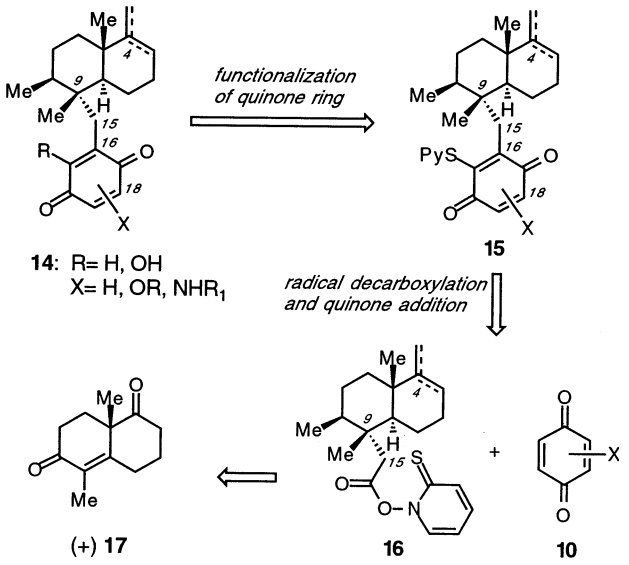
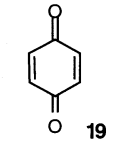
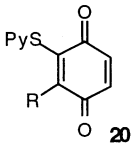
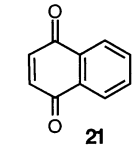
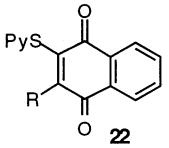
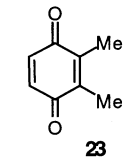
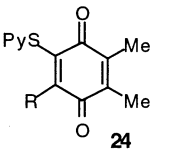
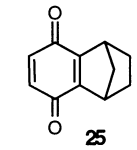
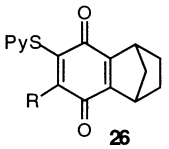
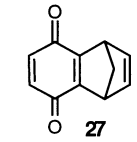
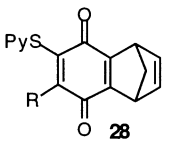
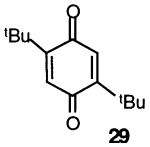


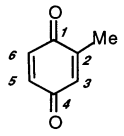
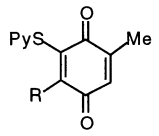
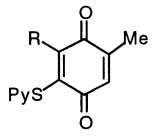
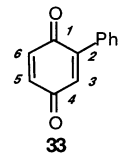
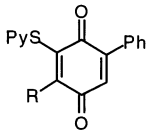
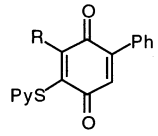
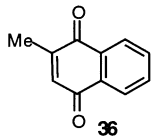
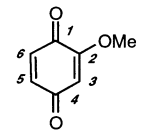
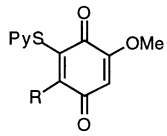
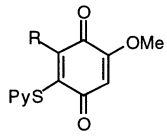
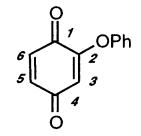
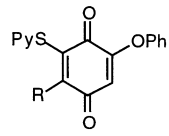
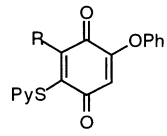
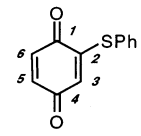
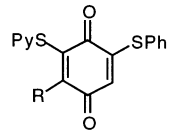
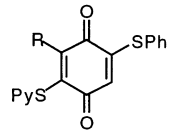
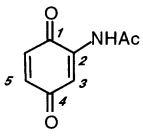
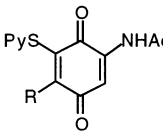
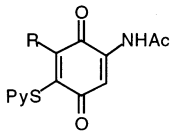
Figure 3. Strategic bond disconnections of quinone sesquiterpenes.

Table 1. Addition of Carbon Radicals to Symmetric Quinones

Entry	Quinone	Thiopyridone derivative	Product	Yield
1	 **19**	**18a**	 **20**	**20a** : 83%
2		**18b**		**20b** : 77%
3		**18c**		**20c** : 48%
4	 **21**	**18a**	 **22**	**22a** : 88%
5		**18b**		**22b** : 71%
6		**18c**		**22c** : 46%
7	 **23**	**18a**	 **24**	**24a** : 77%
8		**18b**		**24b** : 69%
9		**18c**		**24c** : 47%
10	 **25**	**18a**	 **26**	**26a** : 81%
11		**18b**		**26b** : 70%
12	 **27**	**18a**	 **28**	**28a** : 84%
13		**18b**		**28b** : 75%
14	 **29**	**18a**	NR	
15		**18b**		

quinone sesquiterpenes. Starting material for this strategy would then be enone **17**, which following the necessary functionalizations at the C4, C8, C9, and C10 centers could provide thiocarbonyl derivative **16**.

Table 2. Addition of Carbon Radicals to Unsymmetric Quinones

Entry	Quinone	Thiopyridone derivative	Products (Yield)	
1	 **30**	**18a**	 **31a**: 45% **31b**: 42%	 **32a**: 37% **32b**: 32%
2		**18b**		
3	 **33**	**18a**	 **34a**: 39% **34b**: 40%	 **35a**: 36% **35b**: 35%
4		**18b**		
5	 **36**	**18a**	NR	
6		**18b**		
7	 **37**	**18a**	 **38a**: 80% **38b**: 68%	 **39a**: 7% **39b**: 5%
8		**18b**		
9	 **40**	**18a**	 **41a**: 76% **41b**: 72%	 **42a**: 7% **42b**: 6%
10		**18b**		
11	 **43**	**18a**	 **44a**: 72% **44b**: 69%	 **45a**: 4% **45b**: 4%
12		**18b**		
13	 **46**	**18a**	 **47a**: 48% **47b**: 45%	 **48a**: 19% **48b**: 15%
14		**18b**		

Chemoselectivity and Regioselectivity of the Radical Addition to Quinones. The chemoselectivity and regioselectivity of the radical decarboxylation and quinone addition reaction were examined with a variety of symmetric and unsymmetric quinones (Tables 1 and 2, respectively). These studies were performed with primary (2- phenylethyl), secondary (cyclohexyl), and tertiary (*tert*-butyl) carbon radicals generated from precursors **18a**, **18b**, and **18c**, respectively (Figure 4). Optimization of the reaction conditions was performed with benzoquinone (**19**) as the radical trap. Best results were obtained when the thiocarbonyl derivatives were dissolved in dichloromethane together with 3 equiv of **19**, and the radical

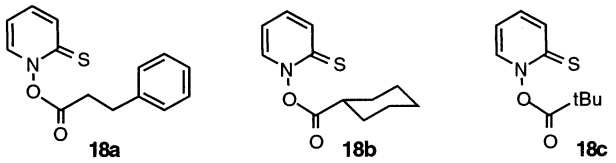


Figure 4. Structures of thiopyridone derivatives **18a**, **18b**, and **18c**.

decarboxylation was performed at 0 °C with two halogen lamps (500 W each). In all cases, the photochemistry was carried out until all starting thiopyridone derivative had been consumed (typically 1−3 h) and the products were purified by chromatography and spectroscopically characterized.[20] Under these conditions the addition products **20a**, **20b,** and **20c** were isolated as the corresponding quinones in 83%, 77%, and 48% yields respectively (Table 1, entries 1−3).[21] Similar yields were obtained with naphthoquinone (**21**) (Table 1, entries 4−6) and suggested that this reaction is synthetically useful in the case of both primary and secondary carbon radicals.

The chemoselectivity of the radical addition was explored with quinones **23**, **25**, and **27** as radical traps. In all these cases the only isolated products were formed from the reaction of radicals with conjugated and unsubstituted double bonds. This chemoselectivity may explain why quinone **29** did not participate as a radical trap in this reaction. In this case, the rearrangement product of the corresponding thiocarbonyl derivative was isolated as the sole product.[22]

To define how alkyl or heteroatom groups on the quinone trap affect the regiochemistry of the radical addition, we tested the reactivity of unsymmetrically substituted quinones. These results are shown in Table 2. Trapping of radicals with quinones **30** and **33** occurred at the nonsubstituted double bonds and gave rise to addition products in good overall yields. As expected, quinone **36** was not reactive under these conditions, reinforcing the previously drawn conclusion that the double bond needs to be unsubstituted at both carbon atoms. It was interesting to observe that the reaction of **18a** with quinone **30** gave rise to two addition products, **31a** and **32a**, isolated in 82% overall yield and a 1.2:1 molar ratio in favor of adduct **31a**. The reaction of **18b** with **30** exhibited comparable regioselectivity, giving rise to products **31b** and **32b** (74% overall yield and 1.3:1 ratio). In both cases, the major products had the carbon radical attached at the C5 carbon center, para to the alkyl substituent of the quinone. This modest regioselectivity of the addition may be explained by the weak, but not negligible, electron-donating effect of the methyl group, which increases the electron density of the C4 carbonyl group. The C1 carbonyl group of **30** is then more electron-deficient, thereby rendering more favorable the attack of the carbon radicals on its β-carbon center (C5 carbon). A similar trend of regioselectivity was observed with quinone **33** and may also be attributed to a weak electron-donating effect of the phenyl group.

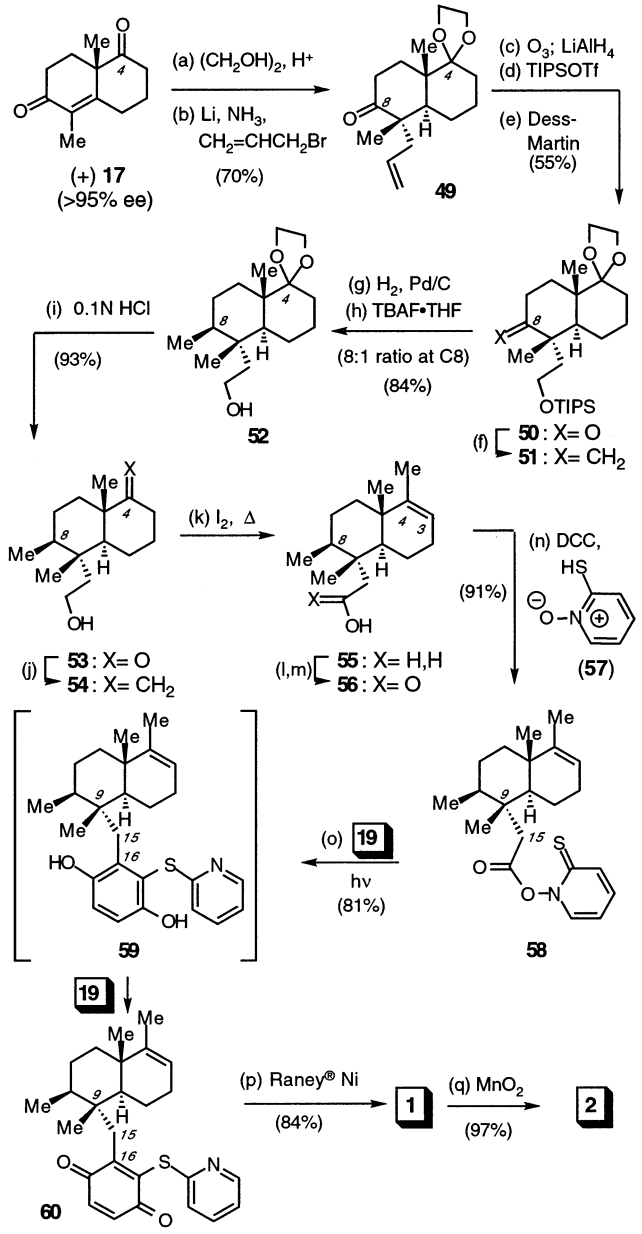
The regioselectivity of the radical addition increased dramatically when the reaction was performed with quinones containing heteroatoms such as **37**, **40**, and **43**. For example, reaction of compound **18a** with methoxybenzoquinone (**37**) afforded diastereomers **38a** and **38b** in 87% overall yield and 12:1 ratio in favor of **38a**. Similar effects were observed in the cases of quinones **40** and **43** with both primary and secondary radicals. The remarkable regioselectivity of these additions can be rationalized on the basis of the strong electron-donating effects of the methoxy-, phenoxy-, and thiophenyl groups, that shield the C4 carbonyl group via a "vinylogous ester" effect.[23] This renders the C5 carbon center a better conjugate electrophile, since it is β to the most electronically deficient C1 carbonyl group. Consequently, the preferred site for new carbon−carbon bond formation is the C6 atom. As expected, the ratio of isomers **47**:**48** is significantly decreased with the weak electron-donating acetamide functionality of quinone **46** as the directing group.

The above studies led us to draw several conclusions regarding the scope and limitations of the radical decarboxylation and quinone addition reaction that are summarized as follows: (a) both primary and secondary carbon radicals can be trapped with a variety of quinones giving rise to addition products in synthetically useful yields; (b) the quinone addition is chemoselective and takes place only at conjugated and unsubstituted double bonds; and (c) the radical addition is strongly influenced by the resonance effect (vinylogous ester effect) of heteroatoms located on the quinone ring. Having defined the chemo- and regioselectivity issues of this reaction, we sought to validate its synthetic utility by applying it to a "unified" synthesis of several members of quinone sesquiterpenes.

Total Synthesis of Avarol (1) and Avarone (2). Our synthetic approach toward the core fragment of avarol (**1**) and avarone (**2**) began with enantiomerically enriched enone **17**, which was readily available through a L-phenylalanine-mediated asymmetric Robinson annulation (60−65% yield, >95% ee) (Scheme 1).[24] Selective protection of the more basic C4 carbonyl group, followed by reductive alkylation of the enone functionality with allyl bromide, afforded ketone **49** in 70% overall yield. Conversion of ketone **49** to silyl ether **50** was accomplished via a sequence of three steps including ozonolysis of the terminal double bond, reduction of the resulting aldehyde, and selective silylation of the primary alcohol (64% combined yield). The C8 ketone functionality that also suffered reduction during the above procedure was subsequently restored upon treatment with Dess−Martin periodinane (87% yield).[25] Functionalization of the C_8 stereocenter was achieved by Wittig olefination, followed by a Pd-catalyzed hydrogenation of the resulting exocyclic methylene unit. This procedure installed the methyl group at the C8 carbon in an 8:1 ratio in favor of the desired β-epimer and 85% combined yield. These stereoisomers were easily separated after fluoride-induced deprotection of the silyl ether functionality, furnishing alcohol **52** in 75% overall yield (starting from **50**). Acid-catalyzed deprotection of the C4 ketal of **52**

(20) For complete experimental procedures and characterization data of all compounds, including copies of ^{1}H and ^{13}C NMR spectra, see Supporting Information.
(21) Thermal decarboxylation of thiopyridone derivatives **18a**−**c** can also be employed as an alternative to the photochemical treatment, by heating a toluene solution of these compounds in the presence of **19**. In this case, however, the addition products **20a**−**c** were isolated in 60−35% yields.
(22) In the absence of any radical trap, decarboxylation of a thiopyridone derivative produces the corresponding thioether of generic structure R−SPy. This compound, referred to herein as rearrangement product, is the major side product of this reaction and accounts for the remaining of the mass balance.
(23) The "vinylogous ester" effect of alkoxy groups in benzoquinone and related compounds has been explored in regioselective Diels−Alder reactions. For selected reviews on this topic, see (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford and New York, 1991; pp 315−399. (b) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70−89.
(24) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308−2311.
(25) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

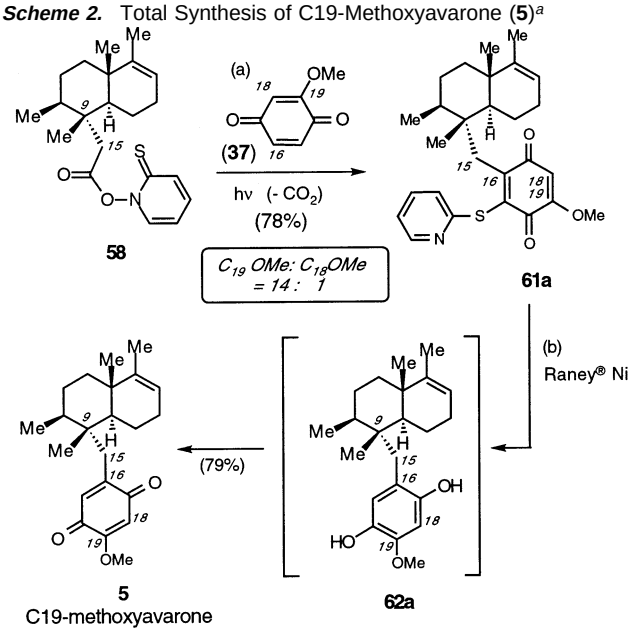
Scheme 1. Total Synthesis of Avarol (**1**) and Avarone (**2**)[a]



[a] Reagents and conditions: (a) 1.0 equiv of $(CH_2OH)_2$, 0.1 equiv of TsOH, 80 °C, benzene, 12 h, 90%; (b) 5.0 equiv of Li(0), NH_3, −80 to −30 °C, 1.0 equiv of H_2O, 5.0 equiv of CH_2=$CHCH_2Br$, −80 to −30 °C, 5 h, 78%; (c) O_3, CH_2Cl_2, −78 °C, then 3.0 equiv of $LiAlH_4$, Et_2O, 0 to 25 °C, 1 h, 65%; (d) 1.0 equiv of TIPSOTf, 1.3 equiv of 2,6-lutidine, CH_2Cl_2, −80 °C, 0.5 h, 98%; (e) 1.6 equiv of Dess−Martin periodinane, CH_2Cl_2, 1 h, 25 °C, 87%; (f) 3.0 equiv of CH_3PPh_3Br, 2.5 equiv of NaHMDS, THF, 65 °C, 10 h, 89%; (g) 0.1 equiv/weight of Pd/C (10%), H_2, CH_3CO_2Et, 25 °C, 12 h, 95% (8:1 ratio at C8); (h) 1.3 equiv of TBAF·THF (1 N), THF, 25 °C, 0.5 h, 100%; (i) 0.1 N HCl, THF, 3 h, 25 °C, 93%; (j) 3.0 equiv of CH_3PPh_3Br, 2.5 equiv of NaHMDS, THF, 65 °C, 10 h, 91%; (k) 0.01 equiv of I_2, xylenes, 150 °C, 12 h, 89%; (l) 1.2 equiv of Dess−Martin periodinane, CH_2Cl_2, 1 h, 25 °C, 90%; (m) 2.0 equiv of $NaClO_2$, 2.0 equiv of NaH_2PO_4, 2.0 equiv of CH_3CH=$C(CH_3)_2$, tBuOH/H_2O 2/1, 25 °C, 1 h, 90%; (n) 1.0 equiv of **56**, 1.0 equiv of **57**, 1.0 equiv of DCC, CH_2Cl_2, 12 h, 25 °C, (dark), 91%; (o) 3.0 equiv of **19**, CH_2Cl_2, *hν* (2 × 500 W), 2 h, 0 °C, 81%; (p) Raney Ni (excess), CH_2Cl_2, 45 °C, 10 min, 84%; (q) 5.0 equiv of MnO_2, Et_2O, 25 °C, 0.5 h, 97%.

gave rise to ketone **53** in 93% yield, which after a second Wittig methylenation provided the exocyclic alkene **54** in 91% yield. Compound **54** has the desired functionalities and stereochemistry encountered in the structure of all quinone sesquiterpenes and is defined as the most advanced common intermediate for our synthetic ventures.

Scheme 2. Total Synthesis of C19-Methoxyavarone (**5**)[a]



[a] Reagents and conditions: (a) 3.0 equiv of **37**, CH_2Cl_2, *hν* (2 × 500 W), 2 h, 0 °C, 84%, **61a**:**61b** = 14:1; (b) Raney Ni (excess), CH_2Cl_2, 45 °C, 10 min; then air [O], 79%.

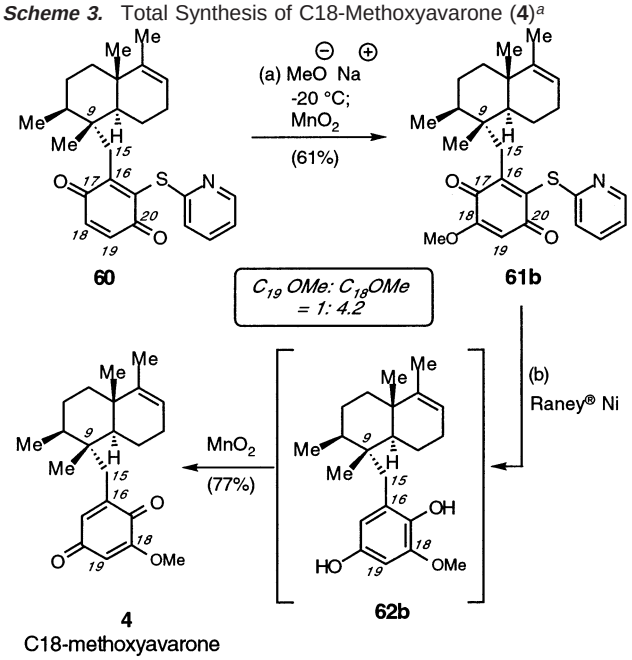
For the synthesis of avarol and related natural products, the exocyclic double bond of **54** was isomerized to produce the more substituted alkene **55**, which, after a two-step oxidation involving Dess−Martin periodinane and sodium chlorite, produced the desired carboxylic acid **56** in 81% overall yield. The stage was now set for the attachment of the aromatic residue on the decalin ring. This was accomplished by DCC-induced esterification of **56** with commercially available 2- mercaptopyridine *N*-oxide (**57**), furnishing the photolabile ester **58** (91% yield). Light-induced decarboxylation of ester **58** in the presence of benzoquinone **19** (3.0 equiv), under identical experimental conditions as optimized during our model studies, produced the substituted quinone **60** in 81% yield. Similar to our previous mechanistic hypothesis, the formation of compound **60** may be rationalized by considering an initial formation of a semiquinone adduct that epimerizes to hydroquinone **59** and is further oxidized in situ with excess **19**.[26] At this point, brief treament of **60** with Raney nickel produced synthetic avarol (**1**) in 84% yield. Consequently, avarone (**2**) was produced from **1** via heterogeneous oxidation with MnO_2 in 97% yield (Scheme 1).[27]

Total Synthesis of C18- and C19-Methoxyavarones. The structure of C19-methoxyavarone (**5**) is highlighted by a benzoquinone unit in which a methoxy functionality is attached para to the decalin core. This regiochemistry suggested that compound **5** can be constructed via a radical decarboxylation and quinone addition reaction with methoxybenzoquinone (**37**) as the radical trap. This synthetic effort is summarized in Scheme 2. Thiopyridone derivative **58** underwent photoinduced decarboxylation in the presence of quinone **37** to produce compound

(26) Compound **59** was independently produced by reduction of **60** with $Na_2S_2O_4$ and was quantitatively reoxidized to **60** upon treatment with benzoquinone (**19**).

(27) Synthetic avarol (**1**) and avarone (**2**) were spectroscopically and analytically identical to the natural compounds, provided to us by Professor D. J. Faulkner (Scripps Institute of Oceanography). See also Supporting Information for more details.

Scheme 3. Total Synthesis of C18-Methoxyavarone (**4**)[a]



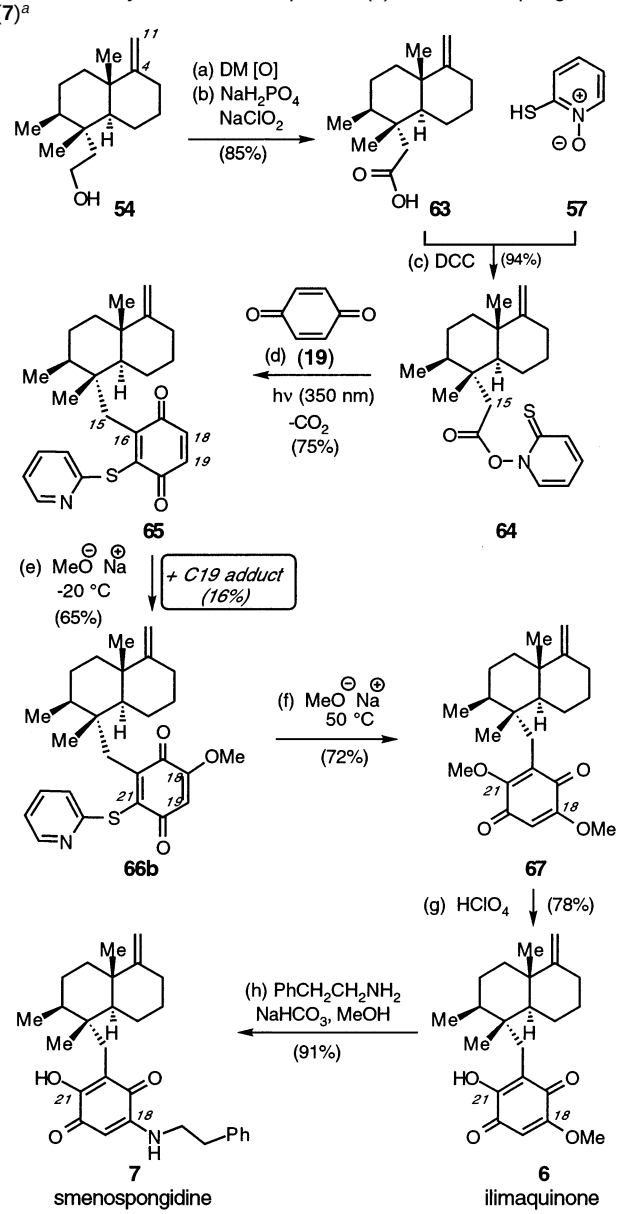
[a] Reagents and conditions: (a) 5.0 equiv of MeONa (0.5 M in MeOH), THF, −20 °C, 2 h; then aqueous NH_4Cl, AcOEt, 5.0 equiv of MnO_2, 25 °C, 1 h, 76%, **61a**:**61b** = 1:4.2; (b) Raney Ni (excess), CH_2Cl_2, 45 °C, 10 min; then 5.0 equiv of MnO_2, 0.5 h, 77%.

61a as the major isomer together with a small amount of the C18 methoxy adduct **61b** (**61a**:**61b** = 14:1, overall yield of 84%) (for the structure of **61b** see Scheme 3). After purification on silica gel, **61a** was subjected to a reductive desulfurization with Raney nickel, producing, after a smooth air oxidation, synthetic C19-methoxyavarone (**5**) in 79% yield.[28]

Although the above sequence can also produce C18-methoxyavarone (**4**) from manipulation of the minor diastereomer **61b**, we decided to examine an alternative approach in order to maximize its formation. With this concept in mind, we turned our attention to quinone **60**, an advanced intermediate produced during the avarone synthesis. We hypothesized that the C17 carbonyl group of **60** is more electronically rich as compared to the C20 functionality due to the electron-donating effect of the thiopyridyl group at C21. By virtue of this effect, the C18 carbon center could be viewed as a better electrophilic carbon for conjugate additions and could be functionalized with methoxide anion.[29] Indeed, treatment of **60** with 5 equiv of sodium methoxide at −20 °C, followed by one-pot oxidation with MnO_2, gave rise to a mixture of **61a** and **61b** in a 1:4.2 ratio in favor of the desired adduct **61b** in 76% overall yield. Treatment of **61b** with Raney nickel, followed by MnO_2 oxidation of the resulting hydroquinone, afforded C18-methoxyavarone (**4**) in 77% yield (Scheme 3).[28]

Total Synthesis of Ilimaquinone (6) and Smenospongidine (7). The chemical structures of ilimaquinone and smenospongidine differ from those of avarone-like molecules at the position of unsaturation of the decalin core and the additional oxygenation at the C21 center of the quinone ring. These issues were addressed as shown in Scheme 4. Alcohol **54**, representing the fully substituted decalin core of **6** and **7**, was oxidized to the corresponding carboxylic acid **63** (Dess−Martin periodinane and sodium chlorite) in 85% combined yield. Coupling of **63** with **57** proceeded in the presence of DCC and afforded compound **64** in 94% yield. Light-induced decarboxylation (>350 nm) of **64** in the presence of excess benzoquinone (**19**) produced the substituted quinone **65** in 75% yield, which upon treatment with sodium methoxide at −20 °C afforded quinone **66b** as the major product in 65% yield. Under these conditions the C19-methoxylated adduct **66a** was also isolated as a minor product

Scheme 4. Synthesis of Ilimaquinone (**6**) and Smenospongidine (**7**)[a]



[a] Reagents and conditions: (a) 1.2 equiv of Dess−Martin periodinane, CH_2Cl_2, 1 h, 25 °C, 96%; (b) 2.0 equiv of $NaClO_2$, 2.0 equiv of NaH_2PO_4, 2.0 equiv of $CH_3CH{=}C(CH_3)_2$, tBuOH/H_2O 2/1, 25 °C, 1 h, 89%; (c) 1.0 equiv of **63**, 1.0 equiv of **57**, 1.0 equiv of DCC, CH_2Cl_2, 12 h, 25 °C, (dark), 94%; (d) 3.0 equiv of **19**, CH_2Cl_2, *hν* (2 × 500 W), 2 h, 0 °C, 75%; (e) 5.0 equiv of MeONa (0.5 M in MeOH), MeOH, −20 °C, 2 h; then aqueous NH_4Cl, CH_2Cl_2, 5.0 equiv of MnO_2, 1 h, 65% for **66b** and 16% for **66a** (C19 adduct); (f) 3.0 equiv of MeONa (0.5 M in MeOH), MeOH, 50 °C, 1 h; 72%; (g) 1.2 equiv of $HClO_4$ (70% aq), THF, 25 °C, 4 h, 78%; (h) 1.5 equiv of $PhCH_2CH_2NH_2$, $NaHCO_3$ (excess), MeOH, 40 °C, 10 h, 91%.

(28) Spectroscopic and analytical data of synthetic methoxyavarones **4** and **5** were identical to the ones reported for the natural products (cited herein as ref 4). See also Supporting Information for more details.

(29) For a related study on vicinally substituted quinones, see Cox, A. L.; Johnston, J. N. *Org. Lett.* **2001**, *3*, 3695−3697.

(16% yield) and was chromatographically separated from desired compound **66b**.

Next task was the exchange of the thiopyridyl group of **66b** with a hydroxyl equivalent. Our initial attempts to perform this displacement in a direct way, by reacting **66b** with hydroxide anion, led to formation of multiple products, arising presumably by reaction of hydroxide anions at both the C18 and C21 centers. This problem was circumvented by using a two-step procedure that involved reaction of **66b** with sodium methoxide at elevated temperature (3 equiv of sodium methoxide at 50 °C) to furnish dimethoxyquinone **67**, followed by selective hydrolysis of the C21 methoxy unit under dilute perchloric acid conditions.[30,31] This sequence of reactions gave rise to synthetic ilimaquinone (**6**) in 56% overall yield.[32] Finally, exposure of **6** to phenylethylamine under basic conditions[33] afforded synthetic smenospongidine (**7**) in 91% yield (Scheme 4).

Conclusion

In summary, we present herein a new application of the Barton's radical decarboxylation reaction, in which the generated radicals are trapped by a quinone trap, giving rise to addition products in good to excellent yields. This addition reaction is characterized by good chemoselectivity, taking place only at conjugated and unsubstituted double bonds, and regioselectivity, being strongly influenced by the resonance effect of heteroatoms located on the quinone ring. The synthetic value of this reaction was demonstrated by the synthesis of selected members of a family of quinone sesquiterpenes. Both symmetric and unsymmetric quinones can be used as radical traps and provide facile access to heteroatom-substituted quinone sesquiterpenes. The versatility of our strategy was further expanded by developing reaction conditions that allow subsequent oxygenation of the quinone adducts, providing access to complementary oxygenated structures.

Acknowledgment. Financial support from the NIH (CA 086079) is gratefully acknowledged. We thank Professor D. John Faulkner (Scripps Institute of Oceanography) for providing us with samples of natural avarone and ilimaquinone and for critical suggestions on the spectroscopic analysis of quinone rings. We also thank Professor Phillip Crews (UC Santa Cruz) for providing us with copies of the NMR data of methoxy avarones **4** and **5**.

Supporting Information Available: Complete experimental procedures and spectroscopic/analytical data of new compounds including copies of ^{1}H NMR and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA027517Q

(30) (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Chem. Pharm. Bull.* **1998**, *46*, 1770−1775. (b) Kubo, I.; Kamikawa, T.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 3825−3828.

(31) The selectivity observed during this step may be explained by considering the relative stability of the tetrasubstituted enol formed by conjugate addition of a hydroxyl unit at the C21 center of quinone **67** versus the less substituted one arising from conjugate addition at the C18 center.

(32) (a) Evans, T. P.; Cornell, L.; Peterson, R. W.; Faulkner, D. J. *Nat. Prod. Lett.* **1994**, *4*, 287−291. (b) Cozzolino, R.; De Giulio, A.; De Rosa, S.; Strazzullo, G.; Gasic, M. J.; Sladic, D.; Zlatovic, M. *J. Nat. Prod.* **1990**, *53*, 699−702.

(33) Synthetic ilimaquinone (**6**) was found to be spectroscopically and analytically identical to the natural compound, provided to us by Professor D. J. Faulkner (Scripps Institute of Oceanography). Spectroscopic and analytical data of synthetic smenospongidine (**7**) was identical to the ones reported for this natural product (see ref 6). See also Supporting Information for more details.