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A Concise Synthesis of (+)-Salvadione B[†,‡]

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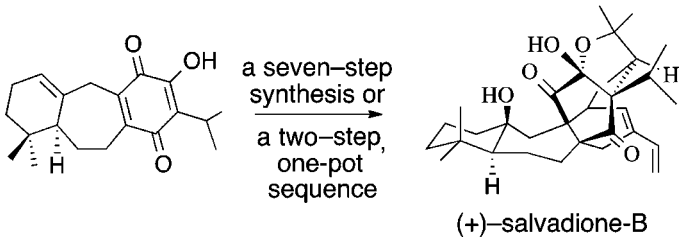
ABSTRACT



The novel hexacyclic triterpene salvadione B was synthesized in seven steps from the chiral quinone shown. The insight gained from this synthesis permitted a two-step, one-pot sequence to introduce the three additional rings and seven chiral centers.

Salvia bucharica is a member of the plant family Lamiaceae (Labiatae),[1a] known throughout Central Asia as "sursaudah". This wild and aromatic shrub, commonly found in dry rocky places of eastern Afghanistan and the Baluchistan region of Pakistan, is used as a traditional medicine for liver disorder,[1b] or as a cooling medicine.[1c]

In 1999, Ahmad and co-workers reported the isolation of salvadione B (**1**)[2a] and salvadiol (**2**)[2b] from the hexane-soluble extract of *Salvia bucharica* (Figure 1). Both of these novel isomeric triterpenes contain complex arrays of six fused and/or bridged rings and eight asymmetric centers. They differ in configuration at only one asymmetric center, suggesting that they can be made via a common strategy.[3] Herein, we describe an efficient seven-step synthesis of (+)−salvadione-B from quinone (*S*)-**4** and a two-step, one-pot sequence.[4]

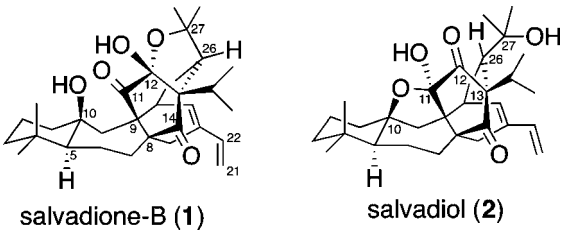


Figure 1. Two isomeric "pseudotriterpenes".[3]

Our strategy to prepare salvadione-B is shown in Scheme 1. We have shown that dienes add to quinone (*S*)-**4** from the α-face, thereby creating the requisite relative configurations at C-8, C-9 and C-25 of salvadione-B.[5] The use of triene-selenide **3** in a Diels−Alder reaction raises the question whether it will react as a 2,4- or as a 4,6-disubstituted butadiene. Scrutiny of conformer **3a** reveals that the methyl substituent at C-2 of this diene hinders the *s*-cis conformer, thus favoring conformer **3b**, so that it will react with quinone (*S*)-**4** to give adduct **5**.

Oxidative radical cyclizations are useful for constructing polycyclic skeletons.[6] After converting the selenide into an

[†] Dedicated to the memory and scientific accomplishments of Professor Mugio Nishizawa, (Tokushima-Bunri University, Japan), 1945−2010.

[‡] Taken in part from the Ph.D. dissertation of Ge Zou, University of Georgia, 2009.

(1) (a) Fujita, E.; Node, M. *Prog. Chem. Org. Nat. Prod.* **1986**, *46*, 77–157. (b) Chopra, R. N.; Nayar, S. L.; Chopra, I. C. *Glossary of Indian Medicinal Plants*; CSIR: New Delhi, 1956; 189. (c) Nasir, E.; Ali, S. I. *Flora of Pakistan*; Fakhri Press: Karachi, 1986, 56, 156.

(2) (a) Isolation of salvadione B: Ahmad, V. U.; Zahid, M.; Ali, M. S.; Jassbi, A. R.; Abbas, M.; Clardy, J.; Lobkovsky, E.; Tareen, R. B.; Iqbal, M. Z. *J. Org. Chem.* **1999**, *64*, 8465–8467. (b) Isolation of salvadiol: Ahmad, V. U.; Zahid, M.; Ali, M. S.; Choudhary, M. I.; Akhtar, F.; Ali, Z.; Iqbal, M. Z. *Tetrahedron Lett.* **1999**, *40*, 7561–7564.

(3) On a biogenetic basis, **1** and **2** and related natural products should be considered as "pseudo-triterpenes" since they are the result of the coupling of a mono- and diterpene and not derived from squalene.

(4) For the synthesis of perovskone, see: (a) Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *11*, 4979–4980. (b) Majetich, G.; Zhang, Y.; Tian, X.; Britton, J. E.; Li, Y.; Phillips, R. *Tetrahedron* **2011**, *67*, 10129–10146. For the synthesis of salvadione A, see: (c) Majetich, G.; Wang, Y.; Li, Y.; Vohs, J. K.; Robinson, G. H. *Org. Lett.* **2003**, *5*, 3847–3850.

(5) For a comprehensive review of the Diels−Alder reactions of quinone (*S*)-**4**, see: Majetich, G.; Zhang, Y.; Tian, X.; Zou, G.; Li, Y.; Wang, Y.; Hu, S.; Huddleston, E. *Molecules* **2013**, *18* (6), 6969–6989 DOI: H.3390/molecules18066969.

(6) (a) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *5*, 6969–6978. (b) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023. (c) Heckrodt, T.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680–4681.

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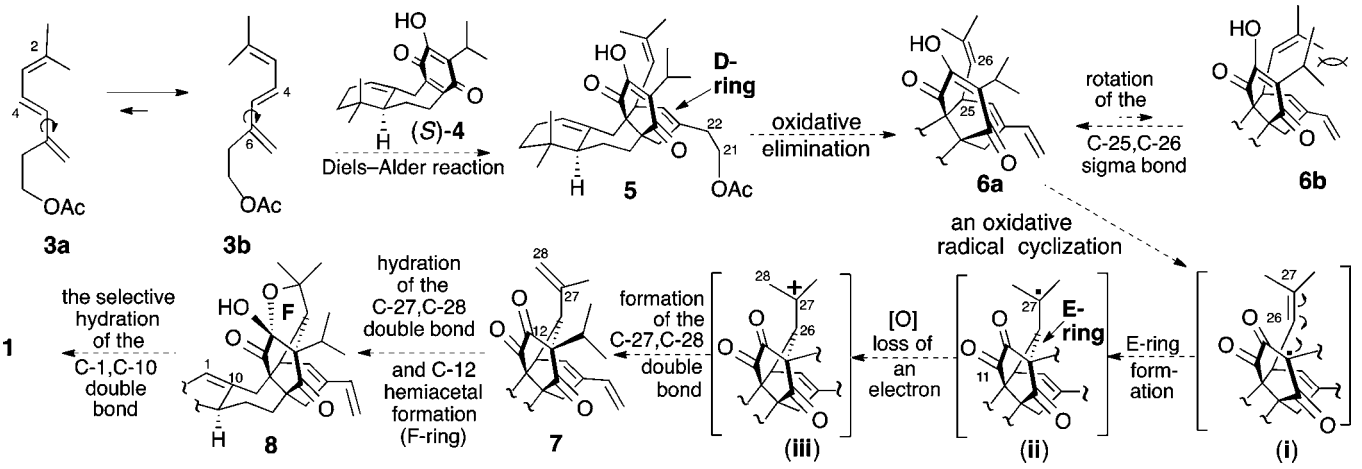
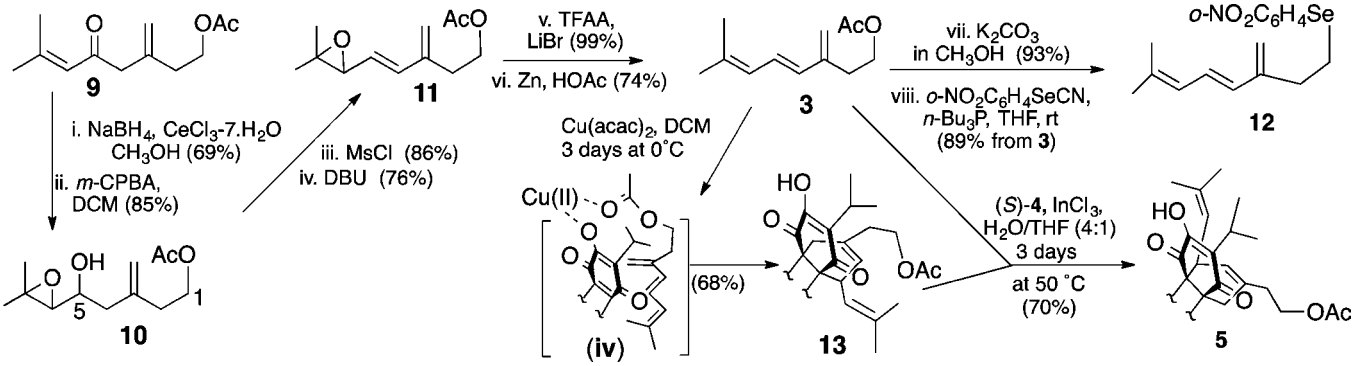
Scheme 1. Retrosynthetic Analysis of Salvadione B



Scheme 2. Preparation and Diels–Alder Reactions of Triene Acetate **12**



alkene, we expected that a free radical cyclization would form the C-13,C-26 σ bond (cf. **6** → **i** → **ii**) and that oxidative elimination of the C-27 radical would produce carbocation **iii** and ultimately tetraene **7**, which has the entire carbon skeleton and all but two of the chiral centers present in **1**. On the basis of our salvadione A synthesis,[4c] nonbonded steric interactions between the C-25 side chain and the C-13 isopropyl group of conformer **6b** would favor the less congested conformer **6a**. This conformational biasing thus controls the C-26 stereochemistry. Hydration of the C-27,C-28 double bond was expected to form hemiacetal **8**, whereas addition of water to the C-1,C-10 double bond of **8** would complete a synthesis of **1**. We were hopeful that the five transformations shown in Scheme 1 were amenable to a cascade process.

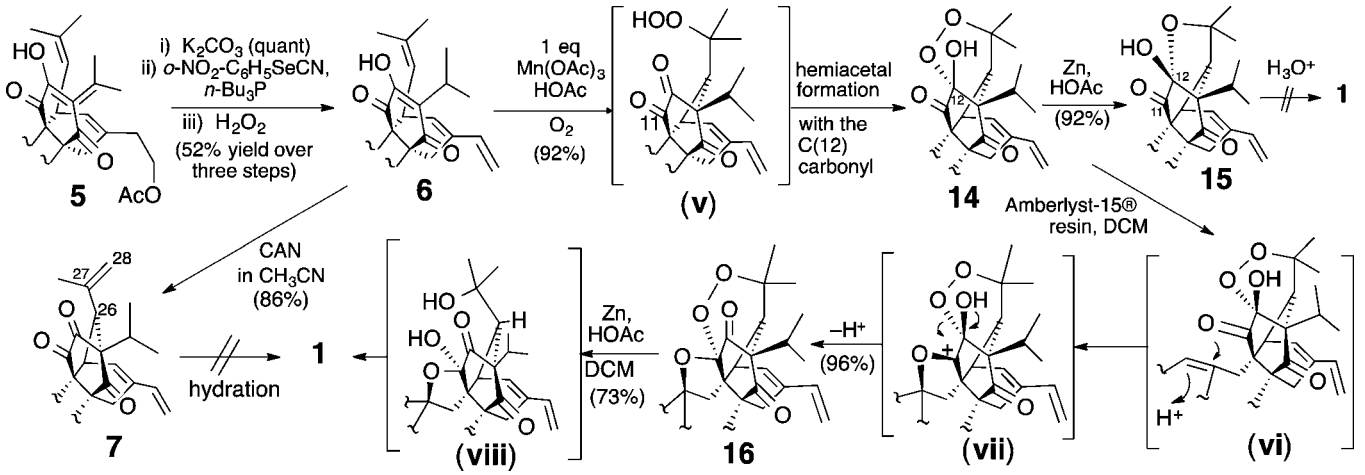
Triene acetate **3** was prepared in six steps from enone **9** (Scheme 2).[7] The Luche reduction of **9** furnished an allylic alcohol in 65% yield, which was selectively epoxidized using *m*-CPBA in DCM. The dehydration of epoxy alcohol **10** was achieved in 63% yield via a mesylation/elimination sequence. Deoxygenation of epoxide **11** was achieved by treating **11** with triflic anhydride and lithium bromide to produce a bromohydrin, which was further reduced by zinc powder to give triene acetate **3** in 73% yield from **11**. Note that saponification of acetate **3** gave a primary alcohol which was converted to selenide **12** using the protocol developed by Grieco, Gilman, and Nishizawa.[8]

The Diels–Alder reaction between triene acetate **3** and quinone (*S*)-**4** was studied to gain insight into the regioselectivity of the cycloaddition. When 1 equiv of triene acetate **3** reacted with 1 equiv of (*S*)-**4** in toluene at 80 °C for 3 h in the presence of a catalytic amount of tris-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedianato-europium [Eu(fod)$_3$], adducts **5** and **13** were produced. The ratio of **5** to **13** improved with longer reaction times and occurred more rapidly when excess **3** was used. Reaction temperatures > 90 °C or prolonged heating caused acetate **3** to polymerize. The more favorable ratio of cycloadduct **5** to its regioisomer **13** after longer reaction times is because adduct **13** undergoes a retro-Diels–Alder reaction more

(7) Garbers, C. F.; Scott, F. *Tetrahedron Lett.* **1976**, 1625–1628.

(8) (a) Rideout, D.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. (b) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897–1900.

Scheme 3. Stepwise Synthesis of Salvadione B



readily than adduct **5** does. Adduct **13** was heated in toluene at 80 °C for 6 h. Workup and analysis showed that all of adduct **13** had been consumed and that only adduct **5**, and unreacted **3** and **4**, were present in the reaction mixture. Continued heating of this mixture for an additional 72 h gave only adduct **5**. In contrast, heating pure adduct **5** under identical conditions produced no adduct **13**. This indicates that adduct **5** is more thermally stable than **13**. Using stronger Lewis acids, even at −78 °C, caused triene **3** to decompose. Note that the reaction of **3** and (*S*)-**4** in DCM at 0 °C, using $Cu(acac)_2$ as the catalyst gave only adduct **13**, presumably via chelate **iv**; further heating converted **13** to **5**.

Water can promote Diels–Alder reactions,[8] so the combination of using water and/or cosolvents with a water-soluble Lewis acid as the catalyst was also investigated. Using $InCl_3$ in water at 50 °C slowed the decomposition rate of **3** so that only 2 equiv of **3** was needed, but (*S*)-**4** was largely insoluble. Dissolving **3** and (*S*)-**4** in a 4:1 mixture of H_2O/THF in the presence of $InCl_3$ improved the quinone's solubility and reduced the reaction time to 3 days. $GaCl_3$, $SmBr_2$, and $Yb(OTf)_3$, which are water-soluble, were less effective than $InCl_3$. For preparative purposes, the $InCl_3$-catalyzed Diels–Alder reactions were stopped after 3 days, adducts **5** and **13** were isolated, and then **13** was heated with additional **3** at 50 °C for an additional 3 days. This two-cycle process gave adduct **5** in 60% yield.

The formation of **6** using the Grieco protocol was complicated by the acidic C-12 hydroxyl group and occurred in only 52% yield (Scheme 3).[9] Treatment of **6** with cerium(IV) ammonium nitrate [CAN] in CH_3CN formed the C-25,C-26 σ bond and introduced the C-27,C-28 double bond in 80% yield (cf. **7**).[10] However, commonly used hydration conditions did not react with any of the four double bonds present in tetraene **7** but instead hydrated the C-12 carbonyl moiety.

When single-electron-transfer cyclizations occur in an oxygen atmosphere, the carbon-free radical produced by cyclization (i.e., **ii**, Scheme 1) reacts with a molecule of oxygen to form a hydroperoxide.[11] Reducing the peroxide linkage would therefore give an alcohol at C-27. Treatment of **6** with $Mn(OAc)_3$ in acetic acid with O_2 bubbled into the reaction mixture produced hydroperoxide **v**. However, since hydroperoxides are good nucleophiles, we were not surprised that hemiacetal **14** was produced. Addition of activated zinc dissolved in acetic acid cleaved the peroxide unit and formed the desired F-ring (cf. **15**).[11]

The hydration of the C-1,C-10 double bond of **15** would complete a synthesis of salvadione B. Unfortunately, this hydration eluded us. Fortunately, exposure of hydroperoxy hemiacetal **14** to the acidic resin Amberlyst-15 in refluxing DCM for 1 h gave diketone **16** in 96% yield. Notice that **16** also has a peroxyacetal moiety with a β-oriented oxygen at C-10. The treatment of peroxyacetal **16** with 6 equiv of acetic acid and 10 equiv of activated zinc powder in DCM cleaved the peroxide moiety and freed the C-27 alcohol (cf. **viii**). The acetic acid present also promoted the interconversion of the C-11 hemiacetal to C-12 and re-established a carbonyl group at C-11. This one-pot reduction/isomerization process produced (+)-salvadione B (**1**), which has spectral data identical to those reported,[2a] in 73% yield from peroxyacetal **16**.

Replacing the acetate in **3** with a selenide would not impact the Diels–Alder reaction or the free-radical cyclization. More importantly, the oxygen added to the radical cyclization should also oxidize the selenide allowing its elimination without requiring the addition of a stronger oxidant (Scheme 4). Indeed, selenide **12** reacted with (*S*)-**4**[4] with 0.2 equiv of $Eu(fod)_3$ neat at 90 °C resulted in its completion in only 2 days. Reactions carried out at reaction temperatures below 70 °C produced Diels–Alder adduct **17** and its regioisomer **18** in a 1:1 ratio. When the

(9) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

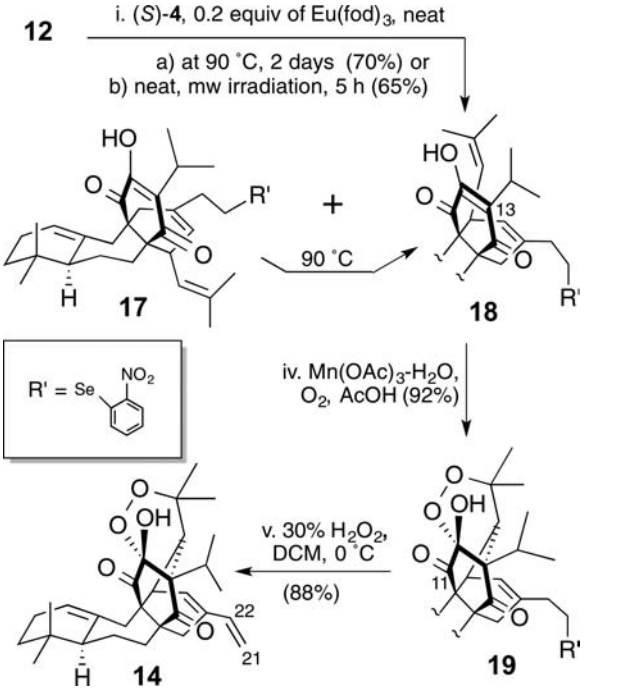
(10) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21–30.

(11) (a) Tategami, S.; Yamada, T.; Nishino, H.; Korp, J. D.; Kurosawa, K. *Tetrahedron Lett.* **1990**, *31*, 6371–6374. (b) Kumabe, R.; Nishino, H. *Tetrahedron Lett.* **2004**, *45*, 703–706.

reaction temperature was maintained at 90 °C, the rate of the retro-Diels–Alder reaction of triene **17** was faster than the retro-cyloaddition rate of **18**, allowing only selenide **18** to be isolated.[5]

In 1986, Gedye and co-workers reported that hydrolysis reactions and some oxidations benefited from microwave irradiation.[12a] Soon afterward, Giguere and Majetich reported their independent observations that microwave-heated Diels–Alder, Claisen, and ene reactions all demonstrated significant rate enhancements compared to traditional heating methods.[12b] Heating quinone (*S*)-**4** with selenide **12**, without solvent, using microwave irradiation at 50 °C for 2 h, followed by further heating at 80 °C for an additional 3 h, cleanly produced adduct **18** in 65% yield. The crude Diels–Alder adduct **18** was dissolved in acetic acid and treated with 1 equiv of manganese(III) acetate, and oxygen gas was vigorously bubbled into the reaction flask.[8] This radical cyclization produced peroxy hemiacetal **19** in 92% yield (along with a trace of product **14**, presumably via the oxidation of **19** by the oxygen gas). Addition of 30% aq H_2O_2 to the solution of crude **19** rapidly gave conjugated diene **14** in 88% yield.

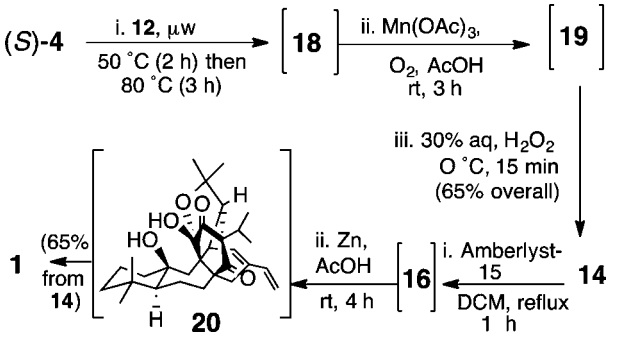
Scheme 4. Conversion of Selenide **12** to Peroxyacetal **14**



The three transformatiomns shown in Scheme 4 were amenable to a one-pot cascade process. In particular, quinone (*S*)-**4**, selenide **12**, and $Eu(Fod)_3$ were dissolved in Et_2O and concentrated to a residue under vacuum (Scheme 5). The resulting homogeneous mixture was heated without solvent in a Milestone Ethos microwave reactor for 2 h at 50 °C, followed by 3 h at 80 °C. The crude Diels–Alder adduct **18** was dissolved in acetic acid, and $Mn(OAc)_3$ hydrated with water was added. Oxygen was vigorously bubbled into the reaction mixture for 3 h or until TLC analysis indicated the reaction was complete. Addition of 30% aq H_2O_2 to the reaction mixture afforded peroxy hemiacetal **14** in 65% overall yield.

Treatment of **14** with Amberlyst-15 resin in refluxing DCM for 1 h provided hydroperoxy acetal **16**. Zinc metal and acetic acid were then added to the reaction mixture, followed by stirring at rt for 4 h. Extractive workup and

Scheme 5. Two One-Pot Syntheses of Salvadione B from (*S*)-**4**



purification gave (+)-salvadione B in 65% yield. In contrast, if the reduction was worked up after 15 min of reaction time, only hemiacetal **20**, which we have named (*iso*)-salvadione-B, was isolated. Reaction times >15 min but <4 h gave mixtures of **20** and **1**, in varying ratios; however, chromatography of the crude mixtures on silica gel gave only **1**. This observation suggests that (*iso*)-salvadione-B (**20**) may never be isolated from Nature. We also observed that pure samples of **1**, when left overnight at room temperature in $CDCl_3$, gave a mixture of **1** and **20**, presumably due to trace amounts of DCl.

In summary, salvadione-B (**1**) was synthesized in seven steps from known quinone (*S*)-**4**. The thermodynamically controlled Diels–Alder adduct required three transformations to make pentaene **6**. An oxidative radical cyclization in the presence of oxygen formed peroxyacetal **14**. The isomerization of the peroxyacetal introduced the C-10 hydroxyl group. Reduction of the peroxide linkage and interchanging the C-11 and C-12 oxidation states culminated in the synthesis of salvadione B. The insight gained from the stepwise synthesis enabled us to synthesize **1** via two-step, one-pot sequences of reactions in 33% overall yield from quinone (*S*)-**4**.

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Supporting Information Available. Experimental procedures and NMR data for new compounds; X-ray crystal data for **14** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L. *Tetrahedron Lett.* **1986**, *27*, 279–282. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.

The authors declare no competing financial interest.