A Synthesis of (+)-Salvadione-A

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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 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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⁽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.

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⁽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 (\pm)- and (+)-Perovskone.



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).

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(10) carbon atom, which should faciliate hydration of the C(1),C(10)-trisubstituted double bond, thereby completing

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a synthesis of salvadione-A (i.e., $6 \rightarrow 7 \rightarrow 1$). 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.

Triene **4** was synthesized from *trans-\beta*-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-

⁽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.



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} Treatment of adduct **12** with excess boron trifluoride etherate in CH₂Cl₂ 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

⁽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 SO₂ 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 SO₂ from the adduct provides pure *trans*- α -ocimene (8). For the total synthesis of *trans*- α -ocimene from the SO₂ 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 C₃₁H₄₄O₄ (**12**): MW = 480.66, orthorhombic, *Pbca*, a = 12.679(5) Å, b = 20.791(10) Å, c = 21.054(10) Å, α , β , $\gamma = 90^{\circ}$, V = 5550(4) Å³, Z = 8, T = 293(2) K, μ (Mo K α) = 0.71073 Å, $D_{calcd} = 1.151$ Mg/m³, R(1) = 8.49% for 6642 observed independent reflections (I > 2σ (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 [α]²⁴_D +37.61 (*c* 0.36, CHCl₃); the reported value is +37.92 (*c* 0.37, CHCl₃).

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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(c) Sandris, C.; Ourisson, G. Bull. Soc. Chim. Fr. 1958, 1524–1526.

⁽¹²⁾ Crystal data for C₃₀H₄₁O₄Br (13): MW = 545.54, monoclinic, P2₁/ c, a = 13.308(4) Å, b = 15.807(5) Å, c = 13.969(4) Å, $\beta = 110.223(5)^{\circ}$, V = 2757.2(14) Å³, Z = 4, T = 293(2) K, μ (Mo K α) = 0.71073 Å, D_{calcd} = 1.314 Mg/m³, R(1) = 7.62% for 5595 observed independent reflections (I > 2 σ (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.