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A Synthesis of (+)-Salvadione-A

George Majetich,* Yanyun Wang, Yang Li, Jason K. Vohs, and Gregory H. Robinson[†]

Department of Chemistry, University of Georgia, Athens, Georgia 30602

majetich@chem.uga.edu

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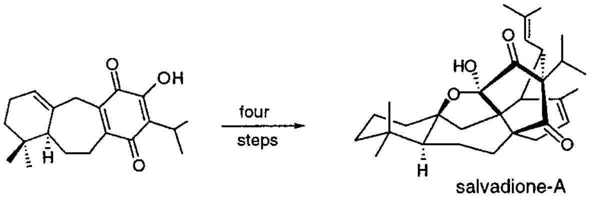
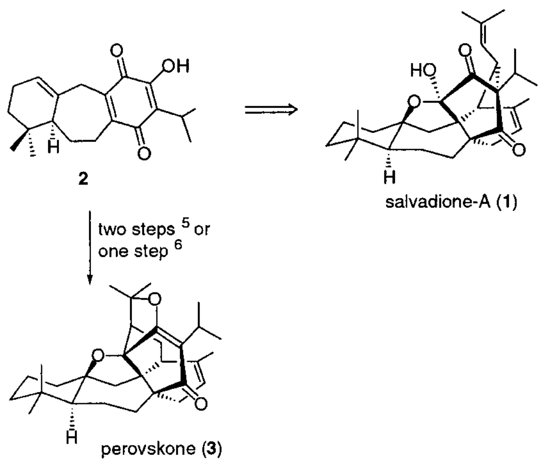
ABSTRACT



The *p*-benzoquinone shown is converted to the novel hexacyclic triterpene salvadione-A in four steps.

The genus *Salvia*, comprising more than 800 species, is the largest genus of the Lamiaceae family.[1] *Salvia bucharica*, popularly known in Pakistan as "sursaudah", is found throughout Central Asia,[2] and is used in popular medicines for liver disorders as well as for its cooling effects. In 1999, salvadione-A (**1**) was isolated from sursaudah by Ahmad and co-workers, and its structure was rigorously established by means of 2D-NMR spectroscopy and X-ray diffraction analysis (Scheme 1).[3] Since salvadione-A possesses many of the salient features of perovskone (**3**),[4] we recognized that it could be synthesized from quinone **2**, a key intermediate in our perovskone synthesis.[5] A detailed discussion of our synthesis of salvadione-A follows.

Scheme 1



Scheme 2 summarizes our retrosynthetic analysis for salvadione-A. We have found that dienes add to the α-face of quinone **2**.[5,6] In addition, the presence of a Lewis acid allows the Diels−Alder reaction to occur at temperatures as low as −20 °C, and also controls the regioselectivity of the cycloaddition when an asymmetric diene, such as isoprene, is used.[5,6]

The use of triene **4** as the diene substrate raises the question of which conjugated diene moiety, the 3,5- or the

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[†] Author for correspondence regarding the X-ray studies.

(1) (a) Fujita, E.; Node, M. Diterpenoids of *Rabdosia Species.* In *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, India, 1956; p 189. (c) Kirtikar, K. R.; Basu, B. D. *Indian Medicinal Plants*; Indian Press: Allahabad, India, 1918; p 1031.

(2) Nasir, E.; Ali, S. I. *Flora of Pakistan*; Fakhri Printing Press: Karachi, Pakistan, 1986; Vol. 56, p 156.

(3) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Ali, Z.; Jassbi, A. R.; Abbas, M.; Clardy, J.; Lobkovsky, E.; Tareen, R. B.; Iqbal, M. Z. *J. Org. Chem.* **1999**, *64*, 8465−8467.

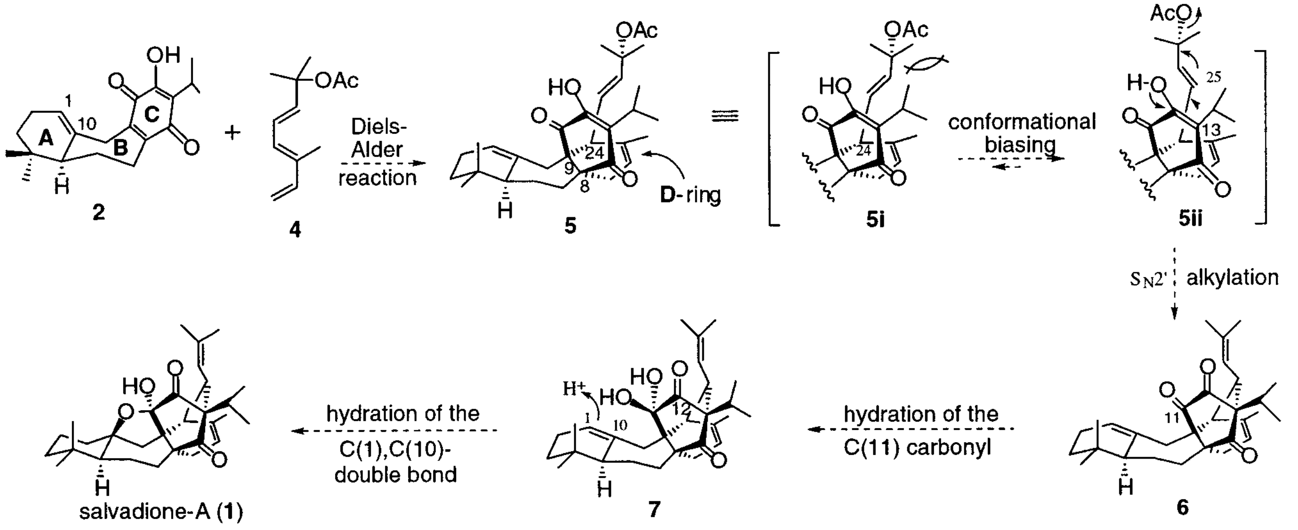
(4) Parvez, A.; Choudhary, M. I.; Akhter, F.; Noorwala, M.; Mohammad, F. V.; Hasan, N. M.; Zamir, T.; Ahmad, V. U. *J. Org. Chem.* **1992**, *57*, 4339−4340.

(5) For our synthesis of (±)-perovskone, see: Majetich, G.; Zhang, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4979−4980.

(6) Optically active *p*-benzoquinone **2** has been prepared in 11 steps and in >50% overall yield. A manuscript detailing this work and a synthesis of (+)-perovskone is under review. See: Majetich, G.; Zhang, Y.; Tian, X.; Britton, J. F.; Wang, Y.; Li, Y. The Total Synthesis of (±)- and (+)-Perovskone.

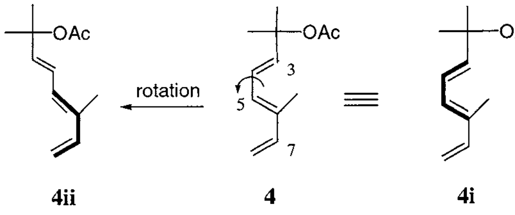
10.1021/ol035380i CCC: $25.00

Scheme 2



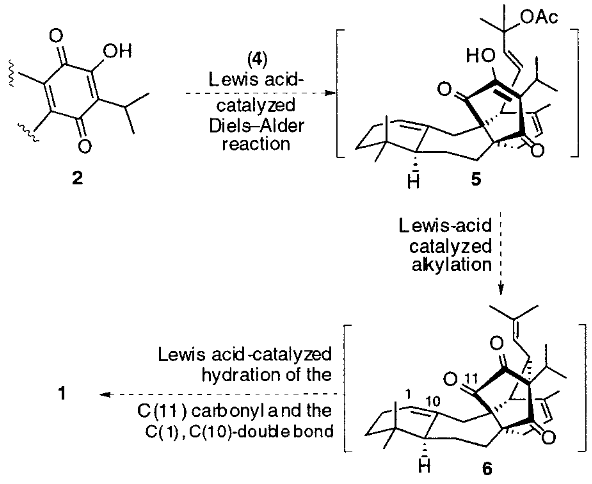
5,7-system, should preferentially take part in the Diels–Alder addition. Scrutiny of triene **4** indicates that the presence of a *Z*-methyl substitutent as part of the 3,5-butadiene moiety reduces its reactivity by hindering the likelihood of the s-cis form (cf. **4i**, Scheme 3), whereas the 5,7-diene readily adopts an s-cis conformation (cf. **4ii**). Hence, the cycloaddition of **2** with **4** will produce only adduct **5**, which has the correct stereochemistry at C(8), C(9), and C(24).

Scheme 3



Protection of the C(2) hydroxyl of triene **4** as an acetate permits the subsequent formation of the C(13),C(25)-bond by means of an intramolecular S_N2'-alkylation of the latent 1,3-dione present in the C-ring.[7] We predicted that simple conformational biasing, prior to the S_N2'-alkylation, would control the C(25) stereochemistry. In particular, nonbonded steric interactions between the C(24) side chain and the C(13) isopropyl unit would disfavor conformer **5i**, thus causing the less sterically congested conformation **5ii** to predominate, leading to the formation of pentacycle **6**. Examination of a Dreiding molecular model of triketone **6** reveals that the C(11) carbonyl oxygen is situated almost directly above the C(10) carbon atom, which should faciliate hydration of the C(1),C(10)-trisubstituted double bond, thereby completing a synthesis of salvadione-A (i.e., **6** → **7** → **1**). Since each of these transformations can in principle be carried out by using Lewis acid catalysis, the judicious choice of catalyst and reaction conditions should permit the Diels–Alder reaction, the intramolecular S_N2'-alkylation, and the sequential hydration of the C(11)-carbonyl and tetrahydrofuran formation to proceed in a tandem cascade fashion (Scheme 4). While the synthesis of salvadione-A via this cascade-based process is our ultimate goal, we decided to first synthesize **1** in a stepwise fashion.

Scheme 4



Triene **4** was synthesized from *trans*-*β*-ocimene (**8**) in three simple steps (Scheme 5).[8] The reaction of **8** with 1 equiv of mCPBA in cold methylene chloride gave a high yield of epoxide **9**,[9] which produced octa-3(*E*),5(*E*)-trien-2-ol (**10**) when treated with excess LDA at 0 °C.

Unfortunately, acetate **4**, derived from tertiary alcohol **10**, was shown to undergo rapid elimination at ambient temper-

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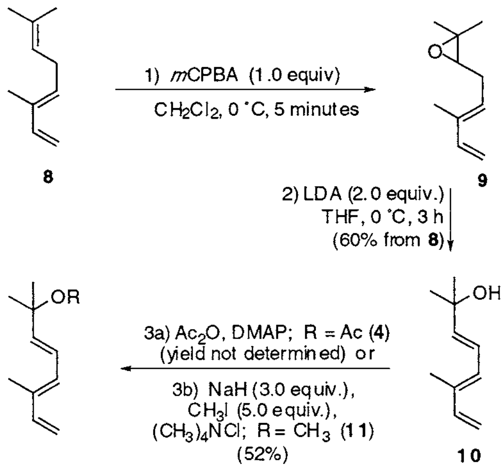
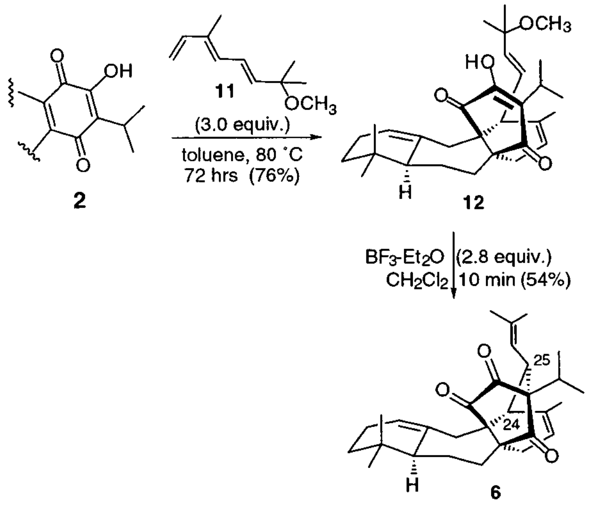
[7] For the alkylation of 1,3-diones with allylic carbonates and allylic acetates, see: Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176–2177.

Scheme 5



ature, upon attempted purification, or upon exposure to mild Lewis acid catalysts (even at low temperatures). Methyl ether **11** was prepared in the hope that the methoxyl group would be less prone to elimination, thereby permitting the Diels–Alder reaction to occur. Triene ether **11** was thermally stable and reacted over a 72-h period with quinone **2** at 80 °C to afford adduct **12** in 76% yield (Scheme 6); an X-ray analysis of adduct **12** confirmed the predicted facial and regioselectivity of this cycloaddition.[10,13]

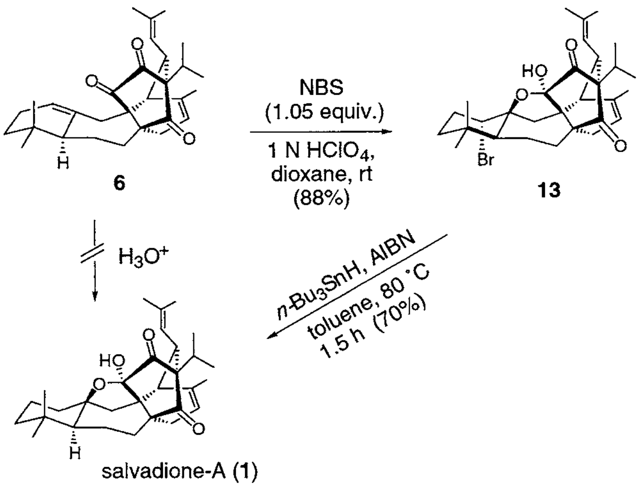
Scheme 6



Treatment of adduct **12** with excess boron trifluoride etherate in CH_2Cl_2 at 0 °C rapidly gave the S_N2'-alkylation product in 54% yield. ^1H NMR data suggested that the 2.7-Hz coupling constant between the C(24) and C(25) methines was indicative of a dihederal angle of almost 120°, indicating that C(25) had the desired stereochemistry; molecular models indicated that the wrong stereochemistry at C(25) would produce a dihedral angle of about 30° and a coupling constant of >6 Hz.

A fundamental tenet in organic chemistry is that carbonyl groups with electron-withdrawing subsitutents are easily hydrated. Indeed, in 1963 Bakule and Long demonstrated that 1,2-cyclohexandiones which cannot enolize, such as **6**, are completely and rapidly hydrated when exposured to dilute aqueous acid.[11] While the reaction of triketone **6** under various aqueous acidic conditions or with water-soluble Lewis acids produced a geminal diol, hydration of the C(1),C(10)-double bond was not observed. These observations suggest that the C(12) carbonyl, which is geometrically unable to assist in the hydration of the C(1),C(10)-double bond, is preferentially hydrated. Fortunately, the observation that the C(11) carbonyl oxygen was near the C(10) carbon atom of the trisubstituted double bond of **6** offered a solution to our hydration difficulties. We speculated that the bromonium ion intermediate generated from the C(1),C(10)-double bond would be opened by the oxygen atom of the C(11) carbonyl to form the desired tetrahydrofuran ring. Treatment of **6** with NBS and 1 N perchloric acid gave bromide **13** in 88% yield (Scheme 7).[12,13] Note that triketone **6** contains two other trisubstituted double bonds which might also react with bromine. However, the steric influence of the C-ring of triketone **6** prevents the bromonium ions derived from

Scheme 7



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(8) Ocimene is sold by International Flavors & Fragrances as a mixture of the C(3),C(4)-*E* and -*Z* isomers. Treatment of this mixture with gaseous SO_2 selectively forms an adduct with the C(3),C(4)-*E* isomer, which is easily separated from the unreacted C(3),C(4)-*Z* isomer by chromatography on silica gel. Extrusion of SO_2 from the adduct provides pure *trans*-α-ocimene (**8**). For the total synthesis of *trans*-α-ocimene from the SO_2 adduct of isoprene, see: Chou, T.; Tso, H.-H.; Chang, L.-J. *J. Chem. Soc., Chem. Commun.* **1984**, 1323–1324.

(9) Conjugation diminishes the reactivity of an alkene in epoxidations; thus, isolated alkenes are usually epoxidized before a conjugated alkene, see: Hiyama, T.; Kanakura, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1978**, 3051–3054.

(10) Crystal data for $C_{31}H_{44}O_4$ (**12**): MW = 480.66, orthorhombic, *Pbca*, $a = 12.679(5)$ Å, $b = 20.791(10)$ Å, $c = 21.054(10)$ Å, α, β, $\gamma = 90°$, $V = 5550(4)$ Å^3, $Z = 8$, $T = 293(2)$ K, μ(Mo Kα) = 0.71073 Å, $D_{calcd} = 1.151$ Mg/m^3, $R(1) = 8.49\%$ for 6642 observed independent reflections ($I > 2\sigma(I)$). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.

these alkenes from opening. Removal of the bromine atom via free radical reduction completed our stepwise synthesis of (±)-salvadione-A. The use of optically active *p*-benzoquinone **2**[6] produced salvadione-A with $[\alpha]^{24}_{D}$ +37.61 (*c* 0.36, $CHCl_3$); the reported value is +37.92 (*c* 0.37, $CHCl_3$).

In summary, salvadione-A, which has six rings and eight chiral centers, was synthesized from quinone **2** in only four steps. The first two steps feature a stereo- and regiospecific Diels−Alder reaction and an intramolecular alkylation, respectively. The C(11) carbonyl was resistant to hydration. A synthesis of salvadione-A was completed by means of an intramolecular bromohydrin reaction, followed by free radical reduction. Our quest to develop conditions to synthesize salvadione-A via a cascade-based process, while perhaps unlikely in light of our many observations, continues.

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(11) (a) Bakule, R.; Long, F. A. *J. Am. Chem. Soc.* **1963**, *85*, 2309−2312. (b) Sandris, C.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1958**, 338−344. (c) Sandris, C.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1958**, 1524−1526.

(12) Crystal data for $C_{30}H_{41}O_4Br$ (**13**): MW = 545.54, monoclinic, $P2_1/c$, $a = 13.308(4)$ Å, $b = 15.807(5)$ Å, $c = 13.969(4)$ Å, $\beta = 110.223(5)°$, $V = 2757.2(14)$ Å^3, $Z = 4$, $T = 293(2)$ K, μ(Mo Kα) = 0.71073 Å, $D_{calcd} = 1.314$ Mg/m^3, $R(1) = 7.62\%$ for 5595 observed independent reflections ($I > 2\sigma(I)$). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated as idealized contributions.

(13) Crystal data and other details for compound **12**, the adduct of quinone **2**, and triene **11** have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Tel +44 1223 336408, Fax +44 1223 336033, E-mail http://www.ccdc.cam.ac.uk); see CCDC 213664. For crystal data and other details for bromide **13**, see CCDC 209551.